Toxicological profile for

Triacetin

This ingredient has been assessed to determine potential human health effects for the consumer. It was considered not to increase the inherent toxicity of the product and thus is acceptable under conditions of intended use.

1. Name of substance and physico-chemical properties

1.1. IUPAC systematic name

2,3-Diacetyloxypropyl acetate (PubChem)

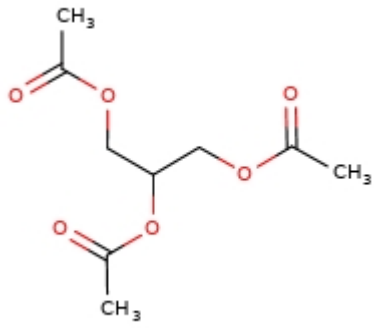
1.2. Synonyms

Acetic, 1,2,3-propanetriyl ester; 1,2,3-Propanetriol triacetate; 1,2,3-Propanetriyl triacetate; 4-02-00-00253 (Beilstein Handbook Reference); AI3-00661; Acetin, tri-; BRN 1792353; CCRIS 9355; EINECS 203-051-9; Enzactin; FEMA No. 2007; Fungacetin; Glycerin triacetate; Glycerol triacetate; Glyceryl triacetate; Glyped; HSDB 585; Kesscoflex TRA; Kodaflex triacetin; NSC 4796; Triacetin; Triacetina [INN-Spanish]; Triacetine [INN-French]; Triacetinum [INN-Latin]; Triacetyl glycerine; Triacetylglycerol; UNII-XHX3C3X673; Vanay; 1,2,3-Propanetriol, 1,2,3-triacetate (ChemIDplus (a))

1.3. Molecular formula

C9 H14 O6

1.4. Structural Formula



(ChemIDplus (a))

1.5. Molecular weight (g/mol)

218.2

1.6. CAS registration number

102-76-1

1.7. Properties

1.7.1. Melting point

(°C): 2-4 or 78 (ChemSpider); 3 (OECD SIDS; US EPA, 2012); -78 (EPISuite, 2017; Merck, 2013)

1.7.2. Boiling point

(°C): 257-260 (ChemSpider; EPISuite, 2017; US EPA, 2012)

1.7.3. Solubility

58,000 mg/L at 25°C (EPISuite, 2017); 58,000-70,000 mg/L at 25°C (US EPA, 2012); 70,000 mg/L (ChemSpider); 52,130 mg/L at 24.5°C or 0.27 M [58,914 mg/L] (PubChem); 64,000 mg/L at 20°C (GESTIS)

1.7.4. pKa

No data available to us at this time.

1.7.5. Flashpoint

(°C): 138 ->145 (Maag et al. 2010); 148-149 (ChemSpider); 138 (closed cup) (PubChem); 137.7 (closed cup) (GSBL, 2021)

1.7.6. Flammability limits (vol/vol%)

Not flammable; explosion limits: 1.05% (lower), 7.73% (upper) (Maag et al. 2010); Lower flammable limit: 1.0% by volume at 373 deg F (189 deg C) (PubChem)

1.7.7. (Auto)ignition temperature

(°C): 432 (Maag et al. 2010); 433 (PubChem); 430 (IGS, 2021)

1.7.8. Decomposition temperature

(°C): No data available to us at this time.

1.7.9. Stability

Stable at normal temperatures and pressure (Maag et al. 2010); Stable. Incompatible with strong oxidizing agents. Combustible (ChemSpider)

1.7.10. Vapor pressure

2.48x10^-3 mmHg at 25°C (EPISuite, 2017); 0.15 kPa [1.125 mmHg] at 20°C (GSBL, 2021)

1.7.11. log Kow

0.25 (EPISuite, 2017); 0.21 (PubChem); 0.34 (ChemSpider); 0.25 at 20°C (GSBL, 2021)

2. General information

2.1. Exposure

Reported levels from use as a flavouring (ppm): (FEMA, 1994)

Food category	**Usual**	**Max**	**Food category**	**Usual**	**Max**
Alcoholic beverages	0.26	0.72	Gelatins, puddings	0.10	0.29
Baked goods	0.40	0.59	Hard candy	0.04	0.05
Chewing gum	0.01	0.01	Nonalcoholic beverages	0.11	0.28
Confection, frosting	0.01	0.02	Soft candy	0.20	0.76

Frozen dairy	0.20	0.64			

Estimated intake from flavouring use: 0.1.6242 mg/kg bw/day.

As taken from Burdock, 2010.

“Occupational exposure to triacetin can occur through dermal contact and inhalation at production sites during operations such as cleaning, sampling, analysis, and drum filling. Triacetin has the following uses in consumer products: a solvent for celluloid and photographic films; a plasticizer for cigarette filters; a fungicide in cosmetics; a fixative in perfumery; and a general purpose food additive.”

“An estimate of the cumulative oral intake in the United Kingdom suggests that an adult might ingest 7.8 mg triacetin/day, and the daily intake was calculated to be 0.111 mg/kg-day (OECD, 2002).”

As taken from US EPA. 2012. Provisional Peer-Reviewed Toxicity Values for Triacetin (CASRN 102-76-1).

“According to the 2012 TSCA Inventory Update Reporting data, 10 reporting facilities estimate the number of persons reasonably likely to be exposed during the manufacturing, processing, or use of triacetin in the United States may be as low as less than 10 workers and as high as 99 workers per plant; the data may be greatly underestimated due to confidential business information (CBI) or unknown values(1). [(1) US EPA; Chemical Data Reporting (CDR). Non-confidential 2012 Chemical Data Reporting information on chemical production and use in the United States. Available from, as of June 2, 2015: http://www.epa.gov/cdr/pubs/guidance/cdr_factsheets.html**PEER REVIEWED**

Occupational exposure to triacetin may occur through inhalation and dermal contact with this compound at workplaces where triacetin is produced or used. Use data indicate that the general population may be exposed to triacetin via dermal contact with consumer products containing triacetin(SRC). **PEER REVIEWED**

Primary use is as a cellulose plasticizer in the manufacture of cigarette filters, and its second largest use is as a component in binders for solid rocket fuels. Smaller amounts are used as a fixative in perfume, as a plasticizer for cellulose nitrate, in the manufacture of cosmetics, and as a carrier in fungicidal compositions. [Morrison LR; Glycerol. Kirk-Othmer Encyclopedia of Chemical Technology (1999-2015). John Wiley & Sons, Inc. Online Posting Date: December 4, 2000] **PEER REVIEWED**

Triacetin is used in pharmaceuticals as a hydrophilic plasticizer in polymeric coatings of capsules, tablets, beads, and granules, with typical concentrations of 10% to 35% w/w. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/EXPL THER/ The FDA approved food additive Triacetin (glyceryl triacetate, GTA) has been safely used for acetate supplementation therapy in Canavan disease, a leukodystrophy due to aspartoacylase (ASPA) mutation. This study characterized the effects of GTA on the proliferation

and differentiation of six primary glioblastoma (GBM)-derived glioma stem-like cells (GSCs) relative to established U87 and U251 GBM cell lines, normal human cerebral cortical astrocytes, and murine neural stem cells. GTA reduced proliferation of GSCs greater than established GBM lines. Moreover, GTA reduced growth of the more aggressive mesenchymal GSCs greater than proneural GSCs. Although sodium acetate induced a dose-dependent reduction of GSC growth, it also reduced cell viability. GTA-mediated growth inhibition was not associated with differentiation, but increased protein acetylation. These data suggest that GTA-mediated acetate supplementation is a novel therapeutic strategy to inhibit GSC growth. [Long PM et al; J Cell Physiol 230 (8): 1929-43 (2015)] **PEER REVIEWED** PubMed Abstract Full text: PMC4414874

Triacetin has been used with prostaglandin E2 (PGE2) to form a gel used for preinduction cervical softening [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

Treatment of onychomycosis (nail fungus), tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corporis (ringworm), monilial impetigo and dermatitis. [Novak, K.M. (ed.). Drug Facts and Comparisons 59th Edition 2005. Wolters Kluwer Health. St. Louis, Missouri 2005., p. 2024] **PEER REVIEWED**"

As taken from HSDB, 2015

"Occupational exposure to triacetin may occur through inhalation and dermal contact with this compound at workplaces where triacetin is produced or used. The general population may be exposed to triacetin via inhalation and dermal contact from use of consumer products containing this compound" (Maag et al. 2010).

"Consumer exposure: intake and dermal/inhalation route through the use as a food additive and topical antifungal and perfume fixative or cigarette filter, respectively" (Maag et al. 2010).

"Due to its uses triacetin soon becomes diffused into small quanties and there is little possibility of large scale human contact or environmental effect after it leaves the manufacturers first line customers' premises. Its use is adhesive may give skin contact. As a carrier and solvent for food soft drinks flavouring materals ingestion will occur. Very small amounts can be found in cigarette smoke through a filter tip using triacetin as the plasticizer" (Maag et al. 2010).

Estimated intake of triacetin in the US is 83 mg/day, which is equivalent to 1.4 mg/kg bw/day (JECFA, 2002)

Triacetin is listed as an ingredient (at given concentrations, where specified) in personal care, inside the home, pesticide (3-5%) and auto products by the CPID.

Triacetin is used as an antimicrobial agent, film forming agent, fragrance, plasticiser and solvent in cosmetics in the EU. As taken from CosIng (undated)

Triacetin is listed as a fragrance ingredient on the US EPA InertFinder Database (2022) and by IFRA.

"The aim was to describe the exposure to excipients among neonates hospitalised in the neonatal intensive care unit (NICU) of a public hospital in Brasilia, Brazil. This was a retrospective study based on medicines that were prescribed electronically to neonates (≤28 days) who were admitted to the NICU of a hospital in Brasilia between January 1 and March 31, 2012. Excipients were identified from the medicine package leaflets and were classified according to toxicity. Seventy-nine infants received a total of 1,303 prescriptions comprising 77 formulations and 70 active drugs. Eighty-six excipients were identified, of which, 9 were harmful excipients (HE) and 48 were potentially harmful excipients (PHE). Almost all the neonates (98.7 %) were exposed to at least one HE and PHE. Preterm neonates (n = 64; 1,502 neonate days) presented high risk of exposure to polysorbate 80 (3.26/100 neonate days), sodium hydroxide (3.39), PG (3.19) and propylparaben (3.06). Full-term neonates (n = 15; 289 neonate days) presented risks in relation to phenol (4.84), ethanol (3.8) and sodium citrate (3.46). CONCLUSION: Neonates in NICUs in Brazil are exposed to

a wide variety of HE and PHE with unpredictable results. Safer alternatives are needed, as well as further studies on the subject". As taken from Souza et al. 2014. Eur. J. Pediatr. 173(7), 935-45. PubMed, 2015 available at http://www.ncbi.nlm.nih.gov/pubmed/24500397.

"This study examined airborne emissions from cigarette butts for styrene, 2-methyl-2-cyclopenten-1-one, naphthalene, triacetin, and nicotine. Ten experiments were conducted by placing butts in a stainless steel chamber and measuring the chemical concentrations in chamber air. Emission rates were determined from the concentrations. Triacetin and nicotine concentrations were roughly 50% of initial concentrations after 100 hours, while concentrations of other chemicals decayed to less than 10% of initial concentrations within 24 hours. Initial emission rates per cigarette butt ranged from 200 to 3500 ng h-1 . Triacetin and nicotine emission rates at 25°C were 1.6 to 2.2 times higher than the rates at 20°C, while the emission rates of other chemicals at 25°C were 1.1 to 1.3 times higher than the rates at 20°C only during the first sampling period. The chemical concentrations and emission rates at 30°C were comparable or lower than the values at 25°C, possibly due to different batches of cigarettes used. The 24-hours emitted mass of nicotine from a cigarette butt at 25°C could be up to 14% of the literature reported nicotine masses emitted from a burning cigarette." As taken from Gong M et al. 2020. Indoor Air 30(4), 711-724. PubMed, 2021 available at https://pubmed.ncbi.nlm.nih.gov/31955455/

"With five trillion generated per year, cigarette butts are some of the most common litter worldwide. However, despite the potential environmental and human health risks from cigarette butts, little effort has been made to understand airborne emissions from cigarette butts. This study examined the influence of temperature, relative humidity and water saturation on airborne chemical emissions from cigarette butts. Experiments were conducted to measure the emitted chemical masses from butts using headspace analysis after the butts were conditioned in a controlled chamber under four conditions (30 °C and 25% relative humidity (RH), 30 °C and 50% RH, 40 °C and 25% RH, 40 °C and 50% RH) and in an outdoor environment (two sets of experiments in both summer and winter). The measured target chemicals included furfural, styrene, ethylbenzene, 2-methyl-2-cyclopenten-1-one, limonene, naphthalene, triacetin, and nicotine. Results indicate that increased temperature increased the emission rates of all target chemicals from the butts conditioned in both chambers and outdoors. In addition, water has considerable influence on the emission rates from the butts. Seven of the eight chemicals were emitted faster from butts at 50% RH compared to 25% RH. During water saturation, chemicals with high water solubility and partition coefficient between water and air, e.g., triacetin and nicotine, mainly migrate into the surrounding environment via aqueous rather than airborne routes. This highlights the importance of rainfall events on airborne emission variability for triacetin and nicotine. Water saturation increased the decay rate (decreased the decay time) of emitted mass measured in headspace analysis for the two carbonyl chemicals: furfural and 2-methyl-2-cyclopenten-1-one, while it decreased the decay rate (increased the decay time) for the three hydrocarbons (styrene, limonene, and naphthalene)." As taken from Poppendieck D et al. 2020. Sci. Total Environ. 712, 136422. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31931215/

"[Triacetin] has been used in the topical treatment of minor dermatophyte infections. It has a role as a plant metabolite, a solvent, a fuel additive, an adjuvant, a food additive carrier, a food emulsifier, a food humectant and an antifungal drug."

As taken from PubChem, 2022

Glycerol triacetate (CAS RN 102-76-1) is used as a cosmetic biocide ("topical use only"), flavour enhancer, fragrance ingredient ("topical use only"), humectant, plasticizer and solvent in non-medicinal and general natural health products (Health Canada, 2022).

2.2. Combustion products

Heating 30g of triacetin in portions to 700ºC until the organic material had disappeared in an air flow of 1.5 l/min, 9 pyrolysis products were identified, including 3 PAHs (Kröller 1968).

This ingredient was investigated in a pyrolysis study. Results are given in Baker and Bishop (2004) J. Anal. Appl. Pyrolysis, 71, 2004, pp. 223-311

Ingredients CAS Number	Chemical Class	Mol. Wt. (M) Bp or Mp (0C)	Max cig Appln. Level (ppm)	Purity of sample Pyrolysed (%)	Composition of pyrolysate (Compound %)	Max level in smoke (ug)
Triacetin CAS 102-76-1	Tri ester	M=218 Mp 32 Bp 131 at 7 mm Hg	1,190	99	Triacetin 98.5 Diacetin 1.4 1 Unidentified compound 0.1	590 8 0.6

In a pyrolysis study, 100% of triacetin added to cigarettes was transferred intact to the smoke (Purkis et al. 2011).

2.3. Ingredient(s) from which it originates

Synthesised by direct reaction of glycerol with acetic acid in the presence of Twitchell's reagent, or in benzene solution of glycerol and boiling acetic acid in the presence of a cationic resin (Zeo-Karb H) pretreated with dilute sulphuric acid.

Reported found in papaya.

As taken from Burdock, 2010.

"Triacetin occurs naturally in small quantities in the seed of European spindletree(1) and papaya(2). [(1) Morrison LR; Glycerol. Kirk-Othmer Encyclopedia of Chemical Technology. (1999-2015). New York, NY: John Wiley & Sons. Online Posting Date: December 4, 2000. (2) USDA; Dr. Duke's Phytochemical and Ethnobotanical Databases. Plants with a chosen chemical. Triacetin. Washington, DC: US Dept Agric, Agric Res Service. Available from, as of May 28, 2015: http://www.ars-grin.gov/duke/**PEER REVIEWED**

Triacetin detections in plants(1).

Genus species	**Family**	**Common name**	**Part**	**Concn (ppm)**
Carica papaya	Caricaceae	Papaya	Fruit	not reported

[(1) USDA; Dr. Duke's Phytochemical and Ethnobotanical Databases. Plants with a chosen chemical. Triacetin. Washington, DC: US Dept Agric, Agric Res Service. Available from, as of May 28, 2015: http://www.ars-grin.gov/duke/**PEER REVIEWED**

Other Environmental Concentrations:

Triacetin is a tobacco ingredient and has been identified in tobacco smoke(1). [(1) Rodgman A, Perfetti TA; The Chemical Components of Tobacco and Tobacco Smoke. 2nd ed., Boca Raton, FL: CRC Press p. 384 (2009)] **PEER REVIEWED**"

As taken from HSDB, 2015

3. Status in legislation and other official guidance

FIFRA Requirements:

Residues of triacetin are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals. Use: solvent, cosolvent. [40 CFR 180.930 (USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of April 20, 2015: http://www.ecfr.gov **PEER REVIEWED**

FDA Requirements:

An ingredient whose use in food or food packaging is subject to a prior sanction or approval within the meaning of section 201(s)(4) of the Act is exempt from classification as a food additive. ... Substances classified as plasticizers, when migrating from food-packaging material shall include ... triacetin. [21 CFR 181.27 (USFDA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of April 20, 2015: http://www.ecfr.gov **PEER REVIEWED**

Substance added directly to human food affirmed as generally recognized as safe (GRAS). [21 CFR 184.1901 (USFDA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of April 20, 2015: http://www.ecfr.gov **PEER REVIEWED**

Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses: triacetin is included in topical antifungal drug products. [21 CFR 310.545(a)(22) (USFDA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of April 20, 2015: http://www.ecfr.gov **PEER REVIEWED**

Triacetin used as a general purpose food additive is generally recognized as safe when used in accordance with good manufacturing or feeding practice. [21 CFR 582.1901(USEPA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of April 20, 2015: http://www.ecfr.gov **PEER REVIEWED**

As taken from HSDB, 2015

Triacetin is included on the FDA’s inventory of “Substances Added to Food (formerly EAFUS)” as a GRAS (generally recognized as safe) flavoring agent or adjuvant, formulation aid, humectant, masticatory substance, processing aid, solvent or vehicle, and surface-finishing agent. It is included under 21 CFR sections 184.1901 (triacetin), 181.27 (plasticizers), 175.300 (resinous and polymeric coatings) and 175.320 (resinous and polymeric coatings for polyolefin films) (FDA, 2022a,b).

There is a REACH Dossier on triacetin (ECHA, undated).

Triacetin (CAS RN 102-76-1) is not classified for packaging and labelling under Regulation (EC) No. 1272/2008 (ECHA, 2022).

Glyceryl triacetate is listed in the US EPA InertFinder Database (2022) as approved for food (as a stabilizer and (co)solvent), non-food and fragrance use pesticide products. For food use it is covered under 40 CFR Parts 180.920 (Inert ingredients used pre-harvest; exemptions from the requirement of a tolerance) and 180.930 (Inert ingredients applied to animals; exemptions from the requirement of a tolerance) (US EPA, 2022b).

Glycerol triacetate (CAS RN 102-76-1) is included on the US EPA list of Safer Chemical Ingredients with functional use: solvents (US EPA, 2022).

Glyceryl triacetate (CAS RN 102-76-1) is listed in the US EPA Toxic Substances Control Act (TSCA) inventory and also on the US EPA 2020 CDR list (Chemical Data Reporting Rule).

US EPA 2020 CDR List. US EPA TSCA inventory1,2,3-Propanetriol, triacetate / glyceryl triacetate (CAS RN 102-76-1) is included on the New Zealand Inventory of Chemicals and does not have an

individual approval but may be used under an appropriate group standard (NZ EPA, 2006). Itis classified according to the New Zealand authorities (NZ EPA CCID).

Triacetin (FEMA no. 2007) has been given GRAS (generally recognized as safe) status by FEMA (Hall RL and Oser BL, 1965).

1,2,3-Propanetriol, triacetate (CAS RN 102-76-1) “poses no unreasonable risk to human health based on Tier I assessment under the NICNAS IMAP assessment framework” (AICIS, 2013).

Glyceryl triacetate (CAS RN 102-76-1, E 1518) is authorised for use as a food additive in the EU under EU Regulation No. 1129/2011 (European Commission, 2011).

Triacetin is included on the US FDA’s list of inactive ingredients for approved drug products. It is permitted for use as an ingredient in various products, at the following maximum potencies per unit dose and maximum daily exposures:

Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency per unit dose	Maximum Daily Exposure (MDE)
TRIACETIN	ORAL	CAPSULE	102761	XHX3C3X673		13mg
TRIACETIN	ORAL	CAPSULE, COATED PELLETS	102761	XHX3C3X673	1.21mg	
TRIACETIN	ORAL	CAPSULE, DELAYED RELEASE	102761	XHX3C3X673	5.1mg	
TRIACETIN	ORAL	CAPSULE, EXTENDED RELEASE	102761	XHX3C3X673		467mg
TRIACETIN	ORAL	CONCENTRATE	102761	XHX3C3X673	50mg/1ml	
TRIACETIN	ORAL	POWDER, FOR SUSPENSION	102761	XHX3C3X673		12mg
TRIACETIN	ORAL	SUSPENSION	102761	XHX3C3X673		7mg
TRIACETIN	ORAL	SUSPENSION, EXTENDED RELEASE	102761	XHX3C3X673		4mg
TRIACETIN	ORAL	TABLET	102761	XHX3C3X673		208mg
TRIACETIN	ORAL	TABLET, CHEWABLE, EXTENDED RELEASE	102761	XHX3C3X673		2mg
TRIACETIN	ORAL	TABLET, COATED	102761	XHX3C3X673	1mg	
TRIACETIN	ORAL	TABLET, DELAYED RELEASE	102761	XHX3C3X673		7mg
TRIACETIN	ORAL	TABLET, EXTENDED RELEASE	102761	XHX3C3X673		11mg

TRIACETIN	ORAL	TABLET, FILM COATED	102761	XHX3C3X673	15.12mg	
TRIACETIN	TRANSDERMAL	SYSTEM	102761	XHX3C3X673	22.1mg	

As taken from FDA, 2022c.

US EPA Regional Removal Management Levels for Chemicals (RMLs)

	TR=1E-04, HQ=1	TR=1E-04, HQ=3		TR=1E-04, HQ=1	TR=1E-04, HQ=3
Oral Slope Factor (mg/kg-day)$^{-1}$ (SFO)	-	-	Soil saturation concentration (mg/kg) (Csat)	-	-
Inhalation Unit Risk (µg/m^3)$^{-1}$ (IUR)	-	-	Resident Soil (mg/kg)	5.1E+06	1.50E+07
Chronic Oral Reference Dose (mg/kg-day) (RfD_0)	8.0E+01	8.0E+01	Industrial Soil (mg/kg)	6.6E+07	2.0E+08
Chronic Inhalation Reference Concentration (mg/m^3) (RFC_i)	-	-	Resident Air (ug/m3)	-	-
Volatile	-	-	Industrial Air (ug/m3)		-
Mutagen	-	-	Tapwater (ug/L)	1.6E+06	4.80E+06
Fraction of contaminant absorbed in gastrointestinal tract (unitless) (GIABS)	1	1	Maximum Contaminant Level (MCL)	-	-
Fraction of contaminant absorbed dermally from soil (unitless) (ABSd)	0.1	0.1	-	-	-

TR=1E-04, HQ=1: 10-4 risk level for carcinogens or a Hazard Quotient (HQ) of 1 for non-carcinogens

TR=1E-04, HQ=3: 10-4 risk level for carcinogens or a Hazard Quotient (HQ) of 3 for non-carcinogens

As taken from US EPA, 2021c.

US EPA Regional Screening Levels for Chemical Contaminants (RSLs)

	TR=1E-06, HQ=1	TR=1E-06, HQ=0.1		TR=1E-06, HQ=1	TR=1E-06, HQ=0.1
Oral Slope Factor (mg/kg-day)$^{-1}$ (SFO)	-	-	Resident Soil (mg/kg)	5.1E+06	5.1E+05
Inhalation Unit Risk (µg/m^3)$^{-1}$ (IUR)	-	-	Industrial Soil (mg/kg)	6.6E+07	6.6E+06
Chronic Oral Reference Dose (mg/kg-day) (RfD_0)	8.0E+01	8.0E+01	Resident Air (ug/m3)	-	-

Chronic Inhalation Reference Concentration (mg/m^3) (RFC_i)	-	-	Industrial Air (ug/m3)	-	-
Volatile	-	-	Tapwater (ug/L)	1.6E+06	1.6E+05
Mutagen	-	-	Maximum Contaminant Level (MCL)	-	-
Fraction of contaminant absorbed in gastrointestinal tract (unitless) (GIABS)	1	1	Risk-based Soil Screening Level (mg/kg)	4.5E+02	4.5E+01
Fraction of contaminant absorbed dermally from soil (unitless) (ABS_d)	0.1	0.1	MCL-based Soil Screening Level (mg/kg)	-	-
Soil saturation concentration (mg/kg) (C_{sat})	-	-	-	-	-

As taken from US EPA, 2021d.

Triacetin (glycerol triacetate) (CAS RN 102-76-1) is listed under Inventory of Food Contact Substances. It is covered under 21 CFR Parts: 175.300, 175.320, 181.27, 184.1901.
FDA (2022d)

Based on the European Commission request the EFSA has included glycerol triacetate/ triacetin (CAS RN 102-76-1) in the the priority list to re-evaluate the risks to public health:
“The EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) was requested by the European Commission to re-evaluate the risks to public health related to the presence of plasticisers such as phthalates, structurally similar substances and replacement substances, as a consequence of migration from food contact materials (FCMs).”
EFSA (2021)

“No safety concern at current levels of intake when used as a flavouring agent.”
TRS 913-JECFA 59/112
JECFA (2005)

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

Triacetin has been administered iv to mongrel dogs. The majority of infused triacetin underwent intravascular hydrolysis, and the majority of the resulting acetate is oxidized. Triacetin was found to be hydrolyzed by human intestinal lipase. [Sheftel, V.O.; Indirect Food Additives and Polymers. Migration and Toxicology. Lewis Publishers, Boca Raton, FL. 2000., p. 284] **PEER REVIEWED**

...Triacetin is rapidly hydrolysed in vitro by all tissues of the organism including the gastrointestinal tract. [WHO; Food Additive Series 8: Toxicological evaluation of some food colours, thickening agents, and certain other substancse (1975). Available from, as of February 15, 2005: http://www.inchem.org/documents/jecfa/jecmono/v08je12.htm **PEER REVIEWED**

Groups of female mongrel dogs to study the metabolic effects of isocaloric and hypercaloric infusions of 5% v/v aqueous triacetin. A primed, continuous infusion of 5 umol/kg (0.3 uCi/kg/min) [(13)C]-acetoacetate and 1.0 uCi/kg (0.01 uCi/kg/min) [(3)H]-glucose was continued for 6 hr. Three

hours after the start of the isotope infusion, dosing with triacetin was started. Six animals were infused at a rate of 47 umol/kg/min and seven were infused at a rate of 70 umol/kg/min triacetin for 3 hr. Blood and breath samples were taken at 15 to 30-min intervals. A group of four animals was infused with 70 umol/kg/min glycerol and used as the control for the hypercaloric infusion. During isocaloric infusion of triacetin, plasma acetate and free fatty acid concentrations were significantly increased at 30 and 60 min, respectively, and remained elevated. During hypercaloric infusion, plasma acetate concentration increased progressively throughout the study, whereas the plasma free fatty acid concentration did not change. Plasma pyruvate and lactate concentrations were significantly decreased after 30 and 90 min, respectively, and throughout the study with both isocaloric and hypercaloric infusion. The plasma insulin concentrations were modestly increased during both infusions. Plasma glucose concentration was significantly decreased during isocaloric triacetin infusion; a slight but significant increase was observed with hypercaloric infusion. Glucose clearance decreased significantly in both groups during the last hour of triacetin infusion. Plasma ketone body concentrations increased significantly by 60 min, and they remained elevated with isocaloric infusion and increased progressively with hypercaloric infusion of triacetin; the increased concentrations were due to increased ketone body production. During the last hour of infusion, resting energy expenditure was significantly increased with isocaloric triacetin. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

Esterases in fungi or in serum act at pH >4 to slowly release acetic acid in situ. Extent of hydrolysis is automatically limited by increased acidity and lowering of pH. [Patty, F. (ed.). Industrial Hygiene and Toxicology: Volume II: Toxicology. 2nd ed. New York: Interscience Publishers, 1963., p. 1871] **PEER REVIEWED**

... The fungistatic activity of triacetin (glyceryl triacetate) results from its hydrolysis by fungalesterases to acetic acid. [Ullmann's Encyclopedia of Industrial Chemistry. 6th ed.Vol 1: Federal Republic of Germany: Wiley-VCH Verlag GmbH & Co. 2003 to Present, p. V10 391 (2003)] **PEER REVIEWED**

As taken from HSDB, 2015

“GTA [triacetin] is rapidly absorbed following ingestion and metabolised like other shorter-chain triglycerides. Several studies confirmed that GTA is hydrolysed to glycerol and acetic acid by digestive enzymes, particularly lipases, liver or plasma carboesterases. GTA is readily hydrolyzed to free glycerol and acetic acid, when incubated with rat intestine in vitro. The chemical infused in dogs undergoes intravascular hydrolysis and the majority of the resulting acetate is oxidized nearly quantitatively. The substance has been shown to be a source of liver glycogen and when fed in amounts equal in caloric value to 15% glucose it was utilised as efficiently as glucose” (Maag et al. 2010).

4.2. Absorption, distribution and excretion

/ALTERNATIVE and IN VITRO TESTS/ In an in vitro study, the penetration of Triacetin into the corium of human skin was determined by topical application of Triacetin to the epidermis (which was later separated from the corium), and then measuring the antimicrobial activity. Using leg skin, a plastic cylinder was attached to the epidermis, and 0.01 cc Triacetin was applied for 20 to 24 hr. The skin was then washed and the epidermis removed. Six-millimeter punches of the corium were taken and implanted on the culture medium, with the epidermal side in contact with the medium. When inhibition of growth around the corium occurred, the radius of inhibition was measured. There was no average inhibition of positive responses with Triacetin cream. The researchers speculated that an antimicrobial agent may penetrate into the corium and not diffuse into the surrounding medium when assayed, and that this might give a false-negative report of its ability to penetrate the epidermis. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

As taken from HSDB, 2015

“Triacetin is readily hydrolyzed to free glycerol and acetic acid, when incubated with rat intestine in vitro. The chemical infused in dogs undergoes intravascular hydrolysis and the majority of the resulting acetate is oxidized nearly quantitatively.”

“A feeding experiment using rams and ewes was conducted for 175 days to study the efficiency of utilization for growth-fattening, of the energy of diets in the ruminal ingesta. Triacetin, employed as a source of acetic acid, was added to the basal diets to comprise 10 % of the total dietary dry matter. Faeces were collected and analysed for the proximate chemical constituents and heat of combustion and samples of urine were analysed for urinary energy. Utilization rates were 62.0 % for the metabolizable energy (ME) provided by the diets containing triacetin in a 175 day feeding study with sheep. No toxicity was reported (Bull et al. 1970).”

As taken from OECD SIDS, Triacetin (102-76-1)

”...Triacetin is more rapidly absorbed from the gastrointestinal tract in 3 hours than the other fats tested. Triacetin has been shown to be a source of liver glycogen and when fed in amounts equal in caloric value to 15% glucose it was utilized as efficiently as was glucose. [WHO; Food Additive Series 8: Toxicological evaluation of some food colours, thickening agents, and certain other substancse (1975). Available from, as of February 15, 2005: http://www.inchem.org/documents/jecfa/jecmono/v08je12.htm **PEER REVIEWED**

Mongrel dogs /were used/ to determine the systemic, hindlimb, gut, hepatic, and renal uptake of acetate during infusion of a 5% v/v aqueous solution of triacetin. A primed, continuous infusion of [1-(14)C]-acetate was continued for 7 hr with 10 animals. Three hours after the start of the tracer infusion, the animals were infused with triacetin at a rate of 47 umol/kg/min for 4 hr. Blood and breath samples were taken at 15-min intervals for the last 30 min. Steady-state conditions were achieved in plasma acetate concentrations and specific activity and in expired [(14)-C02]. Plasma acetate concentrations were 1180, 935, 817, 752, and 473 umol/L /(all values approximate)/ in the aorta, renal vein, portal vein, femoral vein, and hepatic vein, respectively. The acetate turnover rate during triacetin infusion was 2214 umol/min; systemic acetate turnover accounted for 68% of triacetin-derived acetate. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**”

4.3. Interactions

The present studies investigated the effects of intravenous administration of the short-chain triglyceride triacetin on leucine metabolism in dogs. Animals received infusions of triacetin at 1.0 x estimated resting energy expenditure (REE), hyperenergetic triacetin at 1.5 x REE, glycerol, or saline during infusion of [(1-14)C]leucine. During both triacetin infusions, plasma alpha-ketoisocaproate concentrations increased ($p < 0.05$). During triacetin infusion at 1.5 REE, the plasma leucine concentration decreased ($p < 0.05$) and leucine rate of appearance decreased by approximately 19% ($p < 0.05$); this was significantly greater than the changes that occurred during triacetin at 1.0 x REE and glycerol ($p < 0.05$). There was no difference in leucine oxidation between the dogs given triacetin at 1.0 x REE and control groups, whereas leucine oxidation decreased by 53% during triacetin infusion at 1.5 x REE ($p < 0.05$). Nonoxidative leucine disappearance, an indicator of protein synthesis, did not change in any of the studies. [Bailey JW et al; Am J Clin Nutr 58 (6): 912-6 (1993)] **PEER REVIEWED** PubMed Abstract

As taken from HSDB, 2015

5. Toxicity

5.1. Single dose toxicity

Organism	Test Type	Route	Reported Dose (Normalized Dose)	Effect	Source
dog	LD_{50}	intravenous	1500mg/kg (1500mg/kg)		Food and Cosmetics Toxicology. Vol. 16, Pg. 879, 1978.
guinea pig	LDLo	intramuscular	1740mg/kg (1740mg/kg)	LUNGS, THORAX, OR RESPIRATION: DYSPNEA	Journal of Pharmacology and Experimental Therapeutics. Vol. 76, Pg. 189, 1942.
mouse	LD_{50}	intraperitoneal	1400mg/kg (1400mg/kg)	PERIPHERAL NERVE AND SENSATION: SPASTIC PARALYSIS WITH OR WITHOUT SENSORY CHANGE BEHAVIORAL: ALTERED SLEEP TIME (INCLUDING CHANGE IN RIGHTING REFLEX) BEHAVIORAL: STIFFNESS	Federation Proceedings, Federation of American Societies for Experimental Biology. Vol. 22, Pg. 368, 1963.
mouse	LD_{50}	intravenous	1600mg/kg (1600mg/kg)	BEHAVIORAL: CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD LUNGS, THORAX, OR RESPIRATION: RESPIRATORY DEPRESSION	Acta Physiologica Scandinavica. Vol. 40, Pg. 338, 1957.
mouse	LD_{50}	oral	1100mg/kg (1100mg/kg)	PERIPHERAL NERVE AND SENSATION: SPASTIC PARALYSIS WITH OR WITHOUT SENSORY CHANGE BEHAVIORAL: ALTERED SLEEP TIME (INCLUDING CHANGE IN RIGHTING REFLEX) BEHAVIORAL: STIFFNESS	Federation Proceedings, Federation of American Societies for Experimental Biology. Vol. 22, Pg. 368, 1963.
mouse	LD_{50}	subcutaneous	2300mg/kg	BEHAVIORAL:	Proceedings of the

			(2300mg/kg)	SOMNOLENCE (GENERAL DEPRESSED ACTIVITY) LUNGS, THORAX, OR RESPIRATION: DYSPNEA	Society for Experimental Biology and Medicine. Vol. 46, Pg. 26, 1941.
rabbit	LD_{50}	intravenous	750mg/kg (750mg/kg)		Food and Cosmetics Toxicology. Vol. 16, Pg. 879, 1978.
rat	LD_{50}	intraperitoneal	2100mg/kg (2100mg/kg)		Food and Cosmetics Toxicology. Vol. 16, Pg. 879, 1978.
rat	LD_{50}	oral	3gm/kg (3000mg/kg)		AMA Archives of Industrial Health. Vol. 21, Pg. 28, 1960.
rat	LD_{50}	subcutaneous	2800mg/kg (2800mg/kg)	BEHAVIORAL: SOMNOLENCE (GENERAL DEPRESSED ACTIVITY) LUNGS, THORAX, OR RESPIRATION: DYSPNEA	Proceedings of the Society for Experimental Biology and Medicine. Vol. 46, Pg. 26, 1941.

As taken from ChemIDplus (a), available at https://chem.nlm.nih.gov/chemidplus/

/LABORATORY ANIMALS: Acute Exposure/ ...Tested on rabbit eyes has been found to cause no injury... . [Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 931] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ ...Rats made very good weight gains when triacetin replaced fat in diet for extent of 55% of total diet. [Patty, F. (ed.). Industrial Hygiene and Toxicology: Volume II: Toxicology. 2nd ed. New York: Interscience Publishers, 1963., p. 1871] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ Six female mongrel dogs were used to determine the effect of Triacetin on serum phosphorus, calcium, and magnesium metabolism. A 5% v/v aqueous solution of Triacetin was infused intravenously at a rate of 47 umol/kg/min for 3 hr. Arterial blood was sampled at 15 to 30-min intervals, and urine was collected during infusion. No significant

changes in total serum calcium or phosphorus concentrations were observed; however, serum magnesium concentrations were statistically significantly decreased 90 min after the initiation of dosing and remained decreased until the end of the study. During Triacetin infusion, the plasma acetate concentration increased from 0.13 to 1.32 mmol/L at 30 min; the concentration gradually declined to /approximately/ 1 mmol/L during the last hour of the study. No change was observed in the fractional excretion of calcium, magnesium, or phosphorus. The authors speculated that the decrease in serum magnesium was probably because of cellular uptake rather than accelerated excretion. Baseline blood pH was not significantly altered. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ The symptoms of toxicity with triacetin are primarily weakness and ataxia. Animals near death exhibit severe dyspnea, muscular tremors, and occasional convulsions, usually 2-22 min after the injection. Also various degrees of hemorrhage in the lung have been observed. It does not appear to affect the liver, spleen, heart, or kidneys. [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 710] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ In a study examining the effect of Triacetin on nitrogen balance, whole-body kinetics, and muscle and liver fractional protein synthetic rates, /investigators/ infused male Sprague-Dawley rats with isovolemic, isocaloric, and isonitrogenous parenteral diets. Thirty percent of the nonprotein energy of the diets was lipid energy, and for groups of 6, 10, and 6 animals, the lipid energy was composed of 0%, 50%, and 90% Triacetin, respectively. No difference was observed in the plasma acetate concentration of animals that received Triacetin compared to those that did not. The liver weight was significantly decreased in the animals given Triacetin. Protein concentration in the liver and rectus muscle was similar for all three groups. Cumulative nitrogen balance was positive for all animals, and no significant difference in nitrogen balance was observed on days 6 and 7. Lipid composition had very little effect on plasma leucine kinetics. Also, fractional protein synthetic rates in the rectus muscle and liver were similar for all animals. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ The acute dermal LD50 of Triacetin was determined using groups of five albino rabbits. A dose of 5 g/kg was applied to intact and abraded skin. The animals were observed for 7 days after dosing. None of the animals died. The dermal LD50 of Triacetin for rabbits was >5 g/kg. Additional dermal LD50 values were >20 mL/kg for guinea pigs and >2 g/kg for rabbits. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ Groups of 10 mice were dosed with 1.0 to 3.0 cc/kg and groups of 10 rats were dosed with 2.0 to 10.0 cc/kg aqueous triacetin. The mice and rats were observed for 5 and 15 days after dosing, respectively. Two, 2, 7, and 10 mice of the 1.0-, 2.0-, 3.0-, and 3.5-cc/kg groups and 1, 6, and 10 rats of the 2.0-, 3.0-, and 4-10-cc/kg groups died, respectively. The animals usually died within 20 min to 3 or 4 hr after injection. The authors noted marked depression, weakness, prostration, and in some animals, labored respiration just before death. Hemorrhagic areas in the lungs and some swelling of the convoluted tubules of the kidney were observed, along with hydropic degeneration and necrosis of the tubules in some areas. Also, the authors stated that the liver appeared to be congested. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ ... These studies were undertaken to investigate triacetin, the water-soluble triglyceride of acetate when it is incorporated into nutritionally balanced total parenteral nutrition formulas. Male Sprague-Dawley rats (n=22) were fed an isovolemic, isocaloric and isonitrogenous diet for 7 d. The lipid energy represented 30% of the nonprotein energy with short-chain triglycerides representing 0, 50 or 90% of the lipid energy. Plasma acetate concentration was determined as well as indicators of protein metabolism: daily and cumulative nitrogen balance, whole body leucine kinetics and rectus muscle and liver fractional protein

synthetic rates. No overt toxic effects were observed at any point during the study. As the proportion of short-chain triglycerides in the diet increased from 0 to 50 or 90% of the lipid energy, cumulative nitrogen balance increased 50 or 120%, respectively ($p < 0.05$). Whole-body and tissue leucine kinetics (determined during the last 2.5 hr of the 7-d study) were unaffected by the lipid composition of the diet. Plasma acetate concentration was not significantly different among groups. [Bailey JW et al; J Nutr 122 (9): 1823-9 (1992)] **PEER REVIEWED** PubMed Abstract

/LABORATORY ANIMALS: Acute Exposure/ Triacetin, the water-soluble triglyceride of acetate, was infused in mongrel dogs at isocaloric (N=6) or hypercaloric (approximately 1.5 resting energy expenditure (REE), N=7) rates in mongrel dogs for 3 hr. Ketone body and glucose production rates were quantified with [(13)C2] acetoacetate and [3H]glucose, respectively. Four additional animals were infused with glycerol to serve as controls for the hypercaloric triacetin infusion. Energy expenditure was determined in the isocaloric experiments. No evidence of acute toxicity was observed during triacetin infusion at either rate. Plasma acetate concentrations increased from basal levels to approximately 1 and approximately 13 mmol/L in the isocaloric and hypercaloric experiments, respectively. Plasma lactate and pyruvate concentrations decreased dramatically after 30 min of both isocaloric and hypercaloric triacetin infusions. Glucose production rates did not increase in either group, but glucose clearance decreased significantly in both groups ($p < 0.05$) over the last hour of triacetin infusion. Plasma ketone body concentrations increased from 1.4 to 3.5 and 1.8 to 13.5 mumol/kg.min, respectively, during isocaloric and hypercaloric triacetin infusion. Resting energy expenditure increased from 3.0 +/- 0.3 to 4.0 +/- 0.5 kcal/kg.hr during isocaloric triacetin infusion ($p < 0.05$). [Bailey JW et al; JPEN J Patenter Enteral Nutr 15 (1): 32-6 (1991)] **PEER REVIEWED** PubMed Abstract

/OTHER TOXICITY INFORMATION/ Groups of eight Long-Evans rats were given a continuous nasogastric infusion 462 kJ/kg of a diet containing either 16% or 32% triacetin. No adverse effects, such as diarrhea or change in normal activity, were observed. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

The present studies investigated the effects of intravenous administration of the short-chain triglyceride triacetin on leucine metabolism in dogs. Animals received infusions of triacetin at 1.0 x estimated resting energy expenditure (REE), hyperenergetic triacetin at 1.5 x REE, glycerol, or saline during infusion of [(1-14)C]leucine. During both triacetin infusions, plasma alpha-ketoisocaproate concentrations increased ($p < 0.05$). During triacetin infusion at 1.5 REE, the plasma leucine concentration decreased ($p < 0.05$) and leucine rate of appearance decreased by approximately 19% ($p < 0.05$); this was significantly greater than the changes that occurred during triacetin at 1.0 x REE and glycerol ($p < 0.05$). There was no difference in leucine oxidation between the dogs given triacetin at 1.0 x REE and control groups, whereas leucine oxidation decreased by 53% during triacetin infusion at 1.5 x REE ($p < 0.05$). Nonoxidative leucine disappearance, an indicator of protein synthesis, did not change in any of the studies. [Bailey JW et al; Am J Clin Nutr 58 (6): 912-6 (1993)] **PEER REVIEWED** PubMed Abstract

/OTHER TOXICITY INFORMATION/ Triacetin appears to be of low toxicity when swallowed, inhaled or placed on skin. [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 711] **PEER REVIEWED**

As taken from HSDB, 2015

LD_{50}	Rabbit iv	750 mg/kg
LD_{50}	Dog iv	1500 mg/kg
LD_{50}	Mouse sc	2300 mg/kg
LD_{50}	Mouse ip	1400 mg/kg

LD_{50}	Mouse oral	1100 mg/kg
LD_{50}	Mouse iv	1600 mg/kg
LD_{50}	Rat sc	2800 mg/kg
LD_{50}	Rat ip	2100 mg/kg
LD_{50}	Rat oral	3000 mg/kg
LD_{50}	Rabbit oral	> 2000 mg/kg
LC_{50}	Rat inhalation	> 1.721 mg/L/4hr
LD_{50}	Guinea pig dermal	> 20mL/kg
LD_{50}	Rabbit dermal	5 g/kgbw

LD_{50}	Rat oral	6400-12800 mg/kg
LD_{50}	Rat oral	> 2000 mg/kg
LD_{50}	Mouse oral	9300 mg/kg
LD_{50}	Mouse oral	3200-6400 mg/kg
LD_{50}	Rabbit dermal	> 5000 mg/kg
LD_{50}	Rat intraperitoneal	800-1600 mg/kg
LD_{50}	Mouse intraperitoneal	800-1600 mg/kg

As taken from IUCLID Dataset (2000), Triacetin (102-76-1).

Type of Test	**Route of Exposure**	**Species Observed**	**Dose Data**	**Toxic Effects**	**Reference**
LD50 - Lethal dose, 50 percent kill	Oral	Rodent - rat	3 gm/kg	Details of toxic effects not reported other than lethal dose value	AMIHAB AMA Archives of Industrial Health. (Chicago, IL) V.11-21, 1955-60. For publisher information, see AEHLAU. Volume(issue)/page/year: 21,28,1960
LD50 - Lethal dose, 50 percent kill	Intraperitoneal	Rodent - rat	2100 mg/kg	Details of toxic effects not reported other than lethal dose value	FCTXAV Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. Volume(issue)/page/year: 16,879,1978
LD50 - Lethal dose, 50 percent kill	Subcutaneous	Rodent - rat	2800 mg/kg	Behavioral - somnolence (general depressed activity) Lungs, Thorax, or Respiration - dyspnea	PSEBAA Proceedings of the Society for Experimental Biology and Medicine. (Academic Press, Inc., 1 E. First St., Duluth, MN 55802) V.1- 1903/04- Volume(issue)/page/year: 46,26,1941

LD50 - Lethal dose, 50 percent kill	Oral	Rodent - mouse	1100 mg/kg	Peripheral Nerve and Sensation - spastic paralysis with or without sensory change Behavioral - altered sleep time (including change in righting reflex) Behavioral - stiffness	FEPRA7 Federation Proceedings, Federation of American Societies for Experimental Biology. (Bethesda, MD) V.1-46, 1942-87. Volume(issue)/page/year: 22,368,1963
LD50 - Lethal dose, 50 percent kill	Intraperitoneal	Rodent - mouse	1400 mg/kg	Peripheral Nerve and Sensation - spastic paralysis with or without sensory change Behavioral - altered sleep time (including change in righting reflex) Behavioral - stiffness	FEPRA7 Federation Proceedings, Federation of American Societies for Experimental Biology. (Bethesda, MD) V.1-46, 1942-87. Volume(issue)/page/year: 22,368,1963
LD50 - Lethal dose, 50 percent kill	Subcutaneous	Rodent - mouse	2300 mg/kg	Behavioral - somnolence (general depressed activity) Lungs, Thorax, or Respiration - dyspnea	PSEBAA Proceedings of the Society for Experimental Biology and Medicine. (Academic Press, Inc., 1 E. First St., Duluth, MN 55802) V.1- 1903/04- Volume(issue)/page/year: 46,26,1941
LD50 - Lethal dose, 50 percent kill	Intravenous	Rodent - mouse	1600 mg/kg	Behavioral - convulsions or effect on seizure threshold Lungs, Thorax, or Respiration - respiratory depression	APSCAX Acta Physiologica Scandinavica. (Karolinska Institutet, S-10401 Stockholm, Sweden) V.1- 1940- Volume(issue)/page/year: 40,338,1957
LD50 - Lethal dose, 50 percent kill	Intravenous	Mammal - dog	1500 mg/kg	Details of toxic effects not reported other than lethal dose value	FCTXAV Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. Volume(issue)/page/year: 16,879,1978
LD50 - Lethal dose, 50 percent kill	Intravenous	Rodent - rabbit	750 mg/kg	Details of toxic effects not reported other than lethal dose value	FCTXAV Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. Volume(issue)/page/year: 16,879,1978
LDLo - Lowest published	Intramuscular	Rodent - guinea pig	1740 mg/kg	Lungs, Thorax, or Respiration - dyspnea	JPETAB Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins

lethal dose					Co., 428 E. Preston St., Baltimore, MD 21202) V.1-1909/10- Volume(issue)/page/year: 76,189,1942

As taken from RTECS, 2015.

The acute oral and dermal toxicity of GTA [triacetin] is low. In an oral acute toxicity study in rats (OECD 401), a limit dose of 2,000 mg/kg bw caused no mortality and no signs of systemic toxicity during the 14-day observation period. The LD50 in rats by gavage is determined to be >2,000 mg/kg bw for both sexes, and dermal LD50 in rabbits and guinea pigs were >2,000 mg/kg bw. Acute inhalation toxicity is considered to be very low, since the LC50 in an acute inhalation toxicity study in rats was >1,721 mg/m^(3) for both sexes (OECD 403) (Maag et al. 2010).

LC50 (rat) > 1,721 mg/m3/4h (Haz-Map, 2020).

LD50 (rat, intravenous): 1600 ± 81 mg/kg bw (IGS, 2021).

5.2. Repeated dose toxicity

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ In the rat, inhalation of 250 ppm triacetin (6 hr/day, 5 days/wk for 13 weeks) or saturated triacetin vapor (6 hr/day for 5 days) produced no clinical signs of toxicity or histopathological effects. [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 710] **PEER REVIEWED**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ In 3-month feeding studies, growing rats were found to tolerate up to 20% triacetin in the diet, but diets containing 60% triacetin caused marked retardation of body weight gain and considerable increase in deaths. [Sheftel, V.O.; Indirect Food Additives and Polymers. Migration and Toxicology. Lewis Publishers, Boca Raton, FL. 2000., p. 284] **PEER REVIEWED**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Groups of eight male Sprague-Dawley rats that were fed diets containing 30% triacetin (and 30% glycerin or propylene glycol) as a starch substitute for 3 to 4 or 12 to 13 weeks, growth was relatively poor. Liver enlargement was observed in all animals. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ The metabolic effect of Triacetin on intestinal mucosal cells and plasma substrates in male Sprague-Dawley rats was assessed /in a sub-chronic study/. Rats were fed for 30 days a diet in which 28.5% of the total calories were supplied by Triacetin. No overt signs of toxicity were observed. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ /Investigators/ exposed a group of three rats to 250 ppm triacetin /by inhalation/ for 6 hr per day, 5 days per week, for 64 days. The no-observed-effect level (NOEL) was 250 ppm. Three rats were also exposed to 8271 ppm triacetin for 6 hr per day for 64 days. The NOEL was 8271 ppm. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/OTHER TOXICITY INFORMATION/ ... In short-term feeding studies, Triacetin affected weight gain. Triacetin was not toxic in short-term studies when administered via inhalation or parenterally or in subchronic studies when administered via feed or inhalation. [Fiume MZ; Int J Toxicol 22 (Suppl 2): 1-10 (2003)] **PEER REVIEWED**

/OTHER TOXICITY INFORMATION/ Laboratory rats have tolerated diets consisting of 50% triacetin. If hydrolized... /systemic/ acidosis is a possible consequence. [Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. II-203] **PEER REVIEWED**

As taken from HSDB, 2015

“To develop diets which contain virtually all the calories as purified organic compounds for long-duration space missions, growing male rats were fed diets containing triacetin and/or glycerin (20 - 60 %) for 90 days. The animals well tolerated up to 20 % triacetin, which corresponds to 10 g/kg bw/day. Greater percentage caused a decrease in weight gain. A large loss in weight and considerable mortality was associated with diets containing either glycerol or triacetin at 60 % of the diet (Shapira, 1969), while increased liver weight occurred in the 30 % groups (Shapira, 1975). The NOAEL for the feeding study is considered to be 10 g/kg bw/day for male rats.”

As taken from OECD SIDS, Triacetin (102-76-1)

Species	Route	Frequency of treatment	Doses	Frequency	NOAEL
Rats	Inhalation	6h/day, 5days/week	up to 250 ppm	64 days	250 ppm
Rats	Inhalation	6h/day	8271 ppm	64 days	8271 ppm

As taken from IUCLID Dataset (2000), Triacetin (102-76-1).

“…repeated daily exposure of rats to 73,700 mg/m3 produced no sign of toxicity after 5 days” (Maag et al. 2010).

“In a combined repeat dose and reproductive/developmental screening toxicity test (OECD 422), rats were exposed to 40, 200 or 1,000 mg/kg/day by oral gavage for 44 days from 2 weeks prior to mating for males and for 41 – 48 days from 14 days before mating to day 3 postpartum for females. GTA had no effects on clinical signs, body weight, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in either sex. There were no abnormalities in haematological or blood chemical parameters in males. The NOAEL for repeated dose oral toxicity is thus considered to be 1,000 mg/kg bw/day for both sexes” (Maag et al. 2010).

“An inhalation study was conducted in rats given GTA for 90 days at a dose of 249 ppm (2,220 mg/m3). No signs of toxicity were noted during the exposure. The NOAEL is considered to be 249 ppm (2,220 mg/m3) for 90 days. Although the inhalation study is considered to be useful, it does not fully comply with the current testing protocol” (Maag et al. 2010).

“Canavan disease (CD MIM#271900) is a rare autosomal recessive neurodegenerative disorder presenting in early infancy. The course of the disease is variable, but it is always fatal. CD is caused by mutations in the ASPA gene, which codes for the enzyme aspartoacylase (ASPA), which breaks down N-acetylaspartate (NAA) to acetate and aspartic acid. The lack of NAA-degrading enzyme activity leads to excess accumulation of NAA in the brain and deficiency of acetate, which is necessary for myelin lipid synthesis. Glyceryltriacetate (GTA) [triacetin] is a short-chain triglyceride with three acetate moieties on a glycerol backbone and has proven an effective acetate precursor. Intragastric administration of GTA to tremor mice results in greatly increased brain acetate levels, and improved motor functions. GTA given to infants with CD at a low dose (up to 0.25 g/kg/d) resulted in no improvement in their clinical status, but also no detectable toxicity. We present for the first time the safety profile of high dose GTA (4.5 g/kg/d) in 2 patients with CD. We treated 2 infants with CD at ages 8 months and 1 year with high dose GTA, for 4.5 and 6 months respectively. No significant side effects and no toxicity were observed. Although the treatment resulted in no motor improvement, it was well tolerated. The lack of clinical improvement might be explained mainly by the late onset of treatment, when significant brain damage was already

present. Further larger studies of CD patients below age 3 months are required in order to test the long-term efficacy of this drug" (Segel et al. 2011).

Information for the non-peer-reviewed study by Unichema Chemie B.V. (1994) was reported by Fiume (2003); the original citation could not be obtained. Three rats (sex and strain not reported) were exposed to 250 ppm (HEC is 398 mg/m3) by inhalation for 6 hours per day, 5 days per week, for 64 days. Three rats were also exposed to 8,271 ppm (HEC is 13,181 mg/m3) for 6 hours per day for 64 days. No adverse effect was observed. The study author reported a NOAEL of 13,181 mg/m3; a LOAEL was not determined under the conditions tested. Due to the extremely limited toxicity data, this study is not considered suitable for derivation of a subchronic p-RfC. (US EPA 2012)

Information for the peer-reviewed study by Fassett (1963) was reported in a glycerol triacetate safety evaluation by Ellis and Rodford (1996); the original citation could not be obtained. Inhalation concentrations of triacetin averaging 250 ppm (HEC is 398 mg/m3) for 6 hours per day, 5 days per week, for 13 weeks produced no symptoms or histopathology in rats (sex and strain not reported). No changes were reportedly seen in liver and kidney weights, blood counts, or urine analysis. This concentration is considered the NOAEL; a LOAEL is not determined under the conditions tested. Due to the extremely limited toxicity data, this study is not considered suitable for derivation of a subchronic p-RfC.

Information for the non-peer-reviewed study by Fassett (1955) is reported in the OECD Screening Information Dataset (2002) robust summaries; the original citation cannot be obtained. In this study, three rats/sex (strain not reported) were exposed to triacetin vapor by whole–body vapor inhalation exposure for 6 hours/day, 5 days/week, at a concentration of 249 ppm (HEC is 397 mg/m3) for 90 days. A concurrent control group was not exposed. It was stated that inhalation was further extended for another week at 73.72 ppm (HEC is 117 mg/m3), followed by a week at 8,271 ppm (saturated vapor; HEC is 13,181 mg/m3). Treating the animals at 73.72 ppm for an additional week after no observed effect from 13 weeks of treatment at 249 ppm is without apparent reason; therefore, the summary article may be mistaken. Body weights were recorded prior to the first exposure, every 2−9 days during testing, and prior to termination. Limited hematology (red and white blood cell counts and hemoglobin) and urinalysis (albumin and sugar) parameters were measured. Liver and kidneys were weighed, and microscopic findings for trachea, bronchi, lung, kidney, liver, and bladder were reported.

No symptoms of toxicity were noted during the exposure period (Fassett [1955], as summarized in OECD [2002]). Average daily weight gain was 2.2 g/rat and was considered normal. Hematological evaluation and urinalysis showed no abnormalities in any of the animals. No histopathological changes were observed at the time of necropsy. The study author reported an estimated NOAEL of 249 ppm (HEC is 397 mg/m3) for the 90-day study. A LOAEL was not observed under the conditions tested. OECD (2002) stated that, although this inhalation study was considered to be useful, it did not fully comply with the current testing protocol. Due to the limited toxicity data, this study is not considered suitable for derivation of a subchronic p-RfC. (US EPA 2012)

In a peer-reviewed study, Shapira et al. (1969) developed a system capable of serving a regenerative food supply. A mixture of triacetin, glycerol, and Hydrogenomonas eutropha (bacteria, rich in protein) was used as a food supplement and a major portion of the diet. Groups of eight male weanling Sprague-Dawley rats were fed one of 12 different diets for 18 days, containing low, medium, or high protein contents (12, 24, and 48% protein, respectively), along with variable carbohydrate sources, including triacetin. The different protein and carbohydrate contents of the 12 diets are shown in Table B-1.

The adjusted doses for triacetin are calculated to be 13,869, 25,670, and 25,843 mg/kg-day for the diets containing triacetin at 16.1, 29.8, and 30% (by weight), respectively. In addition to the dietary components shown above, all diets contained 5% USP XIV salt mixture (plus 16.5 mg $ZnSO_4$/100 g diet), 5% safflower oil, 2% α-cellulose, 1% vitamins, 1% agar, and a total of 2 parts water to each

part dry weight. After formulation, the diets were stored at 4°C and fed fresh daily. The animals were caged as pairs and weighed daily. No mortality or clinical signs of toxicity were mentioned; however, the study authors did not report any evaluations other than body weights. It is not apparent from the report that statistical analyses were performed on the body-weight data. This study was performed as part of research into regenerative food systems performed at the Ames Research Center for NASA.

The study authors reported that growth was not adversely affected over 18 days when 29.8% triacetin (by weight in the diet; equivalent to 25,670 mg/kg-day) was included with 29.8% glycerol and 27% protein from H. eutropha (minimally affected when protein was casein; see Table B-1). The authors stated that these data show that over 90% of the calories of the diet of growing rats can be composed of a mixture of H. eutropha, glycerol, and triacetin without a detrimental effect on the growth of the animal. However, these results also demonstrate that adequate nutritional needs must be met with regards to protein levels. When fed similar amounts of triacetin (29.8−30%), animals fail to achieve the expected body-weight gain when fed the low protein diet, but not when fed the medium protein diet. The study authors did not define a NOAEL or LOAEL; however, the highest dose of 25,843 mg/kg-day showed no adverse effects; therefore, the NOAEL is 25,843 mg/kg-day. A LOAEL for triacetin is not available under the conditions tested. The study authors reported only limited information to assess the toxicity of this compound in this 18-day study, and the dietary exposure to rats included multiple supplements in addition to triacetin; therefore, this study is not considered suitable for derivation of a subchronic p-RfD.

The report by Shapira et al. (1969) also included general findings related to triacetin from a “number of three month feeding studies.” However, because detailed methodology and data from these studies were not presented, these generalized findings are unsupported and are not included in this report. (US EPA 2012)

In a peer-reviewed study, Lynch et al. (1994), administered to eight Sprague-Dawley male rats one of three diets for 30 days: control diet, diet with 30% of the energy as corn oil, or diet with 30% of the energy as mainly short chain triglycerides (95% triacetin and 5% corn oil). All diets contained 20.6% protein (by percentage of calories), and 1.0%, 3.5%, and 5.0% weight percent vitamins, minerals, and fiber, respectively. The triacetin-diet contained 19.0% triacetin by weight, which is equivalent to an adjusted dose of 16,367 mg/kg-day.

Rats were housed individually in plastic metabolism cages (Lynch et al., 1994). Food intake was measured daily, and body weights were determined at Day 0 and every 5 days thereafter. Animals were euthanized after 30 days, and blood was collected. Nonfasting plasma glucose, triglycerides, total ketone bodies, free fatty acids, lactate, and pyruvate were measured. Jejunal and colon segments were excised and weighed. Intestinal mucosal cells were analyzed for DNA, RNA, and protein content. The protein-DNA ratio for each group was calculated as an index of cell size. Other jejunal and colon segments were fixed in neutral buffered formalin, processed routinely, and analyzed by light microscopy to determine villus height in the jejunum and crypt depth in the colon. Carcasses were eviscerated, frozen, and homogenized with an equivalent weight of water. Aliquots were removed and lyophilized for determination of percent moisture. All data were analyzed by analysis of variance (ANOVA) to determine significant statistical differences among groups caused by diet. When a significant difference was observed, Duncan’s Multiple Range Test was used to further analyze the differences. This study did not include relevant evaluation of hematology, clinical chemistry, urinalysis, organ weights, or gross or microscopic pathology.

Lynch et al. (1994) stated that there were no adverse, treatment-related effects observed on mortality, clinical signs, body weights, food consumption, lactate, ketone body, glucose concentrations, mean villus height, intestinal crypt depth, and carcass composition. Compared to the control group, plasma free fatty acids were decreased ($p < 0.05$) by 44%, and plasma triglycerides were increased ($p < 0.05$) by 22%. DNA content was increased ($p < 0.05$) by approximately 68% in the colon mucosa. RNA content was decreased ($p < 0.05$) by approximately 33% in the jejunum. The protein:DNA ratio was decreased ($p < 0.05$) by 38% in the jejunum. The

study authors reported no NOAEL or LOAEL; however, the only dose of triacetin tested, 16,367 mg/kg-day, showed no toxic effects; therefore, the NOAEL is 16,367 mg/kg-day. A LOAEL is not available under the conditions tested. The study authors reported only limited information to assess the toxicity of this compound in this study; therefore, this study is not suitable for derivation of a subchronic p-RfD.(US EPA 2012)

In a peer-reviewed study by Lynch and Bailey (1995), eight Sprague-Dawley male rats were administered one of three diets for 30 days, with one of the diets containing 19% triacetin by weight (adjusted dose of 16,367 mg/kg-day). The study methodology was the same as described previously in Lynch et al. (1994). In the present study, the adipose cell size and number (as measured by a Coulter counter) for epididymal, perirenal, and inguinal fat depots were reported.

Lynch and Bailey (1995) reported that mean adipose cell size in the triacetin-treated group was less than the control for the epididymal, inguinal, and perirenal fat depots, but cell number was unaffected. A moisture-free sample was used to determine percent lipid with a modified Soxhlet method. Percent protein was determined with the Kjeldahl method, and the percent ash was determined by combustion. The study authors reported no NOAEL or LOAEL; however, the only dose tested, 16,367 mg/kg-day, showed no toxic effects. Therefore, the NOAEL is 16,367 mg/kg-day, and a LOAEL is not available under the conditions tested. The study authors reported only the limited results detailed above to assess the toxicity of this compound in this study; therefore, this study is not suitable for derivation of a subchronic p-RfD. (US EPA 2012)

This study (MHW, 1998) was performed by the Kashima Laboratory of the Mitsubishi Chemical Safety Institute in accordance with the OECD combined repeated dose and reproductive/developmental toxicity screening test guideline (OECD TG 422). Twelve Sprague-Dawley [Crj:CD (SD) IGS] rats/sex (males: 317−375 g; females: 203−240 g; 9 weeks old) were administered triacetin (>98.2% purity) in 3% aqueous gum arabic by gavage once daily at doses of 0, 40, 200, or 1,000 mg/kg-day. Males were dosed for 44 days beginning 2 weeks prior to mating; females were dosed for 41−48 days from 14 days before mating to Postpartum Day (PPD) 3.

In the adults, mortality/morbidity and clinical signs of toxicity were recorded once a day (MHW, 1998). Body weights were measured on Days 0, 3, 7, and 14 of premating in both sexes. Body weights were also measured on Days 21, 28, 35, and 42, and at termination in the males, and on Gestation Days (GD) 0, 7, 14, and 20, PPDs 0 and 4, and at termination in the females. Food consumption (g/rat/day) was recorded for: Days 0−3, 3−7, and 7−14 in both sexes; Days 21−28, 28−35, and 35−42 in the males; and GDs 0−7, 7−14, 14−20, and PPD 0−4 in the females. The following hematological and clinical chemistry parameters were determined in blood collected from males at termination: erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte ratio, thrombocytes, leukocyte differential counts, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, alanine phosphatase, total bilirubin, urea nitrogen, glucose, total cholesterol, triglyceride, total protein, albumin, albumin:globulin ratio, calcium, inorganic phosphorus, sodium, potassium, and chloride. Urinalysis was not performed. It was stated that absolute and relative organ weights were recorded for brain, pituitary, thyroid, heart, liver, kidney, spleen, adrenal gland, thymus, testes, and epididymis; however, data were only presented for thymus, liver, spleen, kidney, adrenal, testes, and epididymis. At necropsy, the following tissues were collected from the controls and 1,000-mg/kg-day group: brain, spinal cord, pituitary, eye, thyroid (with parathyroid), thymus, heart, trachea, lung, liver, kidney, adrenal gland, spleen, stomach, small intestine, large intestine, pancreas, urinary bladder, bone marrow, sciatic nerve, lymph node, testes, epididymis, prostate, seminal vesicle, ovary, uterus, vagina, mammary gland, and any organ that might be expected to have histopathological changes. The following tissues were examined and reported in the histological findings: heart, thymus, spleen, esophagus, stomach, duodenum, liver, kidney, testes, epididymis, ovary, adrenal, brain, and skin. Reproductive data, including reproductive performance indices, delivery data, and litter size, and pup viability indices, pup body weights, and pup body-weight gains were presented. It was stated that the data

were analyzed with the Kruskal-Wallis test for noncontinuous data, Dunnett's test, or Scheffe's test for continuous data, and the Chi-square test for quantal data. It was also stated that the study complied with Good Laboratory Practice (GLP) standards.

One 1,000-mg/kg-day male was found dead on Day 32 (MHW, 1998). This animal was observed grossly to have hemorrhage of the thymus and congestion of the lung, liver, and kidney; microscopic examination revealed slight diffuse hemorrhage of the thymus. In the absence of any evidence of systemic toxicity in any other animal at any dose level, this death is considered incidental to treatment. In the animals that survived to scheduled necropsy, triacetin had no effects on clinical signs of toxicity, body weights, body-weight gains, food consumption, organ weights, or gross or histological pathology findings. Statistically significant decreases were observed in percent of band neutrophils and creatinine in the 40- and 1,000-mg/kg-day males; statistically significant increases in inorganic phosphorus were also noted in the 200-mg/kg-day males. These changes were stated to be within physiological ranges and/or were not dose-dependent. Reproductive and offspring results are discussed under the Reproductive/Developmental Studies section below. In the absence of any reliable finding of toxicity in treated adult rats, the NOAEL was determined to be 1,000 mg/kg-day; a LOAEL was not determined under the conditions tested. (US EPA 2012)

In a peer-reviewed study, Shapira et al. (1975) fed groups of eight male Sprague-Dawley rats diets for 13 weeks containing various carbohydrates in order to investigate the feasibility of replacing starch with alternative carbohydrate sources. The study tested six types of diets: Diet 1 (control, 60% starch), Diet 2 (30% glycerol and 30% propylene glycol), Diet 3 (30% glycerol and 30% triacetin), Diet 4 (30% propylene glycol and 30% triacetin), Diet 5 (40% glycerol and 20% propylene glycol), and Diet 6 (40% glycerol and 20% triacetin). For the diets that included triacetin, the daily adjusted doses of triacetin were 17,228 and 25,843 mg/kg-day for 20 and 30% triacetin diets, respectively. Each diet also contained 27% casein and 5% safflower oil. Identical amounts of cellulose, salts, and vitamins were present in all diets. Rats were kept in pairs in stainless steel cages. For periods of 3−4 and 12−13 weeks, food consumption, body-weight gain, water intake, and liver weight were reported. It is not apparent from the report that statistical analyses were performed.

In this study (Shapira et al., 1975), body weights were decreased by 20% after 12−13 weeks on Diets 3 and 6 (triacetin with glycerol), but body weights were comparable for the control diet and Diet 4 (triacetin with propylene glycol). Water intake varied, and it is not possible to make conclusions without additional test groups where the concentrations of triacetin are varied (while other components remained the same). Body-weight gains as growth percent for periods of 3−4 and 12−13 weeks decreased 29−52% in all triacetin groups compared to the control group. However, due to the other variables in the dietary exposure media (e.g., casein, glycerol, or propylene glycol), it is difficult to attribute changes in body weight to triacetin alone. Alternatively, it is possible that feeding with 30% triacetin may have negatively impacted nutrition over the 13-week period. Regardless, this effect is not considered to be a clear indication of systemic toxicity for triacetin. Relative liver weights were increased by 41−67%. The study authors reported no NOAEL or LOAEL, and the data gaps are such that it is not possible to determine a NOAEL or LOAEL for this study. Insufficient toxicological parameters were examined in this study, and the impact of dietary protein was not sufficiently evaluated; therefore, this study is not considered suitable for derivation of a subchronic p-RfD. (US EPA 2012)

In a peer-reviewed study by Madhavarao et al. (2009), wild-type and tremor rat pups (6−12 males or females per group) received triacetin orally twice daily, initially at a dose of 4.2 g/kg during Postnatal Days (PND)s 7−14, then at 5.8 g/kg during PNDs 15−23, and thereafter in both food (7.5%) and water (5%) for a total treatment period of 110−120 days. The calculated doses in food and water are 7,099 mg/kg-day and 7,504 mg/kg-day, respectively, yielding a total oral dose of 14,603 mg/kg-day after PND 23. The tremor rat model of aspartoacylase deficiency is a natural mutant strain that has the entire aspartoacylase gene deleted. This rat model mimics Canavan disease in humans (described earlier in the Human Studies section [Madhavarao et al., 2009]);

thus, this study was conducted to support the efficacy of oral triacetin supplementation for aspartate deficiency. These rats were bred at the Center of Laboratory Animal Medicine at the Uniformed Services University of the Health Sciences, Bethesda, MD, where the studies were conducted. The study authors did not clearly present the number or sex of rats treated. A subset of rats was treated for approximately 110 days, and food intake and body weights were measured on a regular basis throughout the study (schedule not reported). Another subset of rats was treated for approximately 120 days, euthanized, and histopathology and biochemical analyses (29 different blood serum analytes such as lipids, proteins, electrolytes [e.g., Na, Mg]) were conducted. A limited set of tissues were fixed in 10% neutral-buffered formalin. Brain, spinal cord, lung, heart, liver, kidney, stomach, small and large intestine, and spleen were processed routinely, and slides from 2−4 rats per group were examined microscopically. When the data satisfied the assumptions of normality and equal variance, one-way ANOVA was performed followed by the Holm-Sidak post hoc test. When the data failed the assumptions of normality or equal variance or both, Kruskal-Wallis ANOVA of the ranks was applied, and differences in ranks were compared by Dunn's method.

No significant differences in the mean blood chemistry values occurred between treated and untreated groups, and no lesions indicating toxicity were detectable in any of the tissues examined microscopically (Madhavarao et al., 2009). Although triacetin-treated rats displayed slightly decreased food consumption and decreased body weights, the differences in weights between the treated and untreated groups were not statistically significant (data not presented). The study authors reported no NOAEL or LOAEL; the treated rats showed no adverse effects. Therefore, the NOAEL is 14,603 mg/kg-day, and a LOAEL is not available under the conditions tested. The study authors stated that these data support the use of triacetin supplementation for effective treatment of infants diagnosed with aspartoacylase deficiency. However, the following information was not provided: (a) whether the study complied with GLP standards; (b) the purity of the test compound; and (c) rat husbandry conditions. Hematology, urinalysis, organ weights, and necropsy were not performed or were not reported. Histology was limited to 10 tissues, and samples from only 2−4 rats were examined in each group. Due to these data omissions, this study is not considered suitable for derivation of a subchronic p-RfD. (US EPA 2012)

In a peer-reviewed study, Madhavarao et al. (2009) administered triacetin in infant formula to a 13-month-old girl and an 8-month-old boy for 6 and 4.5 months, respectively. The initial dose was 25 mg/kg twice daily (50 mg/kg-day) for the first week, followed by a doubling each subsequent week up to a maximum dose of 250 mg/kg twice daily (500 mg/kg-day). These infants were previously diagnosed with Canavan disease, a fatal dysmyelinating genetic disorder characterized by mutations in the enzyme aspartoacylase, resulting in a greatly reduced or absent capacity to hydrolyze the brain metabolite N-acetylaspartate to acetate and aspartate. Triacetin was selected for use as a dietary supplement as it is known to be an acetate precursor. The stated aim of this study was to determine the tolerability of low-dose oral triacetin administration in infants having Canavan disease. This study received Institutional Review Board approval and obtained parental consent. The following outcome criteria were evaluated prior to initiation of treatment and reviewed at 4 months of treatment: neurological status, brain magnetic resonance imaging and magnetic resonance spectroscopy, urine N-acetylaspartate levels, and ophthalmoscopic examination. Treatment-related effects were screened clinically and by blood work-up of complete blood count, kidney function, electrolytes, liver function, and venous blood gas measurements. The study authors did not identify a NOAEL or LOAEL; however, they stated that oral administration of triacetin caused no detectable toxicity, and that the infant patients showed no deterioration in their clinical status (Madhavarao et al., 2009). The NOAEL is 500 mg/kg-day; a LOAEL was not determined under the conditions tested. (US EPA 2012)

Similar to the Madhavarao et al. (2009) study above, Segel et al. (2011) administered triacetin in infant formula to a 12-month-old boy and an 8-month-old girl for 6 and 4.5 months, respectively. Both of the infants were previously diagnosed with Canavan disease, and as such, triacetin was being evaluated for efficacy as a dietary supplement (as explained under Madhavarao et al. [2009] above). The stated aim of this study was to determine the tolerability and efficacy of high-dose

triacetin administration in infants with Canavan disease. The initial dose was 500 mg/kg four times daily (2,000 mg/kg-day) for the first 3 days, followed by a doubling of dose every 3 days up to a maximum dose of 4,500 mg/kg-day (the target maximum dose was 5,000 mg/kg-day, but the parents reported 'discomfort' in each child at this specific dose). The children were evaluated prior to treatment and at 4.5 months after the initiation of treatment for the following outcomes: neurological status, brain magnetic resonance imaging and magnetic resonance spectroscopy, urine N-acetylaspartate levels, and ophthalmoscopic examination. Treatment-related effects were screened clinically and by blood work-up of complete blood count, kidney function, electrolytes, liver function, and venous blood gas measurements.

The study authors did not identify a NOAEL or LOAEL; although the study authors did state that administration of triacetin caused no detectable toxicity in either patient at a daily dose of 4,500 mg/kg-day; at the highest dose attempted (5,000 mg/kg-day), the study authors alluded to a potential problem with gastric acidity (Segel et al., 2011). The NOAEL is 4,500 mg/kg-day for lack of effects in human infants; a LOAEL was not determined under the conditions tested. (US EPA 2012)

5.3. Reproduction toxicity

"The combined repeated dose and reproductive/developmental toxicity study in rats at doses of 0 - 1,000 mg/kg bw/day [OECD TG 422] showed no statistically significant adverse effects on reproductive parameters including the mating index, fertility index, gestation length, numbers of corpora lutea and implantations, implantation index, gestation index, delivery index, parturition and maternal behavior at delivery and lactation. In addition, there were no significant differences in numbers of offspring or live offspring, the sex ratio, the live birth index, the viability index or body weight. Developmental toxicity, clinical signs of toxicity, and change in necropsy findings were not found in offspring. Therefore, the NOAEL is considered to be 1,000 mg/kg bw/day for parental animals and offspring."

"Using the OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], SD (Crj: CD) rats received gavage doses of 0 (vehicle; distilled water), 40, 200 and 1,000 mg/kg bw/day; for males for 44 days from 2 weeks prior to mating and for females for 41-48 days from 14 days before mating to day 3 postpartum (MHW, Japan: 1998). Triacetin had no effects on clinical signs, body weight, body weight gain, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed even at the highest dose for both sexes. There were no abnormalities in haematological or blood chemical parameters in males, although urinalysis was not conducted. The NOAEL for repeated dose toxicity is thus considered to be 1,000 mg/kg bw/day for both sexes."

As taken from OECD SIDS, Triacetin (102-76-1)

The study prepared for the Ministry of Health and Welfare, Japan (MHW, 1998) is selected as the principal study and deemed adequate for the derivation of screening level subchronic and chronic p-RfDs**.** In a combined repeated dose and reproductive toxicity screening study, 12 Sprague-Dawley [Crj:CD (SD) IGS] rats/sex were administered triacetin by gavage once daily at doses of 0, 40, 200, or 1,000 mg/kg-day. Males were dosed for 44 days beginning 2 weeks prior to mating; females were dosed for 41−48 days from 14 days before mating to PPD 3. The methodology of this study (MHW, 1998) was previously described under Subchronic Studies above. The results of the offspring and reproductive parameters are reported here. No treatment-related effects were observed on copulation, fertility, implantation, number of corpora lutea, gestation length, or delivery in exposed dams (MHW, 1998). No treatment-related effects were noted for the limited number of developmental parameters examined such as viability, offspring born alive, and offspring alive at PND 4. In addition, offspring body weights for triacetin-treated groups were similar to controls at PNDs 0 and 4. Although the study authors reported no NOAEL or LOAEL for reproductive effects, the highest dose of 1,000 mg/kg-day showed no adverse reproductive effects. Furthermore, triacetin exposure before, during, and immediately after pregnancy did not result in overt toxicity in

offspring. Therefore, the NOAEL for this study is 1,000 mg/kg-day for both offspring (developmental) and reproductive parameters. A LOAEL is not determined under the conditions tested. (US EPA 2012)

5.4. Mutagenicity

“Triacetin was not mutagenic in […] Escherichia coli WP2 uvrA at concentrations up to 5,000 ug /plate, with or without an exogenous metabolic activation system (MHW, Japan: 1998).”

“A chromosomal aberration test according to OECD TG 473 was conducted in cultured Chinese hamster lung (CHL/IU) cells. Induction of chromosome aberrations, however, was observed in the Chinese hamster cultured cells only at the highest concentration (2.2 mg/mL, 10 mM) in the presence of an exogenous metabolic activation system (OECD TG 473). Because of the high toxicity (75 %) and also low pH (4.9) at the end of the treatment, the chromosomal aberration observed might not be biological relevant. Under un-physiological culture condition, such as low pH, it was reported that the frequency of chromosomal aberrations could be increased (Morita et al., 1990). Polyploidy was not induced under any of the conditions on continuous and short-term treatment with and without an exogenous metabolic activation system (MHW, Japan: 1998).”

As taken from OECD SIDS, Triacetin (102-76-1)

/GENOTOXICITY/ /Negative in the Ames test using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 at concentrations of 50, 150, 500, 1500, 5000 ug/plate with and without metabolic activation./ [European Chemicals Bureau; IUCLID Dataset, Triacetin (102-76-1) (2000 CD-ROM edition). Available from, as of February 18, 2005: http://esis.jrc.ec.europa.eu/ **PEER REVIEWED**

/GENOTOXICITY/ The mutagenic potential of Triacetin was determined using adult Drosophila melanogaster. A dose of 0.2 to 0.3 mg Triacetin had a spontaneous mutation rate of approximately one mutation per 750 chromosomes. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/GENOTOXICITY/ The mutagenic potential of Triacetin was evaluated in a suspension test with and without metabolic activation. Test concentrations were 0.0013%, 0.00065%, and 0.000325% with S. typhimurium strains TA1535, TA1537, and TA1538 and 1.25%, 2.5%, and 5.0% with Saccharomyces cerevisiae strain D4. DMSO was used as the solvent. Appropriate negative and positive controls were used and gave expected results. Triacetin was not mutagenic in the suspension tests with or without metabolic activation. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/GENOTOXICITY/ ... Triacetin, with and without metabolic activation, was not mutagenic in the Ames assay or a suspension test. It was also not mutagenic in an in vivo assay using Drosophila. [Fiume MZ; Int J Toxicol 22 (Suppl 2): 1-10 (2003)] **PEER REVIEWED**

As taken from HSDB, 2015

“GTA did not induce gene mutation in Ames test at concentrations up to 5,000 µg/plate (OECD 471 and 472). Induction of chromosome aberrations was observed in the Chinese hamster lung cells at the highest concentration (2.2 mg/mL, 10 mM) in the presence of metabolic activation (OECD 473). Because of high toxicity (75%) that might be caused by low pH (4.9) at the end of the treatment, the chromosomal aberration observed might not be biological relevant. Under un-physiological culture condition, such as low pH, it was reported that the frequency of chromosomal aberrations could be increased. Polyploidy was not induced under any of the conditions tested. Results were equivocal, but taking all data into consideration, GTA could be considered to be non-genotoxic” (Maag et al. 2010).

Litton Bionetics, Inc. (1976a) evaluated the mutagenic potential of triacetin in an Ames plate and suspension test using Salmonella typhimurium (strains TA1535, TA1537, and TA1538) with and

without metabolic activation. Test concentrations were 0.000325%, 0.00065%, and 0.0013% (w/v). Doses were selected based on the results of a preliminary toxicity test. The activation systems included S9 prepared from the liver of male ICR mouse, S-D rat, or Rhesus monkey. A negative control (solvent) and appropriate positive controls were used and gave expected results. Triacetin was not mutagenic with or without metabolic activation. (US EPA 2012)

No evidence of mutagenic potential was obtained in an Ames test using S. typhimurium (strains TA1535, TA1537, TA98, and TA100) with and without metabolic activation at concentrations up to 5,000 µg/plate (Unichema Chemie B.V., 1994). The source document could not be obtained; this information was provided in the Final Report on the Safety Assessment of Triacetin (Fiume, 2003). (US EPA 2012)

Litton Bionetics, Inc. (1976b) evaluated the mutagenic potential of triacetin in a suspension test using Saccharomyces cerevisiae strain D4 with and without metabolic activation. Test concentrations were 1.25%, 2.5%, and 5.0% (w/v). Doses were selected based on the results of a preliminary toxicity test. The activation systems included S9 prepared from the liver of male ICR mouse, S-D rat, or Rhesus monkey. Appropriate negative and positive controls were used and gave expected results. Triacetin did not result in gene conversions in the suspension test with or without metabolic activation. (US EPA 2012)

Efremova (1962) treated adult Drosophila melanogaster with a dose of 0.2−0.3 mg triacetin in an in vivo assay and found triacetin not to be mutagenic. The source document could not be obtained; this information was provided in the Final Report on the Safety Assessment of Triacetin (Fiume, 2003). (US EPA 2012)

Type of Test	Route of Exposure	Species Observed	Dose Data	Reference
Cytogenetic analysis		Rodent - hamster Lung	10 mmol/L/6H	MUREAV Mutation Research. (Elsevier Science Pub. B.V., POB 211, 1000 AE Amsterdam, Netherlands) V.1- 1964- Volume(issue)/page/year: 517,187,2002

As taken from RTECS, 2015.

Triacetin was negative in an Ames test in which Salmonella typhimurium strains TA97, TA98, TA100 and TA1525 were treated with up to 10 mg/plate in dimethyl sulphoxide with and without S9 (NTP).

Purity	:	98.2 %
Test species/strains	:	Salmonella typhimurium TA100, TA1535, TA98, TA1537, Escherichia coli WP2 uvrA
Test method	:	Guidelines for Screening Toxicity Testing of Chemicals (Japan) and OECD Guidelines No. 471 and 472
pÇÇProcedures	:	Pre-incubation method
pÇÇSolvent	:	Distilled water
pÇÇPositive controls	:	-S9 mix; 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide(TA100, TA98, WP2 uvrA), Sodium azide(TA1535) and 9-Aminoacridine(TA1537) +S9 mix; 2-Aminoanthracene(five strains)
pÇÇDoses	:	-S9 mix; 0, 313, 625, 1250, 2500, 5000 µg/plate(five strains)

		+S9 mix; 0, 313 - 5000 µg/plate(five strains)
pÇÇS9	:	Rat liver, induced with phenobarbital and 5,6-benzoflavone
pÇÇPlates/test	:	3
pÇÇNumber of replicates	:	2 and 3(WP2 uvrA without S9 mix)
GLP	:	Yes

Test results: This chemical did not induce gene mutations in S. typhimurium and E. coli strains. Toxicity was not observed at 5000 µg/plate(five strains) with and without an S9 mix.

Genetic effects:

Salmonella typhimurium TA100, TA1535, TA98, TA1537

	+	?	-
Without metabolic activation:	[ ]	[ ]	[*]
With metabolic activation:	[ ]	[ ]	[*]

Escherichia coli WP2 uvrA

As taken from MHLW.

5.5. Cytotoxicity

Type of Test	**Route of Exposure**	**Species Observed**	**Dose Data**	**Reference**
IC50 - Inhibitor Concentration 50 - cell viability (lysosomal damage): neutral red assay etc.	In vitro	Mouse - fibroblast	21.8 mmol/L/48H	TIVIEQ Toxicology In Vitro. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.1- 1987- Volume(issue)/page/year: 27,1357,2013

As taken from RTECS, 2015.

“We identified the most popular electronic cigarette (EC) refill fluids using an Internet survey and local and online sales information, quantified their flavor chemicals, and evaluated cytotoxicities of the fluids and flavor chemicals. “Berries/Fruits/Citrus” was the most popular EC refill fluid flavor category. Twenty popular EC refill fluids were purchased from local shops, and the ingredient flavor chemicals were identified and quantified by gas chromatography-mass spectrometry. Total flavor

chemical concentrations ranged from 0.6 to 27.9 mg/ml, and in 95% of the fluids, total flavor concentration was greater than nicotine concentration. The 20 most popular refill fluids contained 99 quantifiable flavor chemicals; each refill fluid contained 22 to 47 flavor chemicals, most being esters. Some chemicals were found frequently, and several were present in most products. At a 1% concentration, 80% of the refill fluids were cytotoxic in the MTT assay. Six pure standards of the flavor chemicals found at the highest concentrations in the two most cytotoxic refill fluids were effective in the MTT assay, and ethyl maltol, which was in over 50% of the products, was the most cytotoxic. These data show that the cytotoxicity of some popular refill fluids can be attributed to their high concentrations of flavor chemicals." [Note: triacetin was tested in isolation.] As taken from Hua M et al. 2019. Scientific Reports 9, 2782 (15 pp). Available at https://www.nature.com/articles/s41598-019-38978-w.pdf

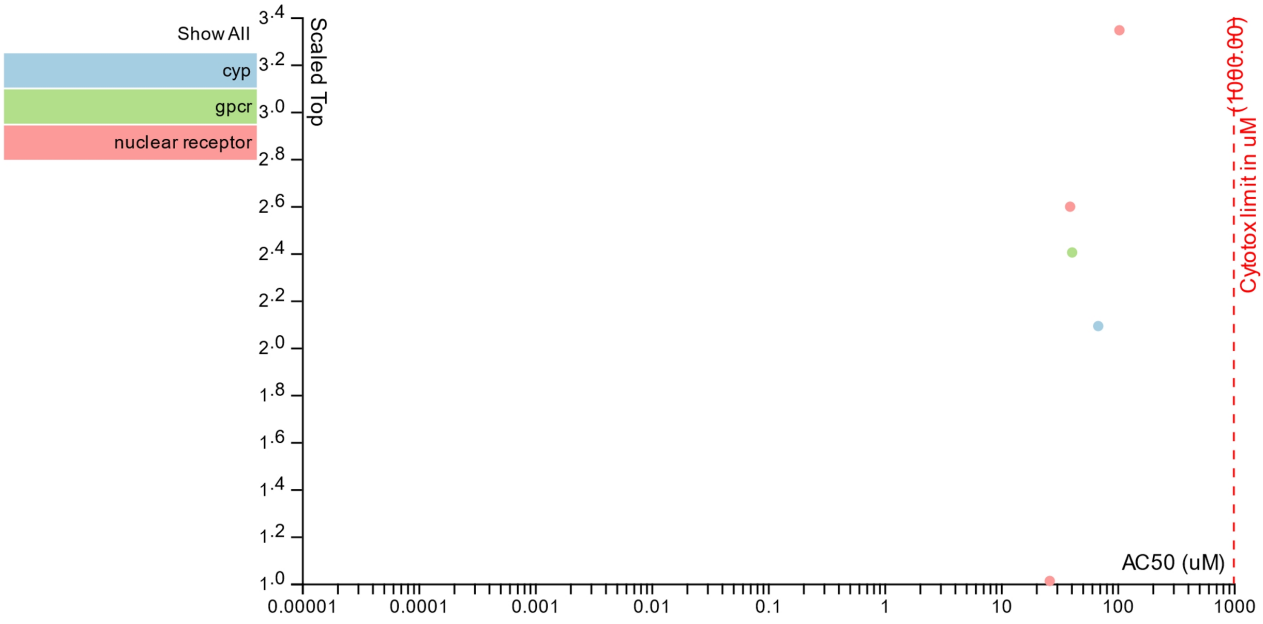
High-throughput Assay Data

The US Environmental Protection Agency (US EPA) evaluated triacetin (CAS RN 102-76-1) in a series of high-throughput assays, which are publicly available on the US EPA's CompTox Dashboard (section BIOACTIVITY / sub-section TOXCAST:SUMMARY), available at the following URL: https://comptox.epa.gov/dashboard

US EPA provides the following data use considerations for ToxCast data: "The activity of a chemical in a specific assay does not necessarily mean that it will cause toxicity or an adverse health outcome. There are many factors that determine whether a chemical will cause a specific adverse health outcome. Careful review is required to determine the use of the data in a particular decision contexts. Interpretation of ToxCast data is expected to change over time as both the science and analytical methods improve."

A summary of the ToxCast assay data on triacetin is provided below in Figure 1. Figure 1 proves an overview of the types of assays where activity was noted with this substance. The complete study details are available on US EPA's CompTox Dashboard.

Figure 1



5.6. Carcinogenicity

Tumor Promotion Studies:

Species:	Mouse
Strain/Sex:	ICR/Female
Route (Promoter):	Dermal
Dose (Promoter):	0, 85 mg, daily for 5 d/wk beginning 1 wk after carcinogen administration for 35 wk, study duration 36 wk
Carcinogen:	7,12-Dimethylbenz(a)anthracene; 57-97-6
Route (Carcinogen):	Dermal
Dose (Carcinogen):	100 ug in 100 ul acetone once at 6 wk of age
Target Tissue: Type of Lesion:	Skin: None
Reference:	[TAKASUKA,N TAKAHASHI,M HORI,Y KITAHASHI,T IIGO,M IMAI,T YOSHIMI,N SUGIMURA,T AND WAKABAYASHI,K; PROMOTION OF MOUSE TWO-STAGE SKIN CARCINOGENESIS BY DIACYLGLYCEROL-RICH EDIBLE OIL; CANCER LETTERS 275(1):150-157, 2009]
Species:	Mouse
Strain/Sex:	ICR/Female
Route (Promoter):	Dermal
Dose (Promoter):	0, 85 mg, twice daily for 5 d/wk beginning 1 wk after carcinogen administration for 35 wk, study duration 36 wk
Carcinogen:	7,12-Dimethylbenz(a)anthracene; 57-97-6
Route (Carcinogen):	Dermal
Dose (Carcinogen):	100 ug in 100 ul acetone once at 6 wk of age
Target Tissue: Type of Lesion:	Skin: None
Reference:	[TAKASUKA,N TAKAHASHI,M HORI,Y KITAHASHI,T IIGO,M IMAI,T YOSHIMI,N SUGIMURA,T AND WAKABAYASHI,K; PROMOTION OF MOUSE TWO-STAGE SKIN CARCINOGENESIS BY DIACYLGLYCEROL-RICH EDIBLE OIL; CANCER LETTERS 275(1):150-157, 2009]

As taken from CCRIS, 2010.

IC50	Human – liver tumor (in vitro)	29 mmol/L/24H	In Vitro Toxicity Studies - cell protein synthesis	TIVIEQ Toxicology In Vitro. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.1- 1987-

				Volume(issue)/page/year: 3,189,1989
IC50	Human – melanoma (in vitro)	4361.2 mg/L/48H	In Vitro Toxicity Studies - cell viability (lysosomal damage): neutral red assay etc.	FCTOD7 Food and Chemical Toxicology. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.20-1982- Volume(issue)/page/year: 50,2084,2012

As taken from RTECS, 2015.

“Glioblastoma multiforme (GBM), grade IV glioma and is aggressive, malignant primary brain cancer. Altered expression and activity of epigenetic proteins such as histone deacetylases (HDACs) are involved in GBM metastasis. Also, acetates are important to brain metabolites that regulate cell proliferation and apoptosis. Here, we have examined the effect of the acetates on the cell-cycle. U87MG cancer cells treated with N-acetyl l-aspartate (NAA) and sodium acetate have exhibited G1 phase cell-cycle arrest whereas U87MG cells treated with Triacetin (TA), and potassium acetate has induced G2/M cell cycle arrest. We have observed inhibition of histone deacetylase (HDAC) mRNA levels in acetate treated U87MG cells. Interestingly, acetates-treated U87MG cells have shown a significant reduction in the mRNA level of class II HDACs than class I HDACs. Acetate treated cells have exhibited an enhanced expression of various microRNAs such as miR-15b, miR-92, miR-101, miR-155, miR-199, miR-200, miR-223, miR-16, and miR-17 that are involved in the inhibition of cancer cell proliferation, invasion, migration, and angiogenesis. Further, these acetate molecules regulate genes involved in mammalian target of rapamycin complex 2 (mTORC2) such as mammalian stress-activated protein kinase-interacting protein (mSIN1), protein observed with Rictor 2 (Protor 2), and protein kinase C α (PKCα). The present study reveals the possible involvement of the mTORC2 complex during acetate-mediated HDAC inhibition, as well as microRNA modulation. Furthermore, molecular modeling studies were employed to understand the binding mode of these acetate molecules to mTOR, Rapamycin-insensitive companion of mammalian target of rapamycin (Rictor), and HDAC-8 proteins. Thus in this study, we have identified the pivotal role of acetates in the modulation of mTOR complex, epigenetic genes and provide structural as well as functional insights that will help in future drug discovery against GBM cancer therapy. (…)

N-acetyl aspartate (NAA) and TA (triacetin) are the most important acetate molecules in the brain. NAA is the most concentrated acetate metabolite in the human brain was found to be involved in the metabolic reprogramming of cancer cells and triacetin is food supplement that acts as an acetate source. We observed NAA and TA caused effective inhibition on the U87MG cell viability at 20 mM and 25 mM concentrations respectively. While the sodium and potassium acetates were inhibited at 240 mM and 100 mM concentrations respectively (...). The normal brain cells (HCN2) does not exhibit much effect on cell viability during the treatment with various acetates. (...)
Triacetin (TA) treatment was found to cause G0/G1 cell-cycle arrest in various cells such as oligodendroglioma cells but was failed to cause cell-cycle arrest in mouse neural stem cells.”

Mekala JR (2021) N-acetyl l-aspartate and Triacetin modulate tumor suppressor MicroRNA and class I and II HDAC gene expression induce apoptosis in Glioblastoma cancer cells in vitro.

5.7. Irritation/immunotoxicity

Skin, Eye and Respiratory Irritations:

“Eye irritant [Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 3503] **PEER REVIEWED**

A Duhring-chamber test was conducted on 20 healthy volunteers. The test substance was applied as 50% dilution for 24 hours. Result: only very mild skin reactions were observed. The substance has a good skin compatibility. [European Chemicals Bureau; IUCLID Dataset, Triacetin (102-76-1)

(2000 CD-ROM edition). Available from, as of February 18, 2005: http://esis.jrc.ec.europa.eu/ **PEER REVIEWED**

/HUMAN EXPOSURE STUDIES/ ... Triacetin (test concentrations not provided) was not an irritant or a sensitizer in a clinical maximization study, and only very mild reactions were seen in a Duhring-chamber test using a 50% dilution. In humans, commercial Triacetin has caused ocular irritation but no injury. [Fiume MZ; Int J Toxicol 22 (Suppl 2): 1-10 (2003)] **PEER REVIEWED** PubMed Abstract

/HUMAN EXPOSURE STUDIES/ A Duhring-chamber test was conducted on 20 healthy volunteers. The test substance was applied as 50% dilution for 24 hours. Result: only very mild skin reactions were observed. The substance has a good skin compatibility. [European Chemicals Bureau; IUCLID Dataset, Triacetin (102-76-1) (2000 CD-ROM edition). Available from, as of February 18, 2005: http://esis.jrc.ec.europa.eu/ **PEER REVIEWED**

/HUMAN EXPOSURE STUDIES/ A maximization test for undiluted triacetin was completed using 33 subjects. Triacetin was applied under an occlusive patch to the volar aspect of the forearm for 48 hr on 5 alternate days. Because a pretest indicated the triacetin was not an irritant, the test site was pretreated for 24 hr with 2% sodium lauryl sulfate (SLS) under an occlusive patch prior to application of the initial test patch. After a 10 to 14-day nontreatment period, challenge patches were applied to a previously unexposed site on the right side of the back. Prior to challenge, 2% SLS was applied for 30 min under an occlusive patch to the left side of the back. Additional SLS control patches and petrolatum patches were placed on the left and right sides, respectively, and used as controls. Undiluted triacetin did not produce an irritant or sensitization reaction. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/SIGNS AND SYMPTOMS/ ... Commercial triacetin may contain diacetin, as well as monoacetin, and when applied to ... human eyes causes severe burning pain and much redness of the conjunctiva, but no injury. Diacetin causes considerably more discomfort than pure triacetin. [Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 932] **PEER REVIEWED**

/SIGNS AND SYMPTOMS/ In sensitive individuals, it may cause slight irritation. [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 711] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ /Investigators examined/ the dermal irritation potential of triacetin in guinea pigs. Doses of 5 and 10 cc/kg were applied under an occlusive patch for 24 hr. Slight erythema was observed. Occlusive patches with 5 to 20 cc/kg were tested using three animals. Slight edema and "1-3 erythema" were observed. Slight skin irritation was observed in the high dose animals. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ Groups of three, three, and two guinea pigs were used to determine the irritation potential of triacetin .... At the end of a 14-day observation period, erythema, slight edema, alopecia, and desquamation were observed. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/OTHER TOXICITY INFORMATION/ Nonaqueous drug vehicles containing triacetin caused local tissue irritation. However, it was neither irritating nor sensitizing when absorbed through guinea pig skin. [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 710] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ In a study using groups of four rabbits, in which ocular tissue sampling was done, 0.1 mL was instilled into both eyes. A control group of four rabbits was not treated. Animals were killed after 2 or 24 hr. In the Draize test, triacetin had a total Draize score of 1 after 2 hr (0 for the cornea and 0.7 for the conjunctiva); corneal thickness did not change. After

2 hr, the corneal percentage of dry weight/wet weight was significantly decreased, but not after 24 hr, compared to controls. No difference was observed for conjunctival percentage of dry weight/wet weight or Evan's blue concentration/dry weight at 2 or 24 hr. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ ...Tested on rabbit eyes has been found to cause no injury... . [Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 931] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ When placed (0.1 mL) undiluted into rabbit eyes, triacetin was slightly to moderately irritating. It was not irritating when immediately irrigated for 6 min. [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 710] **PEER REVIEWED**

/OTHER TOXICITY INFORMATION/ Triacetin appears to be of low toxicity when swallowed, inhaled or placed on skin. [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 711] **PEER REVIEWED**

Therapeutic Uses:

Treatment of onychomycosis (nail fungus), tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corporis (ringworm), monilial impetigo and dermatitis. [Novak, K.M. (ed.). Drug Facts and Comparisons 59th Edition 2005. Wolters Kluwer Health. St. Louis, Missouri 2005., p. 2024] **PEER REVIEWED**"

/LABORATORY ANIMALS: Acute Exposure/ /Investigators examined/ the dermal irritation potential of triacetin in guinea pigs. Doses of 5 and 10 cc/kg were applied under an occlusive patch for 24 hr. Slight erythema was observed. Occlusive patches with 5 to 20 cc/kg were tested using three animals. Slight edema and "1-3 erythema" were observed. Slight skin irritation was observed in the high dose animals. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/OTHER TOXICITY INFORMATION/ ... Triacetin was, at most, slightly irritating to guinea pig skin. However, in one study, it caused erythema, slight edema, alopecia, and desquamation. Triacetin was not sensitizing in guinea pigs; however, test concentrations were not stated. Triacetin caused some irritation in rabbit eyes. [Fiume MZ; Int J Toxicol 22 (Suppl 2): 1-10 (2003)] **PEER REVIEWED**

... The fungistatic activity of triacetin (glyceryl triacetate) results from its hydrolysis by fungalesterases to acetic acid. [Ullmann's Encyclopedia of Industrial Chemistry. 6th ed.Vol 1: Federal Republic of Germany: Wiley-VCH Verlag GmbH & Co. 2003 to Present, p. V10 391 (2003)] **PEER REVIEWED**

As taken from HSDB, 2015

“Not or very weakly irritating for Guinea pig, rabbit and human. No sensitization for human and Guinea pig.”

“A contact eczema in humans caused by triacetin is reported.”

“Minimal tissue irritation in chicken pectoral muscle.”

“Contact with a solution containing 50 % triacetin in ethanol was not irritant to 20 eczema patients in covered test for 24 and 48hr (Unna and Schulz, 1963).”

As taken from OECD SIDS, Triacetin (102-76-1)

“GTA [triacetin} was not found irritating to rabbit skin and eyes in studies following OECD 404 and 405. GTA did not induce sensitisation in guinea pigs” (Maag et al. 2010).

“A case of allergic contact eczema in a 29 year-old patient in a cigarette factory is reported, which was based on sensitisation towards the triacetin used for the production of cigarette filters. The

allergy was demonstrated in a patch test. In addition to triacetin, the di- and mono acetate of glycerol also produced positive tests. It seems reasonable to regard the reaction as an expression of a group sensitisation towards glycerol acetate" (Maag et al. 2010).

Type of Test	Route of Exposure	Species Observed	Dose Data	Reaction Severity	Reference
Standard Draize test	Administration into the eye	Rodent - rabbit	116 mg		JPETAB Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10- Volume(issue)/page/year: 82,377,1944

As taken from RTECS, 2015.

Triacetin is reported to have caused "occupational contact dermatitis in a cigarette manufacturing worker" (Haz-Map 2020).

5.8. All other relevant types of toxicity

/ALTERNATIVE and IN VITRO TESTS/ In an in vitro study, the penetration of Triacetin into the corium of human skin was determined by topical application of Triacetin to the epidermis (which was later separated from the corium), and then measuring the antimicrobial activity. Using leg skin, a plastic cylinder was attached to the epidermis, and 0.01 cc Triacetin was applied for 20 to 24 hr. The skin was then washed and the epidermis removed. Six-millimeter punches of the corium were taken and implanted on the culture medium, with the epidermal side in contact with the medium. When inhibition of growth around the corium occurred, the radius of inhibition was measured. There was no average inhibition of positive responses with Triacetin cream. The researchers speculated that an antimicrobial agent may penetrate into the corium and not diffuse into the surrounding medium when assayed, and that this might give a false-negative report of its ability to penetrate the epidermis. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/OTHER TOXICITY INFORMATION/ Laboratory rats have tolerated diets consisting of 50% triacetin. If hydrolized... /systemic/ acidosis is a possible consequence. [Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. II-203] **PEER REVIEWED**

/OTHER TOXICITY INFORMATION/ Diacetin was slightly less toxic than Triacetin, and the researchers concluded that the order of toxicity of the acetins appears to increase with the degree of acetylation. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

As taken from HSDB, 2015

"BACKGROUND: Most electronic-cigarette liquids contain propylene glycol, glycerin, nicotine and a wide variety of flavors of which many are sweet. Sweet flavors are classified as saccharides, esters, acids or aldehydes. This study investigates changes in cariogenic potential when tooth surfaces are exposed to e-cigarette aerosols generated from well-characterized reference e-liquids with sweet flavors. METHODS: Reference e-liquids were prepared by combining 20/80 propylene glycol/glycerin (by volume fraction), 10 mg/mL nicotine, and flavors. Aerosols were generated by a Universal Electronic-Cigarette Testing Device (49.2 W, 0.2 Ω). Streptococcus mutans (UA159) were exposed to aerosols on tooth enamel and the biological and physiochemical parameters were measured. RESULTS: E-cigarette aerosols produced four-fold increase in microbial adhesion to enamel. Exposure to flavored aerosols led to two-fold increase in biofilm formation and up to a 27% decrease in enamel hardness compared to unflavored controls. Esters (ethyl butyrate, hexyl acetate, and triacetin) in e-liquids were associated with consistent bacteria-initiated enamel

demineralization, whereas sugar alcohol (ethyl maltol) inhibited S. mutans growth and adhesion. The viscosity of the e-liquid allowed S. mutans to adhere to pits and fissures. Aerosols contained five metals (mean ± standard deviation): calcium (0.409 ± 0.002) mg/L, copper (0.011 ± 0.001) mg/L, iron (0.0051 ± 0.0003) mg/L, magnesium (0.017 ± 0.002) mg/L, and silicon (0.166 ± 0.005) mg/L. CONCLUSIONS: This study systematically evaluated e-cigarette aerosols and found that the aerosols have similar physio-chemical properties as high-sucrose, gelatinous candies and acidic drinks. Our data suggest that the combination of the viscosity of e-liquids and some classes of chemicals in sweet flavors may increase the risk of cariogenic potential. Clinical investigation is warranted to confirm the data shown here." As taken from Kim SA et al. 2018. PLoS One 13(9), e0203717. PubMed, 2019 available at https://www.ncbi.nlm.nih.gov/pubmed/30192874

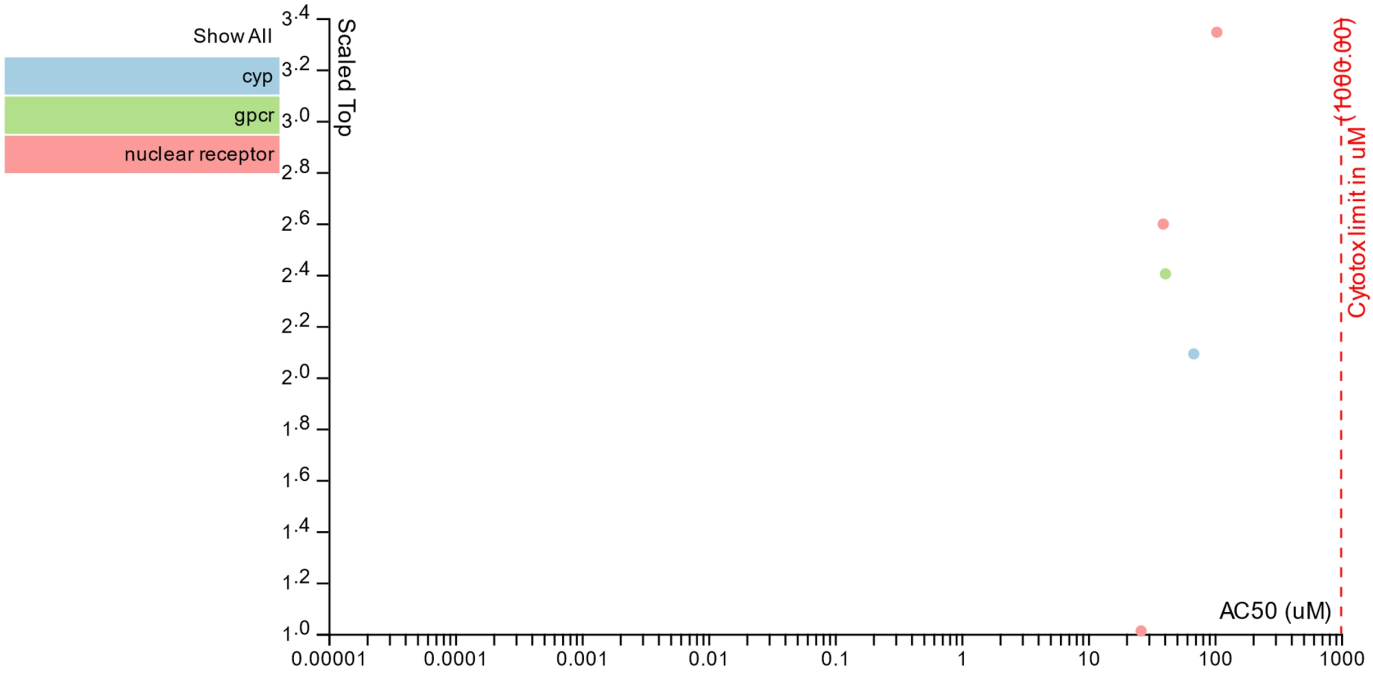
High-throughput Assay Data

The US Environmental Protection Agency (US EPA) evaluated triacetin (CAS RN 102-76-1) in a series of high-throughput assays, which are publicly available on the US EPA's CompTox Dashboard (section BIOACTIVITY / sub-section TOXCAST:SUMMARY), available at the following URL: https://comptox.epa.gov/dashboard

US EPA provides the following data use considerations for ToxCast data: "The activity of a chemical in a specific assay does not necessarily mean that it will cause toxicity or an adverse health outcome. There are many factors that determine whether a chemical will cause a specific adverse health outcome. Careful review is required to determine the use of the data in a particular decision contexts. Interpretation of ToxCast data is expected to change over time as both the science and analytical methods improve."

A summary of the ToxCast assay data on triacetin is provided below in Figure 1. Figure 1 proves an overview of the types of assays where activity was noted with this substance. The complete study details are available on US EPA's CompTox Dashboard.

Figure 1



6. Functional effects on

6.1. Broncho/pulmonary system

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ In the rat, inhalation of 250 ppm triacetin (6 hr/day, 5 days/wk for 13 weeks) or saturated triacetin vapor (6 hr/day for 5 days) produced no clinical signs of toxicity or histopathological effects. [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 710] **PEER REVIEWED**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ /Investigators/ exposed a group of three rats to 250 ppm triacetin /by inhalation/ for 6 hr per day, 5 days per week, for 64 days. The no-observed-effect level (NOEL) was 250 ppm. Three rats were also exposed to 8271 ppm triacetin for 6 hr per day for 64 days. The NOEL was 8271 ppm. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

As taken from HSDB, 2015

“An inhalation study was conducted in rats given triacetin for 90 days at a dose of 249 ppm (2,220 mg/m) under non-GLP condition. No toxic signs were noted during the exposure. The NOAEL is considered to be 249 ppm 3 (2,220 mg/m) for 90 days. Although the inhalation study is considered to be useful, it does not fully comply with the current testing protocol.”

NOEL: 73,7000 mg/m3 was determined by an inhalation study with an 90 days exposure.

As taken from OECD SIDS, Triacetin (102-76-1)

Type of Test	Route of Exposure	Species Observed	Dose Data	Toxic Effects	Reference
ICLo - Inhibitor Concentration Low	In vitro	Human - lung	10 umol/L/8H	In Vitro Toxicity Studies - other assays	TXCYAC Toxicology. (Elsevier Scientific Pub. Ireland, Ltd., POB 85, Limerick, Ireland) V.1- 1973- Volume(issue)/page/year: 287,105,2011

As taken from RTECS, 2015.

6.2. Cardiovascular system

“Triacetin produced a decrease in blood pressure after intravenous application in cats.”

“ Triacetin will produce slight hemolysis in vitro.”

As taken from IUCLID Dataset (2000), Triacetin (102-76-1).

6.3. Nervous system

“/EXPL THER/ Canavan disease (CD) is a fatal genetic neurodegenerative disorder caused by mutations in the gene for aspartoacylase, an enzyme that hydrolyzes N-acetylaspartate (NAA) into L-aspartate and acetate. Because aspartoacylase is localized in oligodendrocytes, and NAA-derived acetate is incorporated into myelin lipids, we hypothesize that an acetate deficiency in oligodendrocytes is responsible for the pathology in CD, and we propose acetate supplementation as a possible therapy. In our preclinical efforts toward this goal, we studied the effectiveness of orally administered glyceryl triacetate (GTA) and calcium acetate for increasing acetate levels in the murine brain. The concentrations of brain acetate and NAA were determined simultaneously after intragastric administration of GTA. We found that the acetate levels in brain were increased in a dose- and time-dependent manner, with a 17-fold increase observed at 1 to 2 hr in 20- to 21-day-old mice at a dose of 5.8 g/kg GTA. NAA levels in the brain were not significantly increased under these conditions. Studies using mice at varying stages of development showed that the dose of

GTA required to maintain similarly elevated acetate levels in the brain increased with age. Also, GTA was significantly more effective as an acetate source than calcium acetate. Chronic administration of GTA up to 25 days of age did not result in any overt pathology in the mice. Based on these results and the current Food and Drug Administration-approved use of GTA as a food additive, we propose that it is a potential candidate for use in acetate supplementation therapy for CD. [Mathew R et al; J Pharmacol Exp Ther 315 (1): 297-303 (2005)] **PEER REVIEWED** PubMed Abstract

/EXPL THER/ The FDA approved food additive Triacetin (glyceryl triacetate, GTA) has been safely used for acetate supplementation therapy in Canavan disease, a leukodystrophy due to aspartoacylase (ASPA) mutation. This study characterized the effects of GTA on the proliferation and differentiation of six primary glioblastoma (GBM)-derived glioma stem-like cells (GSCs) relative to established U87 and U251 GBM cell lines, normal human cerebral cortical astrocytes, and murine neural stem cells. GTA reduced proliferation of GSCs greater than established GBM lines. Moreover, GTA reduced growth of the more aggressive mesenchymal GSCs greater than proneural GSCs. Although sodium acetate induced a dose-dependent reduction of GSC growth, it also reduced cell viability. GTA-mediated growth inhibition was not associated with differentiation, but increased protein acetylation. These data suggest that GTA-mediated acetate supplementation is a novel therapeutic strategy to inhibit GSC growth. [Long PM et al; J Cell Physiol 230 (8): 1929-43 (2015)] **PEER REVIEWED** PubMed Abstract Full text: PMC4414874

/LABORATORY ANIMALS: Acute Exposure/ Patients suffering from traumatic brain injury (TBI) have decreased markers of energy metabolism, including N-acetylaspartate (NAA) and ATP. In the nervous system, NAA-derived acetate provides acetyl-CoA required for myelin lipid synthesis. Acetate can also be oxidized in mitochondria for the derivation of metabolic energy. In the current study, using the controlled cortical impact model of TBI in rats, we investigated the effects of the hydrophobic acetate precursor, glyceryltriacetate (GTA), as a method of delivering metabolizable acetate to the injured brain. We found that GTA administration significantly increased the levels of both NAA and ATP in the injured hemisphere 4 and 6 days after injury, and also resulted in significantly improved motor performance in rats 3 days after injury. [Arun P et al; J Neurotrauma 27 (1): 293-8 (2010)] **PEER REVIEWED** PubMed Abstract Full text: PMC2824219

/LABORATORY ANIMALS: Acute Exposure/ Acetate supplementation reduces neuroglia activation and pro-inflammatory cytokine expression in rat models of neuroinflammation and Lyme neuroborreliosis. Because single-dose glyceryl triacetate (GTA) treatment increases brain phosphocreatine and reduces brain AMP levels, we postulate that GTA modulates adenosine metabolizing enzymes and receptors, which may be a possible mechanism to reduce neuroinflammation. To test this hypothesis, we quantified the ability of GTA to alter brain levels of ecto-5'-nucleotidase (CD73), adenosine kinase (AK), and adenosine A2A receptor using western blot analysis and CD73 activity by measuring the rate of AMP hydrolysis. Neuroinflammation was induced by continuous bacterial lipopolysaccharide (LPS) infusion in the fourth ventricle of the brain for 14 and 28 days. Three treatment strategies were employed, one and two where rats received prophylactic GTA through oral gavage with LPS infusion for 14 or 28 days. In the third treatment regimen, an interventional strategy was used where rats were subjected to 28 days of neuroinflammation, and GTA treatment was started on day 14 following the start of the LPS infusion. We found that rats subjected to neuroinflammation for 28 days had a 28% reduction in CD73 levels and a 43% increase in AK levels that was reversed with prophylactic acetate supplementation. CD73 activity in these rats was increased by 46% with the 28-day GTA treatment compared to the water-treated rats. Rats subjected to neuroinflammation for 14 days showed a 50% increase in levels of the adenosine A2A receptor, which was prevented with prophylactic acetate supplementation. Interventional GTA therapy, beginning on day 14 following the induction of neuroinflammation, resulted in a 67% increase in CD73 levels and a 155% increase in adenosine A2A receptor levels. These results support the hypothesis that acetate supplementation can modulate brain CD73, AK and adenosine A2A receptor levels, and possibly influence

purinergic signaling. [Smith MD et al; J Neuroinflammation 11: 99 doi: 10.1186/1742-2094-11-99 (2014)] **PEER REVIEWED** PubMed Abstract Full text: PMC4050445

/LABORATORY ANIMALS: Neurotoxicity/ Neurotoxic effects of triacetin include tremors and convulsions. [European Chemicals Bureau; IUCLID Dataset, Triacetin (102-76-1) (2000 CD-ROM edition). Available from, as of February 18, 2005: http://esis.jrc.ec.europa.eu/ **PEER REVIEWED**"

As taken from HSDB, 2015

".....To determine the effect(s) that an increase in acetyl-CoA levels has on brain energy metabolism, we measured brain nucleotide, phosphagen and glycogen levels, and quantified cardiolipin content and mitochondrial number in rats subjected to acetate supplementation. Acetate supplementation was induced with glyceryl triacetate (GTA) by oral gavage (6 g/kg body weight). Rats used for biochemical analysis were euthanized using head-focused microwave irradiation at 2, and 4h following treatment to immediately stop metabolism. We found that acetate did not alter brain ATP, ADP, NAD, GTP levels, or the energy charge ratio [ECR, (ATP+½ ADP)/(ATP+ADP+AMP)] when compared to controls. However, after 4h of treatment brain phosphocreatine levels were significantly elevated with a concomitant reduction in AMP levels with no change in glycogen levels. In parallel studies where rats were treated with GTA for 28 days, we found that acetate did not alter brain glycogen and mitochondrial biogenesis as determined by measuring brain cardiolipin content, the fatty acid composition of cardiolipin and using quantitative ultra-structural analysis to determine mitochondrial density/unit area of cytoplasm in hippocampal CA3 neurons. Collectively, these data suggest that an increase in brain acetyl-CoA levels by acetate supplementation does increase brain energy stores however it has no effect on brain glycogen and neuronal mitochondrial biogenesis." As taken from Bhatt DP et al. 2013. Neurochem. Int. 62(3), 296-305. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/23321384

"BACKGROUND: We have found that acetate supplementation significantly reduces neuroglia activation and pro-inflammatory cytokine release in a rat model of neuroinflammation induced with lipopolysaccharide. To test if the anti-inflammatory effect of acetate supplementation is specific to a TLR4-mediated injury, we measured markers of neuroglia activation in rats subjected to B. burgdorferi-induced neuroborreliosis that is mediated in large part by a TLR2-type mechanism. METHODS: In this study, rats were subjected to Lyme neuroborreliosis following an intravenous infusion of B. burgdorferi (B31-MI-16). Acetate supplementation was induced using glyceryl triacetate (6g/kg) by oral gavage. Immunohistochemistry, qPCR, and western blot analyses were used to measure bacterial invasion into the brain, neuroglial activation, and brain and circulating levels of interleukin 1β. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by a Tukey's post hoc tests or using a Student's t test assuming unequal variances when appropriate. RESULTS: We found that acetate supplementation significantly reduced microglia activation by 2-fold as determined by immunohistochemical and western blot analysis. Further, acetate supplementation also reduced the expression of the pro-inflammatory cytokine IL-1β by 2-fold as compared to controls. On the other hand, the inoculation of rats with B. burgdorferi had no effect on astroglial activation as determined by immunocytochemistry and western blot analysis despite significant increases in circulation levels of antigen toward B. burgdorferi and presence of the bacteria in the central nervous system. CONCLUSIONS: These results suggest that microglial activation is an essential component to neuroborreliosis and that acetate supplementation may be an effective treatment to reduce injury phenotype and possibly injury progression in Lyme neuroborreliosis." As taken from Brisette CA et al. 2012. J. Neuroinflammation 9, 249. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/23134838

"BACKGROUND: Long-term acetate supplementation reduces neuroglial activation and cholinergic cell loss in a rat model of lipopolysaccharide-induced neuroinflammation. Additionally, a single dose of glyceryl triacetate, used to induce acetate supplementation, increases histone H3 and H4 acetylation and inhibits histone deacetylase activity and histone deacetylase-2 expression in

normal rat brain. Here, we propose that the therapeutic effect of acetate in reducing neuroglial activation is due to a reversal of lipopolysaccharide-induced changes in histone acetylation and pro-inflammatory cytokine expression. METHODS: In this study, we examined the effect of a 28-day-dosing regimen ofglyceryl triacetate, to induce acetate supplementation, on brain histone acetylation and interleukin-1β expression in a rat model of lipopolysaccharide-induced neuroinflammation. The effect was analyzed using Western blot analysis, quantitative real-time polymerase chain reaction and enzymic histone deacetylase and histone acetyltransferase assays. Statistical analysis was performed using one-way analysis of variance, parametric or nonparametric when appropriate, followed by Tukey's or Dunn's post-hoc test, respectively. RESULTS: We found that long-term acetate supplementation increased the proportion of brain histone H3 acetylated at lysine 9 (H3K9), histone H4 acetylated at lysine 8 and histone H4 acetylated at lysine 16. However, unlike a single dose ofglyceryl triacetate, long-term treatment increased histone acetyltransferase activity and had no effect on histone deacetylase activity, with variable effects on brain histone deacetylase class I and II expression. In agreement with this hypothesis, neuroinflammation reduced the proportion of brain H3K9 acetylation by 50%, which was effectively reversed with acetate supplementation. Further, in rats subjected to lipopolysaccharide-induced neuroinflammation, the pro-inflammatory cytokine interleukin-1β protein and mRNA levels were increased by 1.3- and 10-fold, respectively, and acetate supplementation reduced this expression to control levels. CONCLUSION: Based on these results, we conclude that dietary acetate supplementation attenuates neuroglial activation by effectively reducing pro-inflammatory cytokine expression by a mechanism that may involve a distinct site-specific pattern of histone acetylation and histone deacetylase expression in the brain."As taken from Soliman ML et al. 2012. J. Neuroinflammation 9, 51. PubMed, 2013 available at http://www.ncbi.nlm.nih.gov/pubmed/22413888

In a peer-reviewed study, Madhavarao et al. (2009) administered triacetin in infant formula to a 13-month-old girl and an 8-month-old boy for 6 and 4.5 months, respectively. The initial dose was 25 mg/kg twice daily (50 mg/kg-day) for the first week, followed by a doubling each subsequent week up to a maximum dose of 250 mg/kg twice daily (500 mg/kg-day). These infants were previously diagnosed with Canavan disease, a fatal dysmyelinating genetic disorder characterized by mutations in the enzyme aspartoacylase, resulting in a greatly reduced or absent capacity to hydrolyze the brain metabolite N-acetylaspartate to acetate and aspartate. Triacetin was selected for use as a dietary supplement as it is known to be an acetate precursor. The stated aim of this study was to determine the tolerability of low-dose oral triacetin administration in infants having Canavan disease. This study received Institutional Review Board approval and obtained parental consent. The following outcome criteria were evaluated prior to initiation of treatment and reviewed at 4 months of treatment: neurological status, brain magnetic resonance imaging and magnetic resonance spectroscopy, urine N-acetylaspartate levels, and ophthalmoscopic examination. Treatment-related effects were screened clinically and by blood work-up of complete blood count, kidney function, electrolytes, liver function, and venous blood gas measurements. The study authors did not identify a NOAEL or LOAEL; however, they stated that oral administration of triacetin caused no detectable toxicity, and that the infant patients showed no deterioration in their clinical status (Madhavarao et al., 2009). The NOAEL is 500 mg/kg-day; a LOAEL was not determined under the conditions tested. (US EPA 2012)

Similar to the Madhavarao et al. (2009) study above, Segel et al. (2011) administered triacetin in infant formula to a 12-month-old boy and an 8-month-old girl for 6 and 4.5 months, respectively. Both of the infants were previously diagnosed with Canavan disease, and as such, triacetin was being evaluated for efficacy as a dietary supplement (as explained under Madhavarao et al. [2009] above). The stated aim of this study was to determine the tolerability and efficacy of high-dose triacetin administration in infants with Canavan disease. The initial dose was 500 mg/kg four times daily (2,000 mg/kg-day) for the first 3 days, followed by a doubling of dose every 3 days up to a maximum dose of 4,500 mg/kg-day (the target maximum dose was 5,000 mg/kg-day, but the parents reported 'discomfort' in each child at this specific dose). The children were evaluated prior

to treatment and at 4.5 months after the initiation of treatment for the following outcomes: neurological status, brain magnetic resonance imaging and magnetic resonance spectroscopy, urine N-acetylaspartate levels, and ophthalmoscopic examination. Treatment-related effects were screened clinically and by blood work-up of complete blood count, kidney function, electrolytes, liver function, and venous blood gas measurements.

The study authors did not identify a NOAEL or LOAEL; although the study authors did state that administration of triacetin caused no detectable toxicity in either patient at a daily dose of 4,500 mg/kg-day; at the highest dose attempted (5,000 mg/kg-day), the study authors alluded to a potential problem with gastric acidity (Segel et al., 2011). The NOAEL is 4,500 mg/kg-day for lack of effects in human infants; a LOAEL was not determined under the conditions tested.(US EPA 2012)

Type of Test	**Route of Exposure**	**Species Observed**	**Dose Data**	**Reference**
ICLo - Inhibitor Concentration Low - In Vitro Toxicity Studies - other assays	In vitro	Rat - brain(cerebrum)	2.66 mmol/L/44H	TIVIEQ Toxicology In Vitro. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.1- 1987- Volume(issue)/page/year: 27,1416,2013

As taken from RTECS, 2015.

“We have previously shown that prebiotics (dietary fibres that augment the growth of indigenous beneficial gut bacteria) such as Bimuno™ galacto-oligosaccharides (B-GOS®), increased N-methyl-D-aspartate (NMDA) receptor levels in the rat brain. The current investigation examined the functional correlates of these changes in B-GOS®-fed rats by measuring cortical neuronal responses to NMDA using in vivo NMDA micro-iontophoresis electrophysiology, and performance in the attentional set-shifting task. Adult male rats were supplemented with B-GOS® in the drinking water 3 weeks prior to in vivo iontophoresis or behavioural testing. Cortical neuronal responses to NMDA iontophoresis, were greater (+30%) in B-GOS® administered rats compared to non-supplemented controls. The intake of B-GOS® also partially hindered the reduction of NMDA responses by the glycine site antagonist, HA-966. In the attentional set-shifting task, B-GOS®-fed rats shifted from an intra-dimensional to an extra-dimensional set in fewer trials than controls, thereby indicating greater cognitive flexibility. An initial exploration into the mechanisms revealed that rats ingesting B-GOS® had increased levels of plasma acetate, and cortical GluN2B subunits and Acetyl Co-A Carboxylase mRNA. These changes were also observed in rats fed daily for 3 weeks with glyceryl triacetate, though unlike B-GOS®, cortical histone deacetylase (HDAC1, HDAC2) mRNAs were also increased which suggested an additional epigenetic action of direct acetate supplementation. Our data demonstrate that a pro-cognitive effect of B-GOS® intake in rats is associated with an increase in cortical NMDA receptor function, but the role of circulating acetate derived from gut bacterial fermentation of this prebiotic requires further investigation.” As taken from Gronier B et al. 2018. Eur. Neuropsychopharmacol. 28(1), 211-224. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/29174530

Triacetin is a “CNS Neurotoxin” (Haz-Map, 2020).

6.4. Other organ systems, dependent on the properties of the substance

/LABORATORY ANIMALS: Acute Exposure/ Six female mongrel dogs were used to determine the effect of Triacetin on serum phosphorus, calcium, and magnesium metabolism. A 5% v/v aqueous solution of Triacetin was infused intravenously at a rate of 47 umol/kg/min for 3 hr. Arterial blood was sampled at 15 to 30-min intervals, and urine was collected during infusion. No significant changes in total serum calcium or phosphorus concentrations were observed; however, serum magnesium concentrations were statistically significantly decreased 90 min after the initiation of dosing and remained decreased until the end of the study. During Triacetin infusion, the plasma acetate concentration increased from 0.13 to 1.32 mmol/L at 30 min; the concentration gradually declined to /approximately/ 1 mmol/L during the last hour of the study. No change was observed in the fractional excretion of calcium, magnesium, or phosphorus. The authors speculated that the decrease in serum magnesium was probably because of cellular uptake rather than accelerated excretion. Baseline blood pH was not significantly altered. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ In a study examining the effect of Triacetin on nitrogen balance, whole-body kinetics, and muscle and liver fractional protein synthetic rates, /investigators/ infused male Sprague-Dawley rats with isovolemic, isocaloric, and isonitrogenous parenteral diets. Thirty percent of the nonprotein energy of the diets was lipid energy, and for groups of 6, 10, and 6 animals, the lipid energy was composed of 0%, 50%, and 90% Triacetin, respectively. No difference was observed in the plasma acetate concentration of animals that received Triacetin compared to those that did not. The liver weight was significantly decreased in the animals given Triacetin. Protein concentration in the liver and rectus muscle was similar for all three groups. Cumulative nitrogen balance was positive for all animals, and no significant difference in nitrogen balance was observed on days 6 and 7. Lipid composition had very little effect on plasma leucine kinetics. Also, fractional protein synthetic rates in the rectus muscle and liver were similar for all animals. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ Triacetin, the water-soluble triglyceride of acetate, was infused in mongrel dogs at isocaloric (N=6) or hypercaloric (approximately 1.5 resting energy expenditure (REE), N=7) rates in mongrel dogs for 3 hr. Ketone body and glucose production rates were quantified with [(13)C2] acetoacetate and [3H]glucose, respectively. Four additional animals were infused with glycerol to serve as controls for the hypercaloric triacetin infusion. Energy expenditure was determined in the isocaloric experiments. No evidence of acute toxicity was observed during triacetin infusion at either rate. Plasma acetate concentrations increased from basal levels to approximately 1 and approximately 13 mmol/L in the isocaloric and hypercaloric experiments, respectively. Plasma lactate and pyruvate concentrations decreased dramatically after 30 min of both isocaloric and hypercaloric triacetin infusions. Glucose production rates did not increase in either group, but glucose clearance decreased significantly in both groups ($p < 0.05$) over the last hour of triacetin infusion. Plasma ketone body concentrations increased from 1.4 to 3.5 and 1.8 to 13.5 mumol/kg.min, respectively, during isocaloric and hypercaloric triacetin infusion. Resting energy expenditure increased from 3.0 +/- 0.3 to 4.0 +/- 0.5 kcal/kg.hr during isocaloric triacetin infusion ($p < 0.05$). [Bailey JW et al; JPEN J Patenter Enteral Nutr 15 (1): 32-6 (1991)] **PEER REVIEWED** PubMed Abstract

The present studies investigated the effects of intravenous administration of the short-chain triglyceride triacetin on leucine metabolism in dogs. Animals received infusions of triacetin at 1.0 x estimated resting energy expenditure (REE), hyperenergetic triacetin at 1.5 x REE, glycerol, or saline during infusion of [(1-14)C]leucine. During both triacetin infusions, plasma alpha-ketoisocaproate concentrations increased ($p < 0.05$). During triacetin infusion at 1.5 REE, the plasma leucine concentration decreased ($p < 0.05$) and leucine rate of appearance decreased by

approximately 19% ($p < 0.05$); this was significantly greater than the changes that occurred during triacetin at 1.0 x REE and glycerol ($p < 0.05$). There was no difference in leucine oxidation between the dogs given triacetin at 1.0 x REE and control groups, whereas leucine oxidation decreased by 53% during triacetin infusion at 1.5 x REE ($p < 0.05$). Nonoxidative leucine disappearance, an indicator of protein synthesis, did not change in any of the studies. [Bailey JW et al; Am J Clin Nutr 58 (6): 912-6 (1993)] **PEER REVIEWED** PubMed Abstract

Groups of female mongrel dogs to study the metabolic effects of isocaloric and hypercaloric infusions of 5% v/v aqueous triacetin. A primed, continuous infusion of 5 umol/kg (0.3 uCi/kg/min) [(13)C]-acetoacetate and 1.0 uCi/kg (0.01 uCi/kg/min) [(3)H]-glucose was continued for 6 hr. Three hours after the start of the isotope infusion, dosing with triacetin was started. Six animals were infused at a rate of 47 umol/kg/min and seven were infused at a rate of 70 umol/kg/min triacetin for 3 hr. Blood and breath samples were taken at 15 to 30-min intervals. A group of four animals was infused with 70 umol/kg/min glycerol and used as the control for the hypercaloric infusion. During isocaloric infusion of triacetin, plasma acetate and free fatty acid concentrations were significantly increased at 30 and 60 min, respectively, and remained elevated. During hypercaloric infusion, plasma acetate concentration increased progressively throughout the study, whereas the plasma free fatty acid concentration did not change. Plasma pyruvate and lactate concentrations were significantly decreased after 30 and 90 min, respectively, and throughout the study with both isocaloric and hypercaloric infusion. The plasma insulin concentrations were modestly increased during both infusions. Plasma glucose concentration was significantly decreased during isocaloric triacetin infusion; a slight but significant increase was observed with hypercaloric infusion. Glucose clearance decreased significantly in both groups during the last hour of triacetin infusion. Plasma ketone body concentrations increased significantly by 60 min, and they remained elevated with isocaloric infusion and increased progressively with hypercaloric infusion of triacetin; the increased concentrations were due to increased ketone body production. During the last hour of infusion, resting energy expenditure was significantly increased with isocaloric triacetin. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Groups of eight male Sprague-Dawley rats that were fed diets containing 30% triacetin (and 30% glycerin or propylene glycol) as a starch substitute for 3 to 4 or 12 to 13 weeks, growth was relatively poor. Liver enlargement was observed in all animals. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ The metabolic effect of Triacetin on intestinal mucosal cells and plasma substrates in male Sprague-Dawley rats was assessed /in a sub-chronic study/. Rats were fed for 30 days a diet in which 28.5% of the total calories were supplied by Triacetin. No overt signs of toxicity were observed. [Cosmetic Ingredient Review Expert Panel; International Journal of Toxicology: 22(suppl. 2): 1-10 (2003)] **PEER REVIEWED**

As taken from HSDB, 2015

“To investigate the effects of intravenous administration of triacetin on leucine metabolism in dogs, 14 infusion of L-[1- C]-leucine was conducted at 1.5 kBq/kg bw/min for 6 hr in mongrel dogs (Bailey, et al. 1993). Three hours after initiation of the isotope infusion, animals received infusion of 5 % triacetin at 47 umol/kg bw/min (1.0 x estimated resting energy expenditure: REE), at 70 umol/kg bw/min (1.5 x REE), glycerol (70 umol/kg bw/min), or saline during infusion. No overt toxic effects were observed. Leucine kinetics (the rate of leucine appearance (Ra): an estimate of leucine derived from endogenous protein breakdown, leucine oxidation, and the rate of no oxidized leucine disappearance (NOLD): an indicator of protein synthesis) were not significantly different among animals receiving saline, glycerol, or isoenergitic triacetin infusions. When triacetin was infused at 1.5 x REE, leucine Ra and leucine oxidation decreased 19 % and 53 %, respectively. NOLD did not change in any of the studies. The studies demonstrate that triacetin does not have adverse effects

on protein metabolism and at relatively high doses actually suppresses endogenous proteolysis (Bailey, et al. 1993)."

As taken from OECD SIDS, Triacetin (102-76-1)

"Triacetin fed to rats did not affect the lymphatic transport of endogenous cholesterol from the intestine in comparison with the fasting state, but the uptake of exogenous cholesterol into the intestine wall was increased when triacetin was the vehicle (Sylven & Borgström, 1969)."

As taken from Food & Comestics Toxicology, 2001, (4), 879-881

"AIM: To examine the effect of intra-gastric triacetin on both upper gastrointestinal motility and proximal gastric tone in conscious dogs. METHODS: Three beagle dogs under sedation were surgically implanted with gastrocutaneous fistula in the gastric body and force transducers in the gastric antrum and duodenum. Beginning at week-2 after insertion, the animals were either fasted for 24 h or fed a liquid meal 2-3 h before the experiment. With the animals fully conscious, a polyethylene bag was inserted into the proximal stomach through the gastrocutaneous fistula, followed by 15 min of air inflation (minimal distending pressure of n+ï2 mmHg) and then 20 mL of a low-, mid- or high-concentration triacetin solution (0.5%, 1.0% and 2.0%) or warm water (vehicle control). The proximal stomach receptive volume and gastric antral and duodenal contractions were measured over 10 min. The experiment was repeated twice per week over several months, with each animal receiving at least one infusion of the various triacetin solutions and the vehicle at different times. Intergroup differences were assessed by ANOVA and Bonferroni-Dunn post-hoc testing. RESULTS: Intra-gastric infusion of mid- and high-concentration triacetin induced an increase in the proximal stomach receptive volume, and the average increase induced by the high-concentration at 0-4 min after infusion was significantly greater than that induced by the vehicle control (62.4 ± 9.8 vs 18.4 ± 4.7, $P < 0.01$). The mid- and high-concentration triacetin also produced a temporary inhibition of the gastric antral contractions at 2 min after infusions; however, only the fasted group showed triacetin-induced antral contractile inhibition that was significantly greater than that in the vehicle control group ($P < 0.05$). In addition, only the fasted group showed a high-concentration triacetin-induced increase in duodenal contractions at 9-10 min that was significantly different from that in the vehicle control group ($P < 0.05$). CONCLUSION: Intra-gastric infusion of 1.0%-2.0% triacetin delays gastric emptying by increasing proximal stomach receptive volume, temporarily inhibiting gastric antral contractions and facilitating duodenal contractions." As taken from Oosaka K et al. 2014. World J. Gastroenterol. 20(4), 1054–1060. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24574778

"Cancer is associated with epigenetic (i.e., histone hypoacetylation) and metabolic (i.e., aerobic glycolysis) alterations. Levels of N-acetyl-l-aspartate (NAA), the primary storage form of acetate in the brain, and aspartoacylase (ASPA), the enzyme responsible for NAA catalysis to generate acetate, are reduced in glioma; yet, few studies have investigated acetate as a potential therapeutic agent. This preclinical study sought to test the efficacy of the food additive Triacetin (glyceryl triacetate, GTA) as a novel therapy to increase acetate bioavailability in glioma cells. The growth-inhibitory effects of GTA, compared to the histone deacetylase inhibitor Vorinostat (SAHA), were assessed in established human glioma cell lines (HOG and Hs683 oligodendroglioma, U87 and U251 glioblastoma) and primary tumor-derived glioma stem-like cells (GSCs), relative to an oligodendrocyte progenitor line (Oli-Neu), normal astrocytes, and neural stem cells (NSCs) in vitro. GTA was also tested as a chemotherapeutic adjuvant with temozolomide (TMZ) in orthotopically grafted GSCs. GTA-induced cytostatic growth arrest in vitro comparable to Vorinostat, but, unlike Vorinostat, GTA did not alter astrocyte growth and promoted NSC expansion. GTA alone increased survival of mice engrafted with glioblastoma GSCs and potentiated TMZ to extend survival longer than TMZ alone. GTA was most effective on GSCs with a mesenchymal cell phenotype. Given that GTA has been chronically administered safely to infants with Canavan disease, a leukodystrophy due to ASPA mutation, GTA-mediated acetate supplementation may provide a novel, safe chemotherapeutic adjuvant to reduce the growth of glioma tumors, most notably the more rapidly proliferating, glycolytic and hypoacetylated mesenchymal glioma tumors." As taken from Tsen AR et

al. 2014. Int. J. Cancer 134(6), 1300-1310. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23996800

In a peer-reviewed study, Madhavarao et al. (2009) administered triacetin in infant formula to a 13-month-old girl and an 8-month-old boy for 6 and 4.5 months, respectively. The initial dose was 25 mg/kg twice daily (50 mg/kg-day) for the first week, followed by a doubling each subsequent week up to a maximum dose of 250 mg/kg twice daily (500 mg/kg-day). These infants were previously diagnosed with Canavan disease, a fatal dysmyelinating genetic disorder characterized by mutations in the enzyme aspartoacylase, resulting in a greatly reduced or absent capacity to hydrolyze the brain metabolite N-acetylaspartate to acetate and aspartate. Triacetin was selected for use as a dietary supplement as it is known to be an acetate precursor. The stated aim of this study was to determine the tolerability of low-dose oral triacetin administration in infants having Canavan disease. This study received Institutional Review Board approval and obtained parental consent. The following outcome criteria were evaluated prior to initiation of treatment and reviewed at 4 months of treatment: neurological status, brain magnetic resonance imaging and magnetic resonance spectroscopy, urine N-acetylaspartate levels, and ophthalmoscopic examination. Treatment-related effects were screened clinically and by blood work-up of complete blood count, kidney function, electrolytes, liver function, and venous blood gas measurements. The study authors did not identify a NOAEL or LOAEL; however, they stated that oral administration of triacetin caused no detectable toxicity, and that the infant patients showed no deterioration in their clinical status (Madhavarao et al., 2009). The NOAEL is 500 mg/kg-day; a LOAEL was not determined under the conditions tested. (US EPA 2012)

Similar to the Madhavarao et al. (2009) study above, Segel et al. (2011) administered triacetin in infant formula to a 12-month-old boy and an 8-month-old girl for 6 and 4.5 months, respectively. Both of the infants were previously diagnosed with Canavan disease, and as such, triacetin was being evaluated for efficacy as a dietary supplement (as explained under Madhavarao et al. [2009] above). The stated aim of this study was to determine the tolerability and efficacy of high-dose triacetin administration in infants with Canavan disease. The initial dose was 500 mg/kg four times daily (2,000 mg/kg-day) for the first 3 days, followed by a doubling of dose every 3 days up to a maximum dose of 4,500 mg/kg-day (the target maximum dose was 5,000 mg/kg-day, but the parents reported ‘discomfort’ in each child at this specific dose). The children were evaluated prior to treatment and at 4.5 months after the initiation of treatment for the following outcomes: neurological status, brain magnetic resonance imaging and magnetic resonance spectroscopy, urine N-acetylaspartate levels, and ophthalmoscopic examination. Treatment-related effects were screened clinically and by blood work-up of complete blood count, kidney function, electrolytes, liver function, and venous blood gas measurements.

The study authors did not identify a NOAEL or LOAEL; although the study authors did state that administration of triacetin caused no detectable toxicity in either patient at a daily dose of 4,500 mg/kg-day; at the highest dose attempted (5,000 mg/kg-day), the study authors alluded to a potential problem with gastric acidity (Segel et al., 2011). The NOAEL is 4,500 mg/kg-day for lack of effects in human infants; a LOAEL was not determined under the conditions tested. (US EPA 2012)

7. Addiction

JTI is not aware of any information that demonstrates that this ingredient has any addictive effect.

8. Burnt ingredient toxicity

This ingredient was considered as part of an overall safety assessment of ingredients added to tobacco in the manufacture of cigarettes. An expert panel of toxicologists reviewed the open literature and internal toxicology data of 5 tobacco companies to evaluate a composite list of ingredients used in the manufacture of cigarettes. The conclusion of this report was that these

ingredients did not increase the inherent biological activity of tobacco cigarettes, and are considered to be acceptable under conditions of intended use (Doull et al., 1994 & 1998).

Tobacco smoke condensates from cigarettes containing triacetin and an additive free, reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the condensate was not changed by the addition of triacetin. Table below provides tested level(s) and specific endpoint(s).

Endpoint	**Tested level (ppm)**	**Reference**
Smoke chemistry	54	Carmines, 2002 & Rustemeier et al., 2002
	1,400	Baker et al., 2004a
	100,000	Gaworski et al., 2011 & Coggins et al., 2011f
	225	Roemer et al., 2014
In vitro genotoxicity	54	Carmines, 2002 & Roemer et al., 2002
	1,400	Baker et al., 2004c
	381	fGLH Study Report (2010)
	100,000	Gaworski et al., 2011 & Coggins et al., 2011f
	225	Roemer et al., 2014
In vitro cytotoxicity	54	Carmines, 2002 & Roemer et al., 2002
	1,400	Baker et al., 2004c
	381	fGLH Study Report (2010)
	100,000	Gaworski et al., 2011 & Coggins et al., 2011f
	225	Roemer et al., 2014
Inhalation study	30	Gaworski et al., 1998
	54	Carmines, 2002 & Vanscheeuwijck et al., 2002
	1,400	Baker et al., 2004c
	100,000	Gaworski et al., 2011 & Coggins et al., 2011f
	225	Schramke et al., 2014

In vivo genotoxicity	225	Schramke et al., 2014

In comparison with a CSC of a reference cigarette with sideseam adhesives/cigarette paper corresponding to representative specifications for the majority of commercial cigarettes no differences were observed either in the bacterial mutagenicity, cytotoxicity or mammalian cell genotoxicity of the smoke condensate prepared from cigarettes with sideseam adhesives/cigarette paper containing Triacetin at 0.2448 mg/cig. The smoke chemistry data between test and reference cigarette revealed small changes towards both higher and lower yields per cigarette over all analytical groups. These differences were well within the variability of the analytical methods (JTI NTM Study Report(s)).

“Transfer of triacetin to mainstream smoke was 0.31-0.32mg/cig and 0.25-0.33mg/cig in two samples when the method of application involved the addition of known amounts of triacetin to a Cambridge filter for verification (Lyerly 1967)”.

“The triacetin content of smoke condensate in a study by Hollweg et al. (1981) was 0.66mg/cig.

When triacetin was applied by brush applicator to cigarette filter at a level of 14.9mg/20mm tip, transfer to mainstream smoke over 8 weeks ranged from 9.1% at week 0 to 6.8% at week 4 and up to 7.6% at week 8 (Mathis 1983)”.

“When applied as one of a group of ingredients to tobacco blend at 3 levels, transfer of triacetin to mainstream smoke was estimated at 2.11% (Biggs et al. 1998)”.

In a pyrolysis study, 100% of triacetin added to cigarettes was transferred intact to the smoke (Purkis et al. 2011).

9. Heated/vapor emissions toxicity

Aerosol from heated tobacco stick(s) containing Triacetin was tested in aerosol chemistry and a battery of in vitro test(s). Under the test conditions and within the sensitivity and specificity of the bioassay(s), the activity of the total particulate matter (TPM) and/or gas vapor phase (GVP) were not increased by the addition of this ingredient when compared to TPM and/or GVP from reference combustible cigarettes. The table below provides the highest tested level(s) and specific endpoint(s):

Endpoint	**Tested level (mg/stick)**	**Reference**
Aerosol chemistry	18.9	Labstat International Inc. (2020a) Labstat International Inc. (2021a)
In vitro genotoxicity	18.9	Labstat International Inc. (2020b) Labstat International Inc. (2021b)
In vitro cytotoxicity	18.9	Labstat International Inc. (2020b) Labstat International Inc. (2021b)

“The e-liquids used in electronic cigarettes (E-cigs) consist of propylene glycol (PG), vegetable glycerin (VG), nicotine, and chemical additives for flavoring. There are currently over 7,700 e-liquid flavors available, and while some have been tested for toxicity in the laboratory, most have not. Here, we developed a 3-phase, 384-well, plate-based, high-throughput screening (HTS) assay to rapidly triage and validate the toxicity of multiple e-liquids. Our data demonstrated that the PG/VG vehicle adversely affected cell viability and that a large number of e-liquids were more toxic than PG/VG. We also performed gas chromatography-mass spectrometry (GC-MS) analysis on all tested e-liquids. Subsequent nonmetric multidimensional scaling (NMDS) analysis revealed that e-

liquids are an extremely heterogeneous group. Furthermore, these data indicated that (i) the more chemicals contained in an e-liquid, the more toxic it was likely to be and (ii) the presence of vanillin was associated with higher toxicity values. Further analysis of common constituents by electron ionization revealed that the concentration of cinnamaldehyde and vanillin, but not triacetin, correlated with toxicity. We have also developed a publicly available searchable website (www.eliquidinfo.org). Given the large numbers of available e-liquids, this website will serve as a resource to facilitate dissemination of this information. Our data suggest that an HTS approach to evaluate the toxicity of multiple e-liquids is feasible. Such an approach may serve as a roadmap to enable bodies such as the Food and Drug Administration (FDA) to better regulate e-liquid composition." As taken from Sassano MF et al. 2018. PLoS One 16(3), e2003904. PubMed, 2018 available at

https://www.ncbi.nlm.nih.gov/pubmed/29584716

"Tobacco products containing flavorings, such as electronic nicotine delivery devices (ENDS) or e-cigarettes, cigars/cigarillos, waterpipes, and heat-not-burn devices (iQOS) are continuously evolving. In addition to increasing the exposure of teenagers and adults to nicotine containing flavoring products and flavoring enhancers, chances of nicotine addiction through chronic use and abuse also increase. These flavorings are believed to be safe for ingestion, but little information is available about their effects on the lungs. In this review, we have discussed the in vitro and in vivo data on toxicity of flavoring chemicals in lung cells. We have further discussed the common flavoring agents, such as diacetyl and menthol, currently available detection methods, and the toxicological mechanisms associated with oxidative stress, inflammation, mucociliary clearance, and DNA damage in cells, mice, and humans. Finally, we present potential biomarkers that could be utilized for future risk assessment. This review provides crucial parameters important for evaluation of risk associated with flavouring agents and flavoring enhancers used in tobacco products and ENDS. Future studies can be designed to address the potential toxicity of inhaled flavorings and their biomarkers in users as well as in chronic exposure studies." As taken from Kaur G et al. 2018. Toxicology Letters 288, 143-155. PubMed, 2018 available at

https://www.ncbi.nlm.nih.gov/pubmed/29481849

The health effects of inhaled electronic cigarette (e-cigarette) flavoring compounds are largely unknown. Earlier reports of their chemical reactivity have been conflicting, with some claiming, for example, that the degradation of flavoring chemicals in e-cigarettes to aldehydes is statistically insignificant. It is thus important to understand how these molecules react to afford enhanced aerosol products. The purpose of the current study was to investigate the origin of formaldehyde, acrolein, and acetaldehyde in e-cigarettes that contain the popular additive, triacetin (TA). By using 13C labeling and a combination of 1H NMR and 13C NMR, we were able to identify that ester hydrolysis of TA occurs to form acetic acid (HOAc) during aerosolization. The released HOAc acts as a catalyst in the degradation of propylene glycol (PG) and glycerol (GLY), increasing the formation of formaldehyde hemiacetals, acrolein, and acetaldehyde. A solution of 10% TA in 1:1 PG/GLY e-liquid was aerosolized using two different e-cigarettes at two wattages. Each device exhibited a significant increase in aldehyde levels, of up to 185% compared to the aerosol from a 1:1 PG/GLY e-liquid. In addition, the GLY formaldehyde hemiacetal was more predominant within the presence of HOAc, indicating that GLY may be relatively more prone to degradation from protonation. As taken from Vreeke S et al. (2018). Triacetin enhances levels of acrolein, formaldehyde hemiacetals, and acetaldehyde in electronic cigarette aerosols. ACS Omega 3(7), 7165-7170. DOI: 10.1021/acsomega.8b00842. PubMed, 2019 available at

https://www.ncbi.nlm.nih.gov/pubmed/30087908

"A suite of untargeted methods has been applied for the characterization of aerosol from the Tobacco Heating System 2.2 (THS2.2), a heated tobacco product developed by Philip Morris Products S.A. and commercialized under the brand name IQOS®. A total of 529 chemical

constituents, excluding water, glycerin, and nicotine, were present in the mainstream aerosol of THS2.2, generated by following the Health Canada intense smoking regimen, at concentrations ≥ 100 ng/item. The majority were present in the particulate phase (n = 402), representing more than 80% of the total mass determined by untargeted screening; a proportion were present in both particulate and gas-vapor phases (39 compounds). The identities for 80% of all chemical constituents (representing > 96% of the total determined mass) were confirmed by the use of authentic analytical reference materials. Despite the uncertainties that are recognized to be associated with aerosol-based untargeted approaches, the reported data remain indicative that the uncharacterized fraction of TPM generated by THS2.2 has been evaluated to the fullest practicable extent. To the best of our knowledge, this work represents the most comprehensive chemical characterization of a heated tobacco aerosol to date. Graphical abstract." As taken from Bentley MC et al. 2020. Anal. Bioanal. Chem. 412(11), 2675-2685. PubMed, 2021 available at https://pubmed.ncbi.nlm.nih.gov/32072212/

10. Ecotoxicity

10.1. Environmental fate

Triacetin's production and use as a topical antifungal, fixative in perfumery, plasticizer, specialty solvent, cosmetic biocide and for removal of carbon dioxide from natural gas, may result in its release to the environment through various waste streams. Triacetin has been found in trace amounts in the seed of Euonymus europaeus. If released to air, a vapor pressure of 2.48X10-3 mm Hg at 25 deg C indicates triacetin will exist solely as a vapor in the atmosphere. Vapor-phase triacetin will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 4 days. Triacetin does not contain chromophores that absorb at wavelengths >290 nm and, therefore, is not expected to be susceptible to direct photolysis by sunlight. If released to soil, triacetin is expected to have very high mobility based upon an estimated Koc of 40. Volatilization from moist soil surfaces is not an important fate process based upon an estimated Henry's Law constant of 1.2X10-8 atm-cu m/mole. Utilizing the Japanese MITI test, 93% of the Theoretical BOD for triacetin in a mixture was reached in 4 weeks indicating that biodegradation is an important environmental fate process in soil and water. If released into water, triacetin is not expected to adsorb to suspended solids and sediment based upon the estimated Koc. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated BCF of 3 suggests the potential for bioconcentration in aquatic organisms is low. A base-catalyzed second-order hydrolysis rate constant of 6.2X10-1 L/mole-sec was estimated using a structure estimation method; this corresponds to half-lives of 130 and 13 days at pH values of 7 and 8, respectively. Occupational exposure to triacetin may occur through inhalation and dermal contact with this compound at workplaces where triacetin is produced or used. Use data indicate that the general population may be exposed to triacetin via dermal contact with consumer products containing triacetin. (SRC) **PEER REVIEWED**

Artificial Pollution Sources:

Triacetin's production and use as a topical antifungal, fixative in perfumery, plasticizer, specialty solvent, as well as its use in the manufacture of cosmetics and removal of carbon dioxide from natural gas(1) may result in its release to the environment through various waste streams(SRC). Triacetin is a byproduct obtained during interesterification processes during the production of

biodiesel. It may be added to the formulation of biodiesel up to 10 wt.%(2). [(1) Lewis RJ Sr, ed; Hawley's Condensed Chemical Dictionary. 15th ed. New York, NY: John Wiley & Sons, p. 1259 (2007) (2) (1) Casas A et al; Chem Engineering Journal 171:1324- 1332 (2011)] **PEER REVIEWED**

Environmental Fate:

TERRESTRIAL FATE: Based on a classification scheme(1), an estimated Koc value of 40(SRC), determined from a structure estimation method(2), indicates that triacetin is expected to have very high mobility in soil(SRC). Volatilization of triacetin from moist soil surfaces is not expected to be an important fate process(SRC) given an estimated Henry's Law constant of 1.2X10-8 atm-cu m/mole(3) based upon its vapor pressure, 2.48X10-3 mm Hg(4), and water solubility, 5.8X10+4 mg/L(5). Triacetin is not expected to volatilize from dry soil surfaces(SRC) based upon its vapor pressure(4). Utilizing the Japanese MITI test, 93% of the Theoretical BOD of a mixture containing triacetin was reached in 4 weeks(6) indicating that biodegradation is an important environmental fate process in soil(SRC). [(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of June 2, 2015: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm (3) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991) (4) Daubert TE, Danner RP; Physical and Thermodynamic Properties of Pure Chemicals Data Compilation. Washington, DC: Taylor and Francis (1989) (5) Riddick JA et al; Techniques of Chemistry. 4th ed. Volume II. New York, NY: John Wiley and Sons p. 402 (1985) (6) NITE; Chemical Risk Information Platform (CHRIP). Biodegradation and Bioconcentration. Tokyo, Japan: Natl Inst Tech Eval. Available from, as of June 2, 2015: http://www.safe.nite.go.jp/english/db.html **PEER REVIEWED**

AQUATIC FATE: Based on a classification scheme(1), an estimated Koc value of 40(SRC), determined from a structure estimation method(2), indicates that triacetin is not expected to adsorb to suspended solids and sediment(SRC). Volatilization from water surfaces is not expected(3) based upon an estimated Henry’s Law constant of 1.2X10-8 atm-cu m/mole(4) derived from its vapor pressure, 2.48X10-3 mm Hg(5), and water solubility, 5.8X10+4 mg/L(6). According to a classification scheme(7), an estimated BCF of 30(SRC), from its log Kow of 0.25(8) and a regression-derived equation(2), suggests the potential for bioconcentration in aquatic organisms is low(SRC). Utilizing the Japanese MITI test, 93% of the Theoretical BOD of a mixture containing triacetin was reached in 4 weeks(9) indicating that biodegradation is an important environmental fate process in water(SRC). [(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of June 2, 2015: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990) (4) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991) (5) Daubert TE, Danner RP; Physical and Thermodynamic Properties of Pure Chemicals Data Compilation. Washington, DC: Taylor and Francis (1989) (6) Riddick JA et al; Techniques of Chemistry. 4th ed. Volume II. New York, NY: John Wiley and Sons p. 402 (1985) (7) Franke C et al; Chemosphere 29: 1501-14 (1994) (8) Hansch C et al; Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Prof Ref Book. Heller SR, consult. Ed., Washington, DC: Amer Chem Soc p. 63 (1995) (9) NITE; Chemical Risk Information Platform (CHRIP). Biodegradation and Bioconcentration. Tokyo, Japan: Natl Inst Tech Eval. Available from, as of June 2, 2015: http://www.safe.nite.go.jp/english/db.html **PEER REVIEWED**

ATMOSPHERIC FATE: According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere(1), triacetin, which has a vapor pressure of 2.48X10-3 mm Hg at 25 deg C(5), is expected to exist solely as a vapor in the ambient atmosphere. Vapor-phase triacetin is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals(SRC); the half-life for this reaction in air is estimated to be 4 days(SRC), calculated from its rate constant of 8.5X10-12 cu cm/molecule-sec at 25 deg C(SRC) that was derived using a structure estimation method(3). Triacetin does not contain chromophores that absorb at wavelengths >290 nm(4) and,

therefore, is not expected to be susceptible to direct photolysis by sunlight(SRC). [(1) Bidleman TF; Environ Sci Technol 22: 361-367 (1988) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of June 3,2015: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm (3) Meylan WM, Howard PH; Chemosphere 26: 2293-99 (1993) (4) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 8-12 (1990) (5) Daubert TE, Danner RP; Physical and Thermodynamic Properties of Pure Chemicals Data Compilation. Washington, DC: Taylor and Francis (1989)] **PEER REVIEWED**

Environmental Biodegradation:

AEROBIC: Triacetin, present at 100 mg/L, reached 91-94% of its theoretical BOD in 4 weeks using an activated sludge inoculum at 30 mg/L and the Japanese MITI test(1). Using a rapid infiltration system for treating primary and secondary effluents, triacetin, present in a feed solution at a concentration of 0.094 ug/L, was not detected in the column effluent(2). The specific loss process was not identified(2). [(1) NITE; Chemical Risk Information Platform(CHRIP). Biodegradation and Bioconcentration. Tokyo, Japan: Natl Inst Tech Eval. Available from, as of June 2, 2015: http://www.safe.nite.go.jp/english/db.html (2) Hutchins SR et al; Environ Toxicol Chem 2: 195-216 (1983)] **PEER REVIEWED**

Environmental Abiotic Degradation:

The rate constant for the vapor-phase reaction of triacetin with photochemically-produced hydroxyl radicals has been estimated as 8.5X10-12 cu cm/molecule-sec at 25 deg C(SRC) using a structure estimation method(1). This corresponds to an atmospheric half-life of about 4 days at an atmospheric concentration of 5X10+5 hydroxyl radicals per cu cm(1). A base-catalyzed second-order hydrolysis rate constant of 6.2X10-1 L/mole-sec(SRC) was estimated using a structure estimation method(2); this corresponds to half-lives of 130 and 13 days at pH values of 7 and 8, respectively(2). Triacetin does not contain chromophores that absorb at wavelengths >290 nm(3) and, therefore, is not expected to be susceptible to direct photolysis by sunlight(SRC). [(1) Meylan WM, Howard PH; Chemosphere 26: 2293-99 (1993) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of June 3, 2015: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 8-12 (1990)] **PEER REVIEWED**

Environmental Bioconcentration:

An estimated BCF of 3 was calculated in fish for triacetin(SRC), using a log Kow of 0.25(1) and a regression-derived equation(2). According to a classification scheme(3), this BCF suggests the potential for bioconcentration in aquatic organisms is low(SRC). [(1) Hansch C et al; Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Prof Ref Book. Heller SR, consult. ed., Washington, DC: Amer Chem Soc p. 63 (1995) (2) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of June 3, 2015: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm/ (3) Franke C et al; Chemosphere 29: 1501-14 (1994)] **PEER REVIEWED**

Soil Adsorption/Mobility:

Using a structure estimation method based on molecular connectivity indices(1), the Koc of triacetin can be estimated to be 40(SRC). According to a classification scheme(2), this estimated Koc value suggests that triacetin is expected to have very high mobility in soil. [(1) US EPA; Estimation Program Interface (EPI) Suite. Ver. 4.1. Nov, 2012. Available from, as of June 3, 2015: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm (2) Swann RL et al; Res Rev 85: 17-28 (1983)] **PEER REVIEWED**

Volatilization from Water/Soil:

The Henry's Law constant for triacetin is estimated as 1.2X10-8 atm-cu m/mole(SRC) derived from its vapor pressure, 2.48X10-3 mm Hg(1), and water solubility, 5.8X10+4 mg/L(2). This Henry's Law constant indicates that triacetin is expected to be essentially nonvolatile from water surfaces(3). Triacetin's estimated Henry's Law constant indicates that volatilization from moist soil surfaces is not expected to occur(SRC). Triacetin is not expected to volatilize from dry soil surfaces(SRC) based upon its vapor pressure(1). [(1) Daubert TE, Danner RP; Physical and Thermodynamic Properties of Pure Chemicals Data Compilation. Washington, DC: Taylor and Francis (1989) (2) Riddick JA et al; Techniques of Chemistry. 4th ed. Volume II. New York, NY: John Wiley and Sons p. 402 (1985) (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990)] **PEER REVIEWED**

Environmental Water Concentrations:

SURFACE WATER: Triacetin was detected in a sample of Tennessee River water collected in Apr 1973 (concn not reported)(1). [(1) Shackelford WM, Keith LH; Frequency of Organic Compounds Identified in Water. USEPA-600/4-76-062 p.226 (1976)] **PEER REVIEWED**

RAIN/SNOW: Triacetin was found in 1 out of 10 snow samples collected early March, 1998 from Finland, Russia and Siberia. The sample that contained 0.8 ug/kg of triacetin was from Moscow State University, Russia(1). [(1) Poliakova OV et al; Toxicol Environ Chem 75: 427-509 (2000)] **PEER REVIEWED**

Effluent Concentrations:

Triacetin was detected at concentrations of 0.024 and 0.51 ug/L in secondary effluent samples from a rapid infiltration site in Fort Polk, LA sampled November 4-5, 1980(1). [(1) Hutchins SR et al; Environ Toxicol Chem 2: 195-216 (1983)] **PEER REVIEWED**

As taken from HSDB, 2015

“GTA (triacetin) appears to be easily biodegradable, it does not bioaccumulate…..The bulk of data on aerobic biodegradability of GTA suggests that the substance is readily biodegradable, e.g. 77% degradation after 14 days based on BOD, 93% after 28 days based on ThCO2 and 94% after 28 days based on TOC (OECD methods 301B, 301C and 301 D). The KOC of 10.5 indicates high mobility in soil (corresponds well with high water solubility and low log KOW), and the calculated BCF = 1.3 implies an insignificant bioaccumulation potential” (Maag et al., 2010).

EPISuite provides the following data:

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]: Bond Method :	1.75^{E}-009 atm-m3/mole (1.77^{E}-004 Pa-m3/mole)	
Group Method:	5.11^{E}-011 atm-m3/mole (5.18^{E}-006 Pa-m3/mole)	
Henrys LC [via VP/Wsol estimate using User-Entered or Estimated values]:	HLC: 6.991^{E}-008 atm-m3/mole (7.084^{E}-003 Pa-m3/mole) VP: 0.00524 mm Hg (source: MPBPVP) WS: 2.15^{E}+004 mg/L (source: WSKOWWIN)]	

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]: Log Kow used:	0.25 (exp database)
Log Kaw used:	-6.299 (exp database)
Log Koa (KOAWIN v1.10 estimate):	6.549

Log Koa (experimental database):	None
Probability of Rapid Biodegradation (BIOWIN v4.10): Biowin1 (Linear Model): Biowin2 (Non-Linear Model) : Biowin3 (Ultimate Survey Model): Biowin4 (Primary Survey Model) : Biowin5 (MITI Linear Model) : Biowin6 (MITI Non-Linear Model): Biowin7 (Anaerobic Linear Model):	1.1662 1.0000 3.1376 (weeks) 4.2198 (days) 1.1436 0.9877 0.9991
Ready Biodegradability Prediction:	YES

Hydrocarbon Biodegradation (BioHCwin v1.01): Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]: Vapor pressure (liquid/subcooled):	1.11 Pa (0.00829 mm Hg)	
Log Koa (Koawin est):	6.549	
Kp (particle/gas partition coef. (m3/ug)):Mackay model: Octanol/air (Koa) model:	2.71^{E}-0068.69^{E}-007	

Fraction sorbed to airborne particulates (phi): Junge-Pankow model:	9.8^{E}-005
Mackay model:	0.000217
Octanol/air (Koa) model:	6.95^{E}-005
Atmospheric Oxidation (25 deg C) [AopWin v1.92]: Hydroxyl Radicals Reaction: OVERALL OH Rate Constant =	8.4987 E-12 cm3/molecule-sec
Half-Life =	1.259 Days (12-hr day; 1.5^{E}6 OH/cm3)
Half-Life =	15.102 Hrs
Ozone Reaction:	No Ozone Reaction Estimation

Fraction sorbed to airborne particulates (phi): 0.000158 (Junge-Pankow, Mackay avg) 6.95^{E}-005 (Koa method)Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00): Koc :	40.73 L/kg (MCI method)
Log Koc:	1.610 (MCI method)
Koc :	8.554 L/kg (Kow method)

Log Koc:	0.932 (Kow method)
Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]: Total Kb for pH > 8 at 25 deg C:	6.172^{E}-001 L/mol-sec
Kb Half-Life at pH 8:	12.997 days
Kb Half-Life at pH 7:	129.965 days

(Total Kb applies only to esters, carbmates, alkyl halides)

Volatilization from Water: Henry LC: 1.23E-008 atm-m3/mole (Henry experimental database) Half-Life from Model River:	7.032^{E}+004 hours (2930 days)
Half-Life from Model Lake:	7.672^{E}+005 hours (3.197^{E}+004 days)
Removal In Wastewater Treatment: Total removal:	1.85 percent
Total biodegradation:	0.09 percent
Total sludge adsorption:	1.76 percent
Total to Air:	0.00 percent

(using 10000 hr Bio P,A,S) **Level III Fugacity Model:**	Mass Amount(percent)	Half-Life(hr)	Emissions(kg/hr)
Air	0.214	30.2	1000
Water	23.6	360	1000
Soil	76.1	720	1000
Sediment	0.083	3.24^{e}+003	0

Persistence Time: 670 hr

The Ecological Categorization Results from the Canadian Domestic Substances List state that 1,2,3-propanetriol, triacetate (CAS RN 102-76-1) is not persistent in the environment:

Media of concern leading to Categorization	Water
Experimental Biodegradation half-life (days)	Not Available
Experimental Biodegradation result (%)	94
Reference (biodegradation result)	CHEMICALS INSPECTION AND TESTING INSTITUTE.; BIODEGRADATION AND BIOACCUMULATION DATA OF EXISTING CHEMICALS BASED ON THE CSCL JAPAN.; JAPAN CHEMICAL INDUSTRY ECOLOGY - TOXICOLOGY AND INFORMATION CENTER.ISBN 4-89074-101-1.; 1992
Predicted Ultimate degradation half-life (days)	15
MITI probability of biodegradation	0.9877
TOPKAT probability of biodegradation	1
EPI Predicted hydrolysis half-life (days)	1.30E+002
EPI Predicted Ozone reaction half-life (days)	999
EPI Predicted Atmospheric Oxidation half-life (days)	1.259

ROBUST STUDY SUMMARY - <u>Persistence</u>

Item	Yes	No
<u>Reference</u>: Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan, 1992. Chemicals Inspection and Testing Institute (Ed.). Published by: Japan Chemical Industry Ecology-Toxicology & Information Center.		
<u>Test Substance</u> (CAS # and name): The list of the substances is attached (see file on N drive)		
Chemical composition of the substance (including purity, by-products)		X
<u>Method</u>		
References	X	
OECD, EU, national, or other standard method?	X	

Justification of the method/protocol if not a standard method was used	Not applicable	
Test design / conditions		
Study type (photodegradation, hydrolysis, biodegradation, other –specify, do not assess): Biodegradation		
Test type (aerobic or anaerobic - specify, do not assess):		
Test medium (air, water, soil, sediment - specify, do not assess):		
Information on stability of the substance in the media of concern is reported?	X	
Controls (positive or negative) Both	X	
Number of replicates (including controls)		X
Temperature (specify) 25±1 ºC	X	
Duration of the experiment (specify) 14 or 28 days	X	
For photodegradation only		
Light source (specify):	Not applicable	
Light spectrum and relative intensity based on sunlight intensity:	Not applicable	
For hydrolysis only		
Measured concentrations reported?	Not applicable	
Basic water properties (pH, hardness, etc.)	Not applicable	
For biodegradation only		
Ready or inherent biodegradation (specify): Both types (see file on N drive)	X	
Innoculum (concentration and source)	X	
Results		
Endpoints: half-life (preferred); degradation, %; etc. (do not assess this item): % biodegradation by BOD or TOC (see file on N drive)		
Information on breakdown products (do not assess this item)		X
Overall score: 8/10 = 80%		
EC Reliability code: 1		
Reliability category (high, satisfactory, low): high		
Comments:		

Data accessed July 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

10.2. Aquatic toxicity

LC50; Species: Cyprinus carpio (Carp); Conditions: static; Concentration: 174 mg/L for 48 hr [European Chemicals Bureau; IUCLID Dataset, Triacetin (102-76-1) (2000 CD-ROM edition). Available from, as of February 18, 2005: http://esis.jrc.ec.europa.eu/ **PEER REVIEWED**

LC50; Species: Leuciscus idus (Ide); Conditions: static; Concentration: 170 mg/L for 48 hr [European Chemicals Bureau; IUCLID Dataset, Triacetin (102-76-1) (2000 CD-ROM edition). Available from, as of February 18, 2005: http://esis.jrc.ec.europa.eu/ **PEER REVIEWED**

As taken from HSDB, 2015

Spec. Sci. Name **Spec. Common Name**	**Exp. Type** **Chem. Anal.**	**Media Type** **Loc**	**Resp. Site** **Obs. Dur. (Days)**	**Endpoint** **BCF**	**Trend** **Eff%**	**Effect** **Effect Meas.**	**Conc (Standardized)** **Appl. Rate**	**Stat. Signif.** **Sig. Level**
CAS #/Chemical: 102761 - Glyceryl triacetate								
Fish; Standard Test Species; U.S. Exotic/Nuisance Species								
Cyprinus carpio	GV	FW				MOR/	F (122-184) mg/kg bw	
Common Carp	U	LAB	2.75			MORT		

As taken from EPA ECOTOX database.

Acute/Prolonged Toxicity to Fish

Type:	static
Species:	Cyprinus carpio (Fish, fresh water)
Exposure period:	48 hour(s)
Unit:	mg/l
LC0:	100
LC50:	174
LC100:	320

Method:	other
Year:	1979
GLP:	yes
Remark: .	Method: Bewertung wassergefährdender Stoffe, Bestimmung der akuten Fischtoxizität, Ad–hoc–Arbeitsgruppe 1 (Obmann Dr. Niemitz), LTwS, Nr. 10, September 1979
Source:	Unichema Chemie B.V. Gouda Unichema Chemicals Ltd Bebington
Type:	static
Species:	Cyprinus carpio (Fish, fresh water)
Exposure period:	48 hour(s)
Unit:	mg/l
Analytical monitoring:	no
LC0:	100
LC50:	174
LC100:	320
Method:	other
Year:	1979
GLP:	yes
Test substance:	as prescribed by 1.1 – 1.4
Remark:	Method: Bewertung wassergefährdender Stoffe, Bestimmung der akuten Fischtoxizität, Ad–hoc–Arbeitsgruppe 1 (Obmann Dr. Niemitz), LTwS, Nr. 10, September 1979.
Source:	UnichemaChemicals Ltd. Merseyside (41)
Type:	static
Species:	Leuciscus idus (Fish, fresh water)
Exposure period:	48 hour(s)
Unit:	mg/l
LC0:	= 100
LC50:	= 170

LC100:	= 300
Method:	other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN38412 Teil15
Source:	Unichema Chemie B.V. Gouda Unichema Chemicals Ltd. Merseyside Unichema Chemicals Ltd Bebington (42)
Test condition:	Test substance directly weighed into test vessel followed by treatment with Ultraturrax.
Species:	Cyprinus carpio (Fish, fresh water)
Remark:	Carp (Cyprinus carpio) force–fed with triacetin were killed at concentrations between 122 and 184 mg/kg
Source:	Unichema Chemie B.V. Gouda Unichema Chemicals Ltd. Merseyside Unichema Chemicals Ltd Bebington(43)
Test condition:	exposure time: 66 h, pH 6.7, 18.3 degr. C

Acute Toxicity to Aquatic Invertebrates

Species:	Daphnia magna (Crustacea)
Exposure period:	48 hour(s)
Unit:	mg/l
EC0:	65
EC50:	380
EC100:	1000
Method:	other: Daphnien–Kurzzeittest, DIN 38412 Teil 11, Bestimmung der Wirkung von Wasserinhaltsstoffen auf Kleinkrebse
Year:	
GLP:	yes
Test substance:	as prescribed by 1.1 – 1.4
Remark:	Test method conforms with OECD Guideline 202A.
Source:	Unichema Chemie B.V. Gouda Unichema Chemicals Ltd. Merseyside Unichema Chemicals Ltd Bebington (44)
Type:	aquatic
Species:	Pseudomonas putida (Bacteria)

Exposure period:	18 hour(s)
Unit:	mg/l
Analytical monitoring:	no
EC0:	> 541.6
Method:	other
Year:	1979
GLP:	yes
Test substance:	as prescribed by 1.1 – 1.4
Source:	Unichema Chemie B.V. Gouda Unichema Chemicals Ltd Bebington(45) (46)
Type:	aquatic
Species:	Pseudomonas putida (Bacteria)
Exposure period:	18 hour(s)
Unit:	mg/l
Analytical monitoring:	no
EC0:	> 541.6
Method:	other
Year:	1979
GLP:	yes
Test substance:	as prescribed by 1.1 – 1.4
Source:	Unichema Chemicals Ltd. Merseyside (47) (46)
Species:	Pseudomonas putida (Bacteria)
Exposure period:	30
Unit:	mg/l
EC0:	> 10000

Method:	other: Pseudomonas–Atmungs–Hemmtest, DIN 38412 Teil 27, in Vorber.,Bestimmung der Hemmwirkung von Abwasser auf die Sauerstoffzehrung von Pseudomonas putida
GLP:	no
Remark:	10000 mg/l was highest concentration tested.
Source:	Unichema Chemie B.V. Gouda Unichema Chemicals Ltd. Merseyside Unichema Chemicals Ltd Bebington (48)
Species:	Pseudomonas putida (Bacteria)
Exposure period:	16
Unit:	mg/l
EC0:	= 3000
EC10:	= 10000
Method:	other: Pseudomonas–Zellvermehrungs–Hemmtest, DIN 38412 Teil 8, zum Gelbdruck verabschiedet, Bestimmung der Hemmwirkung vonWasserinhaltsstoffen auf Bakterien
Test substance:	as prescribed by 1.1 – 1.4
Source:	Unichema Chemie B.V. Gouda Unichema Chemicals Ltd. Mersey Unichema Chemicals Ltd Bebington
Test condition:	10 min. treatment of stock solution with Ultraturrax; test solution was taken from water phase.

As taken from IUCLID Dataset (2000), Triacetin (102-76-1).

“GTA (triacetin) ….. has very moderate toxicity in the aquatic environment….The acute toxicity of GTA to fish has been studied on a number of species such as Pimephales promelas, Oryzias latipes, Cyprinus carpio, Brachydanio rerio and Leuciscus idus. In the test with O. letipes, the lethal level was not reached at the highest test concentration of 100 mg/L, and among the other species the LC50 ranged from 165 to 300 mg/L with P. promelas being the most sensitive species (tested with OECD 203, DIN38412 or ISO 7346/2 (conforming to OECD 203)). In a prolonged test with O. latipes the 14 days LC50 was > 100 mg/L (nomimal) (OECD 204)” (Maag et al., 2010).

“EC50'ies for acute toxicity to D. magna range from 380 to 811 mg/L with the most sensitive result being obtained with the DIN 39412 Teil 11 test, which conforms to OECD 202. The 21 days NOEC on reproduction of D. magna was 100 mg/L in the OECD 211 test. Inhibition of growth of Seleneastrum capricornutum (now known as Pseudokirchneriella subcapitata) in the standard 72 hours static test (OECD 201) could not be determined but was > 1,000 mg/L. The NOEC (72 h) was determined to be 556 mg/L. The toxicity to bacteria, Pseudemonas putida, was determined using the EN ISO 10712 guideline. A 16 hours NOEC = 3,000 mg/L was determined” (Maag et al., 2010).

The Ecological Categorization Results from the Canadian Domestic Substances List state that 1,2,3-propanetriol, triacetate (CAS RN 102-76-1) is not inherently toxic to aquatic organisms:

Pivotal value for iT (mg/l)	153.7
Toxicity to fathead minnow (LC50 in mg/l) as predicted by Topkat v6.1	153.7
Toxicity to fish (LC50 in mg/l) as predicted by Ecosar v0.99g	249.041
Toxicity to fish (LC50 in mg/l) as predicted by Aster	37.777043
Toxicity to fish (LC50 in mg/l) as predicted by PNN	18.83713
Toxicity to daphnia (EC50 in mg/l) as predicted by Topkat v6.1	0.0002601
Toxicity to fish, daphnia, algae or mysid shrimp (EC50 or LC50 in mg/l) as predicted by Ecosar v0.99g	5,386.061
Toxicity to fish (LC50 in mg/l) as predicted by Neutral Organics QSAR in Ecosar v0.99g	1.88E+003

Data accessed July 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

Organism	**Test Type**	**Route**	**Reported Dose (Normalized Dose)**	**Source**
frog	LDLo	oral	150mg/kg	Food and Cosmetics Toxicology. Vol. 16, Pg. 879, 1978.

As taken from ChemIDplus (b), available at https://chem.nlm.nih.gov/chemidplus/

LDLo	Frog oral	150 mg/kg	FCTXAV Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. Volume(issue)/page/year: 16,879,1978

As taken from RTECS, 2015.

ECOSAR version 1.11 reports the following aquatic toxicity data for CAS RN 102-76-1:

Values used to Generate ECOSAR Profile:
Log Kow: 0.363 (EPISuite Kowwin v1.68 Estimate)
Wat Sol: 5.8E+004 (mg/L, PhysProp DB exp value)

ECOSAR v1.11 Class-specific Estimations
Esters

ECOSAR Class	**Organism**	**Duration**	**End Pt**	**Predicted mg/L (ppm)**
Esters :	Fish	96-hr	LC50	263.621
Esters :	Daphnid	48-hr	LC50	652.980
Esters :	Green Algae	96-hr	EC50	360.185

Esters :	Fish		ChV	27.962
Esters :	Daphnid		ChV	714.926
Esters :	Green Algae		ChV	54.264
Esters :	Fish (SW)	96-hr	LC50	443.326
Esters :	Mysid	96-hr	LC50	976.880
Esters :	Fish (SW)		ChV	47.327
Esters :	Mysid (SW)		ChV	2.02e+006 *
Neutral Organic SAR :	Fish	96-hr	LC50	5292.501
(Baseline Toxicity) :	Daphnid	48-hr	LC50	2583.552
	Green Algae	96-hr	EC50	1030.155
	Fish		ChV	432.843
	Daphnid		ChV	165.435
	Green Algae		ChV	192.672

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported.

10.3. Sediment toxicity

No data available to us at this time.

10.4. Terrestrial toxicity

ECOSAR version 1.11 reports the following terrestrial toxicity data for CAS RN 102-76-1:

Values used to Generate ECOSAR Profile:	
Log Kow:	0.363 (EPISuite Kowwin v1.68 Estimate)
Wat Sol:	5.8E+004 (mg/L, PhysProp DB exp value)

ECOSAR v1.11 Class-specific Estimations
Esters

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Esters :	Earthworm	14-day	LC50	9590.474

10.5. All other relevant types of ecotoxicity

EPISuite provides the following data:

Bioaccumulation Estimates (BCFBAF v3.01): Log BCF from regression-based method:	0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL):	-3.7089 days (HL = 0.0001955 days)
Log BCF Arnot-Gobas method (upper trophic):	-0.033 (BCF = 0.927)
Log BAF Arnot-Gobas method (upper trophic):	-0.033 (BAF = 0.927)
log Kow used:	0.25 (expkow database)

The Ecological Categorization Results from the Canadian Domestic Substances List state that 1,2,3-propanetriol, triacetate (CAS RN 102-76-1) is not bioaccumulative in the environment:

Empirical Log Kow	0.25
Log Kow predicted by KowWin	0.36
Log BAF T2MTL predicted by Gobas	0.0208808953605746
Log BCF 5% T2LTL predicted by Gobas	0.0169028689438781
Log BCF Max predicted by OASIS	1.1115379779595
Log BCF predicted by BCFWIN	0.5

Data accessed July 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

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13. Last audited

May 2022

WORLD HEALTH ORGANIZATION

Toxicological evaluation of some food colours, thickening agents, and certain other substancse

WHO FOOD ADDITIVES SERIES NO. 8

The evaluations contained in this publication were prepared by the Joint FAO/WHO Expert Committee on Food Additives which met in Geneva, 14-23 April 1975[1]

World Health Organization, Geneva 1975

[1] Nineteenth Report of the Joint FAO/WHO Expert Committee on Food Additives, Wld Hlth Org. techn. Rep. Ser., 1975, No. 576; FAO Nutrition Meetings Report Series, 1975, No. 55.

The monographs contained in the present volume are also issued by the Food and Agriculture Organization of the United Nations, Rome, as FAO Nutrition Meetings Report Series, No. 55A

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TRIACETIN

BIOLOGICAL DATA

BIOCHEMICAL ASPECTS

Numerous studies have shown that triacetin is rapidly hydrolysed *in vitro* by all tissues of the organism including the gastro-intestinal tract (Bach & Metais, 1970). This property has been utilized for the estimation of tissue esterase concentrations by employing triacetin as enzyme substrate (Gomori, 1945; Archibald, 1946) and has been confirmed in studies comparing lipase and esterase activities, the latter acting far more rapidly and especially the shorter the fatty acid chain length (Desnuelle, 1961; Desnuelle & Savary, 1963; Entressaugles et al., 1961; Greenberger et al., 1966; Isselbacher, 1966; Sampugna et al., 1967). Tissue esterases are active in combination with acetokinase of Lipman (acetyl CoA synthetase) at the cellular level especially in hepatic and cardiac tissue. Triacetin is more rapidly absorbed from the gastro-intestinal tract in three hours than the other fats tested (Deuel & Hallman, 1940). Triacetin has been shown to be a source of liver glycogen (Deuel et al., 1937) and when fed in amounts equal in caloric value to 15% glucose it was utilized as efficiently as was glucose (McManus et al., 1943). The rate of hydrolysis by pancreatic lipase *in vitro* is increased by surface active agents (Nishida, 1957).

TOXICOLOGICAL STUDIES

Acute toxicity

Species	Route	LD_{50} mg/kg body weight	Reference

Mouse	S.c.	2 670	Spector, 1956
	I.p.	1 400-1 700	Gast, 1963
Rat	S.c.	3 250	Spector, 1956

Comments:

Although no formal short and long-term studies are available, it is reasonable to conclude that triacetin is metabolized like other fats in food and to take this into account for evaluation as well as its ready hydrolysis by non-specific tissue esterases.

EVALUATION

Estimate of acceptable daily intake for man

Acceptable daily intake not specified.*

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* The statement "ADI not specified" means that, on the basis of the available data (toxicological, biochemical, and other), the total daily intake of the substance arising from its use or uses at the levels necessary to achieve the desired effect and from its acceptable background in food, does not, in the opinion of the Committee, represent a hazard to health. For this reason, and for the reasons stated in individual evaluations, the establishment of an acceptable daily intake (ADI) in mg/kg bw is not deemed necessary.

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See Also:

Toxicological Abbreviations

Triacetin (ICSC)

TRIACETIN (JECFA Evaluation)

Triacetin (SIDS)

FOREWORD INTRODUCTION

TRIACETIN

CAS N°:102-76-1

SIDS Initial Assessment Report

For

SIAM 15

Boston, 22-25 October 2002

1. Chemical Name: Triacetin

2. CAS Number: 102-76-1

3. Sponsor Country: Japan

National SIDS Contact Points in Sponsor Country:

Mr. Yasuhisa Kawamura
Director
Second Organisations Div.
Ministry of Foreign Affairs
2–2-1, Kasumigaseki, Chiyoda-ku
Tokyo 110

4. Shared Partnership with:

5. Roles/Responsibilities of the Partners:

- Name of industry sponsor /consortium: Dr. Tsuneo Baba
  Daicel Chemical Industries, Ltd.
  E-mail: ts_baba@daicel.co.jp
- Process used:

6. Sponsorship History

- How was the chemical or category brought into the OECD HPV Chemicals Programme ? This substance is sponsored by Japan under the ICCA Initiative and is submitted for first discussion at SIAM 15

7. Review Process Prior to the SIAM: The industry consortium collected new data and prepared the updated IUCLID, draft versions of the SIAR and SIAP. Japanese government peer-reviewed the documents, audited selected studies.

8. Quality check process: No testing (X) Testing ( )

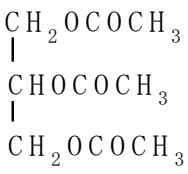
9. Date of Submission: 13 August 2002
Deadline for Circulation: 9 August 2002

10. Date of last Update:

11. Comments: The Industry contact point is Dr. Tsuneo Baba, Daicel Chemical Industries, Ltd. acting on behalf of the Triacetin Consortium

Industries, Ltd. acting on behalf of the Triacetin Consortium (consortium members: Bayer AG, Cognis Deutschland GmbH, Eastman Chemical Company, Tessenderlo Chemie NV and Uniqema)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	102-76-1
Chemical Name	Triacetin
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Triacetin is readily hydrolyzed to free glycerol and acetic acid, when incubated with rat intestine *in vitro.* The chemical infused in dogs undergoes intravascular hydrolysis and the majority of the resulting acetate is oxidized nearly quantitatively.

The acute oral and dermal toxicity of triacetin are very low: in an oral acute toxicity study in rats [OECD TG 401], a limit dose of 2,000 mg/kg bw caused no mortality and no signs of systemic toxicity during the 14-day observation period. The LD_{50} in rats by gavage is determined to be >2,000 mg/kg bw for both sexes, and dermal LD_{50} in rabbits and guinea pigs were >2,000 mg/kg bw. Acute inhalation toxicity is considered to be very low, since the LC_{50} in an acute inhalation toxicity study in rats was >1,721 mg/m^3 for both sexes [OECD 403] and repeated daily exposure of rats to 73,700 mg/m^3 produced no sign of toxicity after 5 days.

In an oral study in rats by the OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], animals received gavage doses of 0 - 1,000 mg/kg bw/day of triacetin for 44 days from 2 weeks prior to mating for males and for 41 - 48 days from 14 days before mating to day 3 postpartum for females. Triacetin had no effects on clinical signs, body weight, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in either sex. There were no abnormalities in haematological or blood chemical parameters in males. The NOAEL for repeated dose oral toxicity is thus considered to be 1,000 mg/kg bw/day for both sexes.

An inhalation study was conducted in rats given triacetin for 90 days at a dose of 249 ppm (2,220 mg/m^3) under non-GLP condition. No toxic signs were noted during the exposure. The NOAEL is considered to be 249 ppm (2,220 mg/m^3) for 90 days. Although the inhalation study is considered to be useful, it does not fully comply with the current testing protocol.

The combined repeated dose and reproductive/developmental toxicity study in rats at doses of 0 - 1,000 mg/kg bw/day [OECD TG 422] showed no statistically significant adverse effects on reproductive parameters including the mating index, fertility index, gestation length, numbers of corpora lutea and implantations, implantation index, gestation index, delivery index, parturition and maternal behavior at delivery and lactation. In addition, there were no significant differences in numbers of offspring or live offspring, the sex ratio, the live birth index, the viability index or body weight. Developmental toxicity, clinical signs of toxicity, and change in necropsy findings were not found in offspring. Therefore, the NOAEL is considered to be 1,000 mg/kg bw/day for parental animals and offspring.

Triacetin did not induce gene mutation in bacteria at concentrations up to 5,000 ug /plate (OECD TG 471 and 472). Induction of chromosome aberrations, however, was observed in the Chinese hamster cultured cells only at the highest concentration (2.2 mg/mL, 10 mM) in the presence of an exogenous metabolic activation system (OECD TG 473). Because of high toxicity (75 %) that might be caused by low pH (4.9) at the end of the treatment, the chromosomal aberration observed might not be biological relevant. Under un-physiological culture condition, such as low pH, it was reported that the frequency of chromosomal aberrations could be increased. Polyploidy was not induced under any of the conditions tested. Taking all data into consideration, triacetin could be considered to be

non-genotoxic.

Triacetin is not irritating to skin [OECD TG 404] and to eyes [OECD TG 405] in rabbits. There is no skin sensitisation in guinea pigs by triacetin. In the tests using human volunteers, triacetin induced no skin irritation or skin sensitization. However, one case concerning allergic contact eczema caused by triacetin has so far been reported in a cigarette factory.

Based on the available data and anticipated daily intake (7.8 mg/day/adult), triacetin and a group of related triglyceride did not represent a hazard to human health (JECFA, 1975, Commission, 1992 and SCF, 1995). Triacetin was given GRAS status by FEMA (1965) and is approved by the FDA for human food use.

Environment

Triacetin is a liquid with a boiling point of 258 °C and vapour pressure of 0.003306 hPa at 25°C. It is soluble in water (70 g/L at 25°C) and miscible with alcohols, aromatic hydrocarbons and diethyl ether.

The generic fugacity model (Mackay Level III Fugacity Model) shows that triacetin will be distributed mainly to water if it is released into water, whereas approximately one third and two third of the chemical will stay in water and soil, respectively when released at equal amounts to water, soil and sediment (1:1:1). An estimated Henry's law constant of 1.23×10^{-8} atm m^3/mol indicates that the compound is essentially non-volatile from water.

The rate constant for the vapour-phase reaction with photochemically produced hydroxyl radicals has been estimated to be 7.81×10^{-12} cm^3/molecule sec at 25°C, which corresponds to an atmospheric half-life of about 48 hours at an atmospheric concentration of 5×10^5 hydroxy radicals/cm^3.

Triacetin is readily biodegradable (OECD TG 301C: 77 % after 14 days based on BOD, OECD TG 301B: 93 % after 28 days based on $ThCO_2$, OECD TG 301D: 79 % after 30 days based on BOD). The chemical is expected to have a low potential for bioaccumulation based on a low Log Pow (0.21).

The half-lives in water at pH 7 and 9 are estimated to be 60.4 days and 16.5 hours at 25 °C, respectively, whereas no hydrolysis at pH 4 occurs at 50 °C in 5 days. Triacetin is expected to have high soil mobility and may leach readily in soil based on Koc value of 10.5 from a regression-derived equation. Therefore, aqueous hydrolysis may be a major degradation process for triacetin in moist alkaline soils.

The 72-h toxicity of triacetin to alga (growth inhibition, *Selenastrum capricornutum*) is > 1,000 mg/L for EC_{50} and 556 mg/L for NOEC [OECD TG 201]. In *Daphnia magna*, EC_{50} values (48 h) for acute toxicity [OECD TG 202] are 768 mg/L, 810.9 mg/L and 380 mg/L, while the NOEC (21-d reproduction) for chronic toxicity [OECD TG 211] is 100 mg/L. The acute toxicity to fish is > 100 mg/L (Medaka; *Oryzias latipes*) and 165.3 mg/L (Fathead minnow; *Pimephales promelas*) for 96 h LC_{50} [OECD TG 203]. The prolonged toxicity to fish (Medaka; *Oryzias latipes*) is 100 mg/L for 14 d LC_0 [OECD TG 204].

Exposure

Triacetin is manufactured in a closed reaction system. The production volume in Japan is approximately 5,000 tonnes/year, while the estimated global production is 10,000-50,000 tonnes/year. Commercially available triacetin contains less than 0.1 % of diacetin and 0.01 % of monoacetin. Since triacetin produced in Japan is used industrially in a variety of applications including a solvent for basic dyes, fixative in perfumery, food additive, pharmaceuticals, CO_2 remover from natural gas and in manufacture of cigarette filters, celluloid, photographic films etc., in consumer products as well as at industrial sites, both workplace and consumer exposure has to be assumed according to the following three scenarios.

(1) Occupational exposure: inhalation and dermal route during operations such as cleaning of strainers, sampling, analysis and drum filling.
(2) Consumer exposure: intake and dermal/inhalation route in food additive and topical antifungal or perfume fixative and cigarette filter.
(3) Environmental exposure: emission to aquatic compartment from waste water and evaporative emissions associated with its use in the perfume and cosmetic industries and its use as a solvent and CO_2 remover from natural gas, and disposal of consumer products containing triacetin.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemical is currently of low priority for further work because of its low hazard potential.

FULL SIDS SUMMARY

CAS NO: 102-76-1		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Unknown	3 °C (276 K)
2.2	Boiling Point		Unknown	258°C (1,013 hPa)
2.3	Density		Unknown	1.1562 g/cm^3 (25 °C)
2.4	Vapour Pressure		Unknown	0.003306 hPa (25 °C)
2.5	Partition Coefficient (Log Pow)		OECD TG 107	0.21 (25 °C)
2.6 A.	Water Solubility		OECD TG 105	70 g/L (25 °C)
			Unknown	58 g/L (25 °C)
B.	pH		Unknown	7
	pKa			None.
2.12	Oxidation: Reduction Potential			None.
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Calculated (Atkinson)	$T_{1/2}$=48 hours (Indirect photolysis)
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4 (50°C). $T_{1/2}$ = 60.4 days at pH 7 (25°C) $T_{1/2}$ = 16.5 hours at pH 9 (25°C)
3.2	Monitoring Data		Unknown	In air : None. In surface water : None. In soil/sediment : None. In biota : None.
3.3	Transport and Distribution		Calculated	Estimated distribution under four emission scenario
			(Mackay Level III Fugacity Model)	Water solubility: 70 g/L (58 g/L) at 25°C
				(Release 100% to air) Air Water Soil Sed. (%) 0.9 (1.1) 20.0 (19.9) 79.1 (79.0) 0.1 (0.1) (Release 100% to water) 0.0 (0.0) 99.7 (99.7) 0.0 (0.0) 0.3 (0.3) (Release 100% to soil) 0.0 (0.0) 12.9 (12.9) 87.1 (87.1) 0.0 (0.0) (Equal emission scenario 1:1:1) 0.3 (0.4) 30.1 (30.2) 69.5 (69.4) 0.1 (0.1)
			(Local exposure)	PEC_{local} : None.
3.5	Biodegradation		OECD TG 301C	Readily biodegradable.
3.7	Bioaccumulation		Calculated (Lyman)	1.3

ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50} (96 hr) > 100 mg/L
			OECD TG 204	LC_{50} (14 d) > 100 mg/L LC_0 (14 d) = 100 mg/L
		Pimephales promelas	OECD TG 203	LC_{50} (96 hr) = 165.3 mg/L
		Cyprinus Carpio	Other (unkown)	LC_{50} (48 hr) = 174 mg/L
		Leuciscus idus	DIN38412	LC_{50} (48 hr) = 170 mg/L
		Branchydanio rerio	ISO-7346/2	LC_{50} (96 hr) = 300 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50} (24 hr) = 888 mg/L EC_{50} (48 hr) = 768 mg/L EC_0 (48 hr) = 309 mg/L
			OECD TG 202	EC_{50} (24 hr) > 974.4 mg/L EC_{50} (48 hr) = 810.9 mg/L EC_0 (48 hr) = 541.1 mg/L
			OECD TG 202	EC_{50} (48 hr) = 380 mg/L EC_0 (48 hr) = 65 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum Capricornutum (ATCC22662)*	OECD TG 201	EC_{50} (72 hr) > 1,000 mg/L NOEC (72 hr) = 556 mg/L (Growth inhibition: growth rate & biomass)
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 211	EC_{50} (21 d) > 100 mg/L (Reproduction) NOEC (21 d) = 100 mg/L (Reproduction) LC_{50} (14 d) > 100mg/L (Parental Daphnia) LC_{50} (21 d) > 100mg/L (Parental Daphnia)
4.6.1	Toxicity to Soil Dwelling Organisms			None.
4.6.2	Toxicity to Terrestrial Plants			None.
4.6.3	Toxicity to Other Non-mammalian Terrestrial Species (Including Birds)			None.

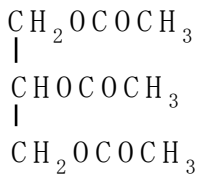
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	OECD TG 401	LD_{50} > 2,000 mg/kg bw (m & f)
		Rat	Other (unknown)	LD_{50} = 3,000 mg/kg bw
		Rat	Other (unknown)	LD_{50} = 6,400-12,800 mg/kg bw
		Rat	Other (unknown)	LD_{50} = 12,700 mg/kg bw
		Mouse	Other (unknown)	LD_{50} = ca. 9,300 mg/kg bw (m)
		Mouse	Other (unknown)	LD_{50} = 1,800 mg/kg bw (m) LD_{50} = 1,100 mg/kg bw (f)
		Mouse	Other (unkown)	LD_{50} = 3,200-6,400 mg/kg bw
5.1.2	Acute Inhalation	Rat	OECD TG 403	LD_{50} > 1,721 mg/m^3 (m & f) No lethal effects observed.
	Toxicity		Other (unkown) (Inhalation for 5 days)	NOAEL=73,700 mg/m^3
5.1.3	Acute Dermal Toxicity	Rabbit	Other (unknown)	LD_{50} > 2,000 mg/kg bw
		Rabbit	Other (unknown)	LD_{50} > 5,000 mg/kg bw
		Guinea pig	Other (unknown)	LD_{50} > 20 mL/kg bw
5.2.1	Skin Irritation	Rabbit	OECD TG 404	Not irritating.
5.2.2	Eye Irritation	Rabbit	OECD TG 405	Not irritating.
5.3	Skin Sensitisation	Guinea pig	Maximization	Not sensitising.
5.4	Repeated Dose Toxicity	Rat	OECD TG 422 (Oral gavage)	NOAEL =1,000 mg/kg bw/day (m) NOAEL =1,000 mg/kg bw/day (f)
		Rat	Other (unknown) (Oral by feed)	NOAEL =10 g/kg bw /day (20 % of the diet)
		Rat	Other (unknown) (Inhalation for 90 days)	NOAEL =2,220 mg/m^3
5.5	Genetic Toxicity *In Vitro*			
A.	Bacterial Test (Gene mutation)	*S.typhimurium, E. coli*	Japanese TG and OECD TG 471 & 472	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial *In Vitro* Test (Chromosomal aberrations)	CHL cells	Japanese TG and OECD TG 473	? (With metabolic activation) - (Without metabolic activation)
5.6	Genetic Toxicity *In Vivo*			None.
5.7	Carcinogenicity			None.
5.8	Toxicity to Reproduction	Rat	OECD TG 422	NOAEL Reproduction=1,000mg/kg bw/day
5.9	Developmental Toxicity/Teratogenicity			NOAEL F1 Offspring=1,000mg/kg bw/day
5.11	Experience with Human Exposure		Duhring-chamber	Very mild skin reaction. One case report of contact eczema.
			Other (a patch test)	Triacetin ingestion : 7.8 mg/day/adult

SIDS Initial Assessment Report

1. IDENTITY

1.1 Identification of the Substance

CAS Number: 102 – 76 – 1
IUPAC Name: Triacetin
Molecular Formula: $C_9H_{14}O_6$
Structural Formula:



Synonyms: (Chemical name)
1, 2, 3-Propanetriol, triacetate
1, 2, 3-Propanetriyl, triacetate
1, 2, 3-Triacetoxypropane
Acetic acid, glycerol triester
Acetic, 1, 2, 3-Propanetriyl ester
Acetin, Tri-
Glycerin triacetate
Glycerol triacetate
Glycerol, triester with acetic acid
Glyceryl triacetate
Propane-1, 2, 3-triyl triacetate
Triacetin
Triacetyl glycerin
Triacetyl glycerine
Triacetyl glycerol

(Trade name)
ENZACTIN
"ESTROBOND" B Plasticizer
FEMA NUMBER 2007
FUNGACETIN
GLYPED
KESSCOFLEX TRA
KODAFLEX TRIACETIN
VANAY

1.2 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

ITEMS	PROTOCOL	RESULTS
Melting Point	Unknown	3 °C (276 K)
Boiling Point	Unknown	258 °C (1,013 hPa)
Density	Unknown	1.1562 g/cm^3 (25 °C)
Vapour Pressure	Unknown	0.003306 hPa (25 °C)
Flash point	DIN 51758/ISO2719	> 145 °C (Closed cup).
Auto flammability	ASTM D2155	432 °C
Partition Coefficient (Log Pow)	OECD TG 107	0.21 (25 °C)
Water Solubility	OECD TG 105 Unknown	70 g/L (25 °C) 58 g/L (25 °C)

2. GENERAL INFORMATION ON EXPOSURE

Triacetin is a liquid with a boiling point of 258 °C and a vapour pressure of 0.003306 hPa at 25 °C. It is soluble in water. The Henry's Law constant (1.23×10^{-8} atm m^3/mol) for triacetin indicates that the compound is essentially non-volatile from water.

Triacetin is produced in a fully closed system in Japan. The production volume of triacetin in Japan is approximately 5, 000 tonnes/year (Daicel, 2001), while estimated global production is 10,000-50,000 tonnes/year according to IUCLID 2001. Other major manufacturers are Eastman (USA), Cognis (Germany) and Uniqema (UK).

Since triacetin has a variety of applications including as a plasticizer for cigarette filters and cellulose nitrate, solvent for the manufacture of celluloid, photographic films, fungicide in cosmetics, fixative in perfumery, component in binders for solid rocket fuels and a general purpose food additive, release of triacetin to the environment may occur at the production sites, specific industrial sites and consumers depending on the conditions of use in Japan.

The exposure of triacetin may occur mainly according to the following three scenarios.

(1) Occupational exposure: inhalation and dermal route in the industries.

(2) Consumer exposure: intake and dermal/inhalation route through the use as a food additive and topical antifungal and perfume fixative or cigarette filter, respectively.

(3) Environmental exposure: emission to aquatic compartment from waste water and evaporative emissions associated with its use in the perfume and cosmetic industries and its use as a solvent and CO_2 remover from natural gas, and disposal of consumer products containing triacetin.

2.1 Environmental Exposure and Fate

2.1.1 Sources of Environmental Exposure

Triacetin is readily biodegradable in activated sludge (OECD 301C: 77 % by BOD and 94 % by TOC (100 mg/L) after 14 days, OECD 301 B: 64 % (10 mg/L) and 93 % (20 mg/L) by $ThCO_2$, after 28 days, OECD 301 D: 69 % (2 mg/L) and 79 % (5 mg/L) by BOD, after 30 days) (Chemicals Evaluation and Research Institute, 1998, Unichema, 1990 and Henkel, 2001, respectively).

This chemical is stable to hydrolysis in water at pH 4, whereas it is hydrolysed at pH 7 and 9 with half-lives of 60.4 days and 16.5 hours at 25 °C, respectively (Chemicals Evaluation and Research Institute, 1998).

Triacetin is a triglyceride, and the shortest-chain fatty acid ester of glycerol, which will be readily hydrolyzed to give acetic acid and glycerol in alkaline environment.

Direct photodegradation is not expected because triacetin has no absorption band in the UV and VIS region, whereas indirect photodegradation may occur as a result of reactions with photochemically generated hydroxy radicals with an estimated rate constant of 7.81×10^{-12} cm^3/molecule*sec (Atkinson, 1987), which corresponds to an atmospheric half-life of about 48 hours at an atmospheric concentration of 5×10^5 hydroxy radicals/cm^3.

Triacetin has low bioaccumulative potential based on its Log Pow (0.21 at 25 °C, Chemicals Evaluation and Research Institute, 1998).

During the course of the regular use of consumer products, triacetin diffuses away into air. Although direct photodegradation is not expected, triacetin in air decomposes and disappears by photolytic reactions with photochemically generated hydroxy radicals.

For these reasons, there will be little potential for accumulation of triacetin in the atmosphere.

2.1.2 Other Information on Environmental Fate

In Japan, the annual quantity of triacetin production is estimated to be 5, 000 tonnes/year and 3.6 tonnes of this chemical is treated by activated sludge through process waste water (Daicel, 2001). Worst case and most likely case scenarios are based on the assumption that all of the annual production of 5,000 tonnes was discharged to water and the process waste water containing 3.6 tonnes of triacetin/year was released without sludge treatment within a single geographical area, respectively.

The Mackay level III fugacity model was employed to estimate the environmental distribution of triacetin in air, water, soil and sediment (Section 4.4). The calculation revealed that in the case of 100 % release to water, more than 99 % of triacetin is expected to stay in water due to its high solubility and low vapour pressure, but if it is released into air and/or soil, it is likely to be distributed to other compartments. The results also show that approximately one third of triacetin will be distributed to water, whereas two third will stay in soil when applied to the equal emission scenario to water, soil and sediment (1:1:1). In addition, the fugacity model using the solubility value of 58 g/L reveals that there is little change in the distribution of triacetin between the three compartments when compared to those obtained from 70 g/L (Section 4.4).

For exposure to surface water, PEC values of 0.00018 mg/L and 0.25 mg/L are calculated for most likely case and worst case modelling evaluations, respectively. PEC values are calculated based on the hypothetical model area such as inlet into the Tokyo bay (for parameters used, refer to Appendix in the SIDS dossier).

Assuming that individuals use untreated water as their sole source of drinking water (2 L/day for a 70 kg adult), EHE values of 0.00000514 mg/kg bw/day (most likely case) and 0.00714 mg/kg bw/day (worst case) are calculated.

Potential exposure via consumption of fish is anticipated to be negligible because triacetin is expected to have a low potential for bioaccumulation and is readily biodegradable in activated sludge (Chemicals Evaluation and Research Institute, 1998, Unichema, 1990, Henkel, 2001)

There is little potential for accumulation of triacetin in the atmosphere because of the decomposition by the reactions with photochemically generated hydroxy radicals with a half-life of ca. 48 hours.

2.2 Human Exposure

2.2.1 Occupational Exposure

Occupational exposure to triacetin can occur through dermal contact and inhalation at the production sites during operations such as cleaning strainer, sampling, analysis and drum filling.

The atmospheric concentration of this chemical was measured at a production site in Japan. The monitored data and Estimated Human Exposure (EHE) for triacetin are shown in Table 2.

Table 2: Workplace Monitoring Data and EHE values for Triacetin production

Operation	Working hours/day	Maximum concentration (mg/m^3)	Average concentration (mg/m^3)	Maximum EHE_{inh}	Average EHE_{inh}
Cleaning strainer	0.50	1.364	1.031	0.0122	0.0092
Sampling	0.25	1.333	1.167	0.0060	0.0052
Analysis	0.25	0.400	0.400	0.0018	0.0018
Drum filling	5.0	0.200	0.092	0.0179	0.0082
Combined EHE_{inh}				0.0379	0.0244
EHE_{der}				49.43	4.94
Combined (EHE_{inh} + EHE_{der})				49.47	4.96

EHE : Estimated Human Exposure

Source: Japan Industrial Safety and Health Association Report 2002

Monitoring method: Air sample was suctioned at the breathing zone (1.5 m in height) of a worker at the suction rate of 1 L/min and was passed through a filter. The substance collected on the filter was dissolved in a solvent and analysed quantitatively by GC method. The identity of the substance was confirmed by GC/MS.

Using the data in Table 2, if a single worker (body weight: 70 kg, respiratory volume: 1.25 m^3/hr) is assigned to implement all daily operation without protection, the highest daily intake (combined EHE_{inh}) is calculated to be 0.0379 mg/kg bw/day (e.g. for cleaning strainer, EHE_{inh} (0.0122) = (0.50 hr/day*1.364 mg/m^3*1.25 m^3/hr)/70 kg) for the worst case (maximum concentration) or as 0.0244 mg/kg bw/day (e.g. for cleaning strainer, EHE_{inh} (0.0092) = (0.50 hr/day*1.031 mg/m^3*1.25 m^3/hr)/70 kg) for most likely case (average concentration), respectively.

Dermal absorption can be a significant route of entry into the body for triacetin, however there is no information for the percutaneous absorption rate.

Based on the EASE model and an absorption rate of 0.1 – 1 mg/cm^2/day (worst case) or 0– 0.1 mg/cm^2/day (most likely case), using body weight (70 kg) and open body area (face + arms = 3,460 cm^2), a worker's daily dermal dose (EHE_{der}) for triacetin is calculated to range from 4.94 mg/kg bw/day (most likely case, EHE_{der}= (0.1 mg/cm^2/day*3,460 cm^2)/70 kg) to 49.43 mg/kg bw/day (worst case, EHE_{der}= (1 mg/cm^2/day*3,460 cm^2)/70 kg).

Typically, workers are using PPE (protective gloves) and RPE (respiratory protective equipment-mask) during these operations at the workplace, triacetin uptake is minimised and is practically negligible.

Triacetin has no significant irritant effects following skin contact or by inhalation.

No occupational exposure limits are established for triacetin (MSDS-OHS, 2001).

2.2.2 Consumer Exposure

According to HSDB 2001, triacetin has the following uses in consumer products: as a solvent for celluloid and photographic films, a plasticizer for cigarette filters, fungicide in cosmetics, fixative in perfumery, and a general purpose food additive.

Concentration of triacetin in consumer products is in the range of about 0.005-2 % for cosmetics, and has been reported to be as high as 15-33 % for one specific antifungal drug (Opdyke, 1978).

Dermal exposure (EHE_{der}) to triacetin by consumers is estimated using the equation based on EASE model.

Dermal dose (EHE_{der}) =($M*W_f*n*R_f$)/(W)

Where, Dermal dose (EHE_{der}): daily dermal dose (mg/kg bw/day)

M (mg) = amount /use (1,000 and 10 mg assumed, for cream for most likely case and antifungal ointment for worst case, respectively)

W_f (%): triacetin content (0.3 and 25 % assumed)

n: exposure frequency/day (1 and 3 assumed)

R_f (%): amount remained on the skin (100 % assumed)

W: body weight (70 kg)

Based on this hypothetical scenario, a consumer's daily dermal dose (EHE_{der}) for triacetin is calculated to range from 0.0429 mg/kg bw/day (most likely case, 1,000 mg*0.3*1/day*1.00/70 kg) to 0.107 mg/kg bw/day (worst case, 10 mg*0.25*3/day*1.00/70 kg).

According to a UK survey, an adult might ingest 7.8 mg triacetin/day as part of a total daily additive intake of 8.0 g (MAFF, 1993) and the daily intake is thus calculated to be 0.111 mg/kg bw/day (most likely case).

3. HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Pharmacokinetics studies according to OECD TG are not available. Instead, a substantial amount of studies were conducted concerning mechanism on enzymatic hydrolysis of triacetin and its favorable effects on carbohydrate and protein metabolism because of the use regarding triacetin as a parenteral nutrient. Among them, two studies are identified as the key study because they were well conducted and described in detail. Details of the studies are described below.

When monoacetin, diacetin and triacetin were incubated with the sacs of everted intestine from rats for 1 hr at 37 °C, the glycerides entered the epithelial cells and were completely hydrolyzed to free glycerol and acetic acid. The acetate released appeared in higher concentrations on the serosal side. The activity of the preparation, as measured by acetate release, increased with the number of acetic acid residues in the glyceride (15 mM). Monoacetin, diacetin and triacetin released 92 ± 4, 206 ± 12 and 307 ± 11 umoles of acetate, respectively. With increasing concentrations of glyceride (5, 10 and 15 mM), the amount of acetate released increased linealy up to about a total amount of 300 umoles of acetates released. There was no absolute positional specificity, and all three ester linkages were split (Barry et al., 1966).

To investigate that triacetin may have a role as a parenteral nutrient, a 5 % (v/v) aqueous solution was administered intravenously to mongrel dogs at a rate of 47 umol/kg bw/min (estimated resting energy expenditure: REE) for an additional 4 hours, after [1-^{14}C] acetate was infused at a rate of ca. 30 kBq/min for 3 hours (continued to the end of study) to allow quantification of organ uptake of acetate as well as systemic turnover and oxidation (Bleiberg, 1993).

Systemic acetate kinetics was obtained in all animals tested. Systemic acetate turnover accounted for approximately 70 % of triacetin-derived acetate, assuming complete hydrolysis of the triglyceride. Aapproximately 80 % of systemic acetate uptake was rapidly oxidized and significant acetate uptake was demonstrated in all tissues (liver, 559 ± 68; intestine, 342 ± 23; hind limb, 89 ± 7; and kidney, 330 ± 37 umol/min). The results demonstrate that during intravenous administration in dogs, the majority of infused triacetin undergoes intravascular hydrolysis, and the majority of the resulting acetate is directly oxidized (Bleiberg, 1993). This is consistent with the generally accepted view that short- and medium-chain fatty acids undergo near quantitative oxidation rather than being reesterificated or elongated to longer fatty acid chain (Groot and Hulsmann, 1973).

Effects on metabolism

(Mineral metabolism)

Triacetin was infused at 47 umol/kg bw/min for 3 hr at an isocaloric rate in mongrel dogs to test its effects on serum phosphorus, calcium, and magnesium metabolism (Bailey, et al. 1989). Arterial blood was sampled at 15-30 min intervals until the end of the study. Urine was collected during the equilibration period and again during triacetin infusion. There were no changes in serum P or Ca. Serum Mg decreased by approximately 20 %, probably because of cellular uptake rather than accelerated excretion and remained at this level for the remainder of the study. Thus, triacetin administered to dogs at a rate approximating resting energy expenditure has no demonstrable adverse effects on mineral metabolism (Bailey, et al. 1989).

(Protein metabolism)

To investigate the effects of intravenous administration of triacetin on leucine metabolism in dogs, infusion of **L**-[1-^{14}C]-leucine was conducted at 1.5 kBq/kg bw/min for 6 hr in mongrel dogs (Bailey, et al. 1993). Three hours after initiation of the isotope infusion, animals received infusion of 5 % triacetin at 47 umol/kg bw/min (1.0 x estimated resting energy expenditure: REE), at 70 umol/kg bw/min (1.5 x REE), glycerol (70 umol/kg bw/min), or saline during infusion. No overt toxic effects were observed. Leucine kinetics (the rate of leucine appearance (Ra): an estimate of leucine derived from endogenous protein breakdown, leucine oxidation, and the rate of no oxidized leucine disappearance (NOLD): an indicator of protein synthesis) were not significantly different among animals receiving saline, glycerol, or isoenergitic triacetin infusions. When triacetin was infused at 1.5 x REE, leucine Ra and leucine oxidation decreased 19 % and 53 %, respectively. NOLD did not change in any of the studies. The studies demonstrate that triacetin does not have adverse effects on protein metabolism and at relatively high doses actually suppresses endogenous proteolysis (Bailey, et al. 1993).

(Lipolysis)

Following ingestion, a natural long-chain triglyceride is eventually hydrolyzed to glycerol and corresponding fatty acid by pancreatic lipase in the presence of colipase, producing 2-monoglyceride, which in turn by the action of 2-monoglyceride lipase in plasma (Fielding, 1981 and Fossati et al., 1992) or liver (Fielding, 1972).

However, such mechanism cannot be necessarily applied to short- and medium-chain triglycerides because shorter-chain 2-monoglycerides are either cleaved by pancreatic lipase or rapidly isomerized to the 1-isomer, which rapidly hydrolyzed (Boudreau, 1965). Several studies confirmed that triacetin is readily hydrolyzed to glycerol and acetic acid by digestive enzymes, particularly intestinal lipase or liver and plasma carboxyesterases (Murphy & Cheever, 1968). Rat everted intestine was found to be equally active on mono-, di- and triacetin to produce glycerol and acetic acid (Barry et al., 1966). An intestinal lipase has been characterized in different species, including man (Serrero, 1975). In addition, the presence of a gastric lipase in adult man with an acidic optimum pH has also been characterized. This lipase is active on short- and medium-chain triglycerides (Cohen, et al., 1971).

Information on structurally related chemicals

(Monoacetin: glyceryl monoacetate)

The oral LD_{50} of monoacetin in rats was determined as 5.0 mL/kg bw (Li et al, 1941). Monoacetin caused no toxic effects in rats when administered at 0.1 mL/kg bw, daily subcutaneously for 70 days, and similar results were observed in dogs (Chenoweth et al, 1951). There are no reports on toxic effects of monoacetin for human beings, and the hazards from handling this chemical appear to be comparatively small.

(Diacetin: glyceryl diacetate)

The oral LD_{50} of diacetin in rats or mice was determined as 4.0 mL or 2.5 mL, respectively (Li et al, 1941). There are no reports on toxic effects of diacetin in man (von Oettingen, 1960).

From these results, it can be concluded that the toxicity of monoacetin and diacetin in mammals is not significant.

(Triproprionin: glyceryl tripropanoate)

The oral LD_{50} of triproprionin in rats was found to be ca. 15 mL/kg bw (Hodge, 1942). Rat exposed to heated vapour (about 750 ppm) for 6 hours/day for 90 days showed no symptoms or abnormalities in clinical data and histopathology (Hodge, 1942). Triproprionin is not a skin irritant or sensitiser in guinea pig (Fassett, 1963).

(Tributyrin: glyceryl tributyrate)

The oral LD_{50} of tributyrin in rats is about 13 g/kg bw. Weakness, ataxia and vasodilatation in the ears and feet were noted. There was no percutaneous absorption or irritation in the guinea pig. Inhalation of 78 ppm for 6 hours caused temporary hyperpnea, but no fatalities or other symptoms in rats (Fassett, 1963).

3.1.2 Acute Toxicity

Studies in Animals

Results from acute toxicities via the oral, inhalation and dermal route using rats, mice, rabbits and guinea pigs are summarized in Table 3.

Table 3: Acute Toxicity of Triacetin in Experimental Animals

Route	Animals	Values	Type	References
Oral	Rat	> 2,000 mg/kg bw (male & female)	LD_{50}	Unichema (1988)[2]
Oral	Rat	3,000 mg/kg bw	LD_{50}	von Oettingen (1960)
Oral	Rat	6,400 - 12,800 mg/kg bw	LD_{50}	Fassett (1955)[1]
Oral	Rat	12,700 mg/kg bw	LD_{50}	Fassett (1948)
Oral	Mouse	ca. 9,300 mg/kg bw (male)	LD_{50}	Lawrence et al. (1974)
Oral	Mouse	1,800 mg/kg bw (male) 1,100 mg/kg bw (female)	LD_{50}	Gast, J.H. (1963)
Oral	Mouse	3,200 - 6,400 mg/kg bw	LD_{50}	Fassett (1955)[1]
Inhalation	Rat	> 1,721 mg/m^3 (4 hrs), (male & female)	LC_{50}	Bayer AG (1985)
Inhalation	Rat	73,700 mg/m^3 (5 days)	NOAEL	Fassett (1955)[2]
Dermal	Rabbit	> 2,000 mg/kg bw	LD_{50}	Unichema (1994)
Dermal	Rabbit	> 5,000 mg/kg bw	LD_{50}	Bailey (1976)
Dermal	Guinea pig	> 20 mL/kg bw	LD_{50}	Fassett (1967)

Among the above, an oral rat study (Unichema, 1988[2]) was identified as the key study because it was well conducted and described in detail in compliance with GLP for non-clinical studies (US FDA, EPA and OECD). Details of the study are described below.

Male and female Wistar rats were administered orally at a single, maximum dose (2,000 mg/kg bw, a limit dose level) to one group of five male and five female rats according to OECD TG 401. No mortality occurred and no signs of systemic toxicity were observed during the 14-day observation period. Gross pathology revealed no treatment-related changes at the end of two weeks for both sexes. From these results, triacetin has no toxic effect when administered as a single oral dose to

rats at a level of 2,000 mg/kg bw. When triacetin was administered orally to rats, in another study, at doses that caused fatality, weakness and ataxia were reported (Fassett, 1955[1]).

Studies in Humans

There is no information available.

Conclusion

Acute toxicity of triacetin is low in rodents because LD_{50} values are greater than 1,000 mg/kg bw by oral or dermal route and greater than 1,000 mg/m^3 by inhalation.

3.1.3 Irritation

Studies in Animals

Skin Irritation

Application of triacetin induced no skin irritation in rabbits (Kaestner, 1988 and Hem, 1974-1975) and slight irritation in guinea pigs (Fasset, 1967).

Eye Irritation

Most of the studies report that triacetin caused no irritation to rabbit eye (Jacobs, 1989, Kaestner, 1988, Conquet, 1977, Lailer, 1976, Hughes, 1976) except one report where slight irritation was observed in rabbits (Fasset, 1967).

Conclusion

Triacetin is neither classified nor labelled as irritant according to European regulation and Directive 67/548/EWG.

Studies in Humans

Human data is not available in detail except one case report (Unna and Schultz, 1963). Triacetin caused mild skin irritation when tested at 50% in 20 volunteers with 24-hr occlusive skin contact (Matthies W., 1988). Triacetin (20 % in petrolatum) did not irritate the skin of 33 volunteers when tested in a 48-hr covered patch test (Epstein, 1976). Contact with a solution containing 50 % triacetin in ethanol was not irritant to 20 eczema patients in covered test for 24 and 48hr (Unna and Schulz, 1963).

No skin reactions occurred in 33 volunteers treated with 20% triacetin in petrolatum in an attempt to induce skin sensitisation using the maximization test (Klingman, 1966, Klingman & Epstein, 1975). However, there is one case report so far concerning allergic contact eczema in a cigarette factory, which was based on sensitisation towards triacetin used for the production of cigarette filters and identified as the key study because of detailed description of the case. The allergy was demonstrated in a patch test. In addition to triacetin, monoacetin and diacetin also produced positive results (Unna and Schulz, 1963).

3.1.4 Sensitisation

Application of triacetin did not induce skin sensitisation in guinea pigs (Opdyke, 1978 and Eastman Kodak Company, 1955).

Conclusion

Triacetin is not irritating to skin and to eyes in rabbits. Triacetin does not induce skin sensitisation in guinea pigs.

3.1.5 Repeated Dose Toxicity

Some of the results from repeated toxicity studies via oral, feeding and inhalation route in rats and sheep are summarized in Table 4.

Table 4: Repeated Dose Toxicity of Triacetin in Experimental Animals

Route	Animals	NOAEL	Exposure period	References
Oral	Rat	1,000 mg/kg bw/day (male) 1,000 mg/ kg bw /day (female)	44 days 41 - 48 days	MHW (1998)
Feed	Rat	10 g/kg bw /day (male)	90 days	Shapira (1969)
Feed	Sheep	10 %/day (male & female)	175 days	Bull (1970)
Inhalation	Rat	2,220 mg/m^3	90 days	Fassett (1955)[2]

Although several studies are available, all but one of these studies were run prior to the publication of GLP standards. In addition, these studies were not conducted according to currently approved laboratory methods for toxicity testing. Therefore, the repeated dose study by gavage conducted by MHW, Japan, 1998 was identified as the best quality and the key study because it was well conducted and described in detail. Other studies including by inhalation (Fassett, 1955[2]) and oral by feed (Bull, et al. 1970 and Shapira, 1969, 1975) were also reviewed because these studies were cited elsewhere and afford the experimental evidences concerning that triacetin is a safe substance in a variety of uses including food, cigarette filters and cosmetics (MSDS-OHS, 2001). Details of these studies are described below.

Oral

(Oral by Gavage)

Using the OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], SD (Crj: CD) rats received gavage doses of 0 (vehicle; distilled water), 40, 200 and 1,000 mg/kg bw/day; for males for 44 days from 2 weeks prior to mating and for females for 41-48 days from 14 days before mating to day 3 postpartum (MHW, Japan: 1998).

Triacetin had no effects on clinical signs, body weight, body weight gain, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed even at the highest dose for both sexes. There were no abnormalities in haematological or blood chemical parameters in males, although urinalysis was not conducted. The NOAEL for repeated dose toxicity is thus considered to be 1,000 mg/kg bw/day for both sexes.

(Oral by Feed)

(Rat) To develop diets which contain virtually all the calories as purified organic compounds for long-duration space missions, growing male rats were fed diets containing triacetin and/or glycerin (20 - 60 %) for 90 days. The animals well tolerated up to 20 % triacetin, which corresponds to 10

g/kg bw/day. Greater percentage caused a decrease in weight gain. A large loss in weight and considerable mortality was associated with diets containing either glycerol or triacetin at 60 % of the diet (Shapira, 1969), while increased liver weight occurred in the 30 % groups (Shapira, 1975). The NOAEL for the feeding study is considered to be 10 g/kg bw/day for male rats.

(Sheep) A feeding experiment using rams and ewes was conducted for 175 days to study the efficiency of utilization for growth-fattening, of the energy of diets in the ruminal ingesta. Triacetin, employed as a source of acetic acid, was added to the basal diets to comprise 10 % of the total dietary dry matter. Faeces were collected and analysed for the proximate chemical constituents and heat of combustion and samples of urine were analysed for urinary energy. Utilization rates were 62.0 % for the metabolizable energy (ME) provided by the diets containing triacetin in a 175 day feeding study with sheep. No toxicity was reported (Bull et al. 1970).

Inhalation

To determine if the plasticiser, when used in cellulose acetate cigarette filters, would have any toxic effect on the individuals inhaling the compound, long-term vapour inhalation toxicity for 90 days was studied for rats at a dose of 249 ppm (2,220 mg/m^3). Average daily weight gain was 2.2 g/rat. Inhalation was further extended for another week at 73.72 ppm (660 mg/m^3) and 8,271 ppm (73,700 mg/m^3, saturated vapour) (Fassett, 1955[2]). No symptoms were noted during the exposure. Haematological studies and urinalysis showed no abnormalities in any of the animals. No histopathological changes were observed at the time of autopsy. The NOAEL is estimated to be 8,271 ppm (73,700 mg/m^3) for the 5-day study and 249 ppm (2,220 mg/m^3) for the 90-day study. Although the inhalation studies are considered to be useful, they do not fully comply with the current testing protocol.

Conclusion

An oral repeated dose study in rats showed no adverse effects even at the highest dose, 1,000 mg/kg bw/day. In a 90-day feeding study with rats up to 10 g/kg bw/day were tolerated without signs of toxicity. An inhalation study reveals no abnormalities attributable to exposures of 8,271 ppm (73,700 mg/m^3) for 5 days and 250 ppm (2,200 mg/m^3) for 90 days. Therefore, the NOAEL for repeated dose oral toxicity in rats is 1,000 mg/kg bw/day for both sexes. The NOAEL for the feeding study is considered to be 10 g/kg bw /day for male rats. The NOAEL for repeated inhalation toxicity in rats is considered to be 8,271 ppm (73,700 mg/m^3) for 5 days and 250 ppm (2,200 mg/m^3) for 90 days.

3.1.6 Mutagenicity

In vitro Studies

Several *in vitro* studies are available. Triacetin did not induce gene mutation in bacteria (MHW, Japan: 1998, Uniquema, 1988[3], Henkel, 1982) and induced chromosomal aberrations in mammalian cultured cells (MHW, Japan: 1998). Among these studies, MHW studies were identified to be the key study because they were most recent, well conducted and published.

A reverse gene mutation assay was conducted using the pre-incubation method (OECD TG 471 and 472). Triacetin was not mutagenic in *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *uvr*A at concentrations up to 5,000 ug /plate, with or without an exogenous metabolic activation system (MHW, Japan: 1998).

A chromosomal aberration test according to OECD TG 473 was conducted in cultured Chinese hamster lung (CHL/IU) cells. Induction of chromosome aberrations, however, was observed in the Chinese hamster cultured cells only at the highest concentration (2.2 mg/mL, 10 mM) in the

presence of an exogenous metabolic activation system (OECD TG 473). Because of the high toxicity (75 %) and also low pH (4.9) at the end of the treatment, the chromosomal aberration observed might not be biological relevant. Under un-physiological culture condition, such as low pH, it was reported that the frequency of chromosomal aberrations could be increased (Morita et al., 1990). Polyploidy was not induced under any of the conditions on continuous and short-term treatment with and without an exogenous metabolic activation system (MHW, Japan: 1998).

In vivo Studies

There are no data on genotoxicity *in vivo* available.

Conclusion

Triacetin is not genotoxic with and without an exogenous metabolic activation system in bacterial tests. The chemical however induced chromosomal aberrations *in vitro* (however under un-physiological conditions). Taking all data into consideration, triacetin should be considered non-genotoxic *in vitro*.

3.1.7 Carcinogenicity

There is no available information on carcinogenicity.

3.1.8 Toxicity for Reproduction

Studies in Animals

One study was available. The data from the OECD repeated dose and reproductive toxicity study by the oral route (MHW, Japan: 1998) was identified as the key study because it was well conducted and reported. Details of this study are as follows.

Effects on Fertility

Using the OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], SD (Crj: CD), rats received gavage doses of 0 (vehicle; distilled water), 40, 200 and 1,000 mg/kg bw/day. Males were exposed for 44 days from 2 weeks prior to mating and females were exposed for 41-48 days from 14 days before mating to day 3 postpartum. Female animals were sacrificed on day 4 of lactation (MHW, Japan: 1998).

No effects related to chemical exposure were observed maternally at any dose levels, although there was a single undelivered animal at 200 mg/kg bw which was not statistically significantly different from the control ($p<0.05$). Similarly, no effects related to the chemical exposure were observed at any dose levels on reproductive parameters including the mating index, fertility index, gestation length, numbers of corpora lutea and implantations, implantation index, gestation index, delivery index, parturition and maternal behaviour at delivery and lactation.

In summary, it can be concluded that reproductive toxicity of triacetin in rats by oral administration was not observed up to the highest dose tested. The NOAEL is thus established to be 1,000 mg/kg bw/day.

Developmental Toxicity

As described the above, using the OECD combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], female rats received gavage doses of 0 - 1,000 mg/kg bw /day, for 41-48 days from 14 days before mating to day 3 postpartum. The animals were sacrificed

on day 4 of lactation to evaluate the potential maternal and developmental parameters of triacetin (MHW, Japan: 1998).

On examination of neonates, there were no statistically significant differences from the control in numbers of offspring or live offspring, the sex ratio, the live birth index, and the viability index or body weight. No abnormal findings ascribable to the compound were found for external features, clinical signs or necropsy of the offspring.

Therefore, the NOAEL for developmental toxicity is considered to be 1,000 mg/kg bw /day for offspring.

Studies in Humans

There is no information on humans available.

Conclusion

Triacetin did not produce any reproductive and developmental effects in rats. The NOAEL for reproductive and developmental toxicity by gavage is established at 1,000 mg/kg bw/day for parental animals and offspring.

3.2 Initial Assessment for Human Health

Triacetin is absorbed following ingestion and metabolised like other shorter-chain triglycerides. Several studies confirmed that triacetin is hydrolysed to glycerol and acetic acid by digestive enzymes, particularly lipases, liver or plasma carboxyesterases. Triacetin infused in dogs undergoes intravascular hydrolysis, and the majority of the resulting acetate is oxidized nearly quantitatively rather than reesterificated or elongated, as is the case with short- and medium-chain fatty acids.

In the oral acute toxicity study in rats (2,000 mg/kg bw, a limit dose level, OECD TG 401), no mortality occurred and no signs of systemic toxicity were observed during the 14-day observation period. Gross pathology revealed no treatment-related changes at the end of two weeks for both sexes. The LD_{50} of triacetin in rats by gavage is thus determined to be > 2,000 mg/kg bw. The LC_{50} in acute inhalation toxicity in rats is > 1.721mg/L (4h) for both sexes [OECD 403].

Most of the studies show that triacetin caused no irritation to rabbit skin [OECD TG 404] and to the rabbit eye [OECD TG 405]. Triacetin is not skin sensitising to guinea pigs.

In the tests using human volunteers, triacetin induced no skin irritation or skin sensitization. However, one case concerning allergic contact eczema caused by triacetin has so far been reported in a cigarette factory.

In an oral rat study according to the combined repeated dose and reproductive/developmental toxicity screening test [OECD TG 422], a dose of 1,000 mg/kg bw/day of triacetin exerted no effects on clinical signs, body weight, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in either sex. The NOAEL for repeated dose toxicity is thus considered to be 1,000 mg/kg bw/day for both sexes.

Growing male rats were fed diets containing triacetin and/or glycerine (20 - 60 %) for 90 days. The animals well tolerated up to 20 % triacetin of the diet. The NOAEL for the feeding study is considered to be 10 g/kg bw/day for male rats.

An inhalation study was conducted in rats given triacetin for 90 days at dose of 249 ppm (2,220 mg/m3) under non-GLP condition. No toxic symptoms were noted during the exposure and all rats appeared to be normal. Haematological studies, urine analyses and autopsy showed no abnormal

observations attributable to the exposure. The NOAEL is considered to be 249 ppm (2,220 mg/m3) for 90 days, although the inhalation studies are considered to be useful, they do not fully comply with the current testing protocol.

In the combined repeated dose and reproductive/developmental oral toxicity study in rats [OECD TG 422], animals received gavage doses of 0, 40, 200 and 1,000 mg/kg bw/day. There were no statistically significant adverse effects on reproductive parameters including the mating index, fertility index, gestation length, numbers of corpora lutea and implantations, implantation index, gestation index, delivery index, parturition and maternal behavior at delivery and lactation. In addition, there were no significant differences in numbers of offspring or live offspring, the sex ratio, the live birth index, the viability index or body weight. No evidence of malformations at any doses ascribable to the compound was found for external features, clinical signs or necropsy of the offspring. Therefore, the NOAEL for reproductive and developmental toxicity by gavage is considered to be 1,000 mg/kg bw/day for parental animals and offspring.

For genotoxicity of triacetin, one non-bacterial in vitro and five bacterial reverse mutation tests are available. Triacetin did not induce gene mutation in bacteria at concentrations up to 5,000 ug /plate (OECD TG 471 and 472). Induction of chromosome aberrations, however, was observed in the Chinese hamster cultured cells only at the highest concentration (2.2 mg/mL, 10 mM) in the presence of an exogenous metabolic activation system (OECD TG 473). Because of high toxicity (75 %) and also low pH (4.9) at the end of treatment, the chromosomal aberration observed might not be biological relevant. Under un-physiological culture condition, such as low pH, it was reported that the frequency of chromosomal aberrations could be increased (Morita et al., 1990). Polyploidy was not induced under any of the conditions tested. Taking all data into consideration, triacetin could be considered to be non-genotoxic.

There is no information on human toxicity available. However, the Joint FAO/WHO Expert Committee on Food Additive (JECFA) considers it unnecessary to assign an acceptable daily intake (ADI) as triacetin is metabolized like other triglycerides in food. In an assessment of triacetin, JECFA concluded that based on the available data, and anticipated daily intake, triacetin did not represent a hazard to health (JECFA, 1975) and in a more recent evaluation, the EU’s Scientific Committee for Food endorsed this position for triacetin (Commission, 1992, SCF, 1995). An estimate of additive intake in the UK suggests that an adult might ingest 7.8 mg triacetin/day as part of a total daily additive intake of 8.0 g (MAFF, 1993).

4. HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute and Chronic Toxicity Test Results

Triacetin has been tested in a limited number of aquatic species. Results from acute and chronic tests on aquatic organisms are summarized in Table 5.

Table 5: Summary of Effects of Triacetin on Aquatic Organisms

Organism	Test duration	Result (mg/L)	Reference
Micro-organisms			
Green alga (*Selenastrum capricornutum*) §	0-72 h (cl, shaken)	(Growth inhibition) EC_{50} (G.rate) > 1,000 (nc*) NOEC = 556 (nc*) EC_{50} (Bms) > 1,000 (nc*) NOEC = 556 (nc*)	EA, Japan (1998)
Invertebrates			
Water flea (*Daphnia magna*)	24 h (op, s) 48 h (op, s)	EC_{50} (Imm) = 888 (nc*) EC_{50} (Imm) = 768 (nc*) EC_0 (Imm) = 309 (nc*)	EA, Japan (1998)
Water flea (*Daphnia magna*)	24 h (op, s) 48 h (op, s)	EC_{50} (Imm) > 974.4 (m) EC_{50} (Imm) = 810.9 (m) EC_0 (Imm) = 541.1 (m)	Lawrence (1995)[1]
Water flea (*Daphnia magna*)	48 h (op, s)	EC_{50} = 380 EC_0 = 65	Henkel KGaA
Water flea (*Daphnia magna*)	21 d (op, ss)	EC_{50} (Rep) > 100 (nc*) NOEC (Rep) = 100 (nc*)	EA, Japan (1998)
Fish			
Medaka (*Oryzias latipes*)	96 h (op, ss)	LC_{50}> 100 (nc*)	EA, Japan (1998)
Medaka (*Oryzias latipes*)	14 d (op, f)	LC_{50} >100 (nc*) LC_0 = 100 (nc*)	EA, Japan (1998)
Fathead minnow (*Pimephales promelas*)	96 h (op, s)	LC_{50} = 165.3 (m)	Lawrence (1995)[2]
Cyprinidae (Carp) (*Cyprinus carpio*)	48 h (op, s)	LC_{50} = 174	Unichema (1988)[1]
Golden orfe (*Leuciscus idus*)	48 h (op, s)	LC_{50} = 170	Henkel KGaA (1988)
Zebra-fish (*Brachydanio rerio*)	96 h (op, ss)	LC_{50} = 300	Henkel KGaA (1982)

cl = closed system m = measured concentration f = flow through
op = open system s = static ss = semi-static
nc = nominal concentration
nc* = calculated based on nominal concentrations, because measured concentrations were >80% of nominal concentrations.
Bms = biomass Imm = immobilization Rep = reproduction
G.rate = Growth rate

§ In the case of green alga, the pH decrease caused by the hydrolysis of triacetin was dependent on the concentration of triacetin and reached the plateau at 556mg/L at pH 5.3. Therefore, the NOEC of 556 mg/L was tentatively assigned for the toxicity of triacetin. It is, however, not clear whether the growth inhibition observed at 1,000 mg/L was due to the pH decrease or the chemical itself in this test.

4.2 Terrestrial Effects

There is no information available.

4.3 Other Environmental Effects

There is no information available.

4.4 Initial Assessment for the Environment

The Mackay level III fugacity model was employed to estimate the environmental distribution of triacetin in air, water, soil and sediment (Daicel, 2002). This was considered the key study and the results are shown below (For details, refer to Appendix in the SIDS Dossier). Table shows the estimated distribution of triacetin obtained from the solubility value (58 g/L) in parenthesis in addition to those obtained from 70 g/L for comparison.

Estimated Distribution Under Four Emission Scenarios

70 g/L (58 g/L)

Compartment	Release 100 % to air	Release 100 % to water	Release 100 % to soil	Equal emission scenario (1:1:1)
Air	0.9 (1.1) %	0.0 (0.0) %	0.0 (0.0) %	0.3 (0.4) %
Water	20.0 (19.9) %	99.7 (99.7) %	12.9 (12.9) %	30.1 (30.2) %
Soil	79.1 (79.0) %	0.0 (0.0) %	87.1 (87.1) %	69.5 (69.4) %
Sediment	0.1 (0.1) %	0.3 (0.3) %	0.0 (0.0) %	0.1 (0.1) %

Triacetin is readily biodegradable (77 % and 94 % based on BOD and TOC, respectively, Chemicals Evaluation and Research Institute, 1998) after 14 days. A half-life of 168 hrs (7 days) is thus derived from the biodegradation data. An estimated half-life of 168 hours is also obtained for water. Given slower transport rate and possible anaerobic change in microbes in soil and sediment, the calculation was made by using 168 hrs x 3 (504 hrs) for both compartments. The calculation revealed that in the case of 100 % release to water, more than 99 % of triacetin is expected to stay in water due to its high solubility and a low vapour pressure, but if it is released into air and/or soil, it is likely to be distributed in other compartments.

The results also show that approximately one third of triacetin will be distributed in water, whereas two third will stay in soil when applied to the equal emission scenario to water, soil and sediment (1:1:1). In addition, the fugacity model using 58 g/L reveals that there is little change in the distribution of triacetin between three compartments when compared to those obtained from 70 g/L.

Based on a water solubility of 58 g/L and a vapour pressure of 0.003306 hPa (0.00248 mmHg) at 25 °C, a Henry's law constant of 1.23 x 10^{-8} atm m^3/mol is estimated. This value indicates that triacetin is essentially non-volatile from water (Lyman, 1990).

Since triacetin is readily biodegradable in activated sludge (Chemicals Evaluation and Research Institute, 1998, Unichema Chemie B.V., 1990, Henkel KGaA, 2001 and Bayer AG), biologically

mediated hydrolysis is the predominant pathway in the primary degradation step when triacetin is discharged to the environment.

This compound is expected to have a low potential for bioaccumulation based on its low Log Pow (0.21, Chemicals Evaluation and Research Institute, 1998).

The BCF is estimated to be 1.3 from a recommended regression-derived equation using a water solubility of 58 g/L at 25 °C (Lyman, 1990), indicating that bioconcentration is of no environmental relevance.

The toxicity results of triacetin to aquatic plants (alga; *Selenastrum capricornutum*) are > 1,000 mg/L for EC_{50} and 556 mg/L for NOEC [growth inhibition, OECD TG 201] (EA, Japan, 1998). The acute (mortality or immobility, [OECD TG 202]) and chronic (reproduction, [OECD TG 211]) toxicity results for *Daphnia magna* are 888 mg/L (EC_{50}, 24 h), 768 mg/L (EC_{50}, 48 h) and 100 mg/L (21 d NOEC), based on nominal concentration (EA, Japan, 1998). The acute toxicity results to fish are > 100 mg/L (Medaka; *Oryzias latipes*) (EA, Japan, 1998) and 165.3 mg/L (Fathead minnow; *Pimephales promelas*) (Lawrence, 1995[2]) for 96 h LC_{50} [OECD TG 203]. In the prolonged toxicity test in fish (Medaka; *Oryzias latipes*), no mortality and any toxic symptom were observed [OECD TG 204]. The 14d LC_{50} and the 14d LC_0 for fish are reported as > 100 mg/L and 100 mg/L, respectively (EA, Japan, 1998).

Thus, triacetin can be regarded as being of low hazard to aquatic organisms.

Based on the acute and prolonged aquatic toxicity data on three trophic levels, a Predicted No Effect Concentration (PNEC) can be calculated. When an assessment factor of 100 was applied to the chronic toxicity for *Daphnia*, the lowest PNEC was determined to be 1.00 mg/L for the aquatic environment.

5. RECOMMENDATIONS

The chemical is currently of low priority for further work because of its low hazard potential.

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ANNEX

(Occupational exposure)

EHE values of 4.94 mg/kg bw/day (most likely case) and 49.43 mg/kg bw/day (worst case) for dermal absorption are defined in Section 2.2 for workers at the production site.

Using these EHE values and the NOAEL of 1,000 mg/kg bw/day, the margin of safety (MOS) for dermal route is calculated as 202 (most likely case) and 20 (worst case), respectively. Similarly, respiratory EHE values of 0.0244 mg/kg bw/day (most likely case) and 0.0379 mg/kg bw/day (worst case) are estimated for workers at the production site. For respiration, the MOS is calculated as 41,000 (most likely case) and 26,000 (worst case), respectively.

At working sites, absorption of triacetin via dermal and inhalation routes may occur simultaneously. Hence, the MOS combined for both routes is calculated as 202 (most likely case) and 20 (worst case), respectively. From these results, workers are not expected to be at risk of toxic health effects from occupational exposure to triacetin under regular conditions of the usage equipped with protective gears.

(Consumer exposure)

EHE values of 0.0429 mg/kg bw/day (most likely case) and 0.107 mg/kg bw/day (worst case) for dermal absorption are defined in Section 2.2 for consumers using products containing 0.3 % and 25 % of triacetin.

Using these EHE values and the NOAEL of 1,000 mg/kg bw/day, the MOS for dermal absorption is calculated as 23,000 (most likely case) and 9,000 (worst case).

The MOS for ingestion is calculated as 9,000 for most likely case.

(Environmental exposure)

EHE values of 0.00000514 mg/kg bw/day (most likely case) and 0.00714 mg/kg bw/day (worst case) are defined in Section 2.2 by assuming that individuals use untreated water as their sole source of drinking water (2 L/day for a 70 kg adult).

The MOS is calculated as 196,000,000 and 140,000 for most likely case and worst case, respectively. The results suggest that adverse effects by triacetin uptake via the environmental route could be negligibly small.

Potential exposure via consumption of fish is anticipated to be negligible because triacetin is expected to have a low potential for bioaccumulation and readily biodegradable.

SIDS DOSSIER

Triacetin

CAS No. 102-76-1

Sponsor Country: Japan

DATE: 9 August 2002

1. GENERAL INFORMATION

1.01 SUBSTANCE INFORMATION

A. CAS number 102 – 76 - 1

B. Name (IUPAC name) Triacetin

C. Name (OECD name) Triacetin

D. CAS Descriptor

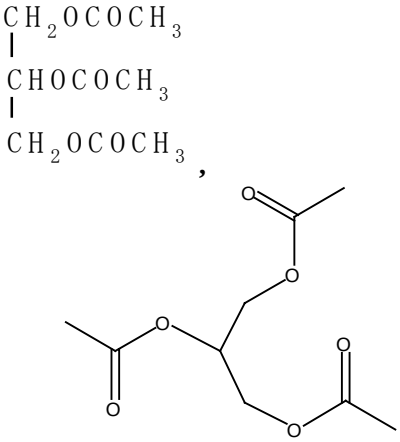
Not applicable in this case.

E. EINECS-Number 203 – 051 - 9

F. Molecular Formula $C_9H_{14}O_6$

G. Structural Formula

C_3H_5-$(OCOCH_3)_3$ or



SMILES Line Notation: CC(OC(C)=O)COCC.O=C.COC(C)=O

H. Substance Group

Not applicable.

I. Substance Remark

None

J. Molecular Weight 218.21

1.02 OECD INFORMATION

A. Sponsor Country: Japan

B. Lead Organisation:

Name of Lead Organisation: Daicel Chemical Industries, Ltd.

Contact person: Mr. Yasuhisa Kawamura, Director

Address: Ministry of Foreign Affairs
Economic Affairs Bureau
Second International Organizations Div.
2-2-1 Kasumigaseki, Chiyoda-ku
Tokyo 100

C. Name of responder

Name: The same as the contact person

Address: The same as the contact person

1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance

element **[ ]**; inorganic **[ ]**; natural substance **[ ]**; organic **[X]**; organometallic **[ ]**; petroleum product **[ ]**

B. Physical State (at 20 °C and 1,013 hPa)

gaseous **[ ]**; liquid **[X]**; solid **[ ]**

C. Purity

99.5-99.8% weight/weight

1.2 SYNONYMS

(Chemical name)
1,2,3-Propanetriol, triacetate
1,2,3-Propanetriyl, triacetate
1,2,3-Triacetoxypropane
Acetic acid, glycerol triester
Acetic, 1,2,3-Propanetriyl ester
Acetin, Tri-
Glycerin triacetate
Glycerol triacatate
Glycerol, triester with acetic acid
Glyceryl triacetate
Propane-1,2,3-triyl triacetate
Triacetin
Triacetyl glycerin
Triacetyl glycerine
Triacetyl glycerol

(Trade name)
ENZACTIN

"ESTROBOND" B Plasticizer
FEMA NUMBER 2007
FUNGACETIN
GLYPED
KESSCOFLEX TRA

KODAFLEX TRIACETIN
VANAY

1.3 IMPURITIES

CAS No.:	26446-35-5
EINECS No.:	247-704-6
Name:	1,2,3-Propanetriol, monoacetate (Monoacetin)
Value:	< 0.01 %
Remarks:	None.
Reference:	Company data (Daicel Chemical, 2001).

CAS No.:	25395-31-7
EINECS No.:	246-941-2
Name:	1,2,3-Propanetriol, diacetate (Diacetin)
Value:	< 0.1 %
Remarks:	None.
Reference:	Company data (Daicel Chemical, 2001).

1.4 ADDITIVES

Not stated.

1.5 QUANTITY

Remarks:	In Japan, ca. 5,000 tonnes/year, produced by three Japanese companies. Estimated global production is 10,000-50,000 tonnes/year; Other major manufacturers are Eastman (USA), Cognis (Germany) and Uniqema (UK).
Reference:	Company data (Daicel Chemical, 2001).

1.6 LABELLING AND CLASSIFICATION (USE AND/OR TRANSPORTATION)

Labelling

Type:	As in Directive 67/548/EEC
Specific limits:	No
Symbols:	None
Nota:	
R-phrases:	None
Text of S-phrases:	
Remarks:	Not stated.

Classification

Type:	As in Directive 67/548/EEC
Category of danger:	None
Remarks:	EC Classification (Calculated).

Reference: Material safety data sheet, dated 26-1-1994; Unichema International.

1.7 USE PATTERN

A. General

Type of Use: **Category: Non dispersive**

(a) Main industrial use: Chemical industry: intermediate

Type of Use: **Category: Wide dispersive**

(b) Main industrial use:
(1) Metal extraction, refining and processing of metals
(2) Paints, lacquers, varnishes industry
(3) Paper pulp, and board industry
(4) Cigarette industry (Cellulose acetate plasticizer in cigarette filters)
(5) Food industry (Food/foodstuff additives)
(6) Photographic industry (Solvent in photographic films)
(7) Polymer industry
(8) Cosmetic industry (Fixative)

(c) Other: Solvents, adhesives, binding agents, flux agents for casting, impregnation agents, plasticizer for cellulose nitrate, absorbents and adsorbents.

Remarks: Not stated.
Reference: HSDB (2001), National Library of Medicine

B. Uses in Consumer Products

Function	Amount present (%)	Physical state
Soap	0.05-1.0	Solid
Detergent	0.005-0.1	Liquid
Cream, lotion	0.025-0.3	Liquid
Perfume	0.8-2.0	Liquid
Tobacco	3-5	Solid
Antifungal drug	15-25-33	Aerosol-Cream-Powder

Remarks: Not stated.
Reference: Opdyke D.L.J. (1978), Food Cosmet. Toxicol. 16 (Suppl. 1), 879-882. Permitted additives to Tobacco products, UK Department of Health, 1998.

1.8 OCCUPATIONAL EXPOSURE LIMIT

Exposure limit value
Type: Not stated.
Value: Not stated.
Remarks: No occupational exposure limits established.
Reference: MSDS-OHS, OHSN OHS10442 (2001), MDL Information Systems, Inc.

1.9 SOURCES OF EXPOSURE

A. Potential human exposure:

The production process consists of the batchwise controlled reaction of glycerol, acetic acid and acetic anhydride in a closed reaction system with adequate cooling facilities. This is followed by purification using vacuum distillation. The pungent nature of the raw materials demands a totally enclosed plant. Therefore, exposure can be negligible by applying protective measures as written below. The process is operated at three sites in Japan.

(a) At a production site: Exposure is possible when sampling, followed by analysing the product. Based on a calculation, the exposure time is estimated for 0.25 hours/day/person for both sampling

and analysis. During cleaning of the strainer for maintenance production line, the worker is also exposed to the substance and the exposure is estimated for 0.50 hours/day/person (Daicel Chemical Industries, 2001). The exposure time for drum filling is estimated 5.0 hours/day/person. The work place is provided with an air ventilator and workers are equipped with protective gear such as mask, rubber gloves and goggles to prevent exposure (MSDS Daicel Chemical, 2001). Spill is collected and incinerated.

(b) At user's facility: Material is used as a solvent in paints, metal processing and as a plasticizer in cigarette filters in addition to foodstuff additives and fixative cosmetics, etc., all of which are used in the industrial sector. Potential exposure is controlled by the use of efficient exhaust ventilation. Exposure is possible during dispensing the substance from drum or tank lorry into a container at user's facility. Workers may be exposed to the vapour or an intact liquid. They are recommended to put on protective gear such as mask, rubber gloves and goggles to prevent exposure (MSDS Daicel Chemical, 2001). Spill is collected and incinerated.

(c) At consumer's site: Due to its uses triacetin soon becomes diffused into small quantities and there is little possibility of large scale human contact or environmental effect after it leaves the manufacturer's production sites. Its use in adhesives may give skin contact. As foodstuff additives or soft drinks flavouring, ingestion of triacetin will occur. Very small amounts can be found in cigarette smoke drawn through a filter tip using triacetin as the plasticizer. (MSDS Daicel Chemical Industries, 2001).

B. Potential environmental exposure:

(a) At a production site:

Source:	Media release: Process wastewater
	Quantities per media: ca. 1,440 kg/year in a production site in Japan, in which ca. 2,000 t/year of the chemical was produced. (estimated by Daicel Chemical Industries, 2001)
Remarks:	Data used for the estimation:
	Waste water released: ca. 19,200 m^3/year
	Content of triacetin: 0.075 g/L
Reference:	Company data (Daicel Chemical Industries, 2001).

(b) At a user's facility:

	No substantial exposure is probable. Potential exposure is controlled by the use of efficient exhaust ventilation and protective gears.
Remarks:	Not stated.
Reference:	Company data (Daicel Chemical Industries, 2001).

1.10 ADDITIONAL REMARKS

A. Options for disposal

Remarks:	Dispose in accordance with all applicable regulations.
Reference:	MSDS-OHS (2001), MDL Information Systems, Inc.

B. Other remarks

Remarks:	CERCLA Sections 102a/103 Hazardous Substances (40 CFR 302.4): Not regulated. SARA TITLE III Section 302 Extremely Hazardous Substances (40 CFR 355.30): Not regulated. SARA TITLE III Section 304 Extremely Hazardous Substances (40 CFR 355.40): Not regulated. SARA TITLE III SARA Sections 311/312 Hazardous Categories (40 CFR 370.21): Acute: Yes Chronic: No Fire: No Reactive: No Sudden Release: No SARA TITLE III Section 313 (40 CFR 372.65): Not regulated. OSHA Process Safety (29CFR1910.119): Not regulated. State Regulations: California Proposition 65: Not regulated. Canadian Regulations: WHMIS classification: Not determined. German Regulations: Water Hazard Class (WGK): State of Classification: VwVwS, ID-Number 761 Classification under Hazard to Water: 1 (low hazard to waters) European Regulations: Refer to 1.6 LABELLING AND CLASSIFICATION (USE AND/OR TRANSPORTATION)
Reference:	MSDS-OHS (2001), MDL Information Systems, Inc.

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

(a) **Preferred result**

Value:	3 °C
Decomposition:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:	Not specified
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	A thermodynamic melting point of crystalline triacetin.
Reference:	The Sigma-Aldrich Library of Regulatory and Safety Data, confirmed by Chemicals Evaluation and Research Institute (Kurume, Japan) (1998), Test No. 80919BK.

(b)

Value:	4.00 °C
Decomposition:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:	Not specified
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	A thermodynamic melting point of crystalline triacetin.
Reference:	Yumashev, N. V. et al. (1984), J. Gen. Chem. USSR (Engl. Transl.), 54 659-662.

(c)

Value:	4.1 °C
Decomposition:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:	Not specified
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	A thermodynamic melting point of crystalline triacetin.
Reference:	CRC Press Inc. (1975), 2 nd Ed, Cleveland Ohio.

(d)

Value:	3.20 °C
Decomposition:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:	Not specified
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	Ethanol as solvent. A thermodynamic melting point of crystalline triacetin.
Reference:	Hancock et al. (1948), J. Amer. Chem. Soc., 70 424.

(e)

Value:	4.10 °C
Decomposition:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method:	Not specified
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	A thermodynamic melting point of crystalline triacetin.
Reference:	Baur (1945), J. Phys. Chem., 58 380.

(f)

Value:	< -78 °C
Decomposition:	Yes **[ ]** No **[ ]** Ambiguous **[ ]**
	Sublimation: Yes **[ ]** No **[X]** Ambiguous **[ ]**
Method:	Not stated.

GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: A glass transition temperature.
Reference: Hutchings, D. et al., (1993) Pharmaxie 48 (12) 912-914.

(g) Value: < -78 °C
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: A glass transition temperature.
Reference: The Merck Index (1996), 12th edition, Merck & Co., Inc., p. 1636.

(h) Value: < -60 °C
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Sublimation: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: A glass transition temperature.
Reference: Timmermans (1922), Bull. Soc. Chim. Belg., 31 392.

2.2 BOILING POINT

(a) **Preferred result**
Value: 258 °C
Pressure: at 1,013 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: The Sigma-Aldrich Library of Regulatory and Safety Data.
Reference: Chemicals Evaluation and Research Institute (1998), Test No. 80919BK.

(b) Value: 258-259 °C
Pressure: at 1,013 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Prager, R. H. & Yurui Z. (1989) Aust. J. Chem., 6 1003-1005.

(c) Value: 258-259 °C
Pressure: at 1,013 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Perkin & Simonsen (1905), J. Chem. Soc., 87 859.

(d) Value: 258-260 °C
Pressure: at 1,013 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.

Reference: The Merck Index (1996), 12th edition, Merck & Co., Inc., p. 1636.

(e) Value: 258 °C
Pressure: at 1,013 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Jellum & Bjoernstad (1964), J. Lipid Res., 5 314-316.

(f) Value: 171-172 °C
Pressure: at 53 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Baur (1945), J. Phys. Chem. 58 380.

(g) Value: 170 °C
Pressure: at 53 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Togashi & Yamada (1969), Chem. Abstr., 71 101337m.

(h) Value: 135-137 °C
Pressure: at 9.3 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Nitrofanowa et al. (1966), J. Org. Chem. USSR (Engl. Transl.), 2 1748.

(i) Value: 130-131 °C
Pressure: at 5.3 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Golendee (1954), Chem. Abstr. 9914.

(j) Value: 123-124 °C
Pressure: at 9.3 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Umemura et al. (1966), Nippon Kagaku Zasshi, 87 986-990.

(k) Value: 101-113 °C
Pressure: at 2.7 hPa
Decomposition: Yes **[ ]** No **[ ]** Ambiguous **[ ]**

Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Umemura et al. (1966), Nippon Kagaku Zasshi, 87 986-990.

2.3 DENSITY

(a) **Preferred result**
Type: Bulk density **[ ]**; Density **[ ]**; Relative Density **[X]**
Value: 1.1562 g/cm^3
Temperature: 25 °C

Value: 1.1596 g/cm^3
Temperature: 20 °C

Value: 1.1630 g/cm^3
Temperature: 20 °C

Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: 4 °C and 20 °C (Reference Temperature)
Reference: The Merck Index (1996), 12th edition, Merck & Co., Inc., p. 1636.

(b) Type: Bulk density **[ ]**; Density **[ ]**; Relative Density **[X]**
Value: approx. 1.160 g/cm^3
Temperature: 20 °C
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Cognis Deutschland GmbH (2000), Safety Data Sheet.

(c) Type: Bulk density **[ ]**; Density **[ ]**; Relative Density **[X]**
Value: 1.15620 g/cm^3
Temperature: 25 °C

Value: 1.07520 g/cm^3
Temperature: 100 °C

Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: 4 °C (Reference Temperature)
Reference: Jaeger (1917), Z. Anorg. Allg. Chem., 101 70.

(d) Type: Bulk density **[ ]**; Density **[ ]**; Relative Density **[X]**
Value: 1.15960 g/cm^3
Temperature: 20 °C
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: 4 °C (Reference Temperature)
Reference: Dunbar, B. (1956), J. Org. Chem., 21 1041-1043.

(e) Type: Bulk density **[ ]**; Density **[ ]**; Relative Density **[X]**
Value: 1.16450 g/cm^3

Temperature: 20 °C

Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: 4 °C (Reference Temperature)
Reference: Nitrofanowa et al. (1966), J. Org. Chem. USSR (Engl. Transl.), 2 1748.

(f) Type: Bulk density **[ ]**; Density **[ ]**; Relative Density **[X]**
Value: 1.11100 g/cm^3
Temperature: 70 °C
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: 4 °C (Reference Temperature)
Reference: Mohr, M. (1934), Milchwirtsch. Forsch., 16 193.

2.4 VAPOUR PRESSURE

(a) **Preferred result**
Value: 0.003306 hPa (0.00248 mmHg)
Temperature: 25 °C
Method: calculated **[ ]**; measured **[X]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: SRC recommended value.
Reference: Design Institute for Physical Property Data (1989).

(b) Value: 53.3 hPa
Temperature: 78 °C
Method: calculated **[ ]**; measured **[ ]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: MSDS-OHS (2001), MDL Information Systems, Inc.

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

(a) **Preferred result**
Log Pow: 0.21
Temperature: 25 °C.
Method: calculated **[ ]**; measured **[X]**
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Remarks: OECD TG 107 (Shake Flask Method)
Reference: Chemicals Evaluation and Research Institute (1998), Test No. 80919BK.

(b) Log Pow: 0.25
Temperature: No data available.
Method: calculated **[ ]**; measured **[ ]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: American Chemical Society (1995), 63.

(c) Log Pow: 0.1
Temperature: No data available
Method: calculated **[X]**; measured **[ ]**

GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: No information about method.
Reference: Chemical Safety Sheets (1991) Dutch Chemical Industry

Association.

(d) Log Pow: 0.368
Temperature: No data available
Method: calculated **[X]**; measured **[ ]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: version CLOGP 3.3.
Reference: ASTM Spec. Techn. Publ. 11 (1988) 468-489.

(e) Log Pow: 0.30
Temperature: No data available
Method: calculated **[X]**; measured **[ ]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Leo A. J. (1978), EPA files.

(f) Log Pow: 0.44
Temperature: No data available
Method: calculated **[X]**; measured **[ ]**
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Leo A. J. (1978), EPA files.

2.6 WATER SOLUBILITY

A. SOLUBILITY

(a) **Preferred result**
Value: 70 g/L
Temperature: 25°C.
Description: Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[X]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method: OECD TG 105.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Remarks: No dissociation group.
Reference: Chemicals Evaluation and Research Institute (Kurume, Japan) (1998), Test No. 80919BK.

(b) **Preferred result**
Value: 58 g/L
Temperature: 25°C
Description: Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[X]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Riddick J.A. et al. (1986), Techniques of Chemistry, 4th ed.

(c) Value: 80 g/L
Temperature: 20°C.
Description: Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[X]**; Slightly soluble **[ ]**;

Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Cognis Deutschland GmbH (2000), Safety Data Sheet.

(d) Value: 7.17 vol%
Temperature: 15°C
Description: Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: CHEMICAL DIVISION DI SISAS SPA CAVAGLIA.

(e) Value: 5.8 vol %
Temperature: Not specified.
Description: Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[X]**; Slightly soluble **[ ]**;
Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Flick, Industrial Solvent Handbook, 3rd edition.

(f) Value: No data available.
Temperature: No data available.
Description: Miscible **[ ]**; Of very high solubility **[ ]**;
Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[X]**;
Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Soluble in 14parts water.
Reference: The Merck Index (1996), 12th edition, Merck & Co., Inc., p. 1636.

B. pH VALUE, pKa VALUE

(a) pH Value: 7
Temperature: 20°C
Concentration: 10g/L
Method: Not specified
GLP: Yes **[ ]** No **[ ]** ? **[X]**
pKa value: No data available
Remarks: No dissociation group
Reference: Safety Data Sheet (2000), Cognis Deutschland GmbH.

2.7 FLASH POINT (liquids)

(a) **Preferred result**
Value: >145 °C
Type of test: Closed cup **[X]**; Open cup **[ ]**; Other **[ ]**
Method: DIN 51758/ISO 2719 (Pensky-Martens).
GLP: Yes **[ ]** No **[ ]** ? **[X]**

Remarks: Not stated.
Reference: Cognis Deutschland GmbH (2000), Safety Data Sheet.

(b) Value: 137.8 °C
Type of test: Closed cup **[ ]**; Open cup **[ ]**; Other **[X]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Design Institute for Physical Property Data (1989), American Institute of Chemical Engineers.

(c) Value: 138 °C
Type of test: Closed cup **[X]**; Open cup **[ ]**; Other **[ ]**
Method: Not specified
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Database ECDIN; Commission of the EEC, Joint Research Centre Ispra, Italy.

(d) Value: 138 °C
Type of test: Closed cup **[ ]**; Open cup **[X]**; Other **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Sax Dangerous Properties of Industrial Materials, 6th edition, p.2605.

(e) Value: 145 °C
Type of test: Closed cup **[ ]**; Open cup **[X]**; Other **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Unichema International, Material Safety Data Sheet, dated 26-1-1994.

(f) Value: 149 °C
Type of test: Closed cup **[ ]**; Open cup **[ ]**; Other **[X]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Sax, N.I. & Lewis, R.J. (eds.)(1987), Hawley's Condensed Chemical Dictionary, 11th edition.

(g) Value: 151 °C
Type of test: Closed cup **[X]**; Open cup **[ ]**; Other **[ ]**
Method: ASTM D 92.
GLP: Yes **[ ]** No **[X]** ? **[ ]**

Remarks: Not stated.
Reference: Eastman Kodak Company, Unpublished data.

(h) Value: 153 °C
Type of test: Closed cup **[ ]**; Open cup **[X]**; Other **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**

Remarks: Not stated.
Reference: CHEMICAL DIVISION DI SISAS SPA CAVAGLIA.

2.8 AUTO FLAMMABILITY (solid/gases)

(a) **Preferred result**
Value: 432 °C
Pressure: No data available.
Method: ASTM D2155.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Eastman Kodak Company, Unpublished data.

(b) Value: 430 °C
Pressure: No data available.
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: Database ECDIN; Commission of the EEC, Joint Research Centre Ispra, Italy.

(c) Value: 433 °C
Pressure: No data available.
Method: Not specified..
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Not stated.
Reference: National Fire Protection Association
(1991), Fire Protection Guide, on Hazardous Materials. 10th ed.
Quincy, MA.

2.9 FLAMMABILITY

(a) Results: Extremely flammable **[ ]**; Extremely flammable - liquified gas **[ ]**; Highly Flammable **[ ]**; Flammable **[ ]**; Non flammable **[X]**; Spontaneously flammable in air **[ ]**; Contact with water liberates highly flammable gases **[ ]**; Other **[ ]**
Method: ASTM E681.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Remarks: Lower flammability limits of 1.05 % (vol./vol.) at 189 °C and upper flammability limits of 7.75 % (vol./vol.) at 215 °C in air.
Reference: Eastman Kodak Company, Unpublished data.

(b) Results: Extremely flammable **[ ]**; Extremely flammable - liquified gas **[ ]**; Highly Flammable **[ ]**; Flammable **[ ]**; Non flammable **[X]**;

Spontaneously flammable in air **[ ]**; Contact with water liberates highly flammable gases **[ ]**; Other **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Remarks: Not stated.
Reference: National Fire Protection Association (1991), Fire Protection Guide, on Hazardous Materials. 10th ed. Quincy, MA.

2.10 EXPLOSIVE PROPERTIES

Results:	Explosive under influence of a flame **[ ]**; More sensitive to friction than m-dinitrobenzene **[ ]**; More sensitive to shock than m-dinitrobenzene **[ ]**; Not explosive **[X]**; Other **[ ]**
Method:	ASTM E537.
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Remarks:	No exothermic activity to boiling. Test type: Differential thermal analysis.
Reference:	Eastman Kodak Company, Unpublished data.

2.11 OXIDISING PROPERTIES

Remarks:	Stable at normal temperatures and pressure, even under fire exposure conditions.
Reference:	Hazardous Substances Databank (HSDB) (2001), The National Library of Medicine.

ADDITIONAL REMARKS

Remarks:	Sets to a glass at –37 °C
Reference:	Sax, N.I. & Lewis, R.J. (eds.)(1987), Hawley's Condensed Chemical Dictionary, 11th edition.
Remarks:	Solidification point: < -30 °C
Reference:	Cognis Deutschland GmbH (2000), Safety Data Sheet.
Remark:	Solubility: Soluble in acetone, ethanol, benzene and chloroform.
Reference:	Unichema Int. (1994), MSDS.
Remark:	Viscosity (25 °C) : ca. 17 mPa.s
Reference:	Unichema Int. (1994), MSDS.
Remark:	Not compatible with strong oxidizing agents. Stable in usual Industrial conditions. Polymerisation: Not occurring. Combustible liquid when exposed to flame or heat.
Reference:	CHEMICAL DIVISION DI SISAS SPA CAVAGLIA.
Remark:	Solubility: Soluble in acetone, ethanol, benzene and chloroform.
Reference:	Unichema Int. (1994), MSDS.
Remark:	Solubility: Soluble in acetone, ethanol, benzene and chloroform.
Reference:	Unichema Int. (1994), MSDS.
Remarks:	Solubility: Slightly soluble in carbon tetrachloride and carbon disulfide
Reference:	Hazardous Substances Databank (HSDB) (2001), The National Library of Medicine.
Remark:	Wt/Gal: 9.7 LB

Reference: Sax, N.I. & Lewis, R.J. (eds.)(1987), Hawley's Condensed Chemical Dictionary, 11th edition.

Remark: Crystals from alcohol, melting point 4.1 °C
Reference: Lide, D.R. (ed.), CRC Handbook of Chemistry and Physics (1991-1992).

2.12 OXIDATION: REDUCTION POTENTIAL

No studies located.

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

Remark: Triacetin may leach readily in soil based upon an estimated Koc value of 10.5.

Reference: Lyman W.J. et al. (1990), Handbook of Chemical Property

Estimation Methods Washington, DC: Amer Chem Soc p. 4-9.

B. Other data:

No studies located.

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 PHOTODEGRADATION

Type:	Air **[X]**; Water **[ ]**; Soil **[ ]**; Other **[ ]**
Indirect Photolysis:	
Type of sensitizer:	OH
Concentration of sensitizer:	500,000 molecule/cm^3
Rate constant (radical):	$7.810*10^{-12}$ cm^3/molecule*sec
Degradation:	ca. 50 % after 2 day
Method:	calculated **[X]**; measured **[ ]**
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	No data available.
Remarks:	Temperature used in the calculation: 25 °C
Reference:	Atkinson, R (1987), J. Inter. Chem. Kinet., 19 799-828

3.1.2 STABILITY IN WATER

(a)	Type:	Abiotic (hydrolysis) **[X]**; biotic (sediment) **[ ]**;
	Half life:	60.4 days and 16.5 hours at pH 7 and 9 at 25 °C, respectively.
	Degradation:	No hydrolysis at pH 4 at 50 °C in 5 days Hydrolysis at pH 7 (50, 60, 70 °C) and 9 (30 and 40 °C).
	Method:	OECD TG111
	GLP:	Yes **[X]** No **[ ]** ? **[ ]**
	Test substance:	Tokyo Kasei, Lot No. GB 01, Purity: > 98 %, Impurity: not stated.
	Remarks:	Hydrolysis rates at pH 7 and 9 were determined at 50, 60, 70 and 30, 40 °C, respectively and they were extrapolated to 25 °C using Arrhenius relationship. Half life at 25 °C was calculated from the rate constant.
	Reference:	Chemicals Evaluation and Research Institute (Kurume, Japan) (1998), Test No. 80919BK.

(b)	Type:	Abiotic (hydrolysis) **[X]**; biotic (sediment) **[ ]**;
	Half life:	ca. 130 days at pH 7. ca. 13 days at pH 8. ca. 1.3 days at pH 9.
	Degradation:	Hydrolysis at pH 7, 8 and 9.
	Method:	Not specified.
	GLP:	Yes **[ ]** No **[ ]** ? **[X]**
	Test substance:	Not stated.
	Remarks:	Method: Estimation.
	Reference:	US EPA (1991), PCGEMS Graphical Exposure Modeling System PCHYDRO.

3.1.3 STABILITY IN SOIL

No studies located.

3.2 MONITORING DATA (ENVIRONMENTAL)

Type of Measurement: Background **[ ]**; At contaminated site **[ ]**; Other **[X]**
Media: Surface water
Method: Not specified.
Results: Triacetin was detected in a sample of Tennessee River water collected in April 1973.
Remarks: Concentration not reported.
Reference: Shackelford W. M. and Keith L. H (1976), US EPA-600/4-76-062, p.226.

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT

No studies located.

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

(a) **Preferred result**
Media: Air-biota **[ ]**; Air-biota-sediment-soil-water **[X]**; Soil-biota **[ ]**; Water-air **[ ]**; Water-biota **[ ]**; Water-soil **[ ]**; Other **[ ]**
Method: Fugacity leve l I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[X]**; Fugacity level IV **[ ]**; Other (calculation) **[ ]**; Other (measurement) **[ ]**

Results:
Predicted distribution of triacetin using Fugacity level III under four emission scenarios
(1) Results from water solubility of 70 g/L

Compartment	Release 100 % to air	Release 100 % to water	Release 100 % to soil	Equal emission scenario (1:1:1)
Air	0.9 %	0.0 %	0.0 %	0.3 %
Water	20.0 %	99.7 %	12.9 %	30.1 %
Soil	79.1 %	0.0 %	87.1 %	69.5 %
Sediment	0.1 %	0.3 %	0.0 %	0.1 %

(2) Results from water solubility of 58 g/L

Compartment	Release 100 % to air	Release 100 % to water	Release 100 % to soil	Equal emission scenario (1:1:1)
Air	1.1 %	0.0 %	0.0 %	0.4 %
Water	19.9 %	99.7 %	12.9 %	30.2 %
Soil	79.0 %	0.0 %	87.1 %	69.4 %
Sediment	0.1 %	0.3 %	0.0 %	0.1 %

Remarks: Refer to Appendix.
Reference: Daicel Chemical Industries (2002), Predicted distribution of triacetin using Fugacity level III, unpublished report.

(b) Media: Air-biota **[ ]**; Air-biota-sediment-soil-water **[ ]**; Soil-biota **[ ]**; Water-air **[X]**; Water-biota **[ ]**; Water-soil **[ ]**; Other **[ ]**
Method: Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[ ]**; Fugacity level IV **[ ]**; Other (calculation) **[X]**; Other (measurement) **[ ]**
Results: Based on a water solubility of 58 g/L and a vapour pressure of 0.00248 mm Hg (at 25 degree C), a Henry's law constant of $1.23 * 10^{-8}$ atm*m^3/mol is estimated. This value indicates that the compound is essentially non-volatile from water.
Remarks: Not stated.
Reference: Lyman W. J. (1990), Amer. Chem. Soc., p.15-29.

(c) Media: Air-biota **[ ]**; Air-biota-sediment-soil-water **[ ]**; Soil-biota **[ ]**; Water-air **[ ]**; Water-biota **[ ]**; Water-soil **[X]**; Other **[ ]**
Method: Fugacity level I **[ ]**; Fugacity level II **[ ]**; Fugacity level III **[ ]**; Fugacity level IV **[ ]**; Other (calculation) **[X]**; Other (measurement) **[ ]**
Results: Based upon a measured water solubility of 58 g/L at 25 °C, the Koc-value can be estimated to be 10.5 from a regression derived equation. This Koc-value indicates very high soil mobility (Chemical Safety Sheets (1991), Dutch Chemical Industry Association).
Remarks: Not stated.
Reference: Lyman W. J. (1990), Amer. Chem. Soc., p.4-9.
Swann R.L.(1983), Res. Rev., 85 p.23.

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

No studies located.

3.5 BIODEGRADATION

(a) **Preferred result**
Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**; other **[ ]**: sewage treatment plant effluent (biological stage)
Concentration of the chemical: 100 mg/L, related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: (1) 77 % after 14 day based on BOD.
(2) 94 % after 14 day based on TOC.
Results: readily biodeg. **[X];** inherently biodeg. **[ ]**; under test condition no biodegradation observed **[ ]**, other **[ ]**
Kinetic: Not stated.
Method: OECD Guideline 301 C, Modified MITI Test (I)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: As prescribed by 1.1-1.4.
Remarks: Domestic activated sludge was used as inoculum..
Reference: Chemicals Evaluation and Research Institute (Kurume, Japan) (1998), Test No. 20919B.

(b) Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**; other **[ ]**: sewage treatment plant effluent (biological stage)
Concentration of the chemical: (1) 10mg/L, (2) 20mg/L, related to COD **[ ]**; DOC **[ ]**;

Test substance **[X]**

Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: (1) 64 % after 28 day based on $ThCO_2$ (10mg/L).
(2) 93 % after 28 day based on $ThCO_2$ (20mg/L).
Results: readily biodeg. **[X];** inherently biodeg. **[ ]**;
under test condition no biodegradation observed **[ ]**, other **[ ]**
Kinetic: Not stated.
Method: OECD TG 301B, Directive 84/449/EEC, C.5 "Biotic degradation-modified Sturm test"
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: As prescribed by 1.1-1.4.
Remarks: The study was also in accordance with OECD Guideline 301 B. Domestic activated sludge was used as inoculum.
Reference: Chemie B.V. (1990), unpublished data, RCC NOTOX Project 005164.

(c) Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**; other **[ ]**: sewage treatment plant effluent (biological stage)
Concentration of the chemical: 2, 5 mg/L. related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: 69 % (2 mg/L) and 79 % (5 mg/L) after 30 days by BOD.
Results: readily biodeg. **[X];** inherently biodeg. **[ ]**;
under test condition no biodegradation observed **[ ]**, other **[ ]**
Kinetic: 2 mg/L: 5% (5 d); 62% (15 d); 69% (30 d)
5 mg/L: 4% (5 d); 57% (15 d); 79% (30 d)
Method: OECD Guideline 301 D
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: As prescribed by 1.1-1.4.
Remarks: Municipal sewage treatment plant effluent was used as inoculum.
Reference: Henkel KGaA (2001), unpublished data (R0100896).

(d) Type: aerobic **[X]**; anaerobic **[ ]**
Inoculum: adapted **[ ]**; non-adapted **[X]**; other **[ ]**: sewage treatment plant effluent (biological stage)
Concentration of the chemical: 3 mg/L. related to COD **[ ]**; DOC **[ ]**; test substance **[X]**
Medium: water **[X];** water-sediment **[ ];** soil **[ ];** sewage treatment **[ ]**
Degradation: 70 % after 30 day.
Results: readily biodeg. **[X];** inherently biodeg. **[ ]**;
under test condition, no biodegradation observed **[ ]**, other **[ ]**
Kinetic: Not stated.
Method: DEV: H5 modif.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: No data available.
Remarks: Domestic sewage was predominantly used as inoculum.
Reference: Bayer AG, unpublished data.

3.6 BOD_5, COD OR RATIO BOD_5/COD

No studies located.

3.7 BIOACCUMULATION

Species: Fish
Exposure period: No data available.
Temperature: 20 °C

Concentration:	No data available.
BCF:	ca. 1.3.
Elimination:	Yes **[ ]** No **[ ]** ? **[X]**
Method:	Other.
Type of test:	calculated **[X]**; measured **[ ]** static **[ ]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]**
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	No data available.
Remarks:	The BCF was estimated from a recommended regression-derived equation using a water solubility of 58 g/L at 25 °C. This estimated BCF indicates that bioconcentration potential in fish will not be significant.
Reference:	Lyman W.J. et al. (1990), Amer. Chem. Soc., p.5-10.

3.8 ADDITIONAL REMARKS

A. Sewage treatment

Remarks: No additional remarks.

B. Other information

Remarks: No additional remarks.

4. ECOTOXICITY

4.1 ACUTE/PROLONGED TOXICITY TO FISH

A. ACUTE TOXICITY TO FISH

(a) **Preferred result**

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other **[ ]** open-system **[ ]**; closed-system **[ ]**
Species:	Oryzias latipes (Medaka, fresh water)
Exposure period:	96 hour(s)
Results:	LC_{50} (96 h) > 100.0 mg/L based on nominal concentrations.
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 203 (1992).
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1-1.4.
Remarks:	Drinking water was used after dechlorination by passing through activated carbon filter. No vehicle was used. Test was conducted at the nominal concentrations of 0 and 100 mg/L. Test solutions were replaced every 24 hours by newly prepared ones. When test solutions were analysed after 24 hours, the measured concentrations showed more than 80 % of the nominal concentrations. At the nominal concentrations of 0 mg/L, 100 % of fish survived until 96 h; At 100 mg/L, 100 % of fish survived until 96 h; at both doses, no fish showed abnormal swimming behaviour.
Reference:	Environment Agency of Japan (1998).

(b) Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other (e.g. field test) **[ ]**; open-system **[ ]**; closed-system **[ ]**

Species:	Pimephales promelas (Fathead minnow, fresh water)
Exposure period:	96 hour(s)
Results:	LC_{50} (96h) = 165.3 mg/L (178.3, 165.3 mg/L)
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 203 and EEC/Annex V C.1.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1-1.4,Sample ID No.: 3045932, Purity: > 99.5 %.
Remarks:	During the test, 77 - 98.1 % of the initial analysed concentrations was maintained throughout the test. The exposure solutions did not appear to exceed the aqueous solubility of the test article as no particulates or surface slicks were observed in the exposure vessels containing the test article.
Reference:	Lawrence, D.L. and Hirsch, M.P. (1995), Eastman Kodak Company, Environmental Sciences Section, Corporate Health and Environment Laboratories, An acute aquatic effects test with the fathead minnow, Study No.: EN-430-900256-1, Unpublished data.

(c) Type of test: static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other (e.g. field test) **[ ]**; open-system **[ ]**; closed-system **[ ]**

Species:	Cyprinus carpio (Cyprinidae, carp, fresh water)
Exposure period:	48 hour(s)
Results:	LC_{50} (48 h) = 174 mg/L
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	Other.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**

	Test substance:	As prescribed by 1.1-1.4.
	Remarks:	Method used was Bewertung wassergefährdender Stoffe, Bestimmung der akuten Fischtoxizität, Ad-hoc-Arbeitsgruppe 1 (Obmann Dr. Niemitz), LTwS, Nr. 10, September 1979.
	Reference:	Unichema Chemie B.V. (1988), unpublished data, RCC NOTOX 0831/PA45.
(d)	Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other (e.g. field test) **[ ]** open-system **[ ]**; closed-system **[ ]**
	Species:	Brachydanio rerio (Zebra-fish, fresh water)
	Exposure period:	96 hour(s)
	Results:	LC_{50} (96 h) = 300 mg/L
	Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
	Method:	ISO-Guideline 7346/2 which conforms to OECD TG 203.
	GLP:	Yes **[ ]** No **[X]** ? **[ ]**
	Test substance:	As prescribed by 1.1 - 1.4.
	Remarks:	Test was conducted at a concentration of 0, 90, 130, 180, 250, 360 and 500 mg/L. Mortalities are recorded at 0, 6, 24, 48, 72 and 96 hr. The study was carried out before 1990, at a time when GLP was not implemented. However, the study adhered to GLP comparable conditions.
	Reference:	Henkel KGaA (1982), unpublished data (R-0100930).
(e)	Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other (e.g. field test) **[ ]** open-system **[ ]**; closed-system **[ ]**
	Species:	Leuciscus idus (Golden orfe, fresh water)
	Exposure period:	48 hour(s)
	Results:	LC_{50} (48 h) = 170 mg/L
	Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
	Method:	Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN38412 Teil15.
	GLP:	Yes **[ ]** No **[X]** ? **[ ]**
	Test substance:	As prescribed by 1.1 - 1.4.
	Remarks:	Test substance directly weighed into test vessel followed by treatment with Ultraturrax. Test was conducted at a concentration of 0, 100, 300 and 1,000 mg/L. Fish did not show any abnormal behaviour. LC_0 (48 h) and LC_{100} (48 h) were 100 mg/L and 300 mg/L, respectively. The study was carried out before 1990, at a time when GLP was not implemented. However, the study adhered to GLP comparable conditions.
	Reference:	Henkel KGaA (1988), unpublished data (R-0100933).
(f)	Type of test:	static **[ ]**; semi-static **[ ]**; flow-through **[ ]**; other (e.g. field test) **[ ]**; open-system **[ ]**; closed-system **[ ]**
	Species:	Cyprinus carpio (Cyprinidae, carp, fresh water)
	Exposure period:	66 hour(s)
	Results:	LC_{50} (Not stated)
	Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
	Method:	Not stated.
	GLP:	Yes **[ ]** No **[ ]** ? **[X]**
	Test substance:	As prescribed by 1.1 - 1.4.
	Remarks:	Carp (Cyprinus carpio) force-fed with triacetin were killed at concentrations between 122 mg/kg bw (minimum) and 184 mg/kg bw (maximum). Alkalinity, Water temperature and pH were 10 mg/L $CaCO_3$, 18.3 °C and 6.7, respectively.
	Reference:	Loeb, H.A. & Kelly, W.H (1963), US Fish Wildl. Serv., Sp. Sci. Rep.-Fish No. 471.

B. PROLONGED TOXICITY TO FISH

Type of test:	static **[ ]**; semi-static **[ ]**; flow-through **[X]**; other (e.g. field test) **[ ]**; open-system **[ ]**; closed-system **[ ]**
Species:	Oryzias latipes (Medaka, fresh water)
Exposure period:	14 days.
Results:	LC_{50} (7 days) > 100.0 mg/L (nominal concentration) LC_{50} (14 days) > 100.0 mg/L (nominal concentration)
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 204.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1-1.4.
Remarks:	Test was conducted at the nominal concentrations of 0, 30.9 (27.7), and 55.6 (51.6), 100 (97.0) mg/L (measured mean concentration of test chemical during test period). No reduction of food intake and no abnormal behaviours were observed at all doses tested during 14-day exposure period. There was no significant difference in fish body weight between all treated groups and in control.
Reference:	Environment Agency of Japan (1998).

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

(a) **Preferred result**

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]** open-system **[ ]**; closed-system **[ ]**
Species:	Daphnia magna (Crustacea)
Exposure period:	48 hour(s)
Results:	EC_{50} (24 h) = 888 mg/L EC_{50} (48 h) = 768 mg/L EC_0 (48 h) = 309 mg/L
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 202
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1-1.4.
Remarks:	Test concentration: 95, 171, 309, 556, 1,000 mg/L. All the test solutions showed more than 90 % of the nominal concentrations after 48 hours.
Reference:	Environment Agency of Japan (1998).

(b)

Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]** open-system **[ ]**; closed-system **[ ]**
Species:	Daphnia magna (Crustacea)
Exposure period:	48 hour(s)
Results:	EC_{50} (24 h) > 974.4 mg/L (974.4, 1006.7 mg/L) EC_{50} (48 h) = 810.9 mg/ L (810.9, 904.2 mg/L) EC_0 (24 h) = 974.4 mg/L (974.4, 1006.7 mg/L) EC_0 (48 h) = 541.1 mg/L (541.1, 558.5 mg/L)
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 202 and EEC/Annex V C.2.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1-1.4,Sample ID No.: 3045932, Purity: > 99.5 %.

Remarks:	The exposure solutions (nominally 95.0, 171.5, 308.5, 555.5, and 1,000.0 mg/L) were prepared by direct addition of the appropriate amounts of the test article to tanks of water. The exposure solutions did not appear to exceed the aqueous solubility of the test article, as throughout the test, there were no particulates, surface slicks or precipitates observed within the exposure solutions containing the test article.
Reference:	Lawrence, D.L. and Hirsch, M.P. (1995), Eastman Kodak Company, Environmental Sciences Section, Corporate Health and Environment Laboratories, An acute aquatic effects test with the daphnid, Study No.: EN-431-900256-1, Unpublished data.

(c) Type of test:	static **[X]**; semi-static **[ ]**; flow-through **[ ]**; other **[ ]** open-system **[ ]**; closed-system **[ ]**
Species:	Daphnia magna (Crustacea)
Exposure period:	48 hour(s)
Results:	EC_0 (48 h) = 65 mg/L EC_{50} (48 h) = 380 mg/L EC_{100} (48 h) = 1000 mg/L
Analytical monitoring:	Yes **[ ]** No **[ ]** ? **[X]**
Method:	Daphnien-Kurzzeittest, DIN 38412 Teil 11, Bestimmung der Wirkung von Wasserinhaltsstoffen auf Kleinkrebse
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Test method conforms to OECD Guideline 202A.
Reference:	Henkel KGaA, unpublished data. (Report-No. R 9400102).

B. Other aquatic organisms

No studies located.

4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

Species:	Selenastrum capricornutum ATCC 22662
Endpoint:	Biomass **[X]**; Growth rate **[X]**; Other **[ ]**
Exposure period:	72 h.
Results:	EC_{50} (0-72 h) > 1,000 mg/L (Growth inhibition: growth rate & biomass) NOEC (0-72 h) = 556 mg/L (Growth inhibition: growth rate & biomass)
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 201(1984) open-system **[ ]**; closed-system **[X]**
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1-1.4.
Remarks:	All the test groups (95, 171, 309, 556 except 1,000 mg/L) showed normal and similar growth (170-224 fold increase after 72 hr) to control (207-fold increase after 72 hr).
Reference:	Environment Agency of Japan (1998).

4.4 TOXICITY TO BACTERIA

(a) Type:	Aquatic **[X]**; Field **[ ]**; Soil **[ ]**; Other **[ ]**
Species:	Pseudomonas putida (Bacteria)
Exposure Period:	18 hour(s)
Results:	EC_0 (18 h) > 541.6 mg/L

Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	Not stated.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Bacteriotoxicity was determined according to Bewertung Wassergefährdender Stoffe, III Bestimmung der akuten Bakterientoxizität Ad-hoc-Arbeitsgruppe 1 (Obmann Dr. Niemitz), LTWS, Nr. 10 September 1979.
Reference:	Unichema Chemie B.V. (1988), unpublished data , RCC NOTOX B.V. 0831/PS9.

(b) Type:	Aquatic **[ ]**; Field **[ ]**; Soil **[ ]**; Other **[ ]**
Species:	Pseudomonas putida MIGULA (Bacteria)
Exposure Period:	30 min
Results:	EC_0 (30 min) = 10,000 mg/L
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	Pseudomonas oxygen consumption inhibition test, German standard method DIN 38412 Part 27
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Pseudomonas oxygen consumption inhibition test. Test was conducted at a concentration of 0 and 10,000 mg/L. The study was carried out before 1990, at a time when GLP was not implemented. However, the study adhered to GLP comparable conditions.
Reference:	Henkel KGaA (1988), unpublished data (R-0100931).

(c) Type:	Aquatic **[ ]**; Field **[ ]**; Soil **[ ]**; Other **[ ]**
Species:	Pseudomonas putida MIGULA (Bacteria)
Exposure Period:	16 hour(s)
Results:	NOEC (16 h) = 3,000 mg/L FOEC (16 h) = 10,000 mg/L NOEC: First Observed Effect Concentration, the highest measured substance concentration with an effect below 10 %. FOEC: First Observed Effect Concentration, the lowest measured substance concentration with an effect above 10 %.
Analytical monitoring:	Yes **[ ]** No **[X]** ? **[ ]**
Method:	Pseudomonas cell multiplication inhibition test in accordance to EU-Guideline EN ISO 10712 of December 1995
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Pseudomonas oxygen consumption inhibition test. Test was conducted at a concentration of 0, 3,000 and 10,000 mg/L. The study was carried out before 1990, at a time when GLP was not implemented. However, the study adhered to GLP comparable conditions.
Reference:	Henkel KGaA (1988), unpublished data (R-0100932).

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

No studies located.

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

INVERTEBRATES

Type of test:	static **[ ]**; semi-static **[X]**; flow-through **[ ]**; other (e.g. field test) **[ ]**; open-system **[ ]**; closed-system **[ ]**
Species:	Daphnia magna
Endpoint:	Mortality **[ ]**; Reproduction rate **[X]**; Other **[ ]**
Exposure period:	21 days.
Results:	EC50 (14-d, reproduction) > 100 mg/L EC50 (21-d, reproduction) > 100 mg/L NOEC (21-d, reproduction) = 100 mg/L (Calculated based based on nominal concentration)
Analytical monitoring:	Yes **[X]** No **[ ]** ? **[ ]**
Method:	OECD TG 211 (1997)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1-1.4.
Remarks:	A single exposure group (100 mg/L) against control group was studied. Mean cumulative numbers of juveniles produced per adult alive for 21 days: Control: 93.8, 100 mg/L: 91.8. Time-weighted means of measured concentration of test chemical (100 mg/L) during 21-d exposure: 94 mg/L. LC50 for parental Daphnia (14-d) > 100 mg/L LC50 for parental Daphnia (21-d) > 100 mg/L (Calculated based on nominal concentrations)
Reference:	Environment Agency of Japan (1998).

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No studies located.

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No studies located.

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No studies located.

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No studies located.

4.8 BIOTRANSFORMATION AND KINETICS

No studies located.

4.9 ADDITIONAL REMARKS

Remarks:	Toxicity towards tadpoles (Rana temporaria): Threshold concentration for complete narcosis at 5000 mg/L.
Reference:	Lipnick, R.L.(1988), ASTM Spec. Techn. Publ. 11, 468-489.

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

(a) Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	> 2,000 mg/kg bw.
Discriminating dose:	2,000 mg/kg bw (a limit dose level).
Method:	Referred to Remarks.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Method: OECD TG 401, EEC Directive 84/449/EEC, Annex V of the EEC Directive 67/548/EEC and Bewertung Wassergefährdender Stoffe, II Bestimmung der akuten oralen Saugetiertoxizität, Ad-hoc-Arbeitsgruppe I (Obmann: Dr. Niemitz), LTWS, Nr. 10 September 1979.
Reference:	Unichema Chemie B.V. (1988), unpublished data , RCC NOTOX 0831/1056.

(b) Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	6,400 – 12,800mg/kg bw.
Discriminating dose:	No data available.
Method:	Not specified.
GLP:	Yes **[ ]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose levels (800-12,800 mg/kg bw), 5 animal per dose level, 14 day observation, no necropsy. Time to death was 37min. Weakness and ataxia were observed.
Reference:	Fassett, D.W. (1955), Eastman Kodak Company, Corporate Health and Environment Laboratories, Unpublished data.

(c) Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	12,700 (11 mL) mg/kg bw (as $d^{20} = 1.1562$)
Discriminating dose:	580 (0.5 mL), 2,500 (2.2 mL), 5,500 (4.8 mL), 10,500 (9.1 mL), 14,600 (12.6 mL), 27,200 (23.5 mL), 52,800 (44.8 mL) mg/kg bw (as $d^{20} = 1.1562$)
Method:	Not specified.
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 7 dose levels (580-52,800 mg/kg bw), 5 animal per dose level, 24 day observation, no necropsy.
Reference:	Fassett, D.W. (1948), Eastman Kodak Company, Corporate Health And Environment Laboratories, Report No. 900256006, Unpublished data.

(d) Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rat
Value:	3,000 mg/kg bw
Discriminating dose:	No data available.
Method:	No data available.

	GLP:	Yes **[ ]** No **[ ]** ? **[X]**
	Test substance:	As prescribed by 1.1 - 1.4.
	Remarks:	Not stated.
	Reference:	AMA Arch Ind. Health, 21 (1960), 28. Sax, Dangerous Properties of Industrial Materials, 6th ed. p. 2605
(e)	Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
	Species/strain:	Mouse
	Value:	ca. 9,300 mg/kg bw
	Discriminating dose:	No data available.
	Method:	Refer to Remarks.
	GLP:	Yes **[X]** No **[ ]** ? **[ ]**
	Test substance:	Triacetin supplied by Matheson..
	Remarks:	The LD50 value was calculated from the given literature value of 8.0 mL/kg bw and the density of 1.16 g/cm^3. 7-Day observation period. Triacetin was administered at fixed level of 0.5, 1.0, 2.0, 4.0, 8.0 and 16 mL/kg bw.
	Reference:	Lawrence, W.H., Malik, M, Autian, J. (1974), J. Biomed. Mater. Res. 8, 11.
(f)	Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
	Species/strain:	Mouse/Swiss
	Value:	1,800 mg/kg bw (male) 1,100 mg/kg bw (female)
	Discriminating dose:	No data available.
	Method:	No data available.
	GLP:	Yes **[ ]** No **[ ]** ? **[X]**
	Test substance:	As prescribed by 1.1 - 1.4.
	Remarks:	Triacetin in 50 % ethylalcohol was administerd.
	Reference:	Gast, J.H. (1963), Fed. Proc. Fed. AM. Soc. Exp. Biol, 22 368.
(g)	Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
	Species/strain:	Mouse
	Value:	3,200 – 6,400 mg/kg bw
	Discriminating dose:	No data available.
	Method:	No data available.
	GLP:	Yes **[ ]** No **[ ]** ? **[X]**
	Test substance:	As prescribed by 1.1 - 1.4.
	Remarks:	Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose levels (1,600-25,600 mg/kg bw), 5 animal per dose level, 14 day observation period, no necropsy. Time to death was 6 min-1 hr. Weakness and ataxia were observed. Test was done in 1955.
	Reference:	Fassett, D.W. (1955), Eastman Kodak Company, Corporate Health and Environment Laboratories, Unpublished data.
(h)	Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
	Species/strain:	Mouse
	Value:	3,200 – 6,100 mg/kg bw
	Discriminating dose:	No data available.
	Method:	No data available.
	GLP:	Yes **[ ]** No **[ ]** ? **[X]**
	Test substance:	As prescribed by 1.1 - 1.4.
	Remarks:	Not stated.
	Reference:	Patty's Industrial Hygiene and Toxicology, 1983, Vol. 2A, p. 2321.

(i) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Mouse
Value: 3,000 mg/kg bw
Discriminating dose: No data available.
Method: No data available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: No data available.
Remarks: Not stated.
Reference: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA".

(j) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rabbit
Value: > 2,000 mg/kg bw
Discriminating dose: No data available.
Method: No data available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Not stated.
Reference: Material safety data sheet, dated 26-1-1994, Unichema International.

(k) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[X]**; Other **[ ]**
Species/strain: Frog
Value: 150 mg/kg bw
Discriminating dose: No data available.
Method: No data available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Not stated.
Reference: National Institute for Occupational Safety and Health (1976) cited in Food Cosmet. Toxicol. 16 (Suppl. 1), 879-882.

5.1.2 ACUTE INHALATION TOXICITY

(a) Type: LC_0 **[ ]**; LC_{100} **[ ]**; LC_{50} **[X]**; LCL_0 **[ ]**; Other **[ ]**
Species/strain: Rat/Wistar SPF-Cpb
Exposure time: 4 hours
Value: > 1.721 mg/L (analytical concentration)
Method: OECD 403.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: No data available.
Remarks: An aerosol of triacetin was tested. No vehicle was used. 100 % of particles < 5 um-diameter. Head only exposure. Five male and 5 female rats were tested in treated and control groups.
Effect: 0/5 males died, 0/5 females died.
No clinical symptoms were observed. No necropsy findings.
Reference: Bayer AG data. Report No. 13888 (P), 1985.

5.1.3 ACUTE DERMAL TOXICITY

(a) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rabbit
Value: > 5,000mg/kg bw
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: As prescribed by 1.1 - 1.4.

Remarks:	Not stated
Reference:	Bailey D.E. (1976); Report to RIFM, 21 May; cited in Opdyke D.L.J. (1978), Food Cosmet. Toxicol. 16 (Suppl. 1), 879-882.

(b) Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Rabbit
Value:	> 2,000 mg/kg bw
Method:	No data available.
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Not stated.
Reference:	Material safety data sheet, dated 26-1-1994; Unichema International.

(c) Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Guinea pig
Value:	> 20 mL/kg bw
Method:	No data available.
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 3 dose groups (0, 5 - 20 mL/kg bw), resp. 3, 3 and 3 animals per group, 14 days observation. Unit : mL/kg bw. Slight Oedema and erythema. No dead animal was observed. No evidence of skin absorption.
Reference:	Fassett, D.W. (1967), Eastman Kodak Company. Unpublished data, Corporate Health and Environment Laboratories.

(d) Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Guinea pig
Value:	> 20 mL/kg bw
Method:	No data available.
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 3 dose groups (0, 5 - 20 mL/kg bw), resp. 3, 3 and 3 animals per group, 14 days observation. Unit : mL/kg bw. Slight erythema and 1 - 3 erythema. Sparse hair and slight desquamation on high dose at one week. Sparse hair at 2 weeks. No evidence of absorption.
Reference:	Fassett, D.W. (1959), Eastman Kodak Company. Unpublished data, Corporate Health and Environment Laboratories.

(e) Type:	LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain:	Guinea pig
Value:	> 10 mL/kg bw
Method:	No data available.
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 3 dose groups (0, 5, 10 mL/kg bw), resp. 3, 3 and 2 animals per group, 14 days observation. Unit : mL/kg bw. No edema and slight redness.
Reference:	Fassett, D.W. (1955), Eastman Kodak Company. Unpublished data, Corporate Health and Environment Laboratories.

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

(a) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rat
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available.
Value: 800 – 1,600 mg/kg bw.
Method: No data available.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose groups (400-6,400 mg/kg bw), 5 animal per group, 14 days observation, no necropsy. Weakness, incoordination, gasping and unconsciousness were observed. Time to death was 6 –13 min. Test was done in 1955.
Reference: Fassett, D.W. (1955), Eastman Kodak Company, Corporate Health and Environment Laboratories, Unpublished data.

(b) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rat
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available.
Value: 800 – 1,600 mg/kg bw.
Method: No data available.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose groups (200-6,400 mg/kg bw), 12 animals per group, 14 days observation, no necropsy. Immediate squirming and gasping with cardiac arrest-death within 15min in high levels-others normal to moderately Weak-some initial gasping-no irritation at autopsy-testes normal. Test was done in 1967.
Reference: Fassett, D.W. (1967), Eastman Kodak Company, Unpublished data, Corporate Health and Environment Laboratories.

(c) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rat
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available.
Value: 1,600 mg/kg bw.
Method: No data available.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose groups (200 - 3,200 mg/kg bw), 2 animals per group, 14 days observation, necropsy at termination. Time to death was 1 - 4 hr.
Reference: Fassett, D.W. (1968), Eastman Kodak Company, Unpublished data, Corporate Health and Environment Laboratories.

(d) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rat
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available.
Value: 2,100 mg/kg bw.

Method: No data available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Not stated.
Remarks: A limited number of adult rats was employed.
Reference: Gast, J.H. (1963), Fed. Proc. Fed. AM. Soc. Exp. Biol, 22 368.

(e) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rat
Route of Administration: i.m. **[ ]**; i.p. **[ ]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[X]**; other **[ ]**
Exposure time: 15 Days after a single injection.
Value: 2.8 mL/kg bw.
Method: Refer to Remarks.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Not stated.
Remarks: Inbred albino rats weighing 200-300 g were used. At least 10 animals were used at each dose level (2.0, 3.0 4-10 mL/kg bw). Not more than 1 mL was given at one site. Animals receiving fatal doses usually died from 20 min to 3 or 4 hours after injection. Symptoms of marked depression, weakness, prostration, and labored respiration just before death were noted. Triacetin was slightly haemolytic and relatively incompatible with blood stream.
Reference: Li, R.C. et al.(1941) Proc. Soc. Exp. Biol. Med., 46 26-28.

(f) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Mouse/Swiss
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available.
Value: 1,700 mg/kg bw (male).
1,400 mg/kg bw (female).
Method: No data available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Not stated.
Remarks: Peripheral nerve and sensation (Spastic paralysis 13), with/without sensory change. Behavioural (Altered sleeptime; stiffness).
Reference: Gast, J.H. (1963), Fed. Proc. Fed. AM. Soc. Exp. Biol, 22 368.

(g) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Mouse/ICR
Route of Administration: i.m. **[ ]**; i.p. **[X]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available.
Value: ca. 1.52 mL/kg bw (male).
Method: Refer to Remarks.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Triacetin supplied by Matheson..
Remarks: 7-Day observation period. Triacetin was administered at fixed level of 0.5, 1.0, 2.0, 4.0, 8.0 and 16 mL/kg bw.
Reference: Lawrence W.H. et al. (1974), J. Biomed. Mater. Res., 8 11-34

(h) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Mouse
Route of Administration: i.m. **[ ]**; i.p. **[ ]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[X]**; other **[ ]**
Exposure time: No data available.
Value: 2.3 mL/kg bw.
Method: Refer to Remarks.
GLP: Yes **[ ]** No **[ ]** ? **[X]**

Test substance: Not stated.
Remarks: Inbred white mice weighing 17-21 g were used. At least 10 animals were used at each dose level (1.0, 2.0, 2.5, 3.0 mL/kg bw). Not more than 1 mL was given at one site. Animals receiving fatal doses usually died in from 20 min to 3 or 4 hours after injection. Symptoms of marked depression, weakness, prostration, and laboured respiration just before death were noted. Triacetin was slightly haemolytic and relatively incompatible with blood stream.
Reference: Li, R.C. et al.(1941) Proc. Soc. Exp. Biol. Med., 46 26-28.

(i) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[ ]**; LDL_0 **[X]**; Other **[ ]**
Species/strain: Guinea pig
Route of Administration: i.m. **[X]**; i.p. **[ ]**; i.v. **[ ]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: One week.
Value: 1.5 mL (1,740 mg)/kg bw.
Method: Refer to Remarks.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Data not available.
Remarks: Triacetin (0.5 or 1.0 mL) was injected into the upper part of the leg of the test animal. Lungs, thorax or respiration (dyspnoea) were affected.
Reference: Lipschitz, W.L. et al. (1942), J. Pharmacol. Exp. Ther. 76 189.

(j) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Mouse
Route of Administration: i.m. **[ ]**; i.p. **[ ]**; i.v. **[X]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available.
Value: 1,600 mg/kg bw.
Method: Refer to Remarks.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Synthetically prepared by esterification of glycerin and acetic acid.
Remarks: Ten mice at each dose were used. Triacetin was administered in volumes between 2 and 40 mL/kg bw as 25% emulsion in 5% glucose. Injection of triacetin caused almost immediate convulsions, failure of the righting reflexes and respiratory arrest.
Reference: Wretlind, A. (1957), Acta Physiol. Scand., 40 338.

(k) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Rabbit
Route of Administration: i.m. **[ ]**; i.p. **[ ]**; i.v. **[X]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available.
Value: 750 mL/kg bw.
Method: No data available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: No data available.
Remarks: Not stated.
Reference: Fassett, D.W. (1963), Eastman Kodak Company, Corporate Health and Environment Laboratories, Unpublished data.

(l) Type: LD_0 **[ ]**; LD_{100} **[ ]**; LD_{50} **[X]**; LDL_0 **[ ]**; Other **[ ]**
Species/strain: Dog
Route of Administration: i.m. **[ ]**; i.p. **[ ]**; i.v. **[X]**; infusion **[ ]**; s.c. **[ ]**; other **[ ]**
Exposure time: No data available.
Value: 1.5-2.0 mL/kg bw.

Method:	No data available.
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	No data available.
Remarks:	Not stated.
Reference:	Fassett, D.W. (1963), Eastman Kodak Company, Corporate Health and Environment Laboratories, Unpublished data.

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

(a)

Species/strain:	Rabbit
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification:	Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[X]**
Method:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion" and Off. J. Europ. Commun. 27, L251 (1984)
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Triacetin was tested for its primary skin irritation under occlusive conditions on the shaved back skin of 4 rabbits. After a contact time of 4 hours, the skin reactions were evaluated. Only one animal showed slight skin redness one hour after the application. The other animals had no skin reactions at all.
Reference:	Kaestner, W. (1988) Unpublished data Henkel KGaA. Rep. No. 880236.

(b)

Species/strain:	Guinea pig
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**; Not irritating **[ ]**
Classification:	Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[ ]**; Irritating **[X]**; Not irritating **[ ]**
Method:	Other (referred to Remarks).
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 3 dose groups, resp. 3, 3 and 2 animals per dose group, and 14 days observation for signs of irritation. Findings erythema, slight oedema, alopecia and desquamation under the conditions of the test. Test was done in 1967.
Reference:	Fassett, D.W. (1967), Corporate Health and Environment Laboratories, Eastman Kodak Company Unpublished data.

(c)

Species/strain:	Chicken/Hubbard Crossbred broiler (male)
Results:	Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification:	Irritating **[ ]**; Not irritating **[X]**; Risk of serious damage to eyes **[ ]**
Method:	Other (referred to Remarks).
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Test substance:	As prescribed by 1.1 - 1.4.
Remarks:	Tissue irritation evaluation was conducted by injecting 0.5 mL

of triacetin 1/2" deep in the right and left pectoral muscle of 7-8 week old chickens (six). Tissue irritation was evaluated at the injection sites at 1, 3, 7 days post injection. Triacetin caused very little irritation and was totally free of irritation by the 7th day after injection.

Reference: Hem S.L. et al. (1974-1975), Drug Dev Commun, 1,471-477.

(d) Species/strain: Human
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification: Highly corrosive (causes severe burns) **[ ]**; Corrosive (causes burns) **[ ]**; Irritating **[ ]**; Not irritating **[X]**
Method: Other: Patch Test (geschlossener Epicutan-Test).
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Not stated.
Reference: Epstein W. L. (1976), Report to RIFM, 27 May, cited in Opdyke D.L.J. (1978), Food Cosmet. Toxicol. 16 (Suppl. 1), 879-882.

5.2.2 EYE IRRITATION/CORROSION

(a) Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification: Irritating **[ ]**; Not irritating **[X]**; Risk of serious damage to eyes **[ ]**
Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: The conjunctival reactions were mild and disappeared totally within 6 to 24 hours after the application. According to the criteria in Off. J. Europ. Commun. 26 (L 257) 1983, the test substance doesn't need to be classified regarding its eye irritation potential. Reactions on the cornea and iris were not observed. As prescribed by 1.1 - 1.4.
Reference: Kaestner, W. (1988) Unpublished data Henkel KGaA. Rep. No. 880228.

(b) Species/strain: Rabbit (male and female albino rabbit)
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification: Irritating **[ ]**; Not irritating **[X]**; Risk of serious damage to eyes **[ ]**
Method: Draize procedure recommended by FDA (1965) and Other (referred to Remarks).
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Triacetin, Eastman Ref. No.256: Eastman Organic Chemicals, Rochester, New York 14650.
Remarks: This study compared the subjective Draize score to several objective procedures, namely, corneal thickness measurement, evaluation of corneal and conjunctival water content, and conjunctival and aqueous humour concentration of a dye bound to plasma proteins after intravenous injection. After a single instillation of 100 uL of undiluted triacetin in the rabbit eye, evaluation of the above parameter was made at 2 and 24 hr. Draize score and corneal thickness were further determined daily for additional days. A linear correlation was found between Draize total score and tissue changes. There was a significant correlation between Draize

corneal score corneal oedema or thickness only on Day one. Therefore, in addition to the standard Draize method, corneal thickness measurements should be performed.

Reference: Conquet, Ph. et al. (1977), Toxic. Appl. Pharmac., 39 129-139.

(c) Species/strain: Rabbit/Rsk:NZW
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification: Irritating **[ ]**; Not irritating **[X]**; Risk of serious damage to eyes **[ ]**
Method: Annex V, Part B of Directive 79/831/EEC and Annex VI, Part IID of Directive 83/467/EEC.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Purity: > 99 % (Fluca A.G., Buchs, Switzerland).
Remarks: The undiluted test substance (100 uL) was placed into one healthy eye of each animal. The other eye served as a blank. The eyes were not washed following instillation of triacetin. The eyes were examined and the grade of ocular reaction was recorded at 4, 24, 48, 72, 96, and 168 hr. Corneal swelling was determined by the ultrasonic pachometer technique. Good correlations were found between the mean percentage corneal swelling after 24, 48 and 72 hr and the mean corneal opacity (r=0.94) and erythema scores (r=0.93) after the same observation times.
Reference: Jacobs, G.A. and Martens, M.A. (1989), Fd Chem. Toxic., 27,255-258.

(d) Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**; Not irritating **[ ]**
Classification: Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method: Other (referred to Remarks).
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 2 rabbits received 1 drop of test substance in one eye. The eye of 1 rabbit was washed. Signs of irritation were evaluated 1, 24 and 48 hours after administration of the test substance.
Reference: Fassett, D.W. (1967), Corporate Health and Environment Laboratories, Eastman Kodak Company Unpublished data.

(e) Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification: Irritating **[ ]**; Not irritating **[X]**; Risk of serious damage to eyes **[ ]**
Method: Other (referred to Remarks).
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Purity: ca. 98%.
Remarks: Triacetin was applied topically to both eyes of albino rabbits (2 males and 2 females). Triacetin was applied 1, 3, 6, 7 and 13 times over the following periods: 2, 4, 7, 26 and 50 hours. The instilled volume (0.1m) was delivered with a micropipette. Evaluation was conducted in terms of corneal and conjunctival oedema, serum extravasion in conjunctivae and blood/aqueous humour barrier disruption. No effects were reported except a possible reduction in corneal dry weight. However, injection of the neat liquid into the rabbit cornea (0.1 mL) resulted in some irritation.
Reference: Lailer J. et al. (1976), Proc. Eur. Soc. Toxic., 17 336-350.

(f) Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[X]**
Classification: Irritating **[ ]**; Not irritating **[X]**; Risk of serious damage to eyes **[ ]**
Method: Other (referred to Remarks).
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Data not available.
Remarks: No irritation occurred when one drop (ca. 0.05 mL) of neat triacetin was applied to rabbit eyes every 2 seconds for 6 min. The ocular reaction was observed over a period of 7-14 days.
Reference: Hughes W. F. Jr. (1976), Bull. Johns Hopkins Hosp., 82 338-353.

(g) Species/strain: Rabbit
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[ ]**; Not irritating **[ ]**
Classification: Irritating **[ ]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method: Other (referred to Remarks).
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: No data available.
Remarks: No injury when tested on rabbits eyes.
Reference: Grant W.M. (1986), Toxicology of the Eye, 3rd ed. Springfield, IL: Charles C. Thomas Publisher, p 931.

(h) Species/strain: Data not available.
Results: Highly corrosive **[ ]**; Corrosive **[ ]**; Highly irritating **[ ]**; Irritating **[ ]**; Moderate irritating **[ ]**; Slightly irritating **[X]**; Not irritating **[ ]**
Classification: Irritating **[X]**; Not irritating **[ ]**; Risk of serious damage to eyes **[ ]**
Method: Other (referred to Remarks).
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Data not available.
Remarks: Not stated.
Reference: CHEMICAL DIVISION DI SISAS SPA CAVAGLIA".

5.3 SKIN SENSITISATION

(a) Type: Other.
Species/strain: Human.
Results: Sensitizing **[ ]**; Not sensitizing **[X]**; Ambiguous **[ ]**
Classification: Sensitizing **[ ]**; Not sensitizing **[ ]**
Method: Maximization test.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Substance concentration: 20 % in petrolatum; group size: 33 volunteers.
Reference: Epstein, WL (1976), Report to RIFM, cited in Opdyke D.L.J. (1978), Food Cosmet. Toxicol. 16 (Suppl. 1), 879-882.

(b) Type: Other.
Species/strain: Guinea pig.
Results: Sensitizing **[ ]**; Not sensitizing **[X]**; Ambiguous **[ ]**
Classification: Sensitizing **[ ]**; Not sensitizing **[X]**
Method: Not stated.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4.

Remarks: Method: Eastman Kodak Company, Laboratory of Industrial MedicineProtocol, 0.05 ml of 0.1M solution of test material in solvent composed of acetone, dioxane and guinea pig fat (7:2:1), dosing 3 times in 5 days, challenges at 1, 2 or 3 weeks after initial exposure. Vehicle control and a positive control (phenyl hydrazine) included. Test was conducted in 1955.
Reference: Eastman Kodak Company (1955). Unpublished data, Corporate Health and Environment Laboratories.

(c) Type: Other.
Species/strain: Human.
Results: Sensitizing **[ ]**; Not sensitizing **[ ]**; Ambiguous **[ ]**
Classification: Sensitizing **[ ]**; Not sensitizing **[ ]**
Method: Not specified.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: A contact eczema in humans caused by triacetin is reported.
Reference: Unna, P.J., Schulz (1963), K.H. Hautarzt 14, 423-25.

(d) Type: No data available.
Species/strain: Guinea pig.
Results: Sensitizing **[ ]**; Not sensitizing **[X]**; Ambiguous **[ ]**
Classification: Sensitizing **[ ]**; Not sensitizing **[X]**
Method: No data available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Not stated.
Reference: Patty's Industrial Hygiene and Toxicology, 1983, Vol. 2A, p.2321
Opdyke D.L.J. (1978), Food Cosmet. Toxicol. 16 (Suppl. 1), 879-882.

5.4 REPEATED DOSE TOXICITY

(a) Species/strain: Rat / Crj:CD (SD) IGS
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral (gavage)
Exposure period: (male) 44 days
(female) From 14 days before mating to day 3 of lactation (41-48days)
Frequency of treatment: One administration/day
Post exposure observation period: None.
Dose: 0, 40, 200, 1,000 mg/kg bw/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL: 1,000 mg/kg bw/day (male)
1,000 mg/kg bw/day (female)
LOAEL: Not determined under the conditions studied.
Method: OECD combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422).
Results: Triacetin had no effects on clinical signs, body weight, and food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in either sex. There were no haematological or blood chemical parameters in males. The NOAEL for repeat dose toxicity is thus considered to be 1,000 mg/kg bw/day for both sexes.
GLP: Yes **[X]** No **[ ]** ? **[ ]**

Test substance: Daihachi Chemical Industries Co. Ltd., purity: >98.2 wt %
Remarks: None
Reference: Ministry of Health & Welfare (MHW), Japan (1998), Toxicity Testing Reports of Environmental Chemicals vol.6 127-147.

(b) Species/strain: Rat
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Inhalation
Exposure period: 90 Days.
Frequency of treatment: Six hours per day for 5 days per week.
Post exposure observation period: 2 weeks.
Dose: 249 ppm (measured average concentration), 3 rats.
Control group: Yes **[ ]**; No **[X]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOAEL: 249 ppm (2,220 mg/m^3)/3 rats
LOAEL: Not stated.
Results: Average daily weight gain was 2.2 g/rat. No symptoms were noted at any time during the exposure, and all rats appeared to be normal. Haematological studies and urine analyses were done at intervals without finding anything abnormal in any of the animals. At the time of autopsy, no abnormalities attributable to the exposure were found. The weight of both liver and kidney when calculated as per cent of total body weight were found to be within the normal range. Under the conditions of the study no toxic effects caused by the inhalation of triacetin could be found.
Method: Not stated.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Plasticizer 88, Eastman Kodak Company.
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, whole body exposure to vaporized (heated at 150 °C) test substance. The range of exposure was 14 to 918 ppm (130 to 8190 mg/m^3).
Reference: Fassett, D.W. (1955), Corporate Health and Environment Laboratories, Eastman Kodak Company Unpublished data.

(c) Species/strain: Rat
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Inhalation
Exposure period: Five days.
Frequency of treatment: Six hours per day for 5 days per week.
Post exposure observation period: One week.
Dose: 73.72 ppm (660 mg/m^3), 8271 ppm (73,700 mg/m^3, saturated concentration) (measured average concentration)/3 rats
Control group: Yes **[ ]**; No **[X]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOAEL: 8271 ppm
LOAEL: Not available.
Results: No damage to the rats was caused in five days exposure to saturated vapours of triacetin.
Method: Other.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Plasticizer 88, Eastman Kodak Company.
Remark: Method: Eastman Kodak Company, Laboratory of Industrial

Medicine Protocol, whole body exposure to vaporized (heated) test substance.
Triacetin was heated at 315 °C and the animals were exposed to saturated vapours at the temperature (28 °C) of the animal chamber. After the 90 days tests on rats inhaling the vapours of triacetin, an exposure to saturated vapours for one week was done to determine the effect on rats. Autopsy was done for 1 rat only.

Reference: Fassett, D.W. (1955), Corporate Health and Environment Laboratories, Eastman Kodak Company Unpublished data.

(d) Species/strain: Rat
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[X]**
Route of Administration: Inhalation
Exposure period: Five days.
Frequency of treatment: Six hours per day.
Post exposure observation period: Data not available.

Dose: Saturated vapour (plus some mist).
Control group: Yes **[ ]**; No **[ ]**; No data **[X]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOAEL: Not stated.
LOAEL: Not stated.
Results: No symtoms or histopathology.
Method: Not stated.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Data not available.
Remark: Not stated.
Reference: Patty's Industrial Hygiene and Toxicology, 1983, vol 2A, 2321.

(e) Species/strain: Rat/ Sprague-Dawley (weanling)
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Oral feed.
Exposure period: 90 days
Frequency of treatment: Daily.
Post exposure observation period: Data not available.
Dose: The diet containing 20 %, 60 % of triacetin by weight or a mixture of triacetin and glycerol.
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL: 20 % of the diet (10 g/kg bw/day).
LOAEL: Not stated.
Results: The animals tolerated up to 20 % triacetin.
Greater percentage caused a decrease in weight gain. A large loss in weight and considerable mortality was associated with diets containing either glycerol or triacetin as 60% (31 g/kg bw/day) of the diet. A diet containing a mixture of 40% glycerol and 20 % triacetin was tolerated fairly well.
Thus, the toxicity of these two compounds was not additive.
Method: Data not available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: No data available.
Remark: Not stated.
Reference: Shapira, J. et al. (1969), Life Sci. Space Res. 7 123-129.

(f) Species/strain: Rat/ Sprague-Dawley

Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Route of Administration: Oral feed.
Exposure period: 13 weeks
Frequency of treatment: Daily.
Post exposure observation period: Data not available.
Dose: Total 60 % of the diet by weight with a mixture of triacetin (20 % or 30 %) and glycerol (40 % or 30 %) or propylene glycol (30 %).
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL: Not stated.
LOAEL: Not stated.
Results: Eight male rats were used with each diet. Growth occurred with all diets but relative to starch control it was best in diet containing glycerol (30 % or 40 %) and propylene glycol (30 % or 20 %). With triacetin present (20 % or 40 %) in the diets, growth was relatively poor. Compared to the control diet, liver enlargement occurred in all animals on experimental diets.
Method: Data not available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: No data available.
Remark: Not stated.
Reference: Shapira, J. et al. (1975), Proc. West. Pharm. Soc. 18 339-343.

(g) Species/strain: Rat/(weanling)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration: Oral feed.
Exposure period: 60 days
Frequency of treatment: Daily.
Post exposure observation period: Not stated.
Dose: 55 % of the diet by weight (77 % of the calories).
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL: Not stated.
LOAEL: Not stated.
Results: Triacetin allowed fair growth when compared to the control diet (coconut oil control).
Method: Four rats, two males and two females, weighing approximately 50 g at the age of weaning, were placed in wire bottom screen cages, and allowed to eat of the diet ad libitum. The food cups were weighed, cleaned, and refilled daily, and record kept of the food consumed.
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Eastman Kodak Company, Purity: No data available.
Remark: Not stated.
Reference: Cox, W. M. Jr. (1933), J. Biol. Chem. 103 777-790.

(h) Species/strain: Mouse/Swiss
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[X]**
Route of Administration: Oral gavage.
Exposure period: Three to five weeks.
Frequency of treatment: Not stated.
Post exposure observation period: Data not available.
Dose: Data not available.
Control group: Yes **[ ]**; No **[ ]**; No data **[X]**;

Concurrent no treatment **[ ]**; Concurrent vehicle **[ ]**; Historical **[ ]**
NOAEL: Not stated.
LOAEL: Not stated.
Results: No symptoms or histopathology.
Method: Preliminary studies showed growth depression, unkempt appearance but no effect on activity over the test period.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: Commercial preparations were used in 50 % ethanol.
Remark: Not stated.
Reference: Gast, J.H. (1963), Fed. Proc. Fed. AM. Soc. Exp. Biol, 22 368.

5.5 GENETIC TOXICITY IN VITRO

A BACTERIAL TEST

(a) **Preferred result**

Type: Bacterial reverse mutation assay
System of testing: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, Escherichia coli WP2 uvr A
Concentration: 0, 313, 625, 1,250, 2,500, 5,000 ug/plate (with and without S 9)
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results: Negative.
Cytotoxicity conc: With metabolic activation: Not observed up to 5,000 ug/plate (five strains)
Without metabolic activation: Not observed up to 5,000 ug/plate (five strains)
Precipitation conc: Not stated.
Genotoxic effects: Negative.

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: OECD Guidelines No.471 and 472 Guidelines for Screening Toxicity Testing of Chemicals (Japan)
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Daihachi Chemical Industries Co. Ltd., purity: >98.2 wt %
Remarks: For metabolic activation, mammalian metabolic preparations were used (pre-incubation assay).
Reference: Ministry of Health & Welfare (MHW), Japan (1998), Toxicity Testing Reports of Environmental Chemicals vol.6 127-147.

(b) Type: Bacterial reverse mutation assay
System of testing: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537,
Concentration: 0, 50, 150, 500, 1,500, 5,000 ug/plate (with and without S 9)
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results: Negative.
Cytotoxicity conc: With metabolic activation: Not observed up to 5,000 ug/plate (four strains).
Without metabolic activation: Not observed up to 5,000 ug/plate (four strains).
Precipitation conc: Not stated.
Genotoxic effects: Negative.

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Other (Referred to Remarks).

GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Method: According Ames et al. (1975), Mutation Research, 31 347-364, and modifications according Maron et al. (1981), Mutation Research, 88 343-350 and Maron et al. (1983), Mutation Research, 113 173-215.
Reference: Uniqema unpublished data (1988), ESL Sample No.S 16674 TO1 .

(c) Type: Bacterial reverse mutation assay
System of testing: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538.
Concentration: 0, 4, 20,100, 500, 2,500 ug/plate (with and without S 9).
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results: Negative.
Cytotoxicity conc: With metabolic activation: No data available.
Without metabolic activation: No data available.
Precipitation conc: Data not available.
Genotoxic effects: Negative.

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Ames test. Test conditions were not available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Triacetin suspension in water was prepared with the help of Tween 80.
Reference: Wallat, S. (1982), Unpublished data Henkel KGaA. Rep. No. TBD 820113.

(d) Type: Bacterial and yeast reverse mutation assay
System of testing: Salmonella typhimurium strains TA1535, TA1537, TA1538
Saccaromyces cerevisiae strain D4
Concentration: 0, 0.000325, 0.000650, 0.001300 w/v (with and without S 9) (bacteria)
0, 1.25, 2.50, 5.00 w/v (with and without S 9) (yeast)
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results: Negative.
Cytotoxicity conc: Without metabolic activation: The 50% survival level was determined. (bacteria) 0.001300 w/v (yeast) 5.00 w/v
Precipitation conc: Not stated.
Genotoxic effects: Negative.

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Other (Referred to Remarks).
GLP: Yes **[ ]** No **[X]** ? **[ ]**
Test substance: Triacetin (Kressco).
Remarks: LBI project No. 2468.
Reference: NTIS PB Report (1976), PB-257871.

(e) Type: Bacterial reverse mutation assay.
System of testing: Salmonella typhimurium strains TA1535.
Concentration: Data not available.
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results: Negative.
Cytotoxicity conc: With metabolic activation: No data available.
Without metabolic activation: No data available.

Precipitation conc: Data not available.
Genotoxic effects: Negative.

	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[ ]**	**[ ]**	**[X]**

Method: Data not available.
GLP: Yes **[ ]** No **[ ]** ? **[X]**
Test substance: As prescribed by 1.1 - 1.4.
Remarks: Not stated.
Reference: Inveresk Research International (1981), Musselburgh, EH21 7UB, Scotland, Project 705352.

B. NON-BACTERIAL IN VITRO TEST

(a) Type: In vitro Mammalian Chromosome aberration test
System of testing: Chinese hamster lung (CHL/IU) cells
Concentration: 0, 0.55, 1.1, 2.2 mg/mL
Metabolic activation: With **[ ]**; Without **[ ]**; With and Without **[X]**; No data **[ ]**
Results: Triacetin induced structural chromosome aberrations on short-term treatment with an exogenous metabolic activation system at the maximum concentration of 2.2 mg/mL (10 mM). However, triacetin decreased pH of the medium at 2.2 mg/mL on short-term treatment with an exogenous metabolic activation system. Therefore, chromosome aberrations induced with triacetin were likely to be caused by lowering pH of the medium rather than by damaging DNA per se. It is, however, recognized that changes in pH of the medium caused by triacetin can induce such artifacts in this assay. Polyploidy was not induced under any of the conditions on continuous and short-term treatment with and without an exogenous metabolic activation system.
Cytotoxicity conc: With metabolic activation: Not observed up to 1.2 mg/mL for 6-Hours exposure. The 50 % inhibition of cell proliferation was calculated to be 1.8 mg/mL.
Without metabolic activation: Not observed up to 2.2 mg/mL for 24- and 48- hours exposure.
Precipitation conc: Not observed.
Genotoxic effects: Equivocal.

	Clastogenicity			Polyploidy		
	+	?	-	+	?	-
With metabolic activation:	**[ ]**	**[ ]**	**[X]**	**[ ]**	**[ ]**	**[X]**
Without metabolic activation:	**[..]**	**[X]**	**[ ]**	**[ ]**	**[ ]**	**[X]**

Method: OECD Guidelines No.473 and Guidelines for Screening Toxicity Testing of Chemicals (Japan).

GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Daihachi Chemical Industries Co. Ltd., purity: >98.2 wt %
Remarks: Lowest concentration producing cytogenetic effects in vitro was 2.2 mg/mL with metabolic activation for short-term treatment. For metabolic activation, mammalian metabolic preparations were used.
Reference: Ministry of Health & Welfare (MHW), Japan (1998), Toxicity Testing Reports of Environmental Chemicals vol.6 127-147.

5.6 GENETIC TOXICITY IN VIVO

No studies located.

5.7 CARCINOGENICITY

No studies located.

5.8 TOXICITY TO REPRODUCTION

Type:	Fertility **[ ]**; One-generation study **[ ]**; Two-generation study **[ ]**; Other **[X]**
Species/strain:	Rat / Crj: CD (SD) IGS
Sex:	Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration:	Oral (gavage)
Exposure period:	(male) 44 days (female) from 14days before mating to day 3 of lactation (41-48days).
Post exposure observation period:	None.
Premating exposure period:	male: 14days, female: 14day
Duration of the test:	(male) 44 days (female) 41-48 days
Doses:	0, 40, 200, 1,000 mg/kg bw/day
Control group:	Yes **[X]**; No **[ ]**; No data **[ ]**; Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL Parental:	1,000 mg/kg bw/day (male) 1,000 mg/kg bw/day (female)
NOAEL F1 Offspring:	1,000 mg/kg bw/day
Results:	Triacetin did not exert any toxic effects on reproductive parameters including the mating index, fertility index, gestation length, number of corpora lutea or implantations, implantation index, gestation index, delivery index and parturition or maternal behaviour at delivery and lactation. General parental toxicity: Triacetin had no effects on clinical signs, body weight, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in either sex. There were no haematological or blood chemical parameters in males. The NOAEL for reproductive toxicity is thus considered to be 1,000 mg/kg bw/day for both sexes.
Method:	OECD 422, combined repeat dose and reproductive/developmental toxicity screening test..
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Daihachi Chemical Industries Co. Ltd., purity: >98.2 wt %
Remarks:	Not stated.
Reference:	Ministry of Health & Welfare (MHW), Japan (1998), Toxicity Testing Reports of Environmental Chemicals vol.6 127-147.

5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

Species/strain:	Rat / Crj: CD (SD) IGS
Sex:	Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration:	Oral (gavage)
Exposure period:	(male) 44 days

(female) from 14days before mating to day 3 of lactation(41-48days).
Frequency of treatment: One administration/day
Post exposure observation period: None.
Premating exposure period: male: 14days. , female: 14day
Duration of the test: (male) 44 days
(female) 41-48 days
Doses: 0, 40, 200, 1,000 mg/kg bw/day
Control group: Yes **[X]**; No **[ ]**; No data **[ ]**;
Concurrent no treatment **[ ]**; Concurrent vehicle **[X]**; Historical **[ ]**
NOAEL Maternal Toxicity: 1000 mg/kg bw/day
LOAEL Maternal Toxicity: Not determined under the conditions tested.
NOAEL Teratogenicity:1000 mg/kg bw/day
Results: No teratological or other developmental effects were observed at any dose.
General parental toxicity: Triacetin had no effects on clinical signs, body weight, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in either sex. There were no haematological or blood chemical parameters in males.
Pregnancy/litter data: Triacetin did not exert any toxic effects on reproductive parameters including the mating index, fertility index, gestation length, number of corpora lutea or implantations, implantation index, gestation index, delivery index and parturition or maternal behaviour at delivery and lactation
Toxicity to offspring: On examination of neonates, there were no significant differences in numbers of offspring or live offspring, the sex ratio, the live birth index, the viability index or body weight. No abnormal findings ascribable to the compound were found for external features, clinical signs or necropsy of the offspring.
The NOAEL for reproductive and developmental toxicity is considered to be 1,000 mg/kg bw/day for parental animals and offspring.
Method: OECD 422, combined repeat dose and reproductive/developmental toxicity screening test..
GLP: Yes **[X]** No **[ ]** ? **[ ]**
Test substance: Daihachi Chemical Industries Co. Ltd., purity: >98.2 wt %
Remarks: Not stated.
Reference: Ministry of Health & Welfare (MHW), Japan (1998), Toxicity Testing Reports of Environmental Chemicals vol.6 127-147.

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

(a) Type: Chemobiokinetics general studies.
Species/strain: Lamb / Southdown
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[X]**; No data **[ ]**
Route of Administration:Oral (feed)
Exposure period: 175 days.
Number of animals: 24 Male (rams), 24 female (ewes).
Method: The feeding experiment was factorially designed with two basal diets x two additives (triacetin and glycerol) x two levels of energy input x two sexes x 3 replications. Two basal diets consisted of (a) pelleted, finely ground Cayuga alfalfa hay harvested on May 25 near Ithaca, N.Y.,

partially dried in the field and finished by heat drying without weather damage, and (b) a pelleted mixture containing 50 % of the same hay and 50 % of yellow corn meal. Triacetin, employed as a source of acetic acid, was added to the basal diets in sufficient quantity to comprise 10 % of the total dietary dry matter. An amount of glycerol equivalent to that in triglyceride, triacetin, was added to the other diets.
Urine and faeces were collected totally, but separately, from each of the 48 animals during 7-day periods of months 2, 4 and 6 of the 175-day feeding periods.
Aliquots of faeces were analysed for the proximate chemical constituents and heat of combustion, and samples of urine were analysed for nitrogen. Urinary energy was estimated from urinary nitrogen and the amount of energy represented by the methane loss was computed from the amount of digestible dry matter.

Results: Each of two basal diets (pelleted, ground hay (H), and a pelleted mixture of the same hay and corn meal (HC) was supplemented singly with triacetin (Ac^3) and glycerol (G). A given animal was fed continuously one of the four diets at one of two levels of intake (approximately, 1 or 2.2 times the maintenance level) during the 175-day feeding period. The mean rates with which the metabolizable energy (ME) ingested above the maintenance level of intake was utilized for body-energy gain, were: (in %) H + Ac^3, 59.9; HC + G, 59.5; HC + Ac^3, 63.7; and HC + G, 61.8($p > 0.3$). Ignoring the kind of basal diet, utilization rates were 62.0and 61.2 % for the ME provided by the diets containing triacetin and glycerol, respectively. The mean pooled net utilization of ME for body-energy gain by females (65.5%) was markedly greater ($P<0.01$) than that by males (57.6 %). In a series of respiration-calorimetric experiments, the net utilization of ME provided by the acetic acid moiety of triacetin was 76.4%, between days 50 and 70 of continuous feeding.

(Conclusion) In a 175 day feeding study with sheep, 62 % of metabolic energy was utilized. Concentration of triacetin in food was 10 %. No data on toxicity are reported.

Test substance: Distillation Products Industries (Rochester, N.Y.),
bp=152-154 °C /22mm,
purity: data not available.

Remark: The efficiency of utilization for growth-fattening, of the energy of diets resulting in high (5.4 : 1) and low (3.1 : 1) ratio of acetic acid to propionic acid in the ruminal ingesta was determined in intact 24 male and 24 female sheep by means of a slaughter-analysis experiment.

Reference: Bull, L.S. et al. J. Nutr. 100 (1970), 262-276.

(b) Type: Other.
Results: Triacetin added directly to human food is affirmed as generally recognized as safe (GRAS) and classified as GRAS-substance.
Remark: Not stated.
Reference: 21 CFR 184.1901 (4/1/90).

(c) Type: Other.
Results: Substances classified as plasticizers, when migrating from food packaging shall including triacetin.
Remark: Not stated.
Reference: 21 CFR 181.27 (4/1/90).

(d) Type: Other.
Results: Triacetin used as a general purpose food additive in animal drugs, feeds, and related products are generally recognized as safe when used in accordance with good manufacturing or feeding practice.
Remark: Not stated.
Reference: 21 CFR 582.1901 (4/1/90).

(e) Type: Other.
Results: Pharmacological effect: decrease in blood pressure after i.v. application in cats.
Remark: Not stated.
Reference: Oetting W.F. (1960), Archs Ind. Health 21, 28-65.

(f) Type: Other.
Results: i.v. Study in dogs, lowest lethal value 1.5-2.0 cm^3/kg bw
i.v. Study in rabbits, lowest lethal value 0.75 cm^3/kg bw,
No effect dose 0.5 cm^3/kg bw
Remark: Not stated.
Reference: Patty's Industrial Hygiene and Toxicology, 1983, Vol. 2A, 2321.

(g) Type: Other.
Results: Laboratory rats have tolerated diets consisting of 50% triacetin. If hydrolysed, systematic acidosis is a possible consequence.
Remark: Not stated.
Reference: Gosselin R.E., R.P. Smith, H.C. Hodge (1984), Clinical Toxicology of Commercial Products. 5th edition, Baltimore: Williams and Wilkins, p. II-203.

(h) Type: Other.
Results: Neurotoxic effects of triacetin include tremors and convulsions.
Remark: Not stated.
Reference: O'Donoghue, J.L. (ed) (1985), Neurotoxicity of Industrial and Commercial Chemicals. Vol. I, Boca Raton, FL, CRC Press, Inc., 136.

(i) Type Other.
Results: Minimal tissue irritation in chicken pectoral muscle.
Remark: Not stated.
Reference: Hem S.L., Bright D.R., Banker G.S., Pogue J.P. (1975), Drug Dev. Commun. Vol. I, ISS 5, 471-7.

(j) Type Other.
Results: Triacetin will produce slight haemolysis in vitro.
Remark: Not stated.
Reference: Patty's Industrial Hygiene and Toxicology (1963), Volume II: Toxicology, 2nd ed., p.1870.

B. Toxicodynamics, toxicokinetics

(a) Type: Toxicokinetics
Species/strain: Dog / (mongrel)
Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[X]**
Method: Triacetin was administered intravenously to mongrel dogs (n=10) 2 weeks after surgical placement of blood-sampling catheters in the aorta and in the portal, hepatic, renal, and femoral veins. [1-^{14}C] Acetate was infused to

allow quantification of organ uptake of acetate as well as systemic turnover and oxidation. Systemic acetate turnover accounted for approximately 70 % of triacetin-derived acetate, assuming complete hydrolysis of the triglyceride.

Results: Approximately 80 % of systemic acetate uptake was rapidly oxidized. Significant acetate uptake was demonstrated in all tissues (liver, 559 ± 68; intestine, 342 ± 23; hindlimb, 89 ± 7; and kidney, 330 ± 37 umol/min). (Conclusion) During intravenous administration in dogs, the majority of infused triacetin undergoes intravascular hydrolysis, and the majority of the resulting acetate is oxidized. Thus, energy in the form of short-chain fatty acids can be delivered to a resting gut via intravenous infusion of a short-chain triglyceride.

Test substance: Data not available.

Remarks: Triacetin is a water-soluble short-chain triglyceride that may have a role as a parenteral nutrient.

Reference: Bleiberg, Batia et al., (1993), Am. J. Clin. Nutr. 58 908-911.

(b) Type: Toxicokinetics

Species/strain: Dog / (mongrel)

Sex: Female **[ ]**; Male **[ ]**; Male/Female **[ ]**; No data **[X]**

Method: Triacetin was infused at 47 umol·kg bw^{-1}·min^{-1} for 3 hr at an isocaloric rate in mongrel dogs (n=6) to test its effects on serum phosphorus, calcium, and magnesium metabolism. Arterial blood was sampled at 15-30 min intervals until the end of the study. Urine was collected during the equilibration period and again during triacetin infusion.

Results: There were no changes in serum P or Ca. The serum Mg concentration decreased from 0.7 ± 0.03 to 0.57 ± 0.03 mmol/L ($p < 0.001$) by 90 min and remained at this level for the remainder of the study.
The triacetin infusion did not influence fractional urinary Mg excretion; thus, the decrease in serum Mg was likely because of an increase in cellular transport of this cation.

(Conclusion) An isocaloric infusion of the short-chain triglyceride triacetin in dogs resulted in modest increases in plasma acetate but did not significantly affect serum Ca or P concentrations. Serum Mg decreased by approximately 20 %, probably because of cellular uptake rather than accelerated excretion.
Triacetin administered to dogs at a rate approximating resting energy expenditure
has no demonstrable adverse effects on mineral metabolism.

Test substance: Sigma (St. Louis, MO), purity: data not available.

Remarks: Triacetin is a water-soluble short-chain triglyceride that
may have a role as a parenteral nutrient.

Reference: Bailey, J.W. et al. (1989), Am. J. Clin. Nutr., 49 385-388.

(c) Type: Toxicokinetics

Species/strain: Rat / Sprague-Dawley

Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**

Method: Male Sprague-Dawley rats (n=22) were fed intravenously an isovolemic, isocaloric and isonitrogenous diet for 7 days. The lipid energy represented 30 % of the nonprotein energy with a short-chain triglyceride, triacetin representing 0 % (Lyposyn II; a long-chain triglyceride 20.1 g/L, Abbot Laboratories), 50 % (triacetin 15.2 g/L + Lyposyn II 10.0 g/L) or 90 % (triacetin 27.2 g/L + Lyposyn II 2.0 g/L) of the lipid energy. Plasma acetate concentration was determined as well as indicators of protein

metabolism: daily and cumulative nitrogen balance, whole body leucine kinetics and rectus muscle and liver fractional protein synthetic rates.

Results: Triacetin caused no overt toxic effects at any point during the study. As the proportion of triacetin in the diet increased from 0 to 50 or 90 % of the lipid energy, cumulative nitrogen balance increased 50 or 120 %, respectively ($p < 0.05$). Whole-body and tissue leucine kinetics (determined during the last 2.5 hr of the 7-day study) were unaffected by the lipid composition of the diet. Plasma acetate concentration was not significantly different among groups.
(Conclusion) These results indicate that incorporation of triacetin in nutritionally balanced total parenteral nutrition formulas improves nitrogen balance with no overt toxic effects.

Test substance: Data not available.

Remarks: Triacetin is a water-soluble short-chain triglyceride that may have a role as a parenteral nutrient.

Reference: Bailey, J.W. et al. (1992), J. Nutr., 122 1823-1829.

(d) Type: Toxicokinetics

Species/strain: Dog / (mongrel)

Sex: Female **[X]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**

Method: Animals received infusions of triacetin at 1.0 x estimated resting energy expenditure (REE), hyperenergetic triacetin at 1.5 x REE, glycerol, or saline during infusion of [1-^{14}C]leucine.
(Group 1) Six dogs were infused with a 5 % (vol: vol) triacetin solution at a rate (47 umol·kg bw^{-1}·min^{-1}) providing energy (12.6 kJ·kg bw^{-1}·h^{-1}) equal to REE in dogs.
(Group 2) Seven dogs were studied under identical conditions as those outlined for group 1, except they received triacetin at a rate (70 umol·kg bw^{-1}·min^{-1}) providing energy 50 % above REE.
(Group 3) Four dogs were studied under identical conditions, except they were infused with glycerol alone at a rate of 70 umol·kg bw^{-1}·min^{-1}, which is comparable to the amount of glycerol derived from the complete hydrolysis of the triacetin infused in group 2.
(Group 4) To control for tracer recycling, five animals were infused with saline for the duration of the study. Blood and breath samples were collected at 15-30-min intervals between - 45 and 180 min.

Results: During both triacetin infusions, plasma alfa-ketoisocaproate concentrations increased ($p < 0.05$). During triacetin infusion at 1.5 REE, the plasma leucine concentration decreased ($p < 0.05$) and leucine rate of appearance decreased by approximately 19 % ($p < 0.05$); this was significantly greater than the changes that occurred during triacetin at 1.0 x REE and glycerol ($p < 0.05$).
There was no difference in leucine oxidation between the dogs given triacetin at 1.0 x REE and control groups, whereas leucine oxidation decreased by 53 % during triacetin infusion at 1.5 REE glycerol ($p < 0.05$). Nonoxidative leucine disappearance, an indicator of protein synthesis, did not change in any of the studies.

(Conclusion) These results indicate that triacetin has effects on leucine metabolism similar to those previously reported with long-chain triglyceride emulsions.

Test substance: Sigma (St. Louis, MO), purity: data not available.

Remarks: Triacetin is a water-soluble short-chain triglyceride that

may have a role as a parenteral nutrient because of lack of toxicity and favourable effects on protein metabolism.

Reference: Bailey, J.W. et al. (1993), Am. J. Clin. Nutr., 58 912-916.

(e) Type: Toxicokinetics
Species/strain: Rat / Sheffield
Sex: Female **[ ]**; Male **[X]**; Male/Female **[ ]**; No data **[ ]**
Method: The procedure used in most experiments followed closely that outlined by Parsons et al. (1958) (J. Physiol. 144 387-402). The sacs of the everted intestine, the middle fifth of the combined jejunum and ileum was used. The sacs contained initially 1 mL of bicarbonate saline and shaken for 1 hr at 37 °C. Acetins, glucose, acetate, or metabolic inhibitors were added to the saline. At the end of the incubation, fluid transfer was estimated by weighing the sac and its contents, and acetate determinations were made on samples of the mucosal and serosal fluids.

Results:
(1) When triacetin, mono- and diacetins were incubated with the sacs of rats everted intestine, they entered the epithelial cells and were completely hydrolyzed to free glycerol and acetic acid. The activity of the preparation, as measured by acetate release, increased with the number of acetic acid residues in the glyceride. There is no absolute positional specificity, and all three ester linkages can be split.
(2) The rate limiting step in the process was the entry of glyceride into the epithelial cell.
(3) The three acetins entered the epithelial cells at the same rate.
(4) The acetate released appeared in higher concentrations on the serosal sides.

Test substance: British Drug Houses, purity: data not available.
Remarks: Volatile fatty acids, which released from acetins could be transferred into the cells by the rat intestine against a concentration gradient.
Reference: Barry, R.J.C. et al. (1966), J. Physiol. 185 667-683.

(f) Type: Toxicokinetics
Species/strain: Dog / (Mongrel)
Sex: Female **[X]**; Male **[ ]**; Male/Female **[ ]**; No data **[ ]**
Method: Triacetin was infused in mongrel dogs at isocaloric (N=6) or hypercaloric (ca. 1.5 REE, N=7) rates for 3 hr. Ketone body and glucose production rates were quantified with [$^{13}C_2$]acetoacetate and [^{3}H]glucose, respectively. An additional animals (N=4) were infused with glycerol to serve as control for the hypercaloric triacetin infusion. Energy expenditure was determined in the isocaloric experiments.
Results: Plasma acetate concentrations increased from basal levels to ca. 1 and ca. 13 mmol/L in the isocaloric and hypercaloric experiments, respectively. Plasma lactate and pyruvate concentrations decreased dramatically after 30 min of both isocaloric and hypercaloric triacetin infusions. Glucose production rates did not increase in either group, but glucose clearance decreased significantly in both groups ($p < 0.05$) over the last hour of triacetin infusion. Plasma ketone body concentrations increased from 1.4 to 3.5 and 1,8 to 13.5 umol/kg bw·min, respectively, during isocaloric and hypercaloric triacetin infusions. Resting energy expenditure increased from 3.0 ± 0.3 to 4.0 ± 0.5 kcal/kg bw·hr during isocaloric and hypercaloric triacetin infusions ($p < 0.05$).
(Conclusion) No evidence of acute toxicity such as irritability, somnolence, myoclonic activity, vomiting, diarrhoea, etc. was observed

during the 3-hr infusion of triacetin at either infusion rate. These studies indicate that triacetin can be administered to dogs at high rates without overt toxicity. The decrease in glucose clearance may represent competion between carbohydrate (glucose) and lipid (acetate). Triacetin infusion resulted in significant increases in ketone body production and concentration.

Test substance: Sigma (St. Louis, MO), purity: data not available.

Remarks: Triacetin is a water-soluble short-chain triglyceride that may have a role as a parenteral nutrient.

Reference: Bailey, J.W. et al. (1991), JPEN, 15 32-36.

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(a) Remark: Commercial triacetin may contain diacetin, as well as monoacetin, and when applied to human eyes causes severe burning, pain and much redness of the conjunctiva, but no injury. Diacetin causes considerably more discomfort than pure triacetin.

Reference: Grant W.M. (1986), Toxicology of the Eye, 3rd ed. Springfield, IL: Charles C. Thomas Publisher, p. 932.

(b) Remarks: Glycerol triacetate appears to be innocuous when swallowed, inhaled or in contact with the skin, but may cause slight irritation to sensitive individuals.

Reference: International Labour Office (1983), Encyclopedia of Occupational Health and Safety. Vols I & II, Geneva, Switzerland. International Labour Office, p. 973.

(c) Remarks: A case of allergic contact eczema in a 29 year-old patient in a cigarette factory is reported, which was based on sensitisation towards the triacetin used for the production of cigarette filters. The allergy was demonstrated in a patch test. In addition to triacetin, the di- and mono acetate of glycerol also produced positive tests. It seems reasonable to regard the reaction as an expression of a group sensitisation towards glycerol acetate.

Test substance: Purity: 99 %.

Reference: Unna, P.J. and Schulz, K. H. (1963), Der Hautarzt, 14 423-425.

(d) Remarks: A Duhring-chamber test was conducted on 20 healthy volunteers
The test substance was applied as 50% dilution for 24 hours.

Result: Only very mild skin reactions were observed. The substance has good skin compatibility.

Reference: Matthies, W. (1988), Henkel KGaA., unpublished data. Rep. No. 880716.

(e) Remarks: No skin reactions occurred in 33 volunteers treated with 20% triacetin in petrolatum in an attempt to induce skin sensitisation using the maximization test.

Reference: Klingman, A.M. (1966), J. Invest. Derm., 47 393 and Klingman, A.M. & Epstein W. (1975), Contact Dermatitis, 1231.

(f) Remarks: Triacetin (20 % in petrolatum) did not irritate the skin of 33 volunteers when tested in a 48-hr covered patch test.

Reference: Epstein, W.L. (1976), Report to RIFM, 27 May, unpublished data.

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Appendix : Parameters used in calculation of distribution by Mackay level III fugacity model.
(Part 1)

Physico-Chemical Properties
(water solubility : 70g/L)

Chemical		Triacetin	Method
Molecular weight		218.21	calculated
Melting point [℃]		3	unkown
Vapour pressure [Pa]		0.331	unkown
Water solubility [g/m^3]		70000	measured
log Kow		0.21	measured
Half life [h]	In air	48	estimated
	In water	168	measured
	In soil	504	estimated
	In sediment	504	estimated

Temp. [℃]	25

Emission Scenario

Scenario	emission rate [kg/h]		
case	b.air E_1	b.w. E_2	b.soil E_3
1	1000	0	0
2	0	1000	0
3	0	0	1000
4	600	300	100
5	333	333	333

Theoretical Distribution of Triacetin

Compartment	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
	100% to air	100% to water	100% to soil	60% to air, 30% to	Equal emission
				water, 10% to soi	air:water:soil=1: 1: 1
Air	0.9%	0.0%	0.0%	0.6%	0.3%
Water	20.0%	99.7%	12.9%	31.6%	30.1%
Soil	79.1%	0.0%	87.1%	67.8%	69.5%
Sediment	0.1%	0.3%	0.0%	0.1%	0.1%

Environmental
Parameter

		volume [m3]	depth [m]	area [m2]	organic carbon	lipid content [-]	density [kg/m3]	residense time [h]
Bulk Air	air	1E+13					1.2	100
	water	2E+03						
	total	1E+13	1000	1E+10				
Bulk Water	water	2E+10					1000	1000
	susp. particles	1E+06			0.0		1500	
	fish	2E+05				0.05	1000	
	total	2E+10	10	2E+09				
Bulk Soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
Bulk Sediment	water	8E+07					1000	
	solid	2E+07			0.06		2400	50000
	total	1E+08	0.05	2E+09				

Scenario	emission rate [kg/h]			fugacity [Pa]				concentration [g/m^3]			
case	b.air E_1	b.wat. E_2	b.soil E_3	b.air f_1	b.w. f_2	b.soil f_3	b.sed. f_4	b.air C_1	b.wat. C_2	b.soilC_3	b.sed.C_4
1	1000	0	0	4.3E-06	2.0E-08	3.0E-06	1.3E-08	3.8E-07	4.3E-03	2.1E-01	2.2E-03
2	0	1000	0	1.7E-10	4.6E-08	1.2E-10	2.9E-08	1.5E-11	9.7E-03	8.6E-06	5.1E-03
3	0	0	1000	5.1E-08	1.6E-08	4.2E-06	1.0E-08	4.5E-09	3.5E-03	2.9E-01	1.8E-03
4	600	300	100	2.6E-06	2.8E-08	2.2E-06	1.8E-08	2.3E-07	5.8E-03	1.6E-01	3.0E-03
5	333	333	333	1.4E-06	2.8E-08	2.4E-06	1.8E-08	1.3E-07	5.8E-03	1.7E-01	3.0E-03

Scenario	amount [kg]				total	transformation rate by reaction [kg/h]				transformation rate by advection [kg/h]		
case	b.air m_1	b.wat. m_2	b.soil m_3	b.sed. m_4	[kg]	b.air	b.wat. R_2	b.soil R_3	b.sed. R_4	b.air A_1	b.wat. A_2	b.sed. A_4
1	3.8E+03	8.6E+04	3.4E+05	2.2E+02	4.3E+05	5.4E+01	3.5E+02	4.7E+02	3.1E-01	3.8E+01	8.6E+01	4.5E-03
2	1.5E-01	1.9E+05	1.4E+01	5.1E+02	2.0E+05	2.2E-03	8.0E+02	1.9E-02	7.0E-01	1.5E-03	1.9E+02	1.0E-02
3	4.5E+01	6.9E+04	4.7E+05	1.8E+02	5.4E+05	6.6E-01	2.9E+02	6.4E+02	2.5E-01	4.5E-01	6.9E+01	3.6E-03
4	2.3E+03	1.2E+05	2.5E+05	3.0E+02	3.7E+05	3.3E+01	4.8E+02	3.5E+02	4.2E-01	2.3E+01	1.2E+02	6.1E-03
5	1.3E+03	1.2E+05	2.7E+05	3.0E+02	3.9E+05	1.8E+01	4.8E+02	3.7E+02	4.2E-01	1.3E+01	1.2E+02	6.1E-03

Scenario	transport rate between spheres [kg/h]						
case	air→ water	water→ air	air→ soil	soil→ air	soil→ water	water→ sed.	sed.→ water
1	1.8E+02	1.8E-02	7.3E+02	8.8E+00	2.6E+02	8.6E-01	5.5E-01
2	7.5E-03	4.1E-02	3.0E-02	3.6E-04	1.0E-02	1.9E+00	1.2E+00
3	2.2E+00	1.4E-02	8.8E+00	1.2E+01	3.5E+02	6.9E-01	4.4E-01
4	1.1E+02	2.4E-02	4.4E+02	6.5E+00	1.9E+02	1.2E+00	7.4E-01
5	6.2E+01	2.4E-02	2.5E+02	7.0E+00	2.0E+02	1.2E+00	7.4E-01

Z and D values

	Z_B [mol/m^3·Pa]	D_R [mol/Pa·h]	D_A [mol/Pa·h]
Bulk Air (1)	4.0E-04	5.8E+07	4.0E+07
Bulk Water (2)	8.0E+02	6.6E+10	1.6E+10
Bulk Soil (3)	2.7E+02	5.9E+08	0.0E+00
Bulk Sediment (4	6.6E+02	9.0E+07	1.3E+06

D_{12} [mol/Pa·h]	D_{21} [mol/Pa·h]	D_{13} [mol/Pa·h]	D_{31} [mol/Pa·h]
1.6E+08	4.0E+06	6.6E+08	1.3E+07

D_{32} [mol/Pa·h]	D_{24} [mol/Pa·h]	D_{42} [mol/Pa·h]
3.2E+08	1.6E+08	1.6E+08

Appendix: Parameters used in calculation of distribution by Mackay level III fugacity model.
(Part 2)

Physico-Chemical Properties

(water solubility .58g/L)

Chemical		Triacetin	Method
Molecular weight		218.21	calculated
Melting point [°C]		3	unkown
Vapour pressure [Pa]		0.331	unkown
Water solubility [g/m^3]		58000	measured
log Kow		0.21	measured
Half life [h]	In air	48	estimated
	In water	168	measured
	In soil	504	estimated
	In sediment	504	estimated

Temp. [°C]	25

Emission Scenario

Scenario	emission	rate [kg/h]	
case	b.air E_1	b.w. E_2	b.soil E_3
1	1000	0	0
2	0	1000	0
3	0	0	1000
4	600	300	100
5	333	333	333

Theoretical Distribution of Triacetin

Compartment	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
	100% to air	100% to water	100% to soil	60% to air, 30% to water, 10% to soi	Equal emission air:water:soil=1: 1: 1
Air	1.1%	0.0%	0.0%	0.7%	0.4%
Water	19.9%	99.7%	12.9%	31.7%	30.2%
Soil	79.0%	0.0%	87.1%	67.5%	69.4%
Sediment	0.1%	0.3%	0.0%	0.1%	0.1%

Environmental Parameter

		volume [m^3]	depth [m]	area [m^2]	organic carbon content [-]	lipid content [-]	density [kg/m^3]	residense time [h]
Bulk Air	air	1E+13					1.2	100
	water	2E+03						
	total	1E+13	1000	1E+10				
Bulk Water	water	2E+10					1000	1000
	susp. particles	1E+06			0.0		1500	
	fish	2E+05				0.05	1000	
	total	2E+10	10	2E+09				
Bulk Soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
Bulk Sediment	water	8E+07					1000	
	solid	2E+07			0.06		2400	50000
	total	1E+08	0.05	2E+09				

Scenario	emission rate [kg/h]			fugacity [Pa]				concentration [g/m^3]			
case	b.air E_1	b.wat. E_2	b.soil E_3	b.air f_1	b.w. f_2	b.soil f_3	b.sed. f_4	b.air C_1	b.wat. C_2	b.soilC_3	b.sed.C_4
1	1000	0	0	5.0E-06	2.4E-08	3.6E-06	1.5E-08	4.5E-07	4.2E-03	2.1E-01	2.2E-03
2	0	1000	0	2.5E-10	5.6E-08	1.8E-10	3.5E-08	2.2E-11	9.7E-03	1.0E-05	5.1E-03
3	0	0	1000	7.1E-08	2.0E-08	5.0E-06	1.3E-08	6.2E-09	3.5E-03	2.9E-01	1.8E-03
4	600	300	100	3.0E-06	3.3E-08	2.7E-06	2.1E-08	2.7E-07	5.8E-03	1.5E-01	3.0E-03
5	333	333	333	1.7E-06	3.3E-08	2.9E-06	2.1E-08	1.5E-07	5.8E-03	1.7E-01	3.0E-03

Scenario	amount [kg]				total	transformation rate by reaction [kg/h]				transformation rate by advection [kg/h]		
case	b.air m_1	b.wat. m_2	b.soil m_3	b.sed. m_4	[kg]	b.air	b.wat. R_2	b.soil R_3	b.sed. R_4	b.air A_1	b.wat. A_2	b.sed. A_4
1	4.5E+03	8.4E+04	3.3E+05	2.2E+02	4.2E+05	6.4E+01	3.5E+02	4.6E+02	3.0E-01	4.5E+01	8.4E+01	4.4E-03
2	2.2E-01	1.9E+05	1.6E+01	5.1E+02	2.0E+05	3.1E-03	8.0E+02	2.2E-02	7.0E-01	2.2E-03	1.9E+02	1.0E-02
3	6.2E+01	6.9E+04	4.7E+05	1.8E+02	5.4E+05	9.0E-01	2.9E+02	6.4E+02	2.5E-01	6.2E-01	6.9E+01	3.6E-03
4	2.7E+03	1.2E+05	2.5E+05	3.0E+02	3.7E+05	3.9E+01	4.8E+02	3.4E+02	4.2E-01	2.7E+01	1.2E+02	6.0E-03
5	1.5E+03	1.2E+05	2.7E+05	3.0E+02	3.8E+05	2.2E+01	4.8E+02	3.7E+02	4.2E-01	1.5E+01	1.2E+02	6.0E-03

Scenario	transport rate between spheres [kg/h]						
case	air→ water	water→ air	air→ soil	soil→ air	soil→ water	water→ sed.	sed.→ water
1	1.8E+02	2.1E-02	7.2E+02	1.0E+01	2.5E+02	8.4E-01	5.4E-01
2	8.9E-03	4.9E-02	3.5E-02	4.9E-04	1.2E-02	1.9E+00	1.2E+00
3	2.5E+00	1.7E-02	1.0E+01	1.4E+01	3.5E+02	6.9E-01	4.4E-01
4	1.1E+02	2.9E-02	4.3E+02	7.5E+00	1.9E+02	1.2E+00	7.4E-01
5	6.1E+01	2.9E-02	2.4E+02	8.1E+00	2.0E+02	1.2E+00	7.4E-01

Z and D Values

	Z_B [$mol/m^3 \cdot Pa$]	D_R [$mol/Pa \cdot h$]	D_A [$mol/Pa \cdot h$]
Bulk Air (1)	4.0E-04	5.8E+07	4.0E+07
Bulk Water (2)	8.0E+02	6.6E+10	1.6E+10
Bulk Soil (3)	2.7E+02	5.9E+08	0.0E+00
Bulk Sediment (4	6.6E+02	9.0E+07	1.3E+06

D_{12} [$mol/Pa \cdot h$]	D_{21} [$mol/Pa \cdot h$]	D_{13} [$mol/Pa \cdot h$]	D_{31} [$mol/Pa \cdot h$]
1.6E+08	4.0E+06	6.6E+08	1.3E+07

D_{32} [$mol/Pa \cdot h$]	D_{24} [$mol/Pa \cdot h$]	D_{42} [$mol/Pa \cdot h$]
3.2E+08	1.6E+08	1.6E+08

ROBUST STUDY SUMMARIES
Triacetin CAS No. 102–76–1

Sponsor Country: Japan

DATE: 9 August 2002

PHYSICAL/CHEMICAL ELEMENTS

MELTING POINT

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Eastman Chemical Company, Purity: 99 %, Impurity: Not stated.

METHOD

- **Method/guideline:** Not stated.
- **GLP:** Not stated.
- **Year:** Not stated.
- **Remarks:** Not stated.

RESULTS

- **Melting point value:** 3 °C (276 K).
- **Decomposition:** Not stated.
- **Sublimation:** Not stated.
- **Remarks:** The temperature of 3 °C is a true thermodynamic melting point of crystalline triacetin, whereas the temperatures of - 60 to - 78 °C, those described elsewhere are a glass transition temperature.

CONCLUSIONS

Melting point is 3 °C (276 K).

DATA QUALITY

- **Reliabilities:** Valid with restriction.
- **Remarks:** The Sigma-Aldrich Library of Regulatory and Safety Data. Data confirmed by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES (Free Text)

Chemicals Evaluation and Research Institute (Kurume, Japan) (1998), Test No. 80919BK.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

BOILING POINT

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Eastman Chemical Company, Purity: 99 %, Impurity: Not stated.

METHOD

- **Method:** Not stated.
- **GLP:** Not stated.
- **Year:** Not stated.
- **Remarks:** Not stated.

RESULTS

- **Boiling point value:** 258 °C
- **Pressure:** 1,013
- **Pressure unit:** hPa
- **Decomposition:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

Boiling point is 258 °C at 1,013hPa.

DATA QUALITY

- **Reliabilities:** Valid with restriction.
- **Remarks:** The Sigma-Aldrich Library of Regulatory and Safety Data. Data Confirmed by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES

Chemicals Evaluation and Research Institute (Kurume, Japan) (1998), Test No. 80919BK.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

VAPOR PRESSURE

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Unavailable.

METHOD

- **Method:** Not stated.
- **GLP:** Not stated.
- **Year:** Not stated.
- **Remarks:** Not stated.

RESULTS

- **Vapor Pressure value:** 0.003306 hPa (0.00248 mmHg)
- **Temperature:** 25 °C
- **Decomposition:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

Vapor pressure is 0.003306 hPa at 25 °C.

DATA QUALITY

- **Reliabilities:** Valid with restriction.
- **Remarks:** SRC recommended value.

REFERENCES

Design Institute for Physical Property Data (1989); American Institute of Chemical Engineers, Hemisphere Pub. New York, NY, Vol. 4.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

PARTITION COEFFICIENT

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Tokyo Kasei, Lot No. GB 01(Class: TCI-GR), Purity: > 98 %, Impurity: Not stated. Stability during use confirmed by IR spectrometry. Kept at cold temperature until use.

METHOD

- **Method/guideline:** OECD TG 107 (Shake Flask Method).
- **GLP:** Yes.
- **Year:** 1998.
- **Remarks field for Test Conditions**
  Not stated.

RESULTS

- **Log P_{ow} :** 0.21
- **Temperature:** 25°C ±1°C
- **Remarks:** Test condition: Test was conducted in duplicate under the following three conditions. Test chemical was analyzed by HPLC.

Test condition	**Condition-1**	**Condition-2**	**Condition-3**
1-Octanol saturated with water	5 mL	10 mL	20 mL
Water saturated with 1-octanol	30 mL	25 mL	15 mL
Test chemical added to 1-octanol saturated with water			
	5.95 mg	5.95 mg	5.95 mg
Test results	**Log Pow**		
	a	**b**	**Mean ±SD**
Condition-1	0.22	0.21	
Condition-2	0.21	0.19	0.21
Condition-3	0.21	0.21	

CONCLUSIONS

Log P_{ow} is 0.21.

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES

Chemicals Evaluation and Research Institute (Kurume, Japan) (1998), Test No. 80919BK.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

WATER SOLUBILITY (1)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks**: Source: Tokyo Kasei, Lot No. GB 01(Class: TCI-GR), Purity: > 98 %, Impurity: Not stated. Stability during use confirmed by IR spectrometry. Kept at cold temperature until use.

METHOD

- **Method:** OECD TG 105 (flask method).
- **GLP:** No.
- **Year:** 1998.
- **Remarks:** Each test solution was shaken for 24, 48 and 72 hours at 30 °C and then allowed to stand for 24 hours at 25 °C.

RESULTS

- **Value:** 70 g/L at 25 °C±1°C
- **Description of solubility:** Soluble.
- **pH value:** No dissociation group.
- **pKa value:** There is no pertinent functional group.
- **Remarks:** Not stated.

Solubility Test results

Shaking time (hr)	Concentration (g/L)	Mean (each shaking time) (g/L)	Mean (24 –72 hr) (g/L)
24	72	70	70
	68		
48	73	70	
	68		
72	71	71	
	70		

CONCLUSIONS

This chemical is soluble in water.

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks:** Well conducted study except GLP, carried out by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES

Chemicals Evaluation and Research Institute (Kurume, Japan), Test No. 80919BK (1998).

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

WATER SOLUBILITY (2)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks**: Source: Data not available.

METHOD

- **Method:** Unknown.
- **GLP:** Unknown.
- **Year:** Unknown.
- **Remarks:** Not stated.

RESULTS

- **Value:** 58 g/L at 25 °C
- **Description of solubility:** Soluble.
- **pH value:** No dissociation group.
- **pKa value:** There is no pertinent functional group.
- **Remarks:** Not stated.

CONCLUSIONS

This chemical is soluble in water.

DATA QUALITY

- **Reliabilities:** Valid with restriction.
  Remarks: This value is quoted elsewhere to calculate a vapour pressure, a Henry's constant and BCF (Lyman, W.J. et al. (1990), Handbook of Chemical Property Estimation).

REFERENCES

Riddick J.A. et al. (1986), Techniques of Chemistry, 4th ed.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

ENVIRONMENTAL FATE AND PATHWAYS ELEMENTS

STABILITY IN WATER

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Tokyo Kasei, Lot No. GB 01(Class: TCI-GR), Purity: > 98 %, Impurity: Not stated. Stability during use confirmed by IR spectrometry. Kept at cold temperature until use.

METHOD

- **Method/guideline:** OECD TG111
- **Type :** Hydrolysis as a function of pH
- **GLP:** Yes
- **Year:** 1998
- **Remarks:** No hydrolysis of test chemical was observed at pH 4 at 50°C ± 1°C for 5 days. Hydrolysis rates at pH 7 (50, 60, 70°C ± 1°C) and at pH 9 (30, 40 °C± 1°C) were determined, respectively. They were extrapolated to 25 °C using Arrhenius relationship. Half-life at 25 °C was calculated from the rate constant.

RESULTS

- **Nominal:** ca. 1,020 mg/L
- **Measured value:**

pH	Rate constant (hr^{-1})	Half-life
pH 7	4.72×10^{-4}	60.4 (day)
pH 9	4.21×10^{-2}	16.5 (hour)

- **Degradation:** No hydrolysis occurred in 5 days at 50 °C at pH 4. At pH 7 and 9, test chemical was hydrolysed at all temperatures studied.
- **Half-life ($t_{(1/2)}$):** At pH 7 and 9, the rate constants were calculated as 4.72×10^{-4} and 4.21×10^{-2}, respectively. By extrapolating against temperature, the half-lives at 25 °C were calculated to be 60.4 days and 16.5 hours, respectively.
- **Breakdown products:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

This chemical is stable to chemical hydrolysis in aqueous water at pH 4 under the condition studied, although it is hydrolysed at pH 7 and 9 at 25 °C with half-life of 60.4 days and 16.5 hours, respectively.

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES

Chemicals Evaluation and Research Institute (Kurume, Japan) (1998), Test No. 80919BK.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Not applicable.

METHOD

- **Test :** Calculation
- **Method :** Mackay Level III Fugacity Model.
- **Year :** 2002
- **Remarks :** The parameters used are shown in Appendix.

RESULTS

- **Media :**
- **Estimated Distribution under three emission scenarios :**

Predicted distribution of triacetin using Fugacity level III under four emission scenarios

(1) Results from water solubility of 70 g/L

Compartment	Release 100 % to air	Release 100 % to water	Release 100 % to soil	Equal emission scenario (1:1:1)
Air	0.9 %	0.0 %	0.0 %	0.3 %
Water	20.0 %	99.7 %	12.9 %	30.1 %
Soil	79.1 %	0.0 %	87.1 %	69.5 %
Sediment	0.1 %	0.3 %	0.0 %	0.1 %

(2) Results from water solubility of 58 g/L

Compartment	Release 100 % to air	Release 100 % to water	Release 100 % to soil	Equal emission scenario (1:1:1)
Air	1.1 %	0.0 %	0.0 %	0.4 %
Water	19.9 %	99.7 %	12.9 %	30.2 %
Soil	79.0 %	0.0 %	87.1 %	69.4 %
Sediment	0.1 %	0.3 %	0.0 %	0.1 %

- **Remarks:** Hydrolysis may be a major degradation process for triacetin in alkaline waters and in moist alkaline soils. Triacetin is readily biodegradable and biodegraded to glycerol and acetic acid, which, in turn, is degraded to carbon dioxide. Based on a vapour pressure of 0.003306 hPa at 25 °C, triacetin is expected to exist almost entirely in the vapour-phase in the ambient atmosphere. Triacetin leach readily in soil based on an estimated K_{OC} value of 10.5.

CONCLUSIONS

The calculation revealed that in the case of 100 % release to water, more than 99 % of triacetin is expected to stay in water due to its high solubility and a low vapour pressure, but if it is released into air and/or soil, it is likely to be distributed in other compartments. The results also show that approximately one third of triacetin will be distributed in water, whereas two third will stay in soil when applied to the equal emission scenario to water, soil and sediment (1:1:1). In addition, the fugacity model using 70 g/L reveals that there is little change in the distribution of triacetin between three compartments when compared to those obtained from 58 g/L.

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks:** Not stated.

REFERENCES

Daicel Chemical Industries Ltd. (2002), unpublished report.

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

BIODEGRADATION

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Tokyo Kasei, Lot No. GB 01(Class: TCI-GR), Purity: > 98 %, Impurity: Not stated. Stability during use confirmed by IR spectrometry. Kept at cold temperature until use.

METHOD

- **Method/guideline:** OECD TG 301C, Modified MITI Test (I)
- **Test Type:** Aerobic
- **GLP:** Yes
- **Year:** 1998
- **Contact time:** 14 days
- **Inoculum:** Sludge samples were collected from the 10 sites such as sewage treatment works, industrial wastewater treatment works, rivers, lakes, and sea throughout Japan and mixed thoroughly. A filtrate (500 mL) of the supernatant of the mixed sludge was then mixed with 5 L of the filtered supernatant of an activated sludge in the present use.

  After the combined sludge solution (pH adjusted at 7.0 ± 1.0) was aerated for 30 min., the supernatant corresponding 1/3 of the whole volume was discarded. An equal volume of pure water was then added to the remaining portion and the supernatant (final concentration: 0.1%) of the resulting sludge solution was mixed with sterile mineral medium and continuously aerated at 25 ± 2°C to allow minimization of residual dissolved organic carbon according to the procedure outlined in the TG.

  The test was conducted in triplicate with triacetin in sterile mineral medium at 100 mg/mL and with a small volume of the activated sludge to give a final MLSS concentration of 30 mg/L in 300 mL.

- **Remarks:** A blank control (sterile mineral medium only), positive control (aniline as reference compound at 100 mg/L) and triacetin control (triacetin in pure water at 100 mg/L) in 300 mL were incubated simultaneously.

  Oxygen consumption resulting from biodegradation of the compounds was measured over 14-day test period using an Okura Electric Closed System Oxygen Consumption measuring apparatus (Coulometer). Removal of dissolved organic carbon (DOC) was determined at the termination of the test (14 days). Percentage biodegradation was calculated based on BOD, TOC and GC analysis.

  The test solutions were maintained in a darkened room at a temperature of 25 ±1°C and continuously stirred by magnetic stir bars over the 14-day test period.
  Percent degradation (%) was obtained from the following equations.

  (BOD)
  Degradation (%) = (BOD - B)/ThOD * 100
  BOD (mg): BOD in Sludge + Triacetin system

B (mg): BOD in Sludge blank
ThOD: theoretical oxygen demand required when triacetin was completely oxidized.

(TOC)
Degradation (%) = (DOC_W - DOC_S)/DOC_W * 100
DOC_W (mgC): Residual DOC in Water + Triacetin system
DOC_S (mgC): Residual DOC in Sludge + Triacetin system

(GC)
Degradation (%) = (S_W - S_S)/S_W * 100
S_W (mg): Residual amount of triacetin detected by GC in Water + Triacetin system
S_S (mg): Residual amount of triacetin detected by GC in Sludge + Triacetin system

RESULTS

- **Degradation:**

Removal of DOC and Mineralization to CO_2 in Biodegradation Test Reactions after 14 Days

		(Water + Triacetin)	(Sludge + Triacetin)				Theoretical amount
		n=1	n=1	n=2	n-3	Mean	
BOD*	**(mg)**	1.40	34.2	31.5	30.6	32.1	41.8
Residual DOC	**(mgC)**	14.8	1.10	0.90	0.80	0.93	14.9
	(%)	99.0	7.00	6.00	6.00	6.33	-
Residual Triacetin	**(mg)**	29.7	0.00	0.00	0.00	0.00	30.1
(by GC)	**(%)**	99.0	0.00	0.00	0.00	0.00	-

***: Results are corrected for corresponding blank values.**

Test and Reference Material Biodegradation after 7 and 14-day test period

	Percent degradation of Triacetin (%) (after 14 days)			
	n=1	n=2	n-3	Mean
BOD	82	75	73	77
TOC	93	94	94	94
GC	100	100	100	100

	Percent degradation of aniline (%)	
	After 7 days	After 14 days
BOD	45	72

- **Results:** Readily biodegradable.
- **Kinetic:** Not stated.
- **Breakdown products:** Not stated.
- **Remarks:** Not stated.

CONCLUSIONS

This chemical is readily biodegradable.

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks:** Well conducted study, carried out by Chemicals Evaluation and Research Institute (Kurume, Japan).

REFERENCES

- Chemicals Evaluation and Research Institute (Kurume, Japan) (1998), Test No. 20919B

OTHER

- **Last changed:**
- **Order number for sorting**
- **Remarks:**

ECOTOXICITY ELEMENTS

ACUTE TOXICITY TO FISH (1)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks**: Source: Wako Pure Chemical Industries, Lot No. TPH 6237, Purity ≥ 98.0 %. Stability during use confirmed by NMR, IR and gas chromatography. Kept at room temperature in a dark place until use.

METHOD

- **Method/guideline followed:** OECD TG 203
- **Type:** Semi-static.
- **GLP :** Yes.
- **Year :** 1998.
- **Species/Strain/Supplier:** *Oryzias latipes* (Medaka): Obtained from commercial domestic hatcheries.
- **Analytical monitoring** Yes. Test solutions were measured using by gas chromatography before and after the first 24-hour exchange of solutions.
- **Exposure period (h):** 96 h.
- **Statistical methods:** Not applicable because a limit test was conducted.
- **Remarks field for Test Conditions:**

  – ***Test fish:***

  · Acclimated for more than 12 days before testing; any groups showing no mortality for 7 days before test started. Fish with 19.8 mm (18.8 - 21.3 mm) in length were selected at random (n=10). Average body weight of fish was 0.1134 g (n=10).

  – ***Test conditions:***

  · Details of test: Semi-static (water exchanged every 24 hours)
  · Dilution water source: Tap water after dechlorinated by passing through activated carbon filter.
  · Dilution water chemistry: Hardness: 25 mg/L as $CaCO_3$; pH: 6.7
  · Stock and test solution and how they are prepared: Pipette or pour the appropriate amount of the solution (0.3 wt% of test chemical) into the test waters.
  · Concentrations dosing rate, flow-through rate, in what medium: Concentrations of 0 and 100 mg/L were tested because no fatality was observed in the preliminary run at 100 mg/L.
  · Vehicle/solvent and concentrations: Not used.
  · Stability of the test chemical solutions: Stable and transparent, no precipitate and colour formed during 96-hour exposure period.
  · Exposure vessel type: 3 L glass beaker.
  · Number of replicates, fish per replicate: 1, 10 individuals/replicate.
  · Water chemistry in test (O_2, pH) in the control and one concentration where effects were observed: Dissolved oxygen readings and pH values were taken daily during 96-hour exposure period.
  · Dissolved oxygen concentration: 5.7 - 9.8 mg/L.
  · pH values: 6.5 - 6.9.

– ***Test temperature range:***
  · Water temperature at 23.5 - 23.8 °C during 96-hour exposure period.
– ***Method of calculating mean measured concentrations:***
  · Geometric mean.

RESULTS

- **Nominal concentrations :**
  0, 100 (mg/L)
- **Measured concentrations :**

Nominal concentration (mg/L)	Measured concentration (mg/L)			Percent of nominal	
	0 hour	24 hour	Geometric mean	0 hour	24 hour
Control (0)	< 1.0	< 1.0	---	---	---
100	88.0	94.0	91.0	88.0	94.0

- **Unit :** mg/L.
- **Element value:**
  Cumulative numbers of died or stressed fish.
- **Statistical results as appropriate:** Not applied.
- **Remarks field for Results:**

– ***Biological observations:*** See below.
– ***Table showing cumulative mortality:***

Percent mortality of Oryzias latipes exposed to the test chemical

Nominal concentration (mg/L)	Cumulative number of died fish (% mortality)			
	24 hour	48 hour	72 hour	96 hour
Control (0)	0 (0)	0 (0)	0 (0)	0 (0)
100	0 (0)	0 (0)	0 (0)	0 (0)

– ***Lowest test substance concentration causing 100% mortality:***
  Not obtained under the test conditions studied.
– ***Mortality of controls:*** No mortality observed during the test period.
– ***Abnormal responses:*** No symptom observed during the test period.
– ***Reference substances (if used) – results:***
  Copper (II) sulfate pentahydrate. 96 h LC_{50} was 0.43 mg/L.
– ***Any observations, such as precipitation that might cause a difference between measured and nominal values:*** No precipitates and colour formation by the test chemical.

CONCLUSIONS

LC_{50} for medaka was determined to be > 100.0 mg/L for 96 hours based on nominal concentrations.

Remarks field with the ability to identify source of comment, i.e. author and/or submitter:

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks field for Data Reliability:**
  Experimental design and analytical procedure were well documented.

REFERENCES

Environment Agency (EA) of Japan (1998).

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

ACUTE TOXICITY TO FISH (2)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks**: Source: Eastman^{R} Triacetin, Sample Reference Identification No.: 43045932,
  Purity ≥ 99.5 %. Stability during use confirmed by GC/FID and mass spectrometry.

METHOD

- **Method/guideline followed:** OECD TG 203 and EEC/Annex V C.1.
- **Type:** Static.
- **GLP :** Yes.
- **Year :** 1995.
- **Species/Strain/Supplier:** *Pimephales promelas* (Fathead minnow, fresh water): Supplied by The Eco-Chem Testing Group, Kodak Park, Rochester, NY (USA).
- **Analytical monitoring** Yes. Measured by gas chromatography (at preparation and after 24 or 96 hours exposure period). Aliquots of the exposure solutions containing 95.0 and 171.5 mg/L (nominally) were analysed at times 0 and 96 hours. Aliquots of the exposure solutions containing 308.5, 555.5 and 1,000 mg/L (nominally) were analysed at times 0 and 24 hours.
- **Exposure period (h):** 96 h.
- **Statistical methods:** A program developed by Stephan (Aquatic Toxicology and Hazard Evaluation, Spec. Tech. Publ.No. 634, American Society for Testing and Materials, Philadelphia, PA, pp.65-84, 1977) and ASTM (Proposed New Standard Practice for Using Probit Analysis, ASTME-47.07, Draft #4, 1988).
- **Remarks field for Test Conditions:**

  – ***Test fish:***

  · Acclimated to the diluent water prior to the test for at least two weeks. Fish with 19.8 mm (18.8 ~ 21.3 mm) in length were selected at random (n=10). Average body weight of fish for set #1 and set #2 at the start of the test was 0.06 and 0.07 g (n=10/set), respectively. Mean body length of fish at the end of the test was 1.61 and 1.57 cm (n=10/set), respectively.

  – ***Test conditions:***

  · Details of test: Static.
  · Dilution water source: The water from Lake Ontario was passed through an activated carbon filter and a set of 3-micron polypropylene filter. The filtered water next received 150 ppb of $Na_2S_2O_3$ to reduce trace level of residual chlorine.
  · Dilution water chemistry: Hardness and total alkalinity: 120 mg/L and 95 mg/L (as $CaCO_3$). pH = 7.4-8.3. DO: 7.1-9.0 mg/L.
  · Lighting: 16 h: 8 h light-darkness cycle.
  · Feeding: Biological loading within test vessels was kept below 1.0 g wet weight/L of test solution.
  · Stock and test solution and how they are prepared:
  The exposure solutions were prepared by direct addition of the appropriate amounts of the triacetin to tanks of water (20 L).

- Concentrations (nominally): 95.0, 171.5, 308.5, 555.5, 1,000.0 mg/L.
- Vehicle/solvent and concentrations: No vehicle used.
- Stability of the test chemical solutions: During the test, 77 - 98.1 % of the initial analysed concentrations was maintained throughout the test.
- Exposure vessel type: Glass 30.5-cm cuboidal jar, each containing 20 L of exposure solution.
- Number of replicates, fish per replicate: 2, 10 individuals/replicate.

– ***Test temperature range:***
- Water temperature at 20 ± 2 °C during 96-hour exposure period.

– ***Method of calculating mean measured concentrations:***
- Geometric Mean.

RESULTS

- **Nominal concentrations :**
  0, 95.0, 171.5, 308.5, 555.5, 1,000.0 (mg/L).
- **Measured concentrations :**

Measured concentration of triacetin during 96-hour exposure of *Pimephales promelas* under static test conditions

Nominal concentration (mg/L)	Concentration determination	Mean conc. (mg/L)	% of Nominal (Series A)	Mean conc. (mg/L)	% of Nominal (Series B)
95.0	**(0, 96-hour)**	78.6	82.7	75.9	80.0
171.5	**(0, 96-hour)**	141.7	82.6	151.4	88.3
308.5	**(0, 24-hour)**	294.2	95.4	302.9	98.2
555.5	**(0, 24-hour)**	547.0	98.5	543.7	97.9
1,000.0	**(0, 24-hour)**	997.2	99.7	1057.5	105.8

- **LC_{50} and LC_0:**

Calculated LC_{50} and LC_0 for *Pimephales promelas* exposed to triacetin under static test conditions

Series	LC_{50} (mg/L)				LC_0 (mg/L)			
	24-hour	**48-hour**	**72-hour**	**96-hour**	**24-hour**	**48-hour**	**72-hour**	**96-hour**
A	220.5	220.5	178.3	178.3	141.7	141.7	78.6	78.6
B	188.3	188.3	177.4	165.3	75.9	75.9	75.9	75.9
Final value				165.3				75.9

- **Unit :** mg/L.
- **Element value:**
  Cumulative numbers of died or signs of stressed fish.
- **Statistical results as appropriate:** Nonlinear interpolation were used to calculate the 24-, 48-, 72- and 96-hour LC_{50} values for replicates A and B at a confidence level of 95 %.
- **Remarks field for Results:**

– ***Biological observations:*** Not described.
– ***Table showing cumulative mortality:*** Data not available.
– ***Lowest test substance concentration causing 100% mortality:***
Not applicable.
– ***Mortality of controls:*** The control mortality was not greater than 10 % when adverse effects

were noted. The minnows in the diluent water control exhibited normal behaviour and appearance throughout the test.

– ***Abnormal responses:*** No descriptions.
– ***Reference substances (if used) – results:***
No descriptions.
– ***Any observations, such as precipitation that might cause a difference between measured and nominal values:*** Throughout the test, there were no particulates, surface slicks, or precipitates observed within the exposure solutions containing the test article.

CONCLUSIONS

LC_{50} (96-hour) =165.3 mg/L

LC_0 (96-hour) = 75.9 mg/L

Remarks field with the ability to identify source of comment, i.e. author and/or submitter:

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks field for Data Reliability:**
Experimental design and analytical procedure were well documented.

REFERENCES

Lawrence, D.L. and Hirsch, M.P. (1995), Eastman Kodak Company, Environmental Sciences Section, Corporate Health and Environment Laboratories, An acute aquatic effects test with the fathead minnow, Study No.: EN-430-900256-1,Unpublished data.

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

PROLONGED TOXICITY TO FISH

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks**: Source: Wako Pure Chemical Industries, Lot No. TPH 6237, Purity ≥ 98.0 %. Stability during use confirmed by NMR, IR and gas chromatography. Kept at room temperature in a dark place until use.

METHOD

- **Method/guideline followed :** OECD TG 204
- **Type :** Flow-through.
- **GLP:** Yes.
- **Year :** 1998.
- **Species/Strain/Supplier:** *Oryzias latipes* (Medaka): Obtained from commercial domestic hatcheries.
- **Analytical monitoring:** Yes. Test solutions were measured by gas chromatography before and after 7 and 14days exposure period.
- **Exposure period :** 14 day.
- **Statistical methods:** Binomial method (TOXDAT MULTI-METHOD PROGRAM, USEPA) was not applied because of no mortality observed at all doses tested**.** Dunnet method was used for fish body weight difference.

- **Remarks field for Test Conditions:**

  – ***Test fish:***

  Acclimated for more than 12 days before testing; any groups showing no mortality for 7 days before test started. Fish with 22.8 mm (21.2 - 24.7 mm) (n=10) in length were selected at random. Average body weight of fish was 0.1638 g (0.1227 - 0.2446 g, n=10). Fish were starved for 24 hours before the test started.

  – ***Test conditions:***

  · Details of test: Flow-through.
  · Dilution water source: Tap water after dechlorinated by passing through an activated carbon filter.
  · Dilution water chemistry: Hardness: 25 mg/L as $CaCO_3$; pH: 6.7.
  · Stock and test solution and how they are prepared: The working solution (0.2 wt % of the test chemical) was prepared by diluting the stock solution (4.0 wt % of the test chemical) with the dilution water. The test solution was supplied continuously by mixing the working solution and the dilution water with the help of a mechanically operated quantitative water-pump.
  · Concentrations dosing rate, flow-through rate, in what medium: Nominal concentrations of 0, 30.9, 55.6 and 100 mg/L were tested.
  · Vehicle/solvent and concentrations: Not used.
  · Stability of the test chemical solutions: Stable, no precipitate and colour formed during the exposure period.
  · Exposure vessel type: 3L glass beaker.
  · Number of replicates, fish per replicate: 10 and one replicate was done**.**
  · Water chemistry in test (O_2, pH) in the control and one concentration where effects were observed: Dissolved oxygen readings and pH values

were taken every 2 - 3 days during the exposure period.
- Dissolved oxygen concentration: 5.9 - 7.8 mg/L.
- pH values: 6.6 - 6.8.
- Lighting: 16 h: 8 h light-darkness cycle.

– ***Test temperature range:***
- Water temperature ranged 23.6 - 24.5°C.

– ***Method of calculating mean measured concentrations:***
- Time-weighted mean.

RESULTS

- **Nominal concentrations :** 0, 30.9, 55.6, 100 (mg/L)

- **Measured concentrations :**

Measured concentration of the test chemical during a 14-day exposure of Medaka (Oryzias latipes) under flow-through test conditions

Nominal concentration (mg/L)	Measured concentration (mg/L)			(percent of nominal)
	0 day	7 day	14 day	Mean
Control (0)	< 1.0	< 1.0	< 1.0	-
30.9	25.8 (83.5)	26.3 (85.1)	31.1 (100.6)	27.7 (89.8)
55.6	49.7 (89.4)	49.2 (88.5)	56.0 (100.7)	51.6 (92.9)
100	90.2 (90.2)	99.2 (99.2)	101.5 (101.5)	97.0 (97.0)

- **Unit :** mg/L
- **Element value:**

LC_{50} (7 days) > 100.0 mg/L (nominal concentration)
LC_{50} (14 days) > 100.0 mg/L (nominal concentration)
LC_0 (14 days) = 100.0 mg/L (nominal concentration)

- **Statistical results as appropriate:**
The mean body weight of fish exposed to the concentrations at 30.9, 55.6 and 100.0 mg/mL (nominal concentration) of the test chemical was not significantly different from the control after 14-day exposure period (alfa=0.05, Dunnet).

– **Calculated LC_{50} values for fish exposed to the test chemical based on nominal concentration under flow-through test conditions:**

Exposure period (day)	LC_{50} (mg/L)	95 % Confidence limits	Statistical method
7	> 100.0	-	Not applied
14	> 100.0	-	Not applied

- **Remarks field for Results.:**

– **Biological observations*:* Not described.**
B. Cumulative mortality:

Percent mortality of Oryzias latipes exposed to the test chemical under flow-through test conditions

Nominal conc. (mg/L)	Cumulative number of died fish (% mortality)													
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 (days)**
Control (0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
30.9	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
55.6	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
100.0	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)

* Threshold level of lethal effect: > 100.0 mg/L

– **Fish weight:**

Nominal conc. (mg/L)	Fish weight (g)										
	No.1	**No.2**	**No. 3**	**No.4**	**No.5**	**No.6**	**No.7**	**No.8**	**No.9**	**No.10**	**Average**
Control	0.1502	0.1302	0.2040	0.2224	0.1895	0.1686	0.2303	0.1789	0.0983	0.1233	0.1696
30.9	0.1220	0.1993	0.2370	0.1815	0.1073	0.0900	0.1572	0.1697	0.1364	0.1331	0.1534
55.6	0.2354	0.1440	0.1227	0.2291	0.1602	0.1892	0.2506	0.1768	0.1350	0.1733	0.1821
100.0	0.1792	0.1463	0.1375	0.1499	0.1176	0.1311	0.1983	0.1626	0.1860	0.1091	0.1518

No significant differences were observed among control and each exposure levels.

– ***Lowest test substance concentration causing 100% mortality:*** Not determined.
– ***Mortality of the control:*** No mortality was observed during the test period (14 days).
– ***Food intake:*** Fish were fed with TetraMin® fish food (2 % of fish body weight/day). No reduction of food intake was observed at all doses tested during 14-day exposure period.
– ***Abnormal responses:*** No abnormal behaviour was observed at all doses tested during 14-day exposure period.
– ***Reference substances (if used) – results:*** Copper (II) sulfate pentahydrate. LC_{50} at 96h was 0.43 mg/L.
– ***Any observations, such as precipitation that might cause a difference between measured and nominal values:*** No precipitates and colour formation by the test chemical.

CONCLUSIONS

LC_{50} (14 days) was determined to be >100.0 mg/L based on nominal concentrations. No fish showed abnormal swimming behaviour.

Remarks field with the ability to identify source of comment, i.e. author and/or submitter:

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks field for Data Reliability:** Experimental design and analytical procedure were well documented.

REFERENCES

Environment Agency (EA) of Japan (1998).

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Wako Pure Chemical Industries, Lot No. TPH 6237, Purity ≥ 98.0 %. Stability during use confirmed by NMR, IR and gas chromatography. Kept at room temperature in a dark place until use.

METHOD

- **Method/guideline followed :** OECD TG 201
- **Test type :** Static.
- **GLP :** Yes
- **Year :** 1998
- **Species/strain # and source:** *Selenastrum capricornutum* ATCC22662 (purchased from ATCC)
- **Element basis:** Growth rate and area under the growth curve.
- **Exposure period:** 72 h.
- **Analytical monitoring:** Yes, measured by gas chromatography at 0 h and 72h.
- **Statistical methods:** Logit analysis for EC_{50} and an ANOVA for NOEC (Bartlett test for homogeneity in variances and One-way Anova (p=0.05), For each analysis, software of EcoTox-Statistics Ver.1.0 beta R1.4 was used.

Remarks field for Test Conditions :

– ***Test organisms:***

· The alga culture was obtained by incubating for 3 days before the exposure to triacetin under the same condition for the main test. The microscopic observation confirmed that there were no deformed or abnormal cells in the culture.
· Laboratory culture: OECD medium
· Method of cultivation: Shaking at 100 rpm
· Control: OECD medium. EC_{50} of potassium dichromate was 0.41 mg/L.

– ***Test Conditions:***

· Test temperature range: 23 ± 2 °C (22.0 - 22.2 °C)
· Growth/test medium: OECD medium.
· Shaking: 100 rpm
· Dilution water source: OECD medium.
· Exposure vessel type: A 300 mL Erlenmeyer flask with a silicon cap, which allows ventilation.
· Medium volume: 100 mL (OECD medium).
· Water chemistry in test (pH) in at least one replicate of each concentration (at start and end of the test): pH=7.5 - 7.6 at start and 5.3 - 8.5 at end of the test (72 h).
· Stock solutions preparation : Test chemical was diluted to 0.2 wt.% (2,000 mg/L) with OECD medium and sterilised with filter before use. Stock solution was not preserved.
· Light levels and quality during exposure: 4,000 - 5,000 lux, continuous illumination.

– ***Test design:***

· Number of replicates: Triplicate

· Concentrations: 0,95, 171, 309, 556 and 1,000 mg/L
· Initial cell number in cells/mL: $1x10^4$

– ***Method of calculating mean measured concentrations:***
· Geometric mean.

RESULTS

- **Nominal concentrations :** 0, 95, 171, 309, 556 and 1,000 (mg/L)

- **Measured concentrations :**

Nominal Concentration (mg/L)	**Measured Concentration (mg/L)**			
	0 hr (at start of the test)	**% of Nominal**	**72 hr (at end of the test)**	**% of Nominal**
Control	< 1.0	-	< 1.0	-
95	95.0	100.3	56.0	58.9
171	163	95.2	110	64.6
309	313	101.3	216	69.8
556	535	96.1	401	72.1
1,000	997	99.7	883	88.3

- **Unit :** Cell density (cells/mL)

- **Results:** (calculated based on nominal concentrations)

(1) Growth inhibition (comparison of the area under growth curve)
EC_{50} (0-72 h) > 1,000 mg/L
NOEC (0-72 h) = 556 mg/L

(2) Growth inhibition (comparison of the growth rates)
EC_{50} (0-72 h) > 1,000 mg/L
NOEC (24-48 h) = 1,000 mg/L
NOEC (24-72 h) = 556 mg/L

Cell density of *Selenastrum capricornutum* at each concentration at different measuring points

Nominal Concentration (mg/L)	**Cell Density ($x10^4$ cells/mL)**				**pH**	
	0 hr	**24 hr**	**48 hr**	**72 hr**	**0 hr**	**24 hr**
Control	1.0 ± 0.00	7.4 ± 0.55	35.6 ± 11.15	207.0 ± 40.96	7.5	8.5
95	1.0 ± 0.00	6.0 ± 0.54	35.9 ± 9.01	220.4 ± 61.00	7.6	7.4
171	1.0 ± 0.00	6.9 ± 0.63	41.4± 4.01	223.7 ± 16.07	7.6	6.8
309	1.0 ± 0.00	5.7 ± 0.97	32.4± 5.80	183.3 ± 28.35	7.6	5.9
556	1.0 ± 0.00	6.5 ±0.23	35.5 ± 11.43	170.4 ± 30.32	7.5	5.3
1,000	1.0 ± 0.00	6.6 ± 0.63	34.7± 6.28	80.0± 18.44	7.5	5.3

(Each value represents the mean of three sample counts ± SD.)

Growth Inhibition of *Selenastrum capricornutum* at each concentration at different intervals

Nominal Concentration (mg/L)	**Area $x10^4$ A(0-72h)**	**Inhibition (%) I_A(0-72h)**	**Rate u(24-48h)**	**Inhibition (%) I_m(24-48h)**	**Rate u (24-72h)**	**Inhibition (%) I_m (24-72h)**
Control	3455	-	0.0642	-	0.0691	-
95	3594	-4.02	0.0735	-14.58	0.0741	-7.17
171	3783	-9.48	0.0748	-16.49	0.0726	-4.96
309	3056	11.57	0.0720	-12.14	0.0722	-4.37
556	2992	13.41	0.0694	-8.21	0.0679	1.76
1,000	1893	45.21	0.0686	-6.88	0.0515	25.52

(Each value represents the mean of three values.)

A: Area under the growth curve
I_A = (Ac – At)/Ac
Ac: Area under the growth curve of control
At: Area under the growth curve at each concentration

u: Growth rate
$I_m = (u_c-u_t)/u_c$
u_c: Average growth rate of control
u_t: Average growth rate at each concentration

- **Was control response satisfactory:**
  Yes: Mean cell density increased to $2.07x10^6$ cells/mL (207-fold increase) after 72 hr (cell density at start = $1.00x10^4$ cells/mL).

- **Statistical results as appropriate:**
  Significant differences in the growth curves were not observed at nominal concentration of 95, 171, 309, and 556 mg/L when compared to that of the control. At such concentrations, 170 - 224 fold increase of cell density was observed.

Remarks field for Results:

– ***Biological observations:***
  · Growth curves: Logarithmic growth until end of the test (72 h).
  · Observations: All test groups (95-556 mg/L) except that of 1,000 mg/L showed normal and similar growth (170.4 - 223.7-fold increase during 72 hr) to that of control (207-fold increase during 72 hr). The 1000 mg/L-group showed only 80-fold increase (38.6 % of the control) after 72 hr, when compared to that of control.

CONCLUSIONS

All the test groups (95, 171, 309, 556 except 1,000 mg/L) showed normal and similar growth (170-224 fold increase after 72 hr) to control (207-fold increase after 72 hr).
EC_{50} (0-72 h) > 1,000 mg/L
NOEC (0-72 h) = 556 mg/L

Remarks field with the ability to identify source of comment, i.e. author and/or submitter:

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks field for Data Reliability:**
  Experimental design and analytical procedure were well documented.

REFERENCES

Environment Agency (EA) of Japan (1998).

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

ACUTE TOXICITY TO AQUATIC INVERTEBRATES (DAPHNIA) (1)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Wako Pure Chemical Industries, Lot No. TPH 6237, Purity ≥ 98.0 %. Stability during use confirmed by NMR, IR and gas chromatography. Kept at room temperature in a dark place until use.

METHOD

- **Method/guideline:** OECD TG 202.
- **Test type:** Static.
- **GLP :** Yes.
- **Year :** 1998.
- **Analytical procedures:** Yes. Measured by gas chromatography (at preparation and after 48 hours exposure period).
- **Species/Strain:** *Daphnia magna*
- **Test details:** Static, open-system.
- **Statistical methods:** TOXDAT MULTI - METHOD PROGRAM (US EPA) Moving average method.

Remarks field for Test Conditions :

– ***Test organisms:***

- Source, supplier, any pre-treatment, breeding method: Supplied by NIES (Japan).
- Age at study initiation: Juveniles within 24h old.
- Control group: Yes.

– ***Test conditions:***

- Stock solutions preparation and stability: No solvent used. Test chemical was diluted to 1.0 wt.% with diluting mineral medium (Elendt M4) before use.
- Test temperature range: 20.1 - 20.4 °C (average temperature within 21±1 °C).
- Exposure vessel type: 100 mL test solution in a 100 ml glass beaker; 4 beakers per treatment.
- Dilution water source: Elendt M4.
- Dilution water chemistry: Hardness: 228 mg/L as $CaCO_3$.
- Lighting: < 1,200 lx, 16h: 8h light-darkness cycle.
- Water chemistry in test: DO= 7.6 - 8.7 mg/L, > 60 % of saturation (8.84 mg/L at 20 °C); pH=7.3 - 7.5.
- Feeding: *Chlorella vulgaris*, 0.1 - 0.2 mgC/day/individual.

– ***Element (unit) basis:*** Cumulative numbers of died or immobilized juveniles.

– ***Test design:*** Number of replicates = 4; individuals per replicate = 5; concentrations: 0,95, 171, 309, 556 and 1,000 mg/L.

– ***Method of calculating mean measured concentrations:***
Geometric mean.

– ***Exposure period:*** 48 hours.

– ***Analytical monitoring:*** By GC analysis, 103.5 - 111.6 % of the nominal concentration at

preparation; 90.8 - 109.5 % after 48 hours exposure period.

Unit : mg/L (calculated based on the nominal concentrations).

RESULTS

- **Nominal concentrations:** 0, 95, 171, 309, 556 and 1,000 mg/L.
- **Measured concentrations:**
  - Triacetin concentration of the test solutions measured at preparation and after 48 hours exposure period.

Measured concentration of triacetin during 48-hour exposure of *Daphnia magna* under static test conditions

Nominal concentration (mg/L)	Measured concentration (mg/L)			Percent of Nominal	
	0-hour (new)	48-hour (old)	Geometric Mean	0-hour (new)	48-hour (old)
Control	< 1.0	< 1.0	-	-	-
95	106	104	105	111.6	109.5
171	178	172	175	103.9	100.7
309	324	323	323	104.8	104.6
556	576	566	571	103.5	101.8
1,000	1,086	908	993	108.6	90.8

new: Freshly prepared test solutions.
old: Test solutions after 48 hours exposure period.

Mortality or immobility of *Daphnia magna* exposed to triacetin under static test conditions.

Nominal concentration (mg/L)	Cumulative numbers of died or immobilized *Daphnia magna* (Percent mortality or immobility)	
Control	**24-hour**	**48-hour**
Control	0 (0)	0 (0)
95	0 (0)	0 (0)
171	0 (0)	0 (0)
309	0 (0)	0 (0)
556	3 (15)	5 (25)
1000	17 (85)	18 (90)
(Mortality: %)		

- **Statistical results as appropriate:**

Calculated EC_{50} values for *Daphnia magna* exposed to triacetin under static test conditions

Exposure period (hour) (hour)	EC_{50} (mg/L)	95% confidence limits (mg/L)	Statistical method
24	888	648-1,489	Moving average
48	768	582-1,176	Moving average

EC_0 and Lowest Concentration in 100 % mortality or immobility values

Exposure period (hour)	EC_0 (mg/L)	Lowest Concentration in 100 % mortality or immobility values (mg/L)
24	309	> 1,000
48	309	> 1,000

Remarks field for Results :

– ***Biological observations:***

- Was control response satisfactory: Yes.
  Cumulative numbers of dead or immobilized *Daphnia* during observation period. 0 (mortality: 0%)

CONCLUSIONS

(Based on nominal concentration)

- EC_{50} (24-hour, mortality or immobility): 888 mg/L
- EC_{50} (48-hour, mortality or immobility): 768 mg/L
- EC_{0} (48-hour, mortality or immobility): 309 mg/L

Remarks field with the ability to identify source of comment, i.e. author and/or submitter:

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks field for Data Reliability:**

Experimental design and analytical procedure were well documented.

REFERENCES

Environment Agency (EA) of Japan (1998).

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

ACUTE TOXICITY TO AQUATIC INVERTEBRATES (DAPHNIA) (2)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Eastman^{R} Triacetin, Sample Reference Identification No.: 43045932,
  Purity ≥ 99.5 %. Stability during use confirmed by GC/FID and mass spectrometry.

METHOD

- **Method/guideline:** OECD TG 202 and EEC/Annex VC.2.
- **Test type:** Static.
- **GLP :** Yes.
- **Year :** 1995.
- **Analytical procedures:** Yes. Measured by gas chromatography (at preparation and after 48 hours exposure period).
- **Species/Strain:** *Daphnia magna*
- **Test details:** Static.
- **Statistical methods:** A program developed by Stephan (Aquatic Toxicology and Hazard Evaluation, Spec. Tech. Publ.No. 634, American Society for Testing and Materials, Philadelphia, PA, pp.65-84, 1977) and ASTM (Proposed New Standard Practice for Using Probit Analysis, ASTME-47.07, Draft #4, 1988).

Remarks field for Test Conditions :

– ***Test organisms:***
  - Source, supplier, any pre-treatment, breeding method: Supplied by The Eco-Chem Testing Group, Kodak Park, Rochester, NY (USA).
  - Age at study initiation: Juveniles between 6 and 24h old.
  - Control group: Yes.

– ***Test conditions:***
  - Stock solutions preparation and stability: No solvent used. The exposure solutions were prepared by direct addition of the appropriate amounts of the triacetin to tanks of water (20 L).
  - Test temperature range: 20±2 °C.
  - Exposure vessel type: 200 mL test solution in a 250 ml glass beaker; Two beakers per treatment.
  - Dilution water source: The water from Lake Ontario was passed through an activated carbon filter and a set of 3-micron polypropylene filter. The filtered water next received 150 ppb of $Na_2S_2O_3$ to reduce trace level of residual chlorine.
  - Dilution water chemistry: Hardness and total alkalinity: 120 mg/L and 95 mg/L (as $CaCO_3$).
  - Lighting: 16 h: 8 h light-darkness cycle.
  - Water chemistry in test: DO: 8.0 - 9.0 mg/L. pH of exposure solution was measured at times 0 and 48 hours (pH = 7.7 - 8.2).
  - Feeding: 5 mL of food/1 L diluent water/100 gravid daphnids.

– ***Element (unit) basis:*** Cumulative numbers of dead or immobilized/stressed organisms.

– ***Test design:*** Number of replicates = 2; individuals per replicate = 10; nominal

concentrations: 0, 95.0, 171.5, 308.5, 555.5 and 1,000.0 mg/L.

– ***Method of calculating mean measured concentrations:***
Geometrical mean.

– ***Exposure period:*** 48 hours.

– ***Analytical monitoring:*** By GC analysis, the mean value of time 0 and 48 hours:
92.2 % (86.6 - 97.4 %) of the nominal concentration (Series A).
95.1 % (86.5 - 100.7 %) of the nominal concentration (Series B).

Unit: ***mg/L (calculated based on the nominal concentrations).***

RESULTS

- **Nominal concentrations:** 0, 95.0, 171.5, 308.5, 555.5 and 1,000.0 mg/L.
- **Measured concentrations:**
  · Triacetin concentration of the test solutions was measured at preparation and after 48 hours exposure period.
  · The analysed mean values of time 0 and 48 hours were calculated.

Measured concentration of triacetin during 48-hour exposure of *Daphnia magna* under static test conditions

Nominal concentration (mg/L)	Mean conc. (mg/L) Series A (0, 48-hour)	% of Nominal	Mean conc. (mg/L) Series B (0, 48-hour)	% of Nominal
95	83.5	87.9	82.2	86.5
171.5	148.5	86.6	156.6	91.3
308.5	283.4	91.9	297.3	96.4
555.5	541.1	97.4	558.5	100.5
1,000.0	974.4	97.4	1006.7	100.7

Calculated EC50 and No-Observed- Effect Concentration (NOEC) for *Daphnia magna* exposed to triacetin under static test conditions

Series	EC_{50} (mg/L)		EC_0 (mg/L)	
	24-hour	48-hour	24-hour	48-hour
A	> 974.4	810.9	974.4	541.1
B	> 1006.7	904.2	1006.7	558.5
Final value	> 974.4	810.9	974.4	541.1

- **Statistical results as appropriate:**
The binominal method and nonlinear interpolation were used to calculate all the EC50 values for replicates A and B at a confidence level of 95 %.

Remarks field for Results :

– ***Biological observations:***
· Was control response satisfactory: Yes.
The control immobility was not greater than 10 % when adverse effects were noted.

CONCLUSIONS

(Based on the measured concentration)

- EC_{50} (24-hour, mortality or immobility): > 974.4 mg/L
- EC_{50} (48-hour, mortality or immobility): 810.9 mg/L
- EC_0 (48-hour, mortality or immobility): 541.1 mg/L

Remarks field with the ability to identify source of comment, i.e. author and/or submitter:

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks field for Data Reliability:**

Experimental design and analytical procedure were well documented.

REFERENCES

Lawrence, D.L. and Hirsch, M.P. (1995), Eastman Kodak Company, Environmental Sciences Section, Corporate Health and Environment Laboratories, An acute aquatic effects test with the fathead minnow, Study No.: EN-430-900256-1,Unpublished data.

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

CHRONIC TOXICITY TO AQUATIC INVERTEBRATES (DAPHNIA)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Wako Pure Chemical Industries, Lot No. TPH 6237, Purity ≥ 98.0 %. Stability during use confirmed by NMR, IR and gas chromatography. Kept at room temperature in a dark place until use.

METHOD

- **Method/guideline:** OECD TG 211 (revised edition of No.202).
- **Test type:** Semi-static.
- **GLP :** Yes.
- **Year :** 1998.
- **Analytical procedures:** Yes. Measured by gas chromatography 2 - 3 times a week (before and after the replacement of the test water.
- **Species/Strain:** *Daphnia magna*
- **Test details:** Semi-static (water renewal: 3 times a week), open-system.
- **Statistical methods:** F & t-test (Yukms StatLight #3).

Remarks field for Test Conditions :

– ***Test organisms:***

- Source, supplier, any pre-treatment, breeding method: Supplied by NIES (Japan).
- Age at study initiation: Juveniles within 24h old.
- Control group: Yes.

– ***Test conditions:***

- Stock solutions preparation and stability: No solvent used. Test chemical was diluted to 1.0 wt.% with diluting mineral medium (Elendt M4) before use.
- Test temperature range: 19.4 - 20.7 °C (average temperature within 20±1 °C).
- Exposure vessel type: 80 mL test solution in a 100 ml glass beaker;
- Dilution water source: Elendt M4.
- Dilution water chemistry: Hardness: 243 mg/L as $CaCO_3$
- Lighting: <1,200 lx, 16 h: 8 h light-darkness cycle
- Water chemistry in test: DO= 7.4 - 8.6 mg/L; pH=7.2.
- Feeding: *Chlorella vulgaris*, 0.1 - 0.2 mgC/day/individual

– ***Element (unit) basis:*** Mean cumulative numbers of juveniles produced per adult (reproduction)

– ***Test design:*** Number of replicates=10; individuals per replicate=1; concentrations: 0 and 100 mg/L (limit test).

– ***Method of calculating mean measured concentrations:***
Time-weighted mean.

– ***Exposure period:*** 21 d

– ***Analytical monitoring:*** By GC analysis, 87.9 - 103.2 % of the nominal concentration at preparation; 75.8 - 100.7 % just before the renewal of the test water (after 2 days exposure).

Unit : ***mg/L (calculated based on measured concentrations)***

RESULTS

- **Nominal concentrations:** 0, 100 mg/L
- **Measured concentrations:**

Time-weighted means of measured concentration of the test chemical during 21-d exposure: 94 mg/L for the test solutions.

Measured concentration of the test chemical during 21-day exposure

Nominal concentration	Measured concentration (mg/L)					
(mg/L)	0 day (new)	2 day (old)	7 day(new)	9 day(old)	14day(new)	16day(old)
Control	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0
100	87.9	75.8	99.4	100.7	103.2	97.4

new: Freshly prepared test solutions.
old: Test solution after 2 days.

Time-weighted means of measured concentration of the test chemical during 21-d exposure

Nominal concentration (mg/L)	Time-weighted mean (mg/L)	Percent of nominal concentration (%)
Control	-	-
100	94.0	94.0

Mean cumulative numbers of juveniles produced per adult during 21-d.

Nominal concentration	Days																				
(mg/L)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Control	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.5	4.8	11.8	17.1	25.8	36.8	44.4	50.5	65.9	73.5	76.9	90.4	91.0	93.8
100	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.9	3.4	8.3	10.5	21.7	33.9	41.0	50.1	68.2	69.9	74.9	90.8	91.3	91.8

Cumulative numbers of dead parental Daphnia during 21-d.

Nominal concentration	Days																				
(mg/L)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Control	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1(10)	1(10)	1(10)
(Mortality: %)																					

- **Statistical results as appropriate:**

There was no statistically significant difference between data from the control and 100 mg/L test groups.

Remarks field for Results :

– ***Biological observations:***

· Cumulative numbers of dead parental *Daphnia*:
Control: 0 (mortality: 0%)
100 mg/L: 1 (mortality: 10 %)

· Time of the first production of juveniles:
Control: 8 - 10 day (Mean: 8.7)
100 mg/L: 8 - 12 day (Mean: 9.1).

· Mean cumulative numbers of juveniles produced per adult alive for 21days:
Control: 93.8

100 mg/L: 91.8
· Was control response satisfactory: Yes.
Mean cumulative numbers of juveniles produced per adult was 93.8 > 60.

CONCLUSIONS

(Based on nominal concentration)

· NOEC (21-d, reproduction) : = 100 mg/L
· EC50 (14-d, reproduction) : > 100 mg/L
· EC50 (21-d, reproduction) : > 100 mg/L
· LC50 for parental *Daphnia* (14-d) : > 100 mg/L
· LC50 for parental *Daphnia* (21-d) : > 100 mg/L;

Remarks field with the ability to identify source of comment, i.e. author and/or submitter:

DATA QUALITY

- **Reliabilities:** Valid without restriction.
- **Remarks field for Data Reliability:**

Experimental design and analytical procedure were well documented.

REFERENCES

Environment Agency (EA) of Japan (1998).

OTHER

- **Last changed :**
- **Order number for sorting :**
- **Remarks field for General Remarks :**

HEALTH ELEMENTS

(a) ACUTE ORAL TOXICITY

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Unichema Chemie B.V., The Netherlands. ESTOL 1579, Purity: approx. 100 %.

METHOD

- **Method/guideline:** OECD TG 401, EEC Directive 84/449/EEC, Annex V of the EEC Directive 67/548/EEC and Bewertung Wassergefährdender Stoffe, II Bestimmung der akuten oralen Saugetiertoxizität, Ad-hoc-Arbeitsgruppe I (Obmann: Dr. Niemitz), LTWS, Nr. 10 September 1979..
- **Test type:** Acute Oral Toxicity Test
- **GLP:** OECD GLP, US FDA (21 CFR 58) and US EPA (40 CFR 160 and 40 CFR 792).
- **Year:** 1988
- **Species:** Rat
- **Strain:** Wistar (SPF)
- **Route of administration:** Oral (by single-dose gavage)
- **Doses/concentration levels:**

  2,000 mg/kg bw/rat
- **Sex:** Male & Female
- **Control group and treatment:** No control and vehicle used.
- **Post exposure observation period:** Two weeks.
- **Statistical methods:** Not applied because of no mortality observed.

REMARKS FIELD FOR TEST CONDITIONS

– ***Test Subjects:***
  - ***Age at study initiation*:** Eight weeks old.
  - ***Weight at study initiation*:** No data available.
  - ***No. of animals per sex per dose*:** Five per sex per dose group.

– ***Study Design:***
  - ***Vehicle*:** No vehicle, undiluted.
  - ***Satellite groups and reasons they were added*:** None
  - ***Clinical observations performed and frequency*:**

Each rat was weighed immediately prior to treatment, the day after and weekly thereafter for two-week post-treatment observation period. Clinical observations were performed on the day of dosing (once every two hours) and once daily thereafter for two-week post-treatment observation period. Any signs of toxicity were recorded along with the time of onset and duration. At the end of the study (day 14), all animals were euthanized and subjected to necropsy.

RESULTS

- **LD_{50}:** ***Male*** **:** > 2,000 mg/kg bw.
  Female**:** > 2,000 mg/kg bw.

REMARKS FIELD FOR RESULTS.

– ***Body weight:*** All rats gained weight during the two-week observation period. No detailed body weight data available.
– ***Food/water consumption:*** No data available.
– ***Clinical signs :***
No mortality occurred and no signs of systemic toxicity were observed during the 14-day observation period.

Individual animal observations

Physical/Clinical		**Animal Number/Sex**									
Parameter		**4488**	**4490**	**4492**	**4494**	**4498**	**4219**	**4221**	**4223**	**4225**	**4229**
		Males					**Females**				
No effect of treatment	DPD	14	14	14	14	14	14	14	14	14	14
Dead	KIL	X	X	X	X	X	X	X	X	X	X
Necropsy findings	NGL	X	X	X	X	X	X	X	X	X	X

Glossary of terms for list of individual findings:
DPD=Days post dosing.
KIL=Killed at necropsy.
NGL=No gross lesions.
X=Positive.

– ***Haematology*****:** Not done.
– ***Biochem:*** Not done.
– ***Ophthalmologic findings:*** Not examined.
– ***Mortality and time to death:***

Mortality of male and female rats dosed orally with the undiluted test material

Dose level (mg/kg bw)	*# Dead / # Treated*		*Time of Death*	
	Males	**Females**	**Males**	**Females**
2,000	0/5	0/5	--	--

– ***Gross pathology incidence and severity:***
No treatment-related lesions were observed upon gross pathological examination of all animals at the end of two weeks for both sexes.

– ***Organ weight changes:*** Not done.

– ***Histopathology (incidence and severity):*** Not done.

CONCLUSIONS

Since no mortality occurred, the oral LD_{50} value for both males and females was noted as exceeding 2,000 mg/kg bw ("Bewertungszahl"1).

DATA QUALITY

- **Reliabilities:** Valid without restriction.

- **Remarks field for Data Reliability**
  Well conducted study, carried out by RCC NOTOX B.V., The Netherlands.

REFERENCES

Unichema Chemie B.V. (1988), "Acute Oral Toxicity of ESTOL 1579 in the Rat", unpublished data, RCC NOTOX 0831/1056.

GENERAL REMARKS

None.

(b) SKIN IRRITATION/CORROSION

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Data not available.
- **pH:** Not stated.

METHOD

- **Method/guideline:** OECD TG 404 and Off. J. Europ. Coimmun. 27, L251 106-108 (1984).
- **Test type:** *In vivo*
- **GLP:** Yes
- **Year:** 1988
- **Species:** Rabbit
- **Strain:** Chbb : HM
- **Sex:** Male
- **Number of animals per sex per dose:** Four.
- **Total dose:** 0.5 mL/animal.
- **Vehicle:** No vehicle used.
- **Exposure time period:** Four hours.

Grading scale: EC, L257/8 of the 16., September 1983 Corrosive action.

Method remarks: Not mentioned.

RESULTS

- **Primary irritation index:** Not applicable because of no irritation.

Results remarks: Triacetin was tested for its primary skin irritation under occlusive conditions on the shaved back skin of 4 rabbits. After a contact time of 4 hours, the skin reactions were evaluated. Only one animal showed slight skin redness one hour after the application. The other animals had no skin reactions at all.

CONCLUSIONS

According to the criteria in Off. J. Europ. Commun. 26, (L257) 1983, triacetin doesn't need to be classified regarding its skin irritation potential.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability

Well conducted study, carried out by Henkel Institut für Toxikologie (Düsseldorf).

REFERENCES

Kaestner, W. (1988), unpublished data Henkel KGaA. Rep. No. 880236.

GENERAL REMARKS

(c) EYE IRRITATION/CORROSION

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Data not available.
- **pH:** Not stated.

METHOD

- **Method/guideline:** OECD TG 405 and Off. J. Europ. Coimmun. L251, 27. Jg., 1984, S.109-112.
- **Test type:** *In vivo.*
- **GLP:** Yes.
- **Year:** 1988.
- **Methods Remarks:**
- **Species:** Rabbit.
- **Strain:** Chbb : HM
- **Sex:** Male.
- **Number of animals per sex per dose:** Four.
- **Doses used:** 0.1 mL/eye/animal.
- **Observation period:** Seventy two hours after the application.
- **Scoring Method used:** 79/831/EWG, Annex V, Part B.

RESULTS:

Reactions on the cornea and iris were not observed.
The conjunctival reactions were mild and disappeared totally within 6 to 24 hours after the application.

Conjunctivale reaktionen nach application der unverdünnten prüfsubstanz triacetin und dauerkontakt.

Tier-Nr.	Stunden nach der behandlung														
	1			6			24			48			72		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
837	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
847	1	0	2	1	0	0	0	0	0	0	0	0	0	0	0
853	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0
854	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0
Mean A		0.25			0.25			0			0			0	
Mean B		0			0			0			0			0	
Mean C		1.75			0			0			0			0	

A=Rotung, B=Chemosis, C=exsudation

- **Corrosive:** Not applicable (see the results).
- **Irritation score (Cornea/Iris):** No irritation (see the results).
- **Irritation score (Conjunctivae): (Redness/Chemosis)** No irritation (see the results).
- **Overall Irritation Score:** 0.
- **Tool used to assess score:** Not stated.
- **Description of lesions (if seen):** Not stated.

Results remarks: Reactions on the cornea and iris were not observed. The conjunctival reactions were mild and disappeared totally within 6 to 24 hours after the application.

CONCLUSIONS

Triacetin is not eye irritant. According to the criteria in Off. J. Europ. Commun. 26 (L 257) 1983, the test substance doesn't need to be classified regarding its eye irritation potential.

DATA QUALITY

Valid without restriction

QUALITY CHECK

Well conducted study, carried out by Henkel Institut für Toxikologie (Düsseldorf).

REFERENCES

Kaestner, W. (1988), unpublished data Henkel KGaA. Rep. No. 880228.

GENERAL REMARKS

(d) SKIN SENSITIZATION (A HUMAN CASE REPORT)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Eastman Kodak, purity: 99 %.
- **pH:** Not stated.

METHOD

- **Method/guideline:** Other.
- **Test type:** *In vivo* (Human patch test).
- **GLP:** No.
- **Year:** 1963
- **Species:** Human.
- **Strain:** Not applicable.
- **Sex:** Female.
- **Number of animals per sex per dose:** Not applicable.
- **Route of administration:** Skin patch test.
- **Induction concentration:** Not applicable.
- **Induction vehicle:** Not applicable.
- **Challenge concentration:** 0.1, 1, 10 and 50 %.
- **Challenge vehicle:** Ethanol.
- **Grading system used:** Not stated.

Method remarks: Not stated.

RESULTS

- **Case report:** The 29 year old female patient attended outpatients' clinic a few months ago with subacute eczema, which extended over both hands and the backs of the fingers as well as the lateral areas of the first three fingers of both hands. In addition on the right hand the ulnar and radial parts of the palm of the hand were affected. The skin was reddened and thickened in these areas, was covered in individual blisters, scales and crusts and displayed lichenification in part. Tonsillectomy in 1959 as a result of chronic recurrent tonsillitis and abscesses on tonsils. In the same year enucleation of a uterine myoma.

Results of the first patch test.

Test substance	Concentration Solvent	Result after 24 hrs	48 hrs	Comments
Potassium bichromate	0.6 % W	0	0	
	0.1 % W	0	0	
Nickel sulphate	5 % W	0	0	
Formalin	2 % W	0	0	
Terpentine	10 % O	0	0	
p-Phenylenediamine bis	1 % S	0	0	
p-Toluylenediamine bis	1 % S	0	0	
Ethyl p-aminobenzoate	2 % O	0	0	
p-aminomethyl-benzosulphoamide (Marfanil)	10 % W	0	0	
Procaine	2 % w	0	0	
Parobalsam	10 % S	0	0	
Tetramethyl-thiuramdisulphide	1 % S	0	0	
Mercaptobenzothiazole	1 % S	0	0	
Triacetin	50 % A	+++	+++	substance taken from
	10 % A	++	++	the Eastman Kodak patent
	1 % A	+	+	
Filter material (treated with triacetin)	pure	++	++	working substances taken from the Eastman Kodak patent
Filter material (not treated with triacetin)	pure	0	0	

W=dissolved in water, O=dissolved in peanut oil, S=incorporated in ointment, A=dissolved in ethanol, + to +++=positive test reaction of varying intensity, 0=negative reaction.

Results of the second patch test.

Test substance	Concentration Solvent	Result after 24 hrs	48 hrs	Comments
Triacetin	10 % A	++	+++	Haarmann u. Reimann, Holzminden
	1 % A	+	++	
	0.1 % A	+	+	
Diacetin	10 % W	+	+	Redistilled, pure
	1 % W	+	+	Chem. Fabrik Fluka AG, Buchs S,
	0.1 % W	0	0	Switzerland
Monoacetin	10 % W	+	+	Chem. Fabrik Fluka AG, Buchs S,
	1 % W	(+)	?	Switzerland
	0.1 % W	0	0	
Glycerol	pure	0	0	analytical grade
Acetic acid	10 % W	0	0	analytical grade
	1 % W	0	0	
Acetic anhydride	1 % W	0	0	analytical grade
Methyl acetate	10 % A	0	0	analytical grade
Ethyl acetate	10 % W	0	0	analytical grade
Sodium acetate	10 % W	0	0	analytical grade
Methyl glycol acetate	10 % W	0	0	analytical grade

W=dissolved in water, O=dissolved in peanut oil, S=incorporated in ointment, A=dissolved in ethanol, + to +++=positive test reaction of varying intensity, 0=negative reaction.

Grades: **0, +, ++, +++ (four grades)**

Results remarks: In the first and second challenge, control tests with 20 other patients who suffered from eczema with several concentration of triacetin as well as with the filter material had negative results.

CONCLUSIONS

A case of allergic eczema in a 29 year-old patient in a cigarette factory is reported, based on sensitization towards triacetin used for the

production of cigarette filters. The allergy was demonstrated in a patch test. In addition to triacetin, monoacetin and diacetin also produced positive results.

DATA QUALITY

- **Reliabilities:** Valid with restriction

Remarks field for Data Reliability

This is only a case report so far available, carried out by the University Skin Clinic Hamburg-Eppendorf (Germany) and published in detail.

REFERENCES

Unna, P.J., Schulz (1963), K.H. Hautarzt, 14 423-25.

GENERAL REMARKS

(e) REPEATED DOSE TOXICITY (ORAL BY GAVAGE)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Daihachi Chemical Industry. Co., Ltd., Lot No. N-80302, Purity > 98.2 %. Stability during use confirmed by gas chromatography.

METHOD

- **Method/guideline:** OECD TG 422
- **Test type:** OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
- **GLP:** Yes
- **Year:** 1998
- **Species:** Rat
- **Strain:** Crj: CD (SD) IGS
- **Route of administration:** Oral (by gavage)
- **Doses/concentration levels:** 0, 40, 200, 1,000 mg/kg bw/day (5 mL/kg bw in 3 % gum arabic solution)
- **Sex:** Male & Female
- **Exposure period:** ***Males;*** for 44 days from 2 weeks prior to mating.
  Females; for 41 - 48 days from 14 days before mating to day 3 postpartum.
- **Frequency of treatment:** Once daily.
- **Control group and treatment:** Concurrent vehicle.
- **Post exposure observation period:** None.
- **Duration of test:** ***Male;*** for 44 days
  Female; for 41 - 48 days
- **Statistical methods:** Kruskal-Wallis test for non-continuous data or Dunnett's or Scheffe's test for continuous data and Chi square test for quantal data.

REMARKS FIELD FOR TEST CONDITIONS

– ***Test Subjects:***
  - ***Age at study initiation*:** 9 week old for males and females
  - ***Weight at study initiation*:** 317 - 375 g for males, 203 - 240 g for females
  - ***No. of animals per sex per dose*:** 12 per sex per dose group

– ***Study Design:***

· ***Vehicle*:** 3 % gum arabic purified water
· ***Satellite groups and reasons they were added*:** None
· ***Clinical observations performed and frequency*:**
General condition was observed once a day and body wt. was determined on the first, day 3, 7 and 14, the last day of the administration, the day sacrificed and once a week during the administration period. For pregnant females, body wt. was determined on the day 0, 14 and 20 of gestation and on day 0 and 4 of lactation. Food consumption was determined on the same day when body wt. was measured for 24 hr. Haematology and biochemistry for males conducted only at time of necropsy after 44 days of chemical exposure. Urinalysis was not conducted.

· ***Organs examined at necropsy:***
Organ weight: for both sexes, brain, pituitary gland, thyroid gland, heart, liver, kidney, spleen, adrenal, thymus, and in addition for males, testes and epididymis.
Microscopic: all animals in control and 1,000 mg/kg bw group, and unfertilized animals in other groups: brain, spinal cord, pituitary gland, eyeball, thyroid gland (including parathyroid gland), thymus, heart, trachea, lung, liver, kidney, adrenal, spleen, stomach, small intestine, large intestine, pancreas, urinary bladder, bone marrow, sciatic nerve, lymph node, testes, epididymis, prostate, seminal vesicle, ovary, uterus, vagina, mammary gland and any organs, which might be expected to have histopathological changes and thymus and lung of dead animals.

RESULTS

- **NOAEL**

***Male*:** 1,000 mg/kg bw/day
***Female*:** 1,000 mg/kg bw/day

- **LOAEL**

Not determined under the conditions tested.

REMARKS FIELD FOR RESULTS.

– ***Body weight:***

For both sexes, no statistically significant difference from controls was observed in body weight and body weight gain during administration period.

– ***Food/water consumption:***

For both sexes, no statistically significant difference from controls was observed in food consumption during administration period.

– ***Clinical signs :***

Males **:** No dose-related changes in general clinical signs.
Females **:** No dose-related changes in general clinical signs.

– ***Haematology :***

Males **:** Decrease in differential leukocyte count (%) in neutrophils

(band) at 40 ($p<0.05$) and 1,000 mg/kg bw ($p<0.01$), but within physiological changes.

Dose level (mg/kg bw/day)	0	40	200	1,000
Differential leukocyte counts (%)				
Neutrophils (band)	0.7 ± 0.8	0.1 ± 0.3*****	0.3 ± 0.6	0.0± 0.0******

Values are expressed as Mean ± SD
***** Significant at $p \leq 0.05$.
****** Significant at $p \leq 0.01$.

– ***Biochem:***

Males **:** Decrease in creatinine at 40 ($p<0.01$) and 1,000 mg/kg bw ($p<0.01$), but within physiological changes. Increase in inorganic phosphorus at 200 mg/kg bw ($p<0.05$), but with no dose-related changes.

Dose level (mg/kg bw/day)	0	40	200	1,000
Creatinine (mg/dL)	0.58 ± 0.06	0.51 ± 0.03******	0.56 ± 0.14	0.49± 0.03******
Inorganic phosphorus (mg/dL)	7.45 ± 0.46	7.72 ± 0.47	8.05 ± 0.60*****	7.94± 0.40

Values are expressed as Mean ± SD
***** Significant at $p \leq 0.05$.
****** Significant at $p \leq 0.01$.

– ***Urinalysis:*** Not examined.
– ***Ophthalmologic findings:*** Not examined.
– ***Mortality and time to death:*** One male at 1,000 mg/kg bw was dead 32 days after the administration started.
– ***Gross pathology incidence and severity:***

No changes in gross pathology in both sexes.

– ***Organ weight changes:***

Male **:** No dose-related changes in organ weight.
Female **:** No dose-related changes in organ weight.

– ***Histopathology***

Tissue pathology revealed no alteration of tissues even in the highest dose groups for both sexes.

CONCLUSIONS

Triacetin had no effects on clinical signs, body weight, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in both sexes. There were no effects on haematological or blood chemical parameters in males.
A NOAEL was thus established at 1,000 mg/kg bw/day for both sexes.

DATA QUALITY

- **Reliabilities:** Valid without restriction

Remarks field for Data Reliability

Well conducted study, carried out by Mitsubishi Chemical Safety Institute Ltd., Kashima Laboratory (Japan).

REFERENCES

Ministry of Health & Welfare (MHW), Japan (1998), Toxicity Testing Reports of Environmental Chemicals vol.6 127-147.

GENERAL REMARKS

This study was conducted to examine both repeated dose toxicity and reproductive/developmental toxicity as an OECD screening combined study. Therefore, biochemical and haematological analysis, and urinalysis in females were not performed. Functional observation, oestrous cycle length and pattern, and sperm examination were not performed because the test was conducted by the TG adopted in 1990.

(f) REPEATED DOSE TOXICITY (INHALATION)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Plasticizer 88, Eastman Kodak Company, Purity: data not available. Stability and composition of the test material during use was confirmed by gas chromatography.

METHOD

- **Method/guideline:** Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, whole body exposure to vaporized (heated at 150 °C) test substance.
- **Test type:** 90 Days vapour inhalation toxicity study.
- **GLP:** No
- **Year:** 1955.
- **Species:** Rat
- **Strain:** Data not available.
- **Route of administration:** Inhalation
- **Doses/concentration levels:**
  The measured average: 249 ppm (2,220 mg/m^3)
  Measured range of exposure: 14 - 918 ppm (130 – 8190 mg/m^3).
- **Sex:** Data not available.
- **Exposure period:** 90 Days.
- **Frequency of treatment:** Six hours each working day from March 7, 1955 to June 3, 1955.
- **Control group and treatment:** No data available.
- **Post exposure observation period:** None.
- **Duration of test:** 103 Days including the exposure period.
- **Statistical methods:** Data not available.

REMARKS FIELD FOR TEST CONDITIONS

– ***Test Subjects:***

· ***Age at study initiation*:** Data not available.
· ***Weight at study initiation*:** 209 g (average of three rats).
· ***No. of animals per sex per dose*:** Three rats.

– ***Study Design:***

- ***Vehicle*:** None
- ***Satellite groups and reasons they were added*:** None
- ***Clinical observations performed and frequency*:**
  Body wt. for each animal was recorded prior to the first exposure and every 2-9 days interval during the test. The final body wt. of each animal was taken prior to the termination. Haematological studies (RBC, HGB, WBC) and urine analyses (albumin, sugar) were done at intervals (50, 64, 101 days, and 51, 65 days, respectively).

- ***Organs examined at necropsy:***
  Organ weight: liver, kidney.
  Microscopic: No data available except trachea, bronchi, lung, kidney, liver, and bladder

RESULTS

- **NOAEL**

  249 ppm (2,220 mg/m^3)

- **LOAEL**

  Not applicable.

REMARKS FIELD FOR RESULTS.

- ***Body weight:***

  The weights of the animals were followed closely on the graph of the average growth curve. The growth of all animals was normal under the conditions of the experiment. Average daily weight gain was 2.2 g/rat.

- ***Food/water consumption:*** Data not available.
- ***Clinical signs :***

  No symptoms were noted at any time during the exposure, and all rats appeared to be normal.

- ***Haematology :***

  Haematological studies revealed that there was nothing abnormal in any of the animals.

- ***Biochem :***

  Data not available.

- ***Urinalysis :***

  Urine revealed that there was nothing abnormal in any of the animals.

- ***Ophthalmologic findings:*** Not examined.
- ***Mortality and time to death:*** No deaths prior to scheduled termination.
- ***Gross pathology incidence and severity:*** No changes in gross pathology.
- ***Organ weight changes:***

  The weight of both liver and kidney when calculated as per cent of total body weight were found to be within the normal range.

- ***Histopathology :***

  At the time of autopsy, no abnormalities attributable to the exposure were found.

CONCLUSIONS

Histopathology, haematology and urine analyses revealed no changes in diagnostic of an adverse treatment-related effect. Under the conditions of the study, no toxic effects caused by the inhalation of triacetin could be found. Therefore, a NOAEL was established at 249 ppm (2,220 mg/m^3) for male rats.

DATA QUALITY

- **Reliabilities:** Valid with restriction because the studies do not fully comply with the current testing protocol.

Remarks field for Data Reliability

Insufficient data in terms of the current testing guideline, however, carefully conducted study, carried out by Corporate Health and Environment Laboratories, Eastman Kodak Company, Rochester, New York.

REFERENCES

Fassett, D.W. (1955), Corporate Health and Environment Laboratories, Eastman Kodak Company Unpublished data.

GENERAL REMARKS

The purpose of this study was to determine if the plasticiser, when used in acetate cigarette filters, would have any toxic effect on the individuals inhaling the compound.

GENETIC TOXICITY IN VITRO (BACTERIAL TEST)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Daihachi Chemical Industry. Co., Ltd., Lot No. N-80302, Purity > 98.2 %. Stability during use confirmed by gas chromatography.

METHOD

- **Method/guideline**: Guideline for Screening Toxicity Testing of Chemicals (Japan) and OECD TG 471 and 472
- **Test type**: Reverse mutation assay
- **GLP**: Yes
- **Year**: 1998
- **Species/Strain:**

  Salmonella typhimurium TA100, TA1535, TA98, TA1537
  Escherichia coli WP2 *uvr*A
- **Metabolic activation:** With and without S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone.
- **Statistical methods**: No statistical analysis was done.

REMARKS FIELD FOR TEST CONDITIONS

- **Study Design:**
  - ***Concentration*:**
    -S9: 0, 313, 625, 1,250, 2,500, 5,000 ug/plate (five strains)
    +S9: 0, 313, 625, 1,250, 2,500, 5,000 ug/plate (five strains)
  - ***Number of replicates*:** 2
  - ***Plates/test*:** 3
  - ***Procedure*:** Pre-incubation method
  - ***Positive controls*:**
    -S9 mix ; 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98, WP2 uvrA), sodium azide (TA1535) and 9-aminoacridine (TA1537)
    +S9 mix ; 2-aminoanthracene (five strains)

RESULTS

- **Cytotoxic concentration:** Toxicity was not observed up to 5,000ug/plate in five strains with and without metabolic activation (S9 mix).

- **Genotoxic effects:**

	+	?	-
– ***With metabolic activation:***	**[ ]**	**[ ]**	**[x]**
– ***Without metabolic activation:***	**[ ]**	**[ ]**	**[x]**

REMARKS FIELD FOR RESULTS.

CONCLUSIONS

Triacetin did not induce gene mutation in *S. typhimurium* and *E. coli* strains with and without metabolic activation.

DATA QUALITY

- **Reliabilities:** Valid without restriction.

Remarks field for Data Reliability

Well conducted study carried out by Hatano Research Institute, Food and Drug Safety Center (Hadano, Japan).

REFERENCES

Ministry of Health & Welfare (MHW), Japan (1998), Toxicity Testing Reports of Environmental Chemicals vol.6 127-147.

GENERAL REMARKS

None.

GENETIC TOXICITY IN VITRO (NON-BACTERIAL IN VITRO TEST)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Daihachi Chemical Industry. Co., Ltd., Lot No. N-80302, Purity > 98.2 %. Stability during use confirmed by gas chromatography.

METHOD

- **Method/guideline**: OECD TG 473 and Guideline for Screening Toxicity Testing of Chemicals (Japan)
- **Test type**: Chromosomal aberration test
- **GLP***:* Yes
- **Year**: 1998
- **Species/Strain:** CHL/IU cell
- **Metabolic activation:** With and without S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone.
- **Statistical methods**: Fisher's exact analysis

REMARKS FIELD FOR TEST CONDITIONS

- **Study Design:**

For continuous treatment, cells were treated for 24 or 48 hrs without S9. For short-term treatment, cells were treated for 6 hrs with and without S9 and cultivated with fresh media for 18 hrs.

· ***Concentration*:**
-S9 (continuous treatment): 0, 0.55, 1.10, 2.20 mg/mL
-S9 (short-term treatment): 0, 0.55, 1.10, 2.20 mg/mL
+S9 (short-term treatment): 0, 0.55, 1.10, 2.20 mg/mL

· ***Plates/test*:** 2
· ***Positive controls*:**
Mitomycin C for continuous treatment
Cyclophosphamide for short-term treatment

RESULTS

- **Cytotoxic concentration:**

Toxicity was not observed up to 2.20 mg/mL in continuous and short-term treatment without S9 mix, although cell growth was retarded with S9 mix at this concentration under the both treatments. IC_{50} of the test chemical was calculated to be 1.80 mg/mL.

Chromosome analysis of Chinese hamster cells (CHL/IU) continuously treated with triacetin (Ta)**

without S9 mix

Group	Conc. (mg/mL)	Time of exposure (h)	No. of cells analysed	No. of structural aberrations gap	ctb	cte	csb	cse	mul[2]	others[3] total	No. of cells with aberrations TAG(%)	TA(%)	Polyploid[4] (%)	Trend test[5] SA	NA	Concurrent cytotoxicity[6] (%)	Mitotic index[7] (%)
Non-treatment			200	0	0	0	0	0	0	1	0 (0.0)	0 (0.0)	0.25			-	-
Solvent[1]	0	24	200	0	1	0	0	0	1	0	1 (0.5)	1 (0.5)	0.50			100.0	-
Ta	0.55	24	200	0	0	2	0	0	2	1	2 (1.0)	2 (1.0)	0.00			100.0	-
Ta	1.10	24	200	0	1	2	0	0	3	1	3 (1.5)	3 (1.5)	0.25	-	-	92.5	-
Ta	2.20	24	200	0	0	0	0	0	0	0	0 (0.0)	0 (0.0)	0.00			90.5	8.6
MC	0.00005	24	200	2	8	26	0	0	36	0	33*(16.5)	31*(15.5)	0.13			-	-
Solvent[1]	0	48	200	0	0	0	0	0	0	0	0 (0.0)	0 (0.0)	0.25			100.0	-
TA	0.55	48	200	0	0	0	0	0	0	0	0 (0.0)	0 (0.0)	0.38			105.0	-
TA	1.10	48	200	0	0	0	0	0	0	1	0 (0.0)	0 (0.0)	0.38	-	-	104.0	-
TA	2.20	48	200	0	0	0	0	0	0	0	0 (0.0)	0 (0.0)	0.13			85.0	6.8
MC	0.00005	48	200	6	13	27	0	4	0	50 4	40*(20.0)	34*(17.0)	0.25			-	-

Abbreviations, gap: chromatid gap and chromosome gap, ctb: chromatid break, cte: chromatid exchange, ctb: chromosome break, cse: chromosome exchange (dicentric and ring), mul: multiple aberrations, TAG: total no. of cells with aberrations, TA: total no. of cells with aberrations except gap, SA: structural aberration, NA: numerical aberration, MC: mitomycin C.
1) DMSO was used as solvent. 2) More than nine aberrations in a cell were scored as 10. 3) Others, such as attenuation and premature chromosome condensation, were excluded from the no. of structural aberrations. 4) Eight hundred cells were analysed in each group. 5) Cochran-Armitage's trend test was done at p<0.01. 6) Cell confluency, representing cytotoxicity, was measured with Monocellater™. 7) Number of metaphase per 500 cells was scored in each dish in order to select the highest dose enable to analyse chromosomes.
*: Significantly different from solvent control at p<0.01 by Fisher's exact test. **: Purity was 98.2 wt%. Diacetin (0.9%) was contained as an impurity.

Chromosome analysis of Chinese hamster cells (CHL/IU) treated with triacetin (Ta)** with and without

S9 mix

Group	Conc. (mg/mL)	S9 mix	Time of exposure (h)	No. of cells analysed	No. of structural aberrations gap	ctb	cte	csb	cse	mul[2]	others[3] total	No. of cells with aberrations TAG(%)	TA(%)	Polyploid[4] (%)	Trend test[5] SA	NA	Concurrent cytotoxicity[6] (%)	Mitotic index[7] (%)
Non-treatment				200	0	0	0	0	0	0	0	0 (0.0)	0 (0.0)	0.00			-	-
Solvent[1]	0	-	6-(18)	200	0	0	0	0	0	0	1	0 (0.0)	0 (0.0)	0.13			100.0	-
Ta	0.55	-	6-(18)	200	0	0	0	4	0	0	4 0	1 (0.5)	1 (0.5)	0.63			100.0	-
Ta	1.10	-	6-(18)	200	0	1	1	0	0	0	2 0	2 (1.0)	2 (1.0)	0.00	-	-	99.5	-
Ta	2.20	-	6-(18)	200	0	0	0	0	0	0	0 0	0 (0.0)	0 (0.0)	0.25			90.5	9.2
CPA	0.005	-	6-(18)	200	0	2	0	2	0	0	4 3	1 (0.5)	1(0.5)	0.50			-	-
Solvent[1]	0	+	6-(18)	200	0	0	0	0	0	0	0 0	0 (0.0)	0 (0.0)	0.25			100.0	-
Ta	0.55	+	6-(18)	200	0	0	0	0	0	0	0 0	0 (0.0)	0 (0.0)	0.50			109.0	-
Ta	1.10	+	6-(18)	200	0	0	1	0	0	0	1 0	1 (0.5)	1 (0.5)	0.25	+	-	104.5	-
Ta	2.20***	+	6-(18)	200	10	59	103	0	0	70	242 1	87*(43.5)	84*(42.0)	0.26			25.5	1.6
CPA	0.005	+	6-(18)	200	4	28	113	1	0	0	146 0	91*(45.5)	90*(45.0)	0.13			-	-

Abbreviations, gap: chromatid gap and chromosome gap, ctb: chromatid break, cte: chromatid exchange, ctb: chromosome break, cse: chromosome exchange (dicentric and ring), mul: multiple aberrations, TAG: total no. of cells with aberrations, TA: total no. of cells with aberrations except gap, SA: structural aberration, NA: numerical aberration, MC: mitomycin C.
1) DMSO was used as solvent. 2) More than nine aberrations in a cell were scored as 10. 3) Others, such as attenuation and premature chromosome condensation, were excluded from the no. of structural aberrations. 4) Eight hundred cells were analysed in each group. 5) Cochran-Armitage's trend test was done at p<0.01. 6) Cell confluency, representing cytotoxicity, was measured with Monocellater™. 7) Number of metaphase per 500 cells was scored in each dish in order to select the highest dose enable to analyse chromosomes. 8) Seven hundred and eighty cells were analysed.
*: Significantly different from solvent control at p<0.01 by Fisher's exact test. **: Purity was 98.2 wt%. Diacetin (0.9%) was contained as an impurity.
***: Medium colour was changed to yellow during the incubation and the pH adjusted to 6.93 at 0 hr lowered to 4.91 after the 6-hr incubation.

- **Genotoxic effects:**

	Clastogenicity			polyploidy		
	+	?	-	+	?	-
– ***Without metabolic activation:***	**[ ]**	**[ ]**	**[x]**	**[ ]**	**[ ]**	**[x]**
– ***With metabolic activation:***	**[ ]**	**[x]**	**[ ]**	**[ ]**	**[ ]**	**[x]**

REMARKS FIELD FOR RESULTS.

Structural chromosomal aberrations were induced on a short-term treatment with an exogenous metabolic activation system at the highest concentration of the test chemical (2.2 mg/mL or 10 mM). Under such conditions, pH of the test medium decreased to pH 4.91 in the presence of the chemical. It is recognised that changes in pH can induce artefacts in this assay. Therefore, it was suggested that chromosomal aberrations induced by the triacetin were due to the lowering pH effect of the chemical rather than DNA damage per se. Polyploidy were not induced under any conditions tested.

CONCLUSIONS

Triacetin induced chromosomal aberration in CHL/IU cells on a short-term treatment with metabolic activation system. It is, however, recognized that chromosomal aberration induced at 2.2 mg/mL can be artefacts in this assay.

DATA QUALITY

- **Reliabilities:** Valid without restriction.

Remarks field for Data Reliability

Well conducted study, carried out by Hatano Research Institute, Food and Drug Safety Center (Hadano, Japan).

REFERENCES

Ministry of Health & Welfare (MHW), Japan (1998), Toxicity Testing Reports of Environmental Chemicals vol.6 127-147.

GENERAL REMARKS

None.

TOXICITY TO REPRODUCTION/DEVELOPMENT

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: Daihachi Chemical Industry. Co., Ltd., Lot No. N-80302, Purity > 98.2 %. Stability during use confirmed by gas chromatography.

METHOD

- **Method/guideline:** OECD TG 422
- **Test type:** OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
- **GLP:** Yes
- **Year:** 1998
- **Species:** Rat
- **Strain:** Crj:CD (SD)IGS
- **Route of administration:** Oral (by gavage)
- **Doses/concentration levels:**

  0, 40, 200, 1,000 mg/kg bw/day (5 mL/kg bw in 3 % gum arabic solution)
- **Sex:** Male & Female
- **Exposure period:** ***Males*****;** for 44 days from 2 weeks prior to mating
  Females**;** for 41 - 48 days from 14 days before mating to day 3 postpartum throughout mating and pregnancy.
- **Frequency of treatment:** Once daily.
- **Control group and treatment:** Concurrent vehicle (3 % gum arabic purified water).
- **Post exposure observation period:** None.
- **Duration of test:** ***Male*****;** for 44 days
  Female**;** for 41 - 48 days
- **Statistical methods:** Kruskal-Wallis test for non-continuous data or Dunnett's or Scheffe's test for continuous data and Chi square test for quantal data.

REMARKS FIELD FOR TEST CONDITIONS

– ***Test Subjects:***

  · ***Age at study initiation*****:** 9 week old for males and females
  · ***Weight at study initiation*****:** 317 - 375 g for males, 203 - 240 g for females

· ***No. of animals per sex per dose*:** 12 per sex per dose group

– ***Study Design:***

The animals were sacrificed on the day 4 of lactation for females. Females with no pregnancy were killed 26 days after the postcoitum date (1/12 in 200mg/kg bw group).

· ***Vehicle*:** 3 % gum arabic purified water.

· ***Satellite groups and reasons they were added*:** None.

· ***Mating procedures*:** Male/female per cage; 1/1, length of cohabitation; 7 days at the longest, until proof of pregnancy (formation of vaginal closing or sperm detection in vagina).

· ***Clinical observations performed and frequency*:**
Parent: General appearance once a day
Foetus: General appearance once a day after birth
Haematology and biochemistry for males conducted only at time of necropsy after 44 days of chemical exposure. Urinalysis was not done.

· ***Organs examined at necropsy*:**
Organ weight: for both sexes, brain, pituitary gland, thyroid gland, heart, liver, kidney, spleen, adrenal, thymus, and in addition for males, testes and epididymis.
Microscopic: all animals in control and 1,000 mg/kg bw group, and unfertilized animals in other groups: brain, spinal cord, pituitary gland, eyeball, thyroid gland (including parathyroid gland), thymus, heart, trachea, lung, liver, kidney, adrenal, spleen, stomach, small intestine, large intestine, pancreas, urinary bladder, bone marrow, sciatic nerve, lymph node, testes, epididymis, prostate, seminal vesicle, ovary, uterus, vagina, mammary gland and any organs, which might be expected to have histopathological changes and thymus and lung of dead animals.
Foetal: full macroscopic examinations on all live and dead pups.

· ***Parameters assessed during study*:**
Body wt. (for males, once a week, and the first, the last day of the administration, the day sacrificed, and for pregnant females, the day 0, 14 and 20 of gestation and on day 0 and 4 of lactation), food/water consumption (once a week, and on the same day when body wt. determined), No. of pairs with successful copulation, copulation index (No. of pairs with successful copulation/No. of pairs mated x 100), pairing days until copulation, No. of pregnant females, fertility index = (No. of pregnant animals/No. of pairs with successful copulation x 100), No. of corpora lutea, No. of implantation sites, implantation index (No. of implantation sites/No. of corpora lutea x 100), No. of living pregnant females, No. of pregnant females with parturition, gestation length, No. of pregnant females with live pups on day 0, gestation index (No. of females with live pups/No. of living pregnant females x 100), No. of pregnant females with live pups on day 4, delivery index (No. of pups born/No. of implantation sites x 100), No. of pups alive on day 0 of lactation, live birth index (No. of live pups on day 0/No. of pups born x 100), sex ratio (Total No. of male

pups/Total No. of female pups), No. of pups alive on day 4 of lactation, viability index (No. of live pups on day 4/No. of live pups on day 0 x 100), body wt. of live pups (on day 0 and 4)

RESULTS

- **NOAEL and LOAEL maternal toxicity:**

  NOAEL: 1,000 mg/kg bw/day

- **NOAEL and LOAEL foetal toxicity:**

  NOAEL: 1,000 mg/kg bw/day

- **Actual dose received by dose level by sex if available:**

  0, 100, 300, 1,000 mg/kg bw/day for 14 consecutive administrations for both sexes.

- **Maternal data with dose level :**

  No effects related to chemical exposure were observed at all doses, although there was a single unsuccessful copulation in control. At 200 mg/kg bw-group, one animal was not delivered of pups.

- **Foetal data with dose level :**

  No effects related to chemical exposure were observed at all doses.

REMARKS FIELD FOR RESULTS.

– ***Mortality and day of death:*** At 1,000 mg/kg bw, one male rat died 32 days after administration, but without apparent relation to the exposure.

– ***Body weight:*** No dose-related changes in body weight and body weight gains for both sexes.

– ***Food/water consumption:*** No dose-related changes in food consumption for both sexes.

– ***Reproductive data:*** No statistically significant difference from controls.

– ***Fetal data :*** No statistically significant difference from controls, although 3, 6, 5 and 1 dead pups at birth or soon after birth were observed at 0, 40, 200 and 1,000 mg/kg bw, respectively.

– ***Grossly visible abnormalities, external, soft tissue and skeletal abnormalities :***
No statistically significant effects were observed at all doses.

Fertility and pregnancy data in rats treated orally with triacetin

Dose level (mg/kg bw/day)	0	40	200	1,000
No. of pairs mated	12	12	12	12
No. of pairs mated with successful copulation	11	12	12	12
Copulation index (%)	91.7	100	100	90
No. of pregnant females	10	12	12	12
Fertility index (%)	90.9	100	90	100

Pairing days until copulation (Mean ± S.D.)	2.6±1.4	2.3±1.4	3.4±1.4	3.0±1.7
No. of estrous stages without mating	0.0±0.0	0.0±0.0	0.1±0.3	0.1±0.3

Copulation index (%)= (No. of pairs with successful copulation / No. of pairs mated) x100
Fertility index (%) =(No. of pregnant females / No. Of pairs with successful copulation) x100

Delivery and litter data in rats treated orally with triacetin

Dose level (mg/kg bw/day)	**0**	**40**	**200**	**1,000**
No. of females examined	10	12	12	12
No. of females with live pups	10	12	11	12
Gestation index (%)	100	100	91.7	100
Gestation length (days, Mean ± SD)	22.6±0.5	22.4±0.5	22.4±0.5	22.6±0.4
No. of corpora lutea (Mean ± SD)	16.6±1.8	16.3±1.9	16.3±1.6	16.8±0.5
No. of implantation sites (Mean ± S.D.)	15.3±4.4	16.0±1.7	14.7±4.4	15.8±1.4
Implantation index (%, Mean ± S.D.)	90.2±23.2	98.2±4.8	89.5±26.4	93.8±4.8
Delivery index (%, Mean ± S.D.)	94.8±7.2	95.1±4.8	90.2±28.5	92.6±3.5
No. of pups born	14.4±4.1	15.3±2.1	15.6±0.8	14.6±1.4
No. of pups alive on day 0 of lactation	14.2±4.1	15.3±2.1	15.5±0.8	14.6±1.4
Live birth index (%)	98.7±2.7	100±0.0	98.9±2.5	100±0.0
Sex ratio (Male/Female)	1.25 (79/63)	0.89 (86/97)	1.18 (92/78)	0.88 (82/93)
No. of pups alive on day 4 of lactation	14.1±4.1	14.8±1.7	15.2±0.8	14.5±1.4
Viability index on day 4 of lactation (%)	14.1±4.1	14.8±1.7	15.2±0.8	14.5±1.4
Body weight of live pups (g)				
(On day 0)				
Male	7.1±0.6	6.8±0.6	6.5±0.6	7.1±0.6
Female	6.7±0.6	6.4±0.6	6.3±0.6	6.7±0.6
(On day 4)				
Male	11.1±1.7	10.8±1.3	10.2±0.5	11.3±1.0
Female	10.7±1.6	10.4±1.2	9.8±0.7	10.9±1.1
Body weight gain of pups (g)				
(On day 0-4)				
Male	4.0±1.1	4.0±0.9	3.7±0.5	4.5±0.7
Female	4.0±1.1	3.9±0.8	3.4±0.5	4.4±0.6

Gestation index (%)=(No. of females with live pups / No. of pregnant females) x100
Delivery index (%) = (No. of pups born/ No. of implantation sites) x100
Live birth index (%) =(No. of live pups on day 0 / No. of pups born) x100
Viability index (%) =(No. of live pups on day 4/ No. of live pups on day 0) x100
Sex ratio =Total No. of male pups/ Total No. of female pups
Values are expressed as Mean±S.D. Except sex ratio.

CONCLUSIONS

No effects related to chemical exposure were observed maternally at all dose levels, although there was a single undelivered animal at 200 mg/kg bw which was not statistically significantly different from the control ($p<0.05$). Similarly, no effects related to the chemical exposure were observed at all dose levels on reproductive parameters including the mating index, fertility index, gestation length, numbers of corpora lutea and implantations, implantation index, gestation index, delivery index, parturition and maternal behaviour at delivery and lactation. Therefore, a NOAEL was established at 1,000 mg/kg bw/day.

DATA QUALITY

- **Reliabilities:** Valid without restriction.

Remarks field for Data Reliability

Well conducted study, carried out by Research Institute for Animal Science in Biochemistry and Toxicology (Japan).

REFERENCES

Ministry of Health & Welfare (MHW), Japan (1998), Toxicity Testing Reports of Environmental Chemicals vol.6 127-147.

Pharmacokinetics (Metabolism)

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: British Drug Houses, purity: not available.

METHOD

- **Method/guideline:** Other.
- **Test type:** *In vitro*.
- **GLP:** No.
- **Year:** 1966.
- **Method:** The procedure used in most experiments followed closely that outlined by Parsons et al. (1958) (J. Physiol., 144 387-402). The sacs of the everted intestine, the middle fifth of the combined jejunum and ileum was used. The sacs contained initially 1 mL of bicarbonate saline and shaken for 1 hr at 37 °C. Acetins, glucose, acetate, or metabolic inhibitors were added to the saline. At the end of the incubation, fluid transfer was estimated by weighing the sac and its contents, and acetate determinations were made on samples of the mucosal and serosal fluids. Acetates were estimated by steam distillation from an all-glass Markham apparatus and titration of the distillate with 0.05 N-NaOH using phenol red as indicator.
- **Species:** White rat.
- **Strain:** Sheffield.
- **Sex:** Male.
- **Age:** Not stated.
- **Body weight:** 230 g.
- **Number of Animals/Donors:** Data not available.
- **Route of administration:** Not applicable.
- **Vehicle:** One mL of bicarbonate saline (Krebs, H. A. and Henseleit, K, 1932, Hoppe-Seyler's Z. Physiol. Chem., 210 33-66)/sac.
- **Doses/concentration levels:** 1, 2, 5, 10, 15, 20, 30, 40, 50 and 70 mM (glyceride)
- **Statistical methods:** Mean ± S.E.M.
- **Actual doses:** Not applicable.
- **Excretion routes:** Not applicable.

- **Body fluids sampled:** Not applicable.
- **Tissues sampled:** Not applicable.
- **Metabolites (CAS):** Acetic acid (64-19-7).
  Glycerol (56-81-5).

RESULTS

Effect of concentration of glyceride on hydrolysis by everted sacs.

	Acetate released (umoles)		
Concentration of glyceride (mM)	**Monoacetin**	**Diacetin**	**Triacetin**
1	-	-	31±1 (5)
2	-	-	61±2 (5)
5	40±3 (5)	84±4 (5)	139±4 (5)
10	71±4 (5)	144±9 (5)	211±12 (5)
15	92±4 (5)	206±12 (11)	307±11 (5)
20	-	231±10 (5)	-
30	195±6 (5)	310±16 (5)	-
40	274±12 (5)	-	
50	295±18 (5)	376±18 (5)	-
70	309±19 (5)	-	
5 mM monoacetin+5 mM diacetin	107±5 (5)	-	
5 mM monoacetin+5 mM triacetin	177±11 (5)	-	
5 mM diacetin+5 mM triacetin	198±11 (5)	-	

***The sacs contained initially I mL bicarbonate saline and were suspended in 15 mL of the same solution for I hr at 37 °C. Values are expressed as umoles/g initial wet wt. of tissue. All values are means S.E.M. with the number of experiments in brackets.**

Effect of concentration on entry into rat intestine from mucosal fluid.

	Glyceride entry rate (umoles)		
Concentration of glyceride (mM)	**Monoacetin**	**Diacetin**	**Triacetin**
1	-	-	10
2	-	-	20
5	40	42	46
10	71	72	70
15	92	103	102
20	-	115	-
30	195	155	-
40	274	-	-
50	295	188	-
70	309	-	-

Final concentration of acetate in mucosal and serosal fluid when glyceride is initially present in the mucosal fluid.

Glyceride (mM)	**Monoacetin**			**Diacetin**			**Triacetin**			
	No. of expts.	**Final mucosal acetate (mM)**	**Final serosal acetate (mM)**	**No. of expts.**	**Final mucosal acetate (mM)**	**Final serosal acetate (mM)**	**No. of expts.**	**Final mucosal acetate (mM)**	**Final serosal acetate (mM)**
1	-	-	-	-	-	-	5	1.39±0.07	5.06±0.06
2	-	-	-	-	-	-	5	2.70±0.17	11.31±0.83
5	5	1.78±0.07	8.50±0.34	10	3.12±0.10	14.67±0.54	5	5.39±0.14	27.75±0.52
10	5	2.78±0.05	16.35±0.51	9	4.98±0.13	27.56±1.24	10	10.56±0.18	40.02±1.45
15	9	4.76±0.09	25.25±0.22	9	6.25±0.22	42.00±1.23	5	17.94±0.18	26.60±1.42
20	-	-	-	9	7.98±0.15	47.78±0.73	-	-	-
30	5	6.19±0.25	43.56±1.72	5	11.31±0.31	54.87±1.41	-	-	-
40	5	8.41±0.25	50.37±0.74	-	-	-	-	-	-
50	6	9.37±0.49	45.62±0.92	5	18.21±0.14	39.75±2.70	-	-	-
70	5	14.31±0.75	46.56±2.12	-	-	-	-	-	-

***The sacs contained initially I mL bicarbonate saline and were suspended in 15 mL of the same solution for I hr at 37 °C. Values are expressed as umoles/g initial wet wt. of tissue. All values are means S.E.M. with the number of experiments in brackets.**

Summary

(1) When triacetin, mono- and diacetins were incubated with the sacs of rats everted intestine, the glycerides entered the epithelial cells and were completely hydrolyzed to free glycerol and acetic acid. The activity of the preparation, as measured by acetate release, increased with the number of acetic acid residues in the glyceride (15 mM). Monoacetin, diacetin and triacetin released 92 ± 4, 206 ± 12 and 307 ± 11 umoles of acetate, respectively. With increasing concentrations of glyceride (5, 10 and 15 mM), the amount of acetate released increased linealy up to about a total amount of 300 umoles of acetates released. There is no absolute positional specificity, and all three ester linkages can be split.

(2) The rate limiting step in the process was the entry of glyceride into the epithelial cell.
(3) The three acetins entered the epithelial cells at the same rate.
(4) The acetate released appeared in higher concentrations on the serosal sides.
(5) Volatile fatty acids, which released from acetins could be transferred into the cells by the rat ..... intestine against a concentration gradient.

CONCLUSIONS

When triacetin, mono- and diacetins were incubated with the sacs of rats everted intestine, every glyceride was hydrolyzed completely to free glycerol and acetic acid. There was no absolute positional specificity for three ester linkages.

DATA QUALITY

- **Reliabilities:** Valid with restriction.

Remarks field for Data Reliability

Data is historic. This study, however, clearly demonstrated that triacetin is hydrolysed to free glycerol and acetic acid by rat intestine without positional specificity for ester linkages.

REFERENCES

Barry, R.J.C. et al. (1966), J. Physiol. 185 667-683.

GENERAL REMARKS

Pharmacokinetics

TEST SUBSTANCE

- **Identity:** Triacetin (CAS No. 102-76-1)
- **Remarks:** Source: data not available.

METHOD

- **Method/guideline:** Other.
- **Test type:** *In vivo*
- **GLP:** No.
- **Year:** 1993.
- **Method:**

Triacetin was administered intravenously to mongrel dogs (n=10) 2 weeks after surgical placement of blood-sampling catheters in the aorta and in the portal, hepatic, renal, and femoral veins.
[1-^{14}C] Acetate was infused to allow quantification of organ uptake of acetate as well as systemic turnover and oxidation.
After 3 hr of tracer infusion, a 5 % (v/v) aqueous solution of triacetin was administered intravenously to mongrel dogs at a rate of 47 umol/kg bw/min (estimated resting energy expenditure: REE) for an additional 4 hours, after [1-^{14}C] acetate was infused at a rate of ca. 30 kBq/min for 3 hours (continued to the end of study) to allow quantification of organ uptake of acetate as well as systemic turnover and oxidation.

- **Species:** Dog.
- **Strain:** Mongrel.
- **Sex:** Data not available.
- **Age:** Data not available.
- **Body weight:** 23.4±0.3 kg.
- **Number of Animals/Donors:** Ten animals.
- **Route of administration:** Infusion via postcava.
- **Vehicle:** 150 mmol NaCl/L containing 2mmole $NaHCO_3$/L.
- **Doses/concentration levels:** 47 umol/kg bw/min (triacetin).
- **Statistical methods:** Average values for plasma acetate concentration and specific activity, mean values for $^{14}CO_2$ excretion rate for breath samples. Systemic acetate turnover and oxidation were determined by using steady-state formulas.

- **Actual doses:** Not applicable.
- **Excretion routes:** Breath.
- **Body fluids sampled:** 15-min Intervals over the last 30 min of the triacetin infusion.
- **Tissues sampled:** Blood.
- **Metabolites:** Not stated.
- **Metabolites CAS:** Not stated.

RESULTS

Plasma acetate concentration after steady-state conditions were achieved.(umol/L)

Aorta	Renal vein	Portal vein	Femoral vein	Hepatic vein
1180	935	817	752	473

Acetate turnover rate during triacetin infusion.
2214±95 umol/min, 68±3 % of the known rate of triacetin-derived acetate infusion, on the assumption that there was complete hydrolysis of the triglyceride.

Acetate oxidation during triacetin infusion.
1876±132 umol/min, 85±5 % of the acetate turnover.

Acetate clearance during triacetin infusion.
2.0±0.1 L/min.

Organ acetate uptake in dogs, postabsorptively.

Tissue	No. of animals	Uptake (umol/min)
Hindlimb	9	89±7
Total skeletal muscle*		445±35
Intestine	10	342±23
Liver	6	559±68
Kidney	4	330±37

*It was assumed that 20 % of whole-body skeletal muscle is represented in the hindlimb.

Systemic acetate kinetics was obtained in all animals tested. Systemic acetate turnover accounted for approximately 70 % of triacetin-derived acetate, assuming complete hydrolysis of the triglyceride. Approximately 80 % of systemic acetate uptake was rapidly oxidized. Significant acetate uptake was demonstrated in all tissues (liver, 559 ± 68; intestine, 342 ± 23; hindlimb, 89 ± 7; and kidney, 330 ± 37 umol/min).

CONCLUSIONS

During intravenous administration in dogs, the majority of infused triacetin undergoes intravascular hydrolysis, and the majority of the resulting acetate is oxidized. Thus, energy in the form of short-chain fatty acids can be delivered to a resting gut via intravenous infusion of a short-chain triglyceride.

DATA QUALITY

- **Reliabilities:** Valid with restriction.

Remarks field for Data Reliability

REFERENCES

Bleiberg, Batia et al., (1993), Am. J. Clin. Nutr. 58 908-911.

GENERAL REMARKS

Triacetin is a water-soluble short-chain triglyceride that may have a role as a parenteral nutrient.

Appendix : Parameters used in calculation of distribution by Mackay level III fugacity model.
(Part 1)

Physico-Chemical Properties
(water solubility : 70g/L)

Chemical		Triacetin	Method
Molecular weight		218.21	calculated
Melting point [℃]		3	unkown
Vapour pressure [Pa]		0.331	unkown
Water solubility [g/m^3]		70000	measured
log Kow		0.21	measured
Half life [h]	In air	48	estimated
	In water	168	measured
	In soil	504	estimated
	In sediment	504	estimated

Temp. [℃]	25

Emission Scenario

Scenario	emission rate [kg/h]		
case	b.air E_1	b.w. E_2	b.soil E_3
1	1000	0	0
2	0	1000	0
3	0	0	1000
4	600	300	100
5	333	333	333

Theoretical Distribution of Triacetin

Compartment	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
	100% to air	100% to water	100% to soil	60% to air, 30% to water, 10% to soi	Equal emission air:water:soil=1: 1: 1
Air	0.9%	0.0%	0.0%	0.6%	0.3%
Water	20.0%	99.7%	12.9%	31.6%	30.1%
Soil	79.1%	0.0%	87.1%	67.8%	69.5%
Sediment	0.1%	0.3%	0.0%	0.1%	0.1%

Environmental Parameter

		volume [m3]	depth [m]	area [m2]	organic carbon	lipid content [-]	density [kg/m3]	residense time [h]
Bulk Air	air	1E+13					1.2	100
	water	2E+03						
	total	1E+13	1000	1E+10				
Bulk Water	water	2E+10					1000	1000
	susp. particles	1E+06			0.0		1500	
	fish	2E+05				0.05	1000	
	total	2E+10	10	2E+09				
Bulk Soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
Bulk Sediment	water	8E+07					1000	
	solid	2E+07			0.06		2400	50000
	total	1E+08	0.05	2E+09				

Scenario	emission rate [kg/h]			fugacity [Pa]				concentration [g/m^3]			
case	b.air E_1	b.wat. E_2	b.soil E_3	b.air f_1	b.w. f_2	b.soil f_3	b.sed. f_4	b.air C_1	b.wat. C_2	b.soilC_3	b.sed.C_4
1	1000	0	0	4.3E-06	2.0E-08	3.0E-06	1.3E-08	3.8E-07	4.3E-03	2.1E-01	2.2E-03
2	0	1000	0	1.7E-10	4.6E-08	1.2E-10	2.9E-08	1.5E-11	9.7E-03	8.6E-06	5.1E-03
3	0	0	1000	5.1E-08	1.6E-08	4.2E-06	1.0E-08	4.5E-09	3.5E-03	2.9E-01	1.8E-03
4	600	300	100	2.6E-06	2.8E-08	2.2E-06	1.8E-08	2.3E-07	5.8E-03	1.6E-01	3.0E-03
5	333	333	333	1.4E-06	2.8E-08	2.4E-06	1.8E-08	1.3E-07	5.8E-03	1.7E-01	3.0E-03

Scenario	amount [kg]				total	transformation rate by reaction [kg/h]				transformation rate by advection [kg/h]		
case	b.air m_1	b.wat. m_2	b.soil m_3	b.sed. m_4	[kg]	b.air	b.wat. R_2	b.soil R_3	b.sed. R_4	b.air A_1	b.wat. A_2	b.sed. A_4
1	3.8E+03	8.6E+04	3.4E+05	2.2E+02	4.3E+05	5.4E+01	3.5E+02	4.7E+02	3.1E-01	3.8E+01	8.6E+01	4.5E-03
2	1.5E-01	1.9E+05	1.4E+01	5.1E+02	2.0E+05	2.2E-03	8.0E+02	1.9E-02	7.0E-01	1.5E-03	1.9E+02	1.0E-02
3	4.5E+01	6.9E+04	4.7E+05	1.8E+02	5.4E+05	6.6E-01	2.9E+02	6.4E+02	2.5E-01	4.5E-01	6.9E+01	3.6E-03
4	2.3E+03	1.2E+05	2.5E+05	3.0E+02	3.7E+05	3.3E+01	4.8E+02	3.5E+02	4.2E-01	2.3E+01	1.2E+02	6.1E-03
5	1.3E+03	1.2E+05	2.7E+05	3.0E+02	3.9E+05	1.8E+01	4.8E+02	3.7E+02	4.2E-01	1.3E+01	1.2E+02	6.1E-03

Scenario	transport rate between spheres [kg/h]						
case	air→ water	water→ air	air→ soil	soil→ air	soil→ water	water→ sed.	sed.→ water
1	1.8E+02	1.8E-02	7.3E+02	8.8E+00	2.6E+02	8.6E-01	5.5E-01
2	7.5E-03	4.1E-02	3.0E-02	3.6E-04	1.0E-02	1.9E+00	1.2E+00
3	2.2E+00	1.4E-02	8.8E+00	1.2E+01	3.5E+02	6.9E-01	4.4E-01
4	1.1E+02	2.4E-02	4.4E+02	6.5E+00	1.9E+02	1.2E+00	7.4E-01
5	6.2E+01	2.4E-02	2.5E+02	7.0E+00	2.0E+02	1.2E+00	7.4E-01

Z and D values

	Z_B [mol/m^3·Pa]	D_R [mol/Pa·h]	D_A [mol/Pa·h]
Bulk Air (1)	4.0E-04	5.8E+07	4.0E+07
Bulk Water (2)	8.0E+02	6.6E+10	1.6E+10
Bulk Soil (3)	2.7E+02	5.9E+08	0.0E+00
Bulk Sediment (4	6.6E+02	9.0E+07	1.3E+06

D_{12} [mol/Pa·h]	D_{21} [mol/Pa·h]	D_{13} [mol/Pa·h]	D_{31} [mol/Pa·h]
1.6E+08	4.0E+06	6.6E+08	1.3E+07

D_{32} [mol/Pa·h]	D_{24} [mol/Pa·h]	D_{42} [mol/Pa·h]
3.2E+08	1.6E+08	1.6E+08

Appendix : Parameters used in calculation of distribution by Mackay level III fugacity model.
(Part 2)

Physico-Chemical Properties

(water solubility : 58g/L)

Chemical		Triacetin	Method
Molecular weight		218.21	calculated
Melting point [℃]		3	unkown
Vapour pressure [Pa]		0.331	unkown
Water solubility [g/m^3]		58000	measured
log Kow		0.21	measured
Half life [h]	In air	48	estimated
	In water	168	measured
	In soil	504	estimated
	In sediment	504	estimated

Temp. [℃]	25

Emission Scenario

Scenario	emission	rate [kg/h]	
case	b.air E_1	b.w. E_2	b.soil E_3
1	1000	0	0
2	0	1000	0
3	0	0	1000
4	600	300	100
5	333	333	333

Theoretical Distribution of Triacetin

Compartment	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
	100% to air	100% to water	100% to soil	60% to air, 30% to water, 10% to soi	Equal emission air:water:soil=1: 1: 1
Air	1.1%	0.0%	0.0%	0.7%	0.4%
Water	19.9%	99.7%	12.9%	31.7%	30.2%
Soil	79.0%	0.0%	87.1%	67.5%	69.4%
Sediment	0.1%	0.3%	0.0%	0.1%	0.1%

Environmental Parameter

		volume [m^3]	depth [m]	area [m^2]	organic carbon content [-]	lipid content [-]	density [kg/m^3]	residense time [h]
Bulk Air	air	1E+13					1.2	100
	water	2E+03						
	total	1E+13	1000	1E+10				
Bulk Water	water	2E+10					1000	1000
	susp. particles	1E+06			0.0		1500	
	fish	2E+05				0.05	1000	
	total	2E+10	10	2E+09				
Bulk Soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
Bulk Sediment	water	8E+07					1000	
	solid	2E+07			0.06		2400	50000
	total	1E+08	0.05	2E+09				

Scenario	emission rate [kg/h]			fugacity [Pa]				concentration [g/m^3]			
case	b.air E_1	b.wat. E_2	b.soil E_3	b.air f_1	b.w. f_2	b.soil f_3	b.sed. f_4	b.air C_1	b.wat. C_2	b.soilC_3	b.sed.C_4
1	1000	0	0	5.0E-06	2.4E-08	3.6E-06	1.5E-08	4.5E-07	4.2E-03	2.1E-01	2.2E-03
2	0	1000	0	2.5E-10	5.6E-08	1.8E-10	3.5E-08	2.2E-11	9.7E-03	1.0E-05	5.1E-03
3	0	0	1000	7.1E-08	2.0E-08	5.0E-06	1.3E-08	6.2E-09	3.5E-03	2.9E-01	1.8E-03
4	600	300	100	3.0E-06	3.3E-08	2.7E-06	2.1E-08	2.7E-07	5.8E-03	1.5E-01	3.0E-03
5	333	333	333	1.7E-06	3.3E-08	2.9E-06	2.1E-08	1.5E-07	5.8E-03	1.7E-01	3.0E-03

Scenario	amount [kg]				total	transformation rate by reaction [kg/h]				transformation rate by advection [kg/h]		
case	b.air m_1	b.wat. m_2	b.soil m_3	b.sed. m_4	[kg]	b.air	b.wat. R_2	b.soil R_3	b.sed. R_4	b.air A_1	b.wat. A_2	b.sed. A_4
1	4.5E+03	8.4E+04	3.3E+05	2.2E+02	4.2E+05	6.4E+01	3.5E+02	4.6E+02	3.0E-01	4.5E+01	8.4E+01	4.4E-03
2	2.2E-01	1.9E+05	1.6E+01	5.1E+02	2.0E+05	3.1E-03	8.0E+02	2.2E-02	7.0E-01	2.2E-03	1.9E+02	1.0E-02
3	6.2E+01	6.9E+04	4.7E+05	1.8E+02	5.4E+05	9.0E-01	2.9E+02	6.4E+02	2.5E-01	6.2E-01	6.9E+01	3.6E-03
4	2.7E+03	1.2E+05	2.5E+05	3.0E+02	3.7E+05	3.9E+01	4.8E+02	3.4E+02	4.2E-01	2.7E+01	1.2E+02	6.0E-03
5	1.5E+03	1.2E+05	2.7E+05	3.0E+02	3.8E+05	2.2E+01	4.8E+02	3.7E+02	4.2E-01	1.5E+01	1.2E+02	6.0E-03

Scenario	transport rate between spheres [kg/h]						
case	air→ water	water→ air	air→ soil	soil→ air	soil→ water	water→ sed.	sed.→ water
1	1.8E+02	2.1E-02	7.2E+02	1.0E+01	2.5E+02	8.4E-01	5.4E-01
2	8.9E-03	4.9E-02	3.5E-02	4.9E-04	1.2E-02	1.9E+00	1.2E+00
3	2.5E+00	1.7E-02	1.0E+01	1.4E+01	3.5E+02	6.9E-01	4.4E-01
4	1.1E+02	2.9E-02	4.3E+02	7.5E+00	1.9E+02	1.2E+00	7.4E-01
5	6.1E+01	2.9E-02	2.4E+02	8.1E+00	2.0E+02	1.2E+00	7.4E-01

Z and D Values

	Z_B [$mol/m^3 \cdot Pa$]	D_R [$mol/Pa \cdot h$]	D_A [$mol/Pa \cdot h$]
Bulk Air (1)	4.0E-04	5.8E+07	4.0E+07
Bulk Water (2)	8.0E+02	6.6E+10	1.6E+10
Bulk Soil (3)	2.7E+02	5.9E+08	0.0E+00
Bulk Sediment (4	6.6E+02	9.0E+07	1.3E+06

D_{12} [$mol/Pa \cdot h$]	D_{21} [$mol/Pa \cdot h$]	D_{13} [$mol/Pa \cdot h$]	D_{31} [$mol/Pa \cdot h$]
1.6E+08	4.0E+06	6.6E+08	1.3E+07

D_{32} [$mol/Pa \cdot h$]	D_{24} [$mol/Pa \cdot h$]	D_{42} [$mol/Pa \cdot h$]
3.2E+08	1.6E+08	1.6E+08

Environmental parameter

		volume [m^3]	depth [m]	area [m^2]	organic carbon content [-]	lipid content [-]	density [kg/m^3]	residence time [h]
bulk air	air	1E+13					1.2	100
	particles	2E+03						
	total	1E+13	1000	1E+10				
bulk water	water	2E+10					1000	1000
	particles	1E+06			0.04		1500	
	fish	2E+05				0.05	1000	
	total	2E+10	10	2E+09				
bulk soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
bulk sediment	water	8E+07					1000	
	solid	2E+07			0.06		2400	50000
	total	1E+08	0.05	2E+09				

FINAL
11-19-2012

Provisional Peer-Reviewed Toxicity Values for

Triacetin
(CASRN 102-76-1)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR TRIACETIN (CASRN 102-76-1)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Triacetin, also known as glyceryl triacetate (CAS No. 102-76-1), is a colorless, oily liquid with a slightly fatty odor and a mild, sweet taste that is bitter at concentrations above 0.05% (see Figure 1). Occupational exposure to triacetin can occur through dermal contact and inhalation at production sites during operations such as cleaning, sampling, analysis, and drum filling. Triacetin has the following uses in consumer products: a solvent for celluloid and photographic films; a plasticizer for cigarette filters; a fungicide in cosmetics; a fixative in perfumery; and a general purpose food additive. A table of physicochemical properties is provided below (see Table 1).

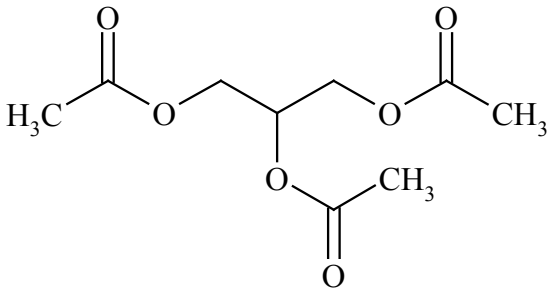


Figure 1. Triacetin Structure

Table 1. Physicochemical Properties of Triacetin (CASRN 102-76-1)[a]

Property (unit)	Value
Boiling point (ºC)	258−259
Melting point (ºC)	3
Density (g/cm^3)	1.1562
Vapor pressure (mm Hg at 25ºC)	0.00248
pH (unitless)	7
Solubility in water (g/100 mL at 25ºC)	5.8−7.0
Relative vapor density (air = 1)	7.52
Molecular weight (g/mol)	218.21

[a]ACGIH (2011), ChemIDPlus (2011), OECD (2002).

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for triacetin is included on the U.S. EPA IRIS database (U.S. EPA, 2010a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). No RfD or RfC values are reported in the HEAST (U.S. EPA, 2010b). The Chemical Assessments and Related Activities (CARA) list does not include a Health and Environmental Effects Profile (HEEP) for triacetin (U.S. EPA,

1994). The toxicity of triacetin has not been reviewed by the ATSDR (2011), and the World Health Organization does not list an Environmental Health monograph for triacetin (WHO, 2011). CalEPA (2008, 2009) has not derived toxicity values for exposure to triacetin. No occupational exposure limits for triacetin have been derived or recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), the National Institute of Occupational Safety and Health (NIOSH, 2010), or the Occupational Safety and Health Administration (OSHA, 2011).

The HEAST (U.S. EPA, 2010b) does not report a cancer weight-of-evidence (WOE) classification or an oral slope factor (OSF) for triacetin. The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of triacetin. Triacetin is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2008) has not derived a quantitative estimate of carcinogenic potential for triacetin.

Triacetin has been reviewed by several committees worldwide and is considered safe under specified exposure scenarios (Ellis and Rodford, 1996). An estimate of the cumulative oral intake in the United Kingdom suggests that an adult might ingest 7.8 mg triacetin/day, and the daily intake was calculated to be 0.111 mg/kg-day (OECD, 2002). The Database of Select Committee on GRAS Substances (SCOGS) Reviews Report No. 30, Glycerin and Glycerides (U.S. FDA, 1975) states that triacetin has been found to be without toxic effects in long-term feeding tests in rats at levels that were several orders of magnitude greater than those to which consumers are exposed. Triacetin was exempted from the requirement of a tolerance when used as a solvent or cosolvent in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals [40 CFR 180.930]. The United States Food and Drug Administration (U.S. FDA) concluded that triacetin is generally recognized as safe (GRAS) when used: as a food additive [21 CFR 184.1901]; in food or food packaging [21 CFR 181.27]; as a general purpose food additive in animal drugs, feeds, and related products [21 CFR 582.1901]; or in certain over the counter drug products [21 CFR 310.545]. The Cosmetic Ingredients Review Expert Panel concluded that triacetin is safe as used in cosmetic formulations (Fiume, 2003). The Joint FAO/WHO Expert Committee on Food Additive (JECFA) considered it unnecessary to assign an acceptable daily intake (ADI), as triacetin is metabolized in the same manner as other dietary triglycerides. In various assessments of triacetin, the JECFA concluded that, based on the available data and anticipated daily intake, triacetin did not represent a hazard to health (JECFA, 1975, 2002). In a separate evaluation, the European Union's Scientific Committee for Food endorsed the JECFA position for triacetin (Commission for the European Communities: Scientific Committee for Food, 1992).

Literature searches were conducted on sources published from 1900 through December 2011 for studies relevant to the derivation of provisional toxicity values for triacetin (CASRN 102-76-1). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications [NSCEP] and National Environmental Publications Internet Site [NEPIS] database); PubMed: MEDLINE and CANCERLIT databases;

SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI; and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); WHO; and Worldwide Science. The following databases outside of HERO were searched for health-related values: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for triacetin and includes all potentially relevant repeated-dose subchronic- and chronic-duration studies. Principal studies are identified. The phrase "statistical significance" used throughout the document, indicates a *p*-value of <0.05.

HUMAN STUDIES

Oral Exposures

The effects of oral exposure of humans to triacetin have been evaluated in two separate subchronic case studies (Madhavarao et al., 2009; Segel et al., 2011).

Subchronic-Duration Studies

Madhavarao et al. (2009)

In a peer-reviewed study, Madhavarao et al. (2009) administered triacetin in infant formula to a 13-month-old girl and an 8-month-old boy for 6 and 4.5 months, respectively. The initial dose was 25 mg/kg twice daily (50 mg/kg-day) for the first week, followed by a doubling each subsequent week up to a maximum dose of 250 mg/kg twice daily (500 mg/kg-day). These infants were previously diagnosed with Canavan disease, a fatal dysmyelinating genetic disorder characterized by mutations in the enzyme aspartoacylase, resulting in a greatly reduced or absent capacity to hydrolyze the brain metabolite *N*-acetylaspartate to acetate and aspartate. Triacetin was selected for use as a dietary supplement as it is known to be an acetate precursor. The stated aim of this study was to determine the tolerability of low-dose oral triacetin administration in infants having Canavan disease. This study received Institutional Review Board approval and obtained parental consent. The following outcome criteria were evaluated prior to initiation of treatment and reviewed at 4 months of treatment: neurological status, brain magnetic resonance imaging and magnetic resonance spectroscopy, urine *N*-acetylaspartate levels, and ophthalmoscopic examination. Treatment-related effects were screened clinically and by blood work-up of complete blood count, kidney function, electrolytes, liver function, and venous blood gas measurements.

The study authors did not identify a NOAEL or LOAEL; however, they stated that oral administration of triacetin caused no detectable toxicity, and that the infant patients showed no deterioration in their clinical status (Madhavarao et al., 2009). The NOAEL is 500 mg/kg-day; a LOAEL was not determined under the conditions tested.

Table 2. Summary of Potentially Relevant Data for Triacetin

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-d)								
Acute[c]	ND							
Short-term[d]	ND							
Subchronic[e]	1/1 infant patients, feeding, 6 mo. exposure (girl) or 4.5 mo. exposure (boy); case study	25 mg/kg twice daily (50 mg/kg-d), doubling weekly to 250 mg/kg twice daily (500 mg/kg-d) (Adjusted)	No effects	500	NDr	NDr	Madhavarao et al. (2009)	PR
Subchronic[e]	1/1 infant patients, feeding, 6 mo. exposure (boy) or 4.5 mo. exposure (girl); case study	500 mg/kg four times daily (2,000 mg/kg-d), doubling every 3 d to 4,500 mg/kg-d	No effects (discomfort reported in both children by parents at 5,000 mg/kg-d; maximum dose titrated back to 4,500 mg/kg-d)	4,500	NDr	NDr	Segel et al. (2011)	PR
Chronic[f]	ND							
2. Inhalation (mg/m^3)								
Acute[c]	ND							
Short-term[d]	ND							
Subchronic[e]	ND							
Chronic[f]	ND							

Table 2. Summary of Potentially Relevant Data for Triacetin

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Animal								
			1. Oral (mg/kg-d)					
Short-term[d]	0/8, S-D rat, feeding, 18 d	13,869; 25,670; 25,843 (Adjusted)	No adverse effects	25,843	NDr	NDr	Shapira et al. (1969) (Concentration of triacetin was not the only variable; multiple other dietary factors included in exposure source confounds interpretation; protein levels impacted body-weight gain)	PR
Subchronic[e]	0/8, S-D rat, feeding, 30 d	16,367 (Adjusted)	No adverse effects	16,367	NDr	NDr	Lynch et al. (1994) (Limited scope of endpoints examined for toxicity; multiple other dietary factors included in exposure source confounds interpretation)	PR
Subchronic[e]	0/8, S-D rat, feeding, 30 d	16,367 (Adjusted)	No adverse effects	16,367	NDr	NDr	Lynch and Bailey (1995) (Limited scope of endpoints examined for toxicity; multiple other dietary factors included in exposure source confounds interpretation)	PR
Subchronic[e]	12/12 S-D rat, gavage, 41−48 d from 14 d prior to mating to Postpartum Day (PPD) 3	0, 40, 200, or 1,000 (Adjusted)	No adverse effects	1,000	NDr	NDr	MHW (1998) (This was a combined OECD repeated dose and reproductive/developmental toxicity screening test [OECD TG 422])	NPR

Table 2. Summary of Potentially Relevant Data for Triacetin

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Subchronic[e]	0/8, S-D rat, feeding, 12−13 wk	17,228; 25,843 (Adjusted)	Decreased body weight, increased liver weight (The toxicological significance of these findings could not be ascertained)	ND	NDr	NDr	Shapira et al. (1975) (Concentration of triacetin was not the only variable; the toxicological significance of these findings could not be ascertained)	PR
Subchronic[e]	Unreported number and sex, rat, feeding and drinking, approximately 110−120 d	4,200 during Postnatal Days (PNDs) 7−14, 5,800 during PNDs 15−22/23, 7099 in food and 7,504 in water, totaling 14,603 for the remaining treatment period (Adjusted)	No adverse effects	14,603 (feed and water doses combined)	NDr	NDr	Madhavarao et al. (2009) (Deficiencies in reporting of study details limits interpretation of results)	PR
Chronic	ND							
Reproductive/ Developmental	**12/12 S-D rat, gavage, 41−48 d from 2 wk prior to mating to PPD 3**	**0, 40, 200, or 1,000 (Adjusted)**	**No adverse effects in dams or offspring**	**F0: 1,000 F1: 1,000**	**NDr**	**NDr**	**MHW (1998)** (Systemic toxicity including reproductive parameters examined in dams; health status of offspring also examined)	**NPR; PS**
Carcinogenicity	ND							
2. Inhalation (mg/m^3)								
Short-term[d]	ND							
Subchronic[e]	3/3 rat, (strain unreported) whole-body vapor inhalation, 6 h/d, 5 d/wk, 103 d	397 for 90 d; 2 additional wk at 117 followed by 13,181 (saturated vapor)	No adverse effects	397	NDr	NDr	Fassett (1955) as summarized in OECD (2002)	NPR; original document could not be obtained

Table 2. Summary of Potentially Relevant Data for Triacetin

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Subchronic[e]	3 rat (sex and strain unreported), 6 h/d, 5 d/wk, 64 d	398; 13,181	No adverse effects	13,181	NDr	NDr	Unichema Chemie B.V. (1994) as summarized by Fiume (2003)	NPR; original document could not be obtained
Subchronic[e]	Unreported number and sex, rat, heated vapor, 6 h/d, 5 d/wk, 13 wk	398	No adverse effects	398	NDr	NDr	Fassett (1963) as summarized by Ellis and Rodford (1996)	PR; original document could not be obtained
Chronic[f]	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects. All long-term exposure values (4 wk and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal developmental studies are not adjusted to a continuous exposure.
HEC_{EXRESP} = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood gas partition coefficient.
[b]Notes: IRIS = Utilized by IRIS, date of last update; PS = principal study, PR = peer reviewed, NPR = not peer reviewed.
[c]Acute = Exposure for 24 hr or less (U.S. EPA, 2002).
[d]Short-term = Repeated exposure for >24 hr ≤30 d (U.S. EPA, 2002).
[e]Subchronic = Repeated exposure for >30 d up to approximately 10% of the lifespan in humans (based on 70-yr typical human lifespan; >30–90 days in typically used laboratory animal species) (U.S. EPA, 2002).
[f]Chronic = Repeated exposure for ≥10% lifespan (U.S. EPA, 2002).

DU = data unsuitable, NA = not applicable, NV = not available, ND = no data, NDr = not determinable, NI = not identified, NP = not provided, NR = not reported, NR/Dr = not reported but determined from data, NS = not selected, S-D = Sprague-Dawley.

Segel et al. (2011)

Similar to the Madhavarao et al. (2009) study above, Segel et al. (2011) administered triacetin in infant formula to a 12-month-old boy and an 8-month-old girl for 6 and 4.5 months, respectively. Both of the infants were previously diagnosed with Canavan disease, and as such, triacetin was being evaluated for efficacy as a dietary supplement (as explained under Madhavarao et al. [2009] above). The stated aim of this study was to determine the tolerability and efficacy of high-dose triacetin administration in infants with Canavan disease. The initial dose was 500 mg/kg four times daily (2,000 mg/kg-day) for the first 3 days, followed by a doubling of dose every 3 days up to a maximum dose of 4,500 mg/kg-day (the target maximum dose was 5,000 mg/kg-day, but the parents reported 'discomfort' in each child at this specific dose). The children were evaluated prior to treatment and at 4.5 months after the initiation of treatment for the following outcomes: neurological status, brain magnetic resonance imaging and magnetic resonance spectroscopy, urine *N*-acetylaspartate levels, and ophthalmoscopic examination. Treatment-related effects were screened clinically and by blood work-up of complete blood count, kidney function, electrolytes, liver function, and venous blood gas measurements.

The study authors did not identify a NOAEL or LOAEL; although the study authors did state that administration of triacetin caused no detectable toxicity in either patient at a daily dose of 4,500 mg/kg-day; at the highest dose attempted (5,000 mg/kg-day), the study authors alluded to a potential problem with gastric acidity (Segel et al., 2011). The NOAEL is 4,500 mg/kg-day for lack of effects in human infants; a LOAEL was not determined under the conditions tested.

Chronic-Duration Studies

No studies were identified.

Developmental Studies

No studies were identified.

Reproduction Studies

No studies were identified.

Carcinogenicity Studies

No studies were identified.

Inhalation Exposures

No studies were identified.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to triacetin have been evaluated in one short-term (Shapira et al., 1969) and five subchronic studies (MHW, 1998; Madhavarao et al., 2009; Lynch et al., 1994; Lynch and Bailey, 1995; Shapira et al., 1975). Additionally, the MHW study (1998) also evaluated reproductive toxicity.

Short-term Studies

Shapira et al. (1969)

In a peer-reviewed study, Shapira et al. (1969) developed a system capable of serving a regenerative food supply. A mixture of triacetin, glycerol, and *Hydrogenomonas eutropha* (bacteria, rich in protein) was used as a food supplement and a major portion of the diet. Groups of eight male weanling Sprague-Dawley rats were fed one of 12 different diets for 18 days, containing low, medium, or high protein contents (12, 24, and 48% protein, respectively), along with variable carbohydrate sources, including triacetin. The different protein and carbohydrate contents of the 12 diets are shown in Table B-1.

The adjusted doses for triacetin are calculated to be 13,869, 25,670, and 25,843 mg/kg-day for the diets containing triacetin at 16.1, 29.8, and 30% (by weight), respectively. In addition to the dietary components shown above, all diets contained 5% USP XIV salt mixture (plus 16.5 mg $ZnSO_4$/100 g diet), 5% safflower oil, 2% α-cellulose, 1% vitamins, 1% agar, and a total of 2 parts water to each part dry weight. After formulation, the diets were stored at 4°C and fed fresh daily. The animals were caged as pairs and weighed daily. No mortality or clinical signs of toxicity were mentioned; however, the study authors did not report any evaluations other than body weights. It is not apparent from the report that statistical analyses were performed on the body-weight data. This study was performed as part of research into regenerative food systems performed at the Ames Research Center for NASA.

The study authors reported that growth was not adversely affected over 18 days when 29.8% triacetin (by weight in the diet; equivalent to 25,670 mg/kg-day) was included with 29.8% glycerol and 27% protein from *H. eutropha* (minimally affected when protein was casein; see Table B-1). The authors stated that these data show that over 90% of the calories of the diet of growing rats can be composed of a mixture of *H. eutropha*, glycerol, and triacetin without a detrimental effect on the growth of the animal. However, these results also demonstrate that adequate nutritional needs must be met with regards to protein levels. When fed similar amounts of triacetin (29.8−30%), animals fail to achieve the expected body-weight gain when fed the low protein diet, but not when fed the medium protein diet. The study authors did not define a NOAEL or LOAEL; however, the highest dose of 25,843 mg/kg-day showed no adverse effects; therefore, the NOAEL is 25,843 mg/kg-day. A LOAEL for triacetin is not available under the conditions tested. The study authors reported only limited information to assess the toxicity of this compound in this 18-day study, and the dietary exposure to rats included multiple supplements in addition to triacetin; therefore, this study is not considered suitable for derivation of a subchronic p-RfD.

The report by Shapira et al. (1969) also included general findings related to triacetin from a "number of three month feeding studies." However, because detailed methodology and data from these studies were not presented, these generalized findings are unsupported and are not included in this report.

Subchronic-Duration Studies

Lynch et al. (1994)

In a peer-reviewed study, Lynch et al. (1994), administered to eight Sprague-Dawley male rats one of three diets for 30 days: control diet, diet with 30% of the energy as corn oil, or diet with 30% of the energy as mainly short chain triglycerides (95% triacetin and 5% corn oil). All diets contained 20.6% protein (by percentage of calories), and 1.0%, 3.5%, and 5.0% weight

percent vitamins, minerals, and fiber, respectively. The triacetin-diet contained 19.0% triacetin by weight, which is equivalent to an adjusted dose of 16,367 mg/kg-day.

Rats were housed individually in plastic metabolism cages (Lynch et al., 1994). Food intake was measured daily, and body weights were determined at Day 0 and every 5 days thereafter. Animals were euthanized after 30 days, and blood was collected. Nonfasting plasma glucose, triglycerides, total ketone bodies, free fatty acids, lactate, and pyruvate were measured. Jejunal and colon segments were excised and weighed. Intestinal mucosal cells were analyzed for DNA, RNA, and protein content. The protein-DNA ratio for each group was calculated as an index of cell size. Other jejunal and colon segments were fixed in neutral buffered formalin, processed routinely, and analyzed by light microscopy to determine villus height in the jejunum and crypt depth in the colon. Carcasses were eviscerated, frozen, and homogenized with an equivalent weight of water. Aliquots were removed and lyophilized for determination of percent moisture. All data were analyzed by analysis of variance (ANOVA) to determine significant statistical differences among groups caused by diet. When a significant difference was observed, Duncan's Multiple Range Test was used to further analyze the differences. This study did not include relevant evaluation of hematology, clinical chemistry, urinalysis, organ weights, or gross or microscopic pathology.

Lynch et al. (1994) stated that there were no adverse, treatment-related effects observed on mortality, clinical signs, body weights, food consumption, lactate, ketone body, glucose concentrations, mean villus height, intestinal crypt depth, and carcass composition. Compared to the control group, plasma free fatty acids were decreased ($p < 0.05$) by 44%, and plasma triglycerides were increased ($p < 0.05$) by 22%. DNA content was increased ($p < 0.05$) by approximately 68% in the colon mucosa. RNA content was decreased ($p < 0.05$) by approximately 33% in the jejunum. The protein:DNA ratio was decreased ($p < 0.05$) by 38% in the jejunum. The study authors reported no NOAEL or LOAEL; however, the only dose of triacetin tested, 16,367 mg/kg-day, showed no toxic effects; therefore, the NOAEL is 16,367 mg/kg-day. A LOAEL is not available under the conditions tested. The study authors reported only limited information to assess the toxicity of this compound in this study; therefore, this study is not suitable for derivation of a subchronic p-RfD.

Lynch and Bailey (1995)

In a peer-reviewed study by Lynch and Bailey (1995), eight Sprague-Dawley male rats were administered one of three diets for 30 days, with one of the diets containing 19% triacetin by weight (adjusted dose of 16,367 mg/kg-day). The study methodology was the same as described previously in Lynch et al. (1994). In the present study, the adipose cell size and number (as measured by a Coulter counter) for epididymal, perirenal, and inguinal fat depots were reported.

Lynch and Bailey (1995) reported that mean adipose cell size in the triacetin-treated group was less than the control for the epididymal, inguinal, and perirenal fat depots, but cell number was unaffected. A moisture-free sample was used to determine percent lipid with a modified Soxhlet method. Percent protein was determined with the Kjeldahl method, and the percent ash was determined by combustion. The study authors reported no NOAEL or LOAEL; however, the only dose tested, 16,367 mg/kg-day, showed no toxic effects. Therefore, the NOAEL is 16,367 mg/kg-day, and a LOAEL is not available under the conditions tested. The

study authors reported only the limited results detailed above to assess the toxicity of this compound in this study; therefore, this study is not suitable for derivation of a subchronic p-RfD.

Ministry of Health and Welfare, Japan (MHW, 1998)

This study (MHW, 1998) was performed by the Kashima Laboratory of the Mitsubishi Chemical Safety Institute in accordance with the OECD combined repeated dose and reproductive/developmental toxicity screening test guideline (OECD TG 422). Twelve Sprague-Dawley [Crj:CD (SD) IGS] rats/sex (males: 317−375 g; females: 203−240 g; 9 weeks old) were administered triacetin (>98.2% purity) in 3% aqueous gum arabic by gavage once daily at doses of 0, 40, 200, or 1,000 mg/kg-day. Males were dosed for 44 days beginning 2 weeks prior to mating; females were dosed for 41−48 days from 14 days before mating to Postpartum Day (PPD) 3.

In the adults, mortality/morbidity and clinical signs of toxicity were recorded once a day (MHW, 1998). Body weights were measured on Days 0, 3, 7, and 14 of premating in both sexes. Body weights were also measured on Days 21, 28, 35, and 42, and at termination in the males, and on Gestation Days (GD) 0, 7, 14, and 20, PPDs 0 and 4, and at termination in the females. Food consumption (g/rat/day) was recorded for: Days 0−3, 3−7, and 7−14 in both sexes; Days 21−28, 28−35, and 35−42 in the males; and GDs 0−7, 7−14, 14−20, and PPD 0−4 in the females. The following hematological and clinical chemistry parameters were determined in blood collected from males at termination: erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte ratio, thrombocytes, leukocyte differential counts, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, alanine phosphatase, total bilirubin, urea nitrogen, glucose, total cholesterol, triglyceride, total protein, albumin, albumin:globulin ratio, calcium, inorganic phosphorus, sodium, potassium, and chloride. Urinalysis was not performed. It was stated that absolute and relative organ weights were recorded for brain, pituitary, thyroid, heart, liver, kidney, spleen, adrenal gland, thymus, testes, and epididymis; however, data were only presented for thymus, liver, spleen, kidney, adrenal, testes, and epididymis. At necropsy, the following tissues were collected from the controls and 1,000-mg/kg-day group: brain, spinal cord, pituitary, eye, thyroid (with parathyroid), thymus, heart, trachea, lung, liver, kidney, adrenal gland, spleen, stomach, small intestine, large intestine, pancreas, urinary bladder, bone marrow, sciatic nerve, lymph node, testes, epididymis, prostate, seminal vesicle, ovary, uterus, vagina, mammary gland, and any organ that might be expected to have histopathological changes. The following tissues were examined and reported in the histological findings: heart, thymus, spleen, esophagus, stomach, duodenum, liver, kidney, testes, epididymis, ovary, adrenal, brain, and skin. Reproductive data, including reproductive performance indices, delivery data, and litter size, and pup viability indices, pup body weights, and pup body-weight gains were presented. It was stated that the data were analyzed with the Kruskal-Wallis test for noncontinuous data, Dunnett's test, or Scheffe's test for continuous data, and the Chi-square test for quantal data. It was also stated that the study complied with Good Laboratory Practice (GLP) standards.

One 1,000-mg/kg-day male was found dead on Day 32 (MHW, 1998). This animal was observed grossly to have hemorrhage of the thymus and congestion of the lung, liver, and kidney; microscopic examination revealed slight diffuse hemorrhage of the thymus. In the absence of any evidence of systemic toxicity in any other animal at any dose level, this death is considered incidental to treatment. In the animals that survived to scheduled necropsy, triacetin

had no effects on clinical signs of toxicity, body weights, body-weight gains, food consumption, organ weights, or gross or histological pathology findings. Statistically significant decreases were observed in percent of band neutrophils and creatinine in the 40- and 1,000-mg/kg-day males; statistically significant increases in inorganic phosphorus were also noted in the 200-mg/kg-day males. These changes were stated to be within physiological ranges and/or were not dose-dependent. Reproductive and offspring results are discussed under the Reproductive/Developmental Studies section below. In the absence of any reliable finding of toxicity in treated adult rats, the NOAEL was determined to be 1,000 mg/kg-day; a LOAEL was not determined under the conditions tested.

Shapira et al. (1975)

In a peer-reviewed study, Shapira et al. (1975) fed groups of eight male Sprague-Dawley rats diets for 13 weeks containing various carbohydrates in order to investigate the feasibility of replacing starch with alternative carbohydrate sources. The study tested six types of diets: Diet 1 (control, 60% starch), Diet 2 (30% glycerol and 30% propylene glycol), Diet 3 (30% glycerol and 30% triacetin), Diet 4 (30% propylene glycol and 30% triacetin), Diet 5 (40% glycerol and 20% propylene glycol), and Diet 6 (40% glycerol and 20% triacetin). For the diets that included triacetin, the daily adjusted doses of triacetin were 17,228 and 25,843 mg/kg-day for 20 and 30% triacetin diets, respectively. Each diet also contained 27% casein and 5% safflower oil. Identical amounts of cellulose, salts, and vitamins were present in all diets. Rats were kept in pairs in stainless steel cages. For periods of 3−4 and 12−13 weeks, food consumption, body-weight gain, water intake, and liver weight were reported. It is not apparent from the report that statistical analyses were performed.

In this study (Shapira et al., 1975), body weights were decreased by 20% after 12−13 weeks on Diets 3 and 6 (triacetin with glycerol), but body weights were comparable for the control diet and Diet 4 (triacetin with propylene glycol). Water intake varied, and it is not possible to make conclusions without additional test groups where the concentrations of triacetin are varied (while other components remained the same). Body-weight gains as growth percent for periods of 3−4 and 12−13 weeks decreased 29−52% in all triacetin groups compared to the control group. However, due to the other variables in the dietary exposure media (e.g., casein, glycerol, or propylene glycol), it is difficult to attribute changes in body weight to triacetin alone. Alternatively, it is possible that feeding with 30% triacetin may have negatively impacted nutrition over the 13-week period. Regardless, this effect is not considered to be a clear indication of systemic toxicity for triacetin. Relative liver weights were increased by 41−67%. The study authors reported no NOAEL or LOAEL, and the data gaps are such that it is not possible to determine a NOAEL or LOAEL for this study. Insufficient toxicological parameters were examined in this study, and the impact of dietary protein was not sufficiently evaluated; therefore, this study is not considered suitable for derivation of a subchronic p-RfD.

Madhavarao et al. (2009)

In a peer-reviewed study by Madhavarao et al. (2009), wild-type and tremor rat pups (6−12 males or females per group) received triacetin orally twice daily, initially at a dose of 4.2 g/kg during Postnatal Days (PND)s 7−14, then at 5.8 g/kg during PNDs 15−23, and thereafter in both food (7.5%) and water (5%) for a total treatment period of 110−120 days. The calculated doses in food and water are 7,099 mg/kg-day and 7,504 mg/kg-day, respectively, yielding a total oral dose of 14,603 mg/kg-day after PND 23. The tremor rat model of aspartoacylase deficiency is a natural mutant strain that has the entire aspartoacylase gene

deleted. This rat model mimics Canavan disease in humans (described earlier in the Human Studies section [Madhavarao et al., 2009]); thus, this study was conducted to support the efficacy of oral triacetin supplementation for aspartate deficiency. These rats were bred at the Center of Laboratory Animal Medicine at the Uniformed Services University of the Health Sciences, Bethesda, MD, where the studies were conducted. The study authors did not clearly present the number or sex of rats treated. A subset of rats was treated for approximately 110 days, and food intake and body weights were measured on a regular basis throughout the study (schedule not reported). Another subset of rats was treated for approximately 120 days, euthanized, and histopathology and biochemical analyses (29 different blood serum analytes such as lipids, proteins, electrolytes [e.g., Na, Mg]) were conducted. A limited set of tissues were fixed in 10% neutral-buffered formalin. Brain, spinal cord, lung, heart, liver, kidney, stomach, small and large intestine, and spleen were processed routinely, and slides from 2−4 rats per group were examined microscopically. When the data satisfied the assumptions of normality and equal variance, one-way ANOVA was performed followed by the Holm-Sidak post hoc test. When the data failed the assumptions of normality or equal variance or both, Kruskal-Wallis ANOVA of the ranks was applied, and differences in ranks were compared by Dunn's method.

No significant differences in the mean blood chemistry values occurred between treated and untreated groups, and no lesions indicating toxicity were detectable in any of the tissues examined microscopically (Madhavarao et al., 2009). Although triacetin-treated rats displayed slightly decreased food consumption and decreased body weights, the differences in weights between the treated and untreated groups were not statistically significant (data not presented). The study authors reported no NOAEL or LOAEL; the treated rats showed no adverse effects. Therefore, the NOAEL is 14,603 mg/kg-day, and a LOAEL is not available under the conditions tested. The study authors stated that these data support the use of triacetin supplementation for effective treatment of infants diagnosed with aspartoacylase deficiency. However, the following information was not provided: (a) whether the study complied with GLP standards; (b) the purity of the test compound; and (c) rat husbandry conditions. Hematology, urinalysis, organ weights, and necropsy were not performed or were not reported. Histology was limited to 10 tissues, and samples from only 2−4 rats were examined in each group. Due to these data omissions, this study is not considered suitable for derivation of a subchronic p-RfD.

Chronic-Duration Studies

No studies were identified.

Developmental Studies

Please refer to offspring data provided in MHW (1998) below.

Reproductive/Developmental Studies

The study prepared for the Ministry of Health and Welfare, Japan (MHW, 1998) is selected as the principal study and deemed adequate for the derivation of screening level subchronic and chronic p-RfDs. In a combined repeated dose and reproductive toxicity screening study, 12 Sprague-Dawley [Crj:CD (SD) IGS] rats/sex were administered triacetin by gavage once daily at doses of 0, 40, 200, or 1,000 mg/kg-day. Males were dosed for 44 days beginning 2 weeks prior to mating; females were dosed for 41−48 days from 14 days before mating to PPD 3. The methodology of this study (MHW, 1998) was previously described under Subchronic Studies above. The results of the offspring and reproductive parameters are reported here.

No treatment-related effects were observed on copulation, fertility, implantation, number of corpora lutea, gestation length, or delivery in exposed dams (MHW, 1998). No treatment-related effects were noted for the limited number of developmental parameters examined such as viability, offspring born alive, and offspring alive at PND 4. In addition, offspring body weights for triacetin-treated groups were similar to controls at PNDs 0 and 4. Although the study authors reported no NOAEL or LOAEL for reproductive effects, the highest dose of 1,000 mg/kg-day showed no adverse reproductive effects. Furthermore, triacetin exposure before, during, and immediately after pregnancy did not result in overt toxicity in offspring. Therefore, the NOAEL for this study is 1,000 mg/kg-day for both offspring (developmental) and reproductive parameters. A LOAEL is not determined under the conditions tested.

Carcinogenicity Studies

No studies were identified.

Inhalation Exposures

The effects of inhalation exposure of animals to triacetin have been evaluated in 3 subchronic studies in rats: Fassett (1955); Unichema Chemie B.V. (1994); and Fassett (1963). The original citations for these studies cannot be obtained; the information from each study is obtained from the indicated summary articles.

Short-term Studies

No studies were identified.

Subchronic-Duration Studies

Fassett (1955), as summarized in OECD (2002)

Information for the non-peer-reviewed study by Fassett (1955) is reported in the OECD Screening Information Dataset (2002) robust summaries; the original citation cannot be obtained. In this study, three rats/sex (strain not reported) were exposed to triacetin vapor by whole–body vapor inhalation exposure for 6 hours/day, 5 days/week, at a concentration of 249 ppm (HEC is 397 mg/m^3) for 90 days. A concurrent control group was not exposed. It was stated that inhalation was further extended for another week at 73.72 ppm (HEC is 117 mg/m^3), followed by a week at 8,271 ppm (saturated vapor; HEC is 13,181 mg/m^3). Treating the animals at 73.72 ppm for an additional week after no observed effect from 13 weeks of treatment at 249 ppm is without apparent reason; therefore, the summary article may be mistaken. Body weights were recorded prior to the first exposure, every 2−9 days during testing, and prior to termination. Limited hematology (red and white blood cell counts and hemoglobin) and urinalysis (albumin and sugar) parameters were measured. Liver and kidneys were weighed, and microscopic findings for trachea, bronchi, lung, kidney, liver, and bladder were reported.

No symptoms of toxicity were noted during the exposure period (Fassett [1955], as summarized in OECD [2002]). Average daily weight gain was 2.2 g/rat and was considered normal. Hematological evaluation and urinalysis showed no abnormalities in any of the animals. No histopathological changes were observed at the time of necropsy. The study author reported an estimated NOAEL of 249 ppm (HEC is 397 mg/m^3) for the 90-day study. A LOAEL was not observed under the conditions tested. OECD (2002) stated that, although this inhalation study was considered to be useful, it did not fully comply with the current testing protocol. Due to the limited toxicity data, this study is not considered suitable for derivation of a subchronic p-RfC.

Unichema Chemie B.V. (1994), as summarized by Fiume (2003)

Information for the non-peer-reviewed study by Unichema Chemie B.V. (1994) was reported by Fiume (2003); the original citation could not be obtained. Three rats (sex and strain not reported) were exposed to 250 ppm (HEC is 398 mg/m^3) by inhalation for 6 hours per day, 5 days per week, for 64 days. Three rats were also exposed to 8,271 ppm (HEC is 13,181 mg/m^3) for 6 hours per day for 64 days. No adverse effect was observed. The study author reported a NOAEL of 13,181 mg/m^3; a LOAEL was not determined under the conditions tested. Due to the extremely limited toxicity data, this study is not considered suitable for derivation of a subchronic p-RfC.

Fassett (1963), as summarized by Ellis and Rodford (1996)

Information for the peer-reviewed study by Fassett (1963) was reported in a glycerol triacetate safety evaluation by Ellis and Rodford (1996); the original citation could not be obtained. Inhalation concentrations of triacetin averaging 250 ppm (HEC is 398 mg/m^3) for 6 hours per day, 5 days per week, for 13 weeks produced no symptoms or histopathology in rats (sex and strain not reported). No changes were reportedly seen in liver and kidney weights, blood counts, or urine analysis. This concentration is considered the NOAEL; a LOAEL is not determined under the conditions tested. Due to the extremely limited toxicity data, this study is not considered suitable for derivation of a subchronic p-RfC.

Chronic-Duration Studies

No studies were identified.

Developmental Studies

No studies were identified.

Reproduction Studies

No studies were identified.

Carcinogenicity Studies

No studies were identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Other studies that are not appropriate for selection of a point of departure (POD) for triacetin and the determination of p-RfD, p-RfC, p-OSF, or p-IUR values may, however, provide supportive data supplementing a WOE approach to hazard identification and dose-response assessment. These studies may include, but are not limited to, information regarding toxic mode-of-action/mechanistic details, metabolism/toxicokinetics, or potential adverse health outcomes following shorter-term (e.g., <30-days) exposure durations. Although some acute/short-term duration studies exist for triacetin, the experimental designs involved the intravenous route of exposure, which is not necessarily relevant for informing hazard or dose response via the oral or inhalation routes and, thus, are not included.

Genotoxicity

Four genotoxicity studies are available indicating that triacetin has no mutagenic potential (Litton Bionetics, Inc. [1976a,b], Unichema Chemie B.V. [1994], and Efremova [1962]) and are presented in Table 3 and summarized briefly below.

Litton Bionetics, Inc. (1976a) evaluated the mutagenic potential of triacetin in an Ames plate and suspension test using *Salmonella typhimurium* (strains TA1535, TA1537, and TA1538) with and without metabolic activation. Test concentrations were 0.000325%, 0.00065%, and 0.0013% (w/v). Doses were selected based on the results of a preliminary toxicity test. The activation systems included S9 prepared from the liver of male ICR mouse, S-D rat, or Rhesus monkey. A negative control (solvent) and appropriate positive controls were used and gave expected results. Triacetin was not mutagenic with or without metabolic activation.

Table 3. Summary of Triacetin Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium* TA1535, TA1537, and TA1538 in the Ames plate test or suspension test with or without S9	0, 0.000325, 0.00065, and 0.0013%	-	-	Negative and positive controls gave the expected results	Litton Bionetics, Inc. (1976a)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA98, and TA100 in the Ames plate test with or without S9	0, 50−5,000 µg/plate	-	-	The source document could not be obtained. This information is from a review	Unichema Chemie B.V. (1994), as summarized by Fiume (2003)
Gene conversion	*Saccharomyces cerevisiae* strain D4 in a suspension test with or without S9	0, 1.25, 2.5, and 5%	-	-	Negative and positive controls gave the expected results	Litton Bionetics, Inc. (1976b)
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	*Drosophila melanogaster*	0.2−0.3 mg	-	-	The source document could not be obtained. This information is from a review	Efremova (1962), as summarized in Fiume (2003)

[a]Lowest effective dose for positive results, or, highest dose tested for negative results.
[b]- = negative, NA = not applicable, ND = no data.

No evidence of mutagenic potential was obtained in an Ames test using *S. typhimurium* (strains TA1535, TA1537, TA98, and TA100) with and without metabolic activation at concentrations up to 5,000 µg/plate (Unichema Chemie B.V., 1994). The source document could not be obtained; this information was provided in the *Final Report on the Safety Assessment of Triacetin* (Fiume, 2003).

Litton Bionetics, Inc. (1976b) evaluated the mutagenic potential of triacetin in a suspension test using *Saccharomyces cerevisiae* strain D4 with and without metabolic activation. Test concentrations were 1.25%, 2.5%, and 5.0% (w/v). Doses were selected based on the results of a preliminary toxicity test. The activation systems included S9 prepared from the liver of male ICR mouse, S-D rat, or Rhesus monkey. Appropriate negative and positive controls were used and gave expected results. Triacetin did not result in gene conversions in the suspension test with or without metabolic activation.

Efremova (1962) treated adult *Drosophila melanogaster* with a dose of 0.2−0.3 mg triacetin in an in vivo assay and found triacetin not to be mutagenic. The source document could not be obtained; this information was provided in the *Final Report on the Safety Assessment of Triacetin* (Fiume, 2003).

DERIVATION OF PROVISIONAL VALUES

Table 4 presents a summary of noncancer reference values. Table 5 presents a summary of cancer values. No cancer values could be derived. IRIS data are indicated in the table, if available.

Table 4. Summary of Noncancer Reference Values for Triacetin

Toxicity Type (Units)	Species/ Sex	Critical Effect	Reference Value	POD Method	POD_{HED}	UFc	Principal Study
Screening Subchronic p-RfD (mg/kg-day)	Rat/M/F	No effects observed	8×10^{1}	NOAEL	240	3	MHW (1998)
Screening Chronic p-RfD (mg/kg-day)	Rat/M/F	No effects observed	8×10^{1}	NOAEL	240	3	MHW (1998)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

NDr = not determinable.

Table 5. Summary of Cancer Values for Triacetin

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	NDr			
p-IUR	NDr			

NDr = not determinable.

DERIVATION OF ORAL REFERENCE DOSE

Derivation of Subchronic and Chronic Provisional RfD (p-RfD)

Studies identified for the oral route of exposure provided no evidence of triacetin toxicity (i.e., highest doses evaluated were all NOAELs). This was due, in part, to the prevalence of factors that confounded interpretation of hazard (resulting in a lack of hazard) and dose-response (e.g., dietary supplements in the exposure medium that might have conferred cytoprotective properties on target tissues). The combined subchronic/developmental/reproductive study performed for the Ministry of Health and Welfare, Japan (MHW, 1998) was the only study identified that did not suffer from confounding study design conditions, and it is deemed the principal study for the derivation of subchronic and chronic p-RfDs. However, because it cannot be conclusively determined that this study is peer reviewed, and the attendant uncertainty of a hazard database comprised only of NOAELs, screening subchronic and chronic p-RfDs are derived in Appendix A.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic and Chronic Provisional RfC (p-RfC)

Three subchronic inhalation studies were located; however, the original documents for these studies could not be obtained. The available data suggest that a saturated triacetin vapor atmosphere of up to 13,181 mg/m^3 can be tolerated without adverse effect for at least 64 days (Unichema Chemie B.V. [1994], as summarized by Fiume [2003]). However, the available summaries for these studies presented only limited experimental details and toxicity data. Due to these limitations, it is not possible to derive subchronic or chronic p-RfCs from these studies.

CANCER WOE DESCRIPTOR

Table 6 identifies the cancer WOE descriptor for triacetin. No data could be located regarding the carcinogenicity of triacetin. Therefore according to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is inadequate information to assess the human carcinogenic potential of triacetin.

Table 6. Cancer WOE Descriptor for Triacetin			
Possible WOE Descriptor	**Designation**	**Route of Entry (oral, inhalation, or both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	NA
"Likely to be Carcinogenic to Humans"	NS	NA	NA
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	NA
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No carcinogenicity studies were identified.**
"Not Likely to be Carcinogenic to Humans"	NS	NA	NA

NA = not applicable; NS = not selected.

MODE OF ACTION DISCUSSION

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) define mode-of-action "…as a sequence of key events and processes starting, with the interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation" (p. 1-10). Examples of possible modes of carcinogenic action for any given chemical include "…mutagenicity, mitogenesis, inhibition of death, cytotoxicity with reparative cell proliferation, and immune suppression" (p. 1-10). No carcinogenicity studies in human or animals were located (see the "Cancer WOE Descriptor" above).

Mutagenic Mode-of-Action

Triacetin was not mutagenic in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, or TA1538 in the Ames plate assay or suspension test, with or without metabolic activation. Triacetin did not result in gene conversion of *Saccharomyces cerevisiae* strain D4 in a suspension test, with or without metabolic activation. Triacetin did not result in mutation in *Drosophila melanogaster*, a eukaryotic organism. There are no available studies to evaluate mutagenic action, and there is no evidence of carcinogenic potential in humans or animals.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of provisional Oral Slope Factor (p-OSF)

No human or animal studies examining the carcinogenicity of triacetin following oral exposure were identified. Therefore, it is not possible to derive a p-OSF.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No human or animal studies examining the carcinogenicity of triacetin following inhalation exposure were identified. Therefore, it is not possible to derive a p-IUR.

APPENDIX A. PROVISIONAL SCREENING VALUES

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional subchronic or chronic p-RfDs for triacetin. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

DERIVATION OF SCREENING LEVEL ORAL REFERENCE DOSES

Derivation of a Screening Level Subchronic Provisional RfD (Screening Subchronic p-RfD)

The two available human studies (Madhavarao et al. [2009] and Segel et al. [2011]) were carefully evaluated in the selection of a principal study and POD. While NOAELs based on a lack of effect in human infants were identified in both of these studies, limitations in study design, questionable exposure compliance during the reported treatment period, and the preexistent disease condition of the infants raises concern over the reliability of the NOAELs. Specifically, only two infants were examined in both the Madhavarao et al. (2009) and Segel et al. (2011) studies. The study authors noted difficulties in maintaining the infants on treatment due to concerns raised by the parents; thus, the difference in exposure period between the male and female infants in each study. In addition, Segel et al. (2011) reported that one of the patients left the country (Israel) two weeks after commencing treatment; follow-up was purportedly monitored by a primary care physician, unrelated to the study, and in the new country of residence (not specified). Lastly, the infants were previously diagnosed with Canavan disease, which results in a significant decrement in acetate levels. Considering that triacetin is an acetate precursor, it is plausible that the triacetin exposures were in part augmenting the deficiency rather than inducing a potential toxicity. Neither human study was considered further for principal study or POD identification.

The study prepared for the Ministry of Health and Welfare, Japan (MHW, 1998) is selected as the principal study and is deemed adequate for the derivation of screening level subchronic and chronic p-RfDs. The MHW (1998) combined subchronic/developmental and reproductive study in rats provides the most complete evaluation of the toxicity of triacetin and identified a NOAEL of 1,000 mg/kg-day for lack of toxicity in either maternal F0 dams or F1 offspring. There are additional subchronic feeding studies (Shapira et al. [1969], Lynch et al. [1994], and Madhavarao et al. [2009]), suggesting that much higher levels of triacetin may be tolerated by rats without adverse effects. For example, the study by Shapira et al. (1969) indicates that triacetin can be tolerated in the diet up to levels that hinder nutrition (e.g., 25,843 mg/kg-day), and the studies by Madhavarao et al. (2009) and Lynch et al. (1994) indicate that rats can tolerate diets containing up to 14,603−16,367 mg/kg-day of triacetin without harm. However, it should be noted that all of these oral repeat-dose studies, except for the MHW (1998) study, employed exposures that included a host of additional dietary supplements (e.g.,

minerals, vitamins, protein, and carbohydrates) that might influence tissue kinetics and dynamics in response to triacetin. Indeed, acute oral exposure to triacetin alone in rats revealed lethal dose (LD_{50}) values ranging from >2,000−12,800 mg/kg (OECD, 2002). Mice appear to be slightly more sensitive, particularly females, to acute oral triacetin exposure with LD_{50}s ranging from 1,100−9,300 mg/kg (OECD, 2002). In addition, many of the repeat-dose studies were severely lacking in the number of toxicological parameters examined, including the studies by Lynch et al. (1994), Lynch and Bailey (1995), Shapira et al. (1969), and Shapira et al. (1975); thus, some caution is warranted in the interpretation of the higher NOAELs identified in these studies compared to MHW (1998).

The principal study (MHW, 1998) was performed by the Kashima Laboratory of the Mitsubishi Chemical Safety Institute in accordance with the OECD combined repeated dose and reproductive/developmental toxicity screening test guideline (OECD TG 422). Because it could not be conclusively determined that this study was peer reviewed and the fact that no effects were observed, screening values are derived below. An adequate number of animals were dosed for a subchronic duration at levels up to 1,000 mg/kg-day and included exposure to progeny during a potentially susceptible lifestage. The parental F0 animals were dosed for 41−48 days from 14 days before mating to PPD3; thus, F1 offspring were exposed throughout gestation and potentially indirectly until PND 4. In the absence of any finding of toxicity in offspring, the NOAEL is considered to be 1,000 mg/kg-day for F1 rats and is selected as the POD to derive both screening subchronic and chronic p-RfDs.

EPA guidance recommends expressing gestational exposures as a daily average during the period of exposure and not to extrapolate to lifetime exposure (U.S. EPA, 1991), so no duration adjustment was needed for each dose in the principal study. However, the POD was extrapolated to a corresponding human equivalent dose using the EPA's guidance document entitled, "Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose" (U.S. EPA, 2011). The Agency endorses a hierarchy of approaches for deriving human equivalent oral exposures (i.e., HEDs) from data in laboratory animals, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches can include using chemical-specific information, in the absence of a complete physiologically-based toxicokinetic model. In lieu of either chemical-specific kinetic models or data to inform the derivation of human equivalent oral exposures, EPA endorses body weight scaling to the ¾ power (i.e., $BW^{3/4}$) as a default approach to extrapolate toxicologically equivalent doses of orally administered agents from adult laboratory animals to adult humans for the purpose of deriving an oral RfD. No physiologically-based toxicokinetic modeling information exists for triacetin. Therefore, consistent with EPA guidance (U.S. EPA, 2011), the POD is converted to a HED employing a standardized dosimetric adjustment factor (DAF) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a BW_a of 0.25 kg for rats and a BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.24. Applying this DAF to the NOAEL identified from the MHW (1998) study yields a $NOAEL_{HED}$ as follows:

$$\begin{aligned} NOAEL_{HED} &= 1{,}000 \text{ mg/kg-day} \times DAF \\ &= 1{,}000 \text{ mg/kg-day} \times 0.24 \\ &= 240 \text{ mg/kg-day} \end{aligned}$$

The screening subchronic p-RfD for triacetin is derived as follows:

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= NOAEL_{HED} \div UF_C \\ &= 240 \text{ mg/kg-day} \div 3 \\ &= 8 \times 10^{1} \text{ mg/kg-day} \end{aligned}$$

Table A-1 summarizes the uncertainty factors (UFs) for the screening subchronic p-RfD for triacetin.

Table A-1. UFs for Screening Subchronic p-RfD of Triacetin

UF	Value	Justification
UF_A	1	A UF_A of 1 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. Although several limitations in the Segel et al. (2011) human study (e.g., preexistent disease condition, confounded exposures) significantly decreases confidence in making inferences regarding potential differences in the toxicokinetics or toxicodynamics of triacetin between rats and humans, the NOAEL of 4,500 mg/kg-day identified in human infants (Madhavarao et al., 2009) is considerably greater than the NOAEL of 1,000 mg/kg-day identified in neonatal rats (MHW, 1998). Therefore, a UF_A of 1 is applied.
UF_D	3	A UF_D of 3 is selected even though there are no acceptable two-generation reproduction studies, or peer-reviewed developmental studies. However, the MHW (1998) study reported no reproductive or developmental toxicity associated with triacetin exposure. Additionally, the Cosmetic Ingredient Review Expert Panel concluded that triacetin does not present a risk of reproductive or developmental toxicity because it is metabolized to glycerol and acetic acid, which are not reproductive or developmental toxicants (Fiume, 2003). Although triacetin appears to be relatively inert in animals and humans during a potentially sensitive lifestage, acute oral exposure studies using triacetin alone have identified LD_{50}s as low as 2,000 mg/kg in rats. Considering the rat developmental POD of 1,000 mg/kg-day, there is some uncertainty in where a LOAEL for a significant biological effect from a triacetin-only repeat-dose (e.g., subchronic or chronic) study may occur along the dose-response continuum between the POD (NOAEL) of 1,000 mg/kg-day and LD_{50} of approximately 2,000 mg/kg. Therefore, a UF_D of 3 is applied.
UF_H	1	A UF_H of 1 is applied for intra-species differences to account for potentially susceptible individuals in human populations. Segel et al. (2011) demonstrated that infants, a sensitive human population, can tolerate daily doses of up to 4,500 mg/kg-d.
UF_L	1	A UF_L of 1 is applied for using a POD based on a NOAEL.
UF_S	1	A UF_S of 1 is applied because the exposure occurred during a developmental lifestage.
UF_C	3	

Derivation of a Screening Chronic Provisional RfD (Screening Chronic p-RfD)

No chronic toxicity study was located. Therefore, MHW (1998) was also used to derive the screening chronic p-RfD. While the principal study, POD, and resultant screening chronic p-RfD are the same as the screening subchronic p-RfD above, the derivation below is shown for completeness.

$$\begin{aligned} \textbf{Screening Chronic p-RfD} &= NOAEL_{HED} \div UF_C \\ &= 240 \text{ mg/kg-day} \div 3 \\ &= 8 \times 10^{1} \text{ mg/kg-day} \end{aligned}$$

Table A-2 summarizes the UFs for the screening chronic p-RfD for triacetin.

Table A-2. UFs for Screening Chronic p-RfD of Triacetin

UF	Value	Justification
UF_A	1	A UF_A of 1 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans. Although several limitations in the Segel et al. (2011) human study (e.g., preexistent disease condition, confounded exposures) significantly decreases confidence in making inferences regarding potential differences in the toxicokinetics or toxicodynamics of triacetin between rats and humans, the NOAEL of 4,500 mg/kg-day identified in human infants (Madhavarao et al., 2009) is considerably greater than the NOAEL of 1,000 mg/kg-day identified in neonatal rats (MHW, 1998). Therefore, a UF_A of 1 is applied.
UF_D	3	A UF_D of 3 is selected even though there are no acceptable two-generation reproduction studies, or peer-reviewed developmental studies. However, the MHW (1998) study reported no reproductive or developmental toxicity associated with triacetin exposure. Additionally, the Cosmetic Ingredient Review Expert Panel concluded that triacetin does not present a risk of reproductive or developmental toxicity because it is metabolized to glycerol and acetic acid, which are not reproductive or developmental toxicants (Fiume, 2003). Although triacetin appears to be relatively inert in animals and humans during a potentially sensitive lifestage, acute oral exposure studies using triacetin alone have identified LD_{50}s as low as 2,000 mg/kg in rats. Considering the rat developmental POD of 1,000 mg/kg-day, there is some uncertainty in a LOAEL for a significant biological effect from a triacetin-only repeat-dose (e.g., subchronic or chronic) study may occur along the dose-response continuum between the POD (NOAEL) of 1,000 mg/kg-day and LD_{50} of approximately 2,000 mg/kg. Therefore, a UF_D of 3 is applied.
UF_H	1	A UF_H of 1 is applied for intraspecies differences to account for potentially susceptible individuals in human populations. Segel et al. (2011) demonstrated that infants, a sensitive human population, can tolerate daily doses of up to 4,500 mg/kg-d.
UF_L	1	A UF_L of 1 is applied for using a POD based on a NOAEL.
UF_S	1	A UF_S of 1 is applied because the exposure occurred during a developmental lifestage.
UF_C	3	

APPENDIX B. DATA TABLES

Table B-1. Initial and Terminal Body Weights of Weanling Male S-D Rats Fed Diets Containing Various Levels of Triacetin for 18 Days[a]

Target Protein Content	Dietary Components by % Weight					Animal weight (g) ± SEM	
	Protein Source		Carbohydrate Source				
	Casein	*H. Eutropha*	Glycerol	Triacetin[b]	Starch	Original	Day 18
12%	13.7	0	0	0	73.3	79.1 ± 2.9	152.8 ± 4.5
	13.7	0	30	30	13.3	78.0 ± 3.4	117.4 ± 4.3
	0	13.4	0	0	73.6	77.0 ± 5.0	148.6 ± 6.3
	0	13.4	30	30	13.6	77.0 ± 3.9	129.4 ± 6.3
24%	27.4	0	0	0	59.6	76.3 ± 2.9	186.9 ± 4.9
	27.4	0	29.8	29.8	0	84.1 ± 2.6	166.8 ± 6.9
	0	26.8	0	0	60.2	76.5 ± 4.2	182.9 ± 3.1
	0	26.8	29.8	29.8	0.2	74.9 ± 4.0	178.8 ± 3.4
48%	54.8	0	0	0	32.2	79.3 ± 1.7	181.0 ± 3.3
	54.8	0	16.1	16.1	0	78.6 ± 4.1	178.1 ± 5.1
	0	53.6	0	0	33.4	78.4 ± 3.2	204.3 ± 13.1
	0	53.6	16.7	16.1	0	83.3 ± 3.1	191.5 ± 8.3

[a]Source: Shapira et al. (1969).
[b]The three dietary levels of triacetin (16.1, 29.8, and 30%) are equivalent to adjusted doses of 13,869, 25,670, and 25,843 mg/kg-day, respectively.

APPENDIX C. BMD OUTPUTS

No BMD modeling was conducted for this assessment.

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WHO FOOD ADDITIVES SERIES: 48

SAFETY EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

ALIPHATIC ACYCLIC DIOLS, TRIOLS, AND RELATED SUBSTANCES

First draft prepared by Dr P.J. Abbott, Professor A.G. Renwick[2] and Professor I.G. Sipes[3]
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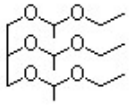
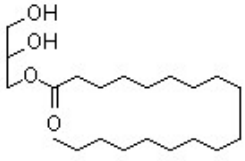
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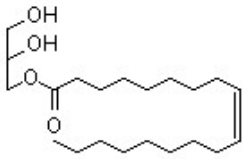
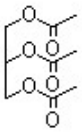
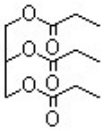
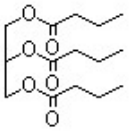
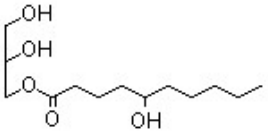
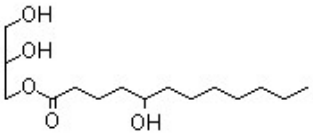
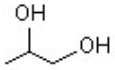
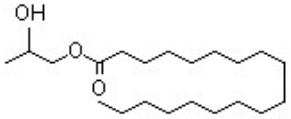
1. EVALUATION

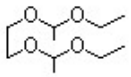
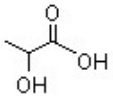
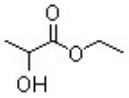
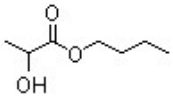
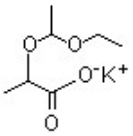
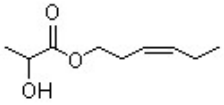
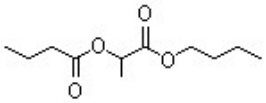
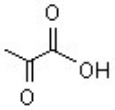
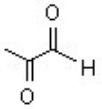
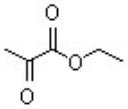
1.1 Introduction

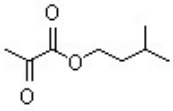
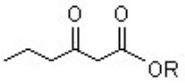
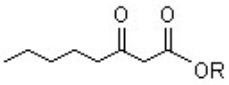
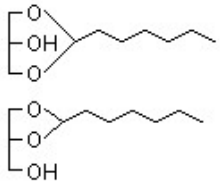
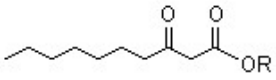
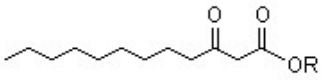
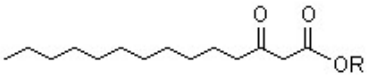
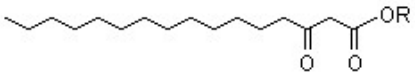
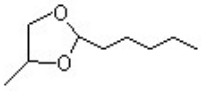
The Committee evaluated a group of 31 flavouring agents[1] that included aliphatic acyclic diols, triols, and related substances (see Table 1) using the Procedure for the Safety Evaluation of Flavouring Agents (see Figure 1, Introduction). All members of this group are aliphatic acyclic primary alcohols, aldehydes, acids, or related esters with one or more additional oxygenated functional groups. The group contains four subgroups: glycerol (No. 909) and 15 related glycerol esters and acetals (Nos 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, and 924); propylene glycol (No. 925) and four related esters, acetals, and ketals (Nos 926, 927, 928, and 929); lactic acid (No. 930) and four lactate esters (Nos 931, 932, 934, and 935); and pyruvic acid (No. 936), its corresponding aldehyde (No. 937), two pyruvate esters (Nos 938 and 939) and one acetal of pyruvic acid (No. 933).

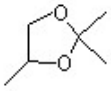
Table 1. Summary of results of safety evaluations of aliphatic acyclic diols, triols, and related substances

Flavouring agent	No.	CAS No. and structure	Step A3[b] Does intake exceed the threshold for human intake?	Step A4 Is the flavouring agent or are its metabolites endogenous?	Conclusion based on current intake
Structural class I					
Glycerol[c,d]	909	56-81-5 	Yes Europe: 17 000 USA: 220 000	Yes Glycerol is endogenous	Evaluation not finalized
1,2,3-Tris[(1′-ethoxy)]-propane	913	67715-82-6 	No Europe: 0 USA: 140	NR	No safety concern
Glyceryl monostearate[c]	918	123-94-4 	No Europe: 0 USA: 230	NR	Evaluation not finalized
Glyceryl monooleate[c]	919		No Europe: ND	NR	Evaluation not finalized

		111-03-5 	USA: 860		
Triacetin[c]	920	102-76-1 	Yes Europe: ND USA: 83 000	Yes Expected to be hydrolysed to glycerol, which is endogenous	Evaluation not finalized
Glyceryl tripropanoate[c]	921	139-45-7 	No Europe: 0.1 USA: 280	NR	Evaluation not finalized
Tributyrin[c]	922	60-01-5 	No Europe: 31 USA: 2	NR	Evaluation not finalized
Glycerol 5-hydroxy-decanoate[c]	923	26446-31-1 	No Europe: 4 USA: 0	NR	Evaluation not finalized
Glycerol 5-hydroxydo-decanoate[c]	924	26446-32-2 	No Europe: 4 USA: 0	NR	Evaluation not finalized
Propylene glycol[c,e]	925	57-55-6 	Yes Europe: ND USA: 2 400 000	Yes Expected to be oxidized to lactic acid, which is endogenous	Evaluation not finalized
Propylene glycol stearate[c]	926	142-75-6 	Yes Europe: ND USA: 66 000	Yes Expected to be oxidized to propylene glycol and subsequently to lactic acid	Evaluation not finalized
1,2-Di[(1-ethoxy)-ethoxy)] propane[c]	927			NR	

		67715-79-1 	No Europe: 7 USA: 150		No safety concern
Lactic acid	930	598-82-3 	Yes Europe: ND USA: 47 000	Yes Lactic acid is endogenous	No safety concern
Ethyl lactate[f]	931	97-64-3 	Yes Europe: 1900 USA: 760	Yes Expected to be hydrolysed to lactic acid, which is endogenous	No safety concern
Butyl lactate	932	138-22-7 	No Europe: 380 USA: 24	NR	No safety concern
Potassium 2-(1′-ethoxy) ethoxy-propanate	933		No Europe: ND USA: 1400	NR	No safety concern
cis-3-Hexenyl lactate	934	61931-81-5 	No Europe: 38	USA: 5NR	No safety concern
Butyl butyryl lactate	935	7492-70-8 	No Europe: 280 USA: 1400	NR	No safety concern
Pyruvic acid	936	127-17-3 	No Europe: 35 USA: 69	NR	No safety concern
Pyruvaldehyde	937	79-98-8 	No Europe: 120 USA: 3	NR	No safety concern
Ethyl pyruvate	938	617-35-6 	No Europe: 1 USA: 20	NR	No safety concern

Isoamyl pyruvate	939	7779--72-8 	No Europe: 0 USA: 0	NR	No safety concern
Structural class III					
3-Oxohexanoic acid glyceride	910	91052-72-1 	Yes Europe: 0 USA: 270	Yes Expected to be hydrolysed to glycerol, which is endogenous	No safety concern
3-Oxooctanoic acid glyceride	911	91052-68-5 	No Europe: 34 USA: 0	NR	No safety concern
Heptanal glyceryl acetal (mixed 1,2 and1,3 acetals)	912	1708-35-6 	No Europe: 4 USA: 0	NR	No safety concern
3-Oxodecanoic acid glyceride[c]	914	91052-69-6 	Yes Europe: 0 USA: 270	Yes Expected to be hydrolysed to glycerol, which is endogenous	Evaluation not finalized
3-Oxododecanoic acid glyceride[c]	915	91052-70-9 	No Europe: 73 USA: 0	NR	Evaluation not finalized
3-Oxotetradecanoic acid glyceride[c]	916	91052-73-2 	Yes Europe: 0 USA: 270	Yes Expected to be hydrolysed to glycerol, which is endogenous	Evaluation not finalized
3-Oxohexadecanoic acid glyceride[c]	917	91052-71-0 	No Europe: 43 USA: 0	NR	Evaluation not finalized
4-Methyl-2-pentyl-1,3- dioxolane	928	26563-74-6 	No Europe: 0 v	NR	No safety concern

2,2,4-Trimethyl-1,3-oxycyclopentane	929	1193-11-9 	No Europe: 0.3 USA: 0.2	NR	No safety concern

CAS: Chemical Abstracts Service; ND: no data available; NR: not required for evaluation because consumption of the substance was determined to be of no safety concern at Step A3 of the Procedure.

[a] *Step 2*: All of the flavouring agents in this group are expected to be metabolized to innocuous products.

[b] The thresholds for human intake are 1800 µg/day for structural class I and 90 µg/day for structural class III. All intake values are expressed in µg/day.

[c] Further information is required to determine whether this substance is currently used as a flavouring agent.

[d] An ADI 'not specified' was established for glycerol by the Committee at its twentieth meeting (Annex 1, reference *41*), which was maintained at the present meeting.

[e] An ADI of 0–25 mg/kg bw was established for propylene glycol by the Committee at its seventeenth meeting (Annex 1, reference *32*), which was maintained at the present meeting.

[f] Ethyl lactate was included in the group ADI 'not specified' for lactic acid and its salts that was established by the Committee at its twenty-sixth meeting (Annex 1, reference *59*), which was maintained at the present meeting.

The Committee previously evaluated three members of the group. Glycerol (No. 909) was considered at the twentieth meeting, when an ADI "not specified" was established (Annex 1, reference *41*). Propylene glycol (No. 925) was considered at the seventh meeting, when an ADI of 0–20 mg/kg bw was established (Annex 1, reference *7*); it was further considered at the seventeenth meeting, when the ADI was increased to 0–25 mg/kg bw (Annex 1, reference *32*). Ethyl lactate (No. 931) was considered at the eleventh (Annex 1, reference *14*), twenty-third (Annex 1, reference *50*), twenty-fourth (Annex 1, reference *53*), and twenty-sixth meetings (Annex 1, reference *59*). At its twenty-sixth meeting, the Committee included ethyl lactate in the group ADI 'not specified'[2] with lactic acid.

Nine of the 31 substances (Nos 909, 929, 930, 931, 932, 934, 936, 937, and 938) have been detected as natural components of foods in cocoa, milk, cider, cognac, asparagus, tomato, and mushrooms (Maarse et al., 1999).

1.2 Estimated per capita intake

The total annual production of the 31 substances in this group of flavouring agents for use in food was reported to be 140 000 kg in Europe (International Organization of the Flavor Industry, 1995) and 21 000 000 kg in the USA (Lucas et al., 1999). These values are equivalent to a total daily *per capita* intake of 20 000 µg in Europe and 2 800 000 µg in the USA. The large difference in the annual volume of production between Europe and the USA is due to the inclusion in the USA of figures on the use of glycerol, triacetin, and propylene glycol as solvents in the preparation of compound flavour mixtures.

In Europe, three flavouring agents, namely, glycerol (17 000 µg/day), ethyl lactate (1900 µg/day), and butyl lactate (380 µg/day), accounted for approximately 97% of the total *per capita* intake. In the USA, three substances, namely glycerol (220 000 µg/day), triacetin (83 000 µg/day), and propylene glycol (2 400 000 µg/day), accounted for 96% of the total annual daily *per capita* intake. The *per capita* intakes of individual substances are shown in Table 2.

Table 2. Annual volumes of use of aliphatic acyclic diols, triols and related substances used as flavouring agents in Europe and the USA

Substance (No.)	Most recent annual volume (kg)	Intake[a]		Annual volume in naturally occurring foods (kg)[b]	Consumption ratio[c]

		µg/day	µg/kg bw per day		
Glycerol (909)					
Europe	120 000	17 000	280	24 000 000	200
USA	1 700 000	220 000	3700		14
1,2,3-Tris[(1'-ethoxy)ethoxy]propane (913)					
Europe	0	0	0	–	
USA	1000	140	2.3		
3-Oxohexadecanoic acid glyceride (917)					
Europe	300	43	0.7	–	
USA	0	0	0		
Glyceryl monostearate (918)					
Europe	0	0	0	–	
USA	1800	230	4		
Glyceryl monooleate (919)					
Europe	NR	NA	NA	–	
USA	6500	860	14		
Triacetin (920)					
Europe	NR	NA	NA	–	
USA	630 000	83 000	1400		
Glyceryl tripropanoate (921)					
Europe	0.5	0.1	0.002	–	
USA	2100	280	5		
Tributyrin (922)					
Europe	220	31	0.5	–	
USA	15	2	0.03		
Glycerol 5-hydroxydecanoate (923)					
Europe	25	4	0.007	–	
USA	0	0	0		

Glycerol 5-hydroxydodecanoate (924)					
Europe	25	4	0.07	–	
USA	0	0	0		
Propylene glycol (925)					
Europe	NR	NA	NA	–	
USA	18 000 000	2 400 000	40 000		
Propylene glycol stearate (926)					
Europe	NR	NA	NA	–	
USA	500 000	66 000	1100		
1,2-Di[(1-ethyoxy)ethyoxy]propane (927)					
Europe	49	7	0.1	–	
USA	1200	150	2.5		
Lactic acid (930)					
Europe	NR	NA	NA	11 000 000	
USA	360 000	47 000	780		30
Ethyl lactate (931)					
Europe	13 000	1900	32	250 000	19
USA	5800	760	13		43
Butyl lactate (932)					
Europe	2600	380	6	+	
USA	190	24	0.4		
Potassium 2-(1′-ethoxy)ethoxypropanate (933)					
Europe	NR	NA	NA	–	
USA	10 000	1400	23		
cis-3-Hexenyl lactate (934)					
Europe	270	38	0.6	+	
USA	36	5	0.1		
Butyl butyryllactate (935)					
Europe	1900	280	5	–	

USA	11 000	1400	24		
Pyruvic acid (936)					
Europe	250	35	0.6	3 900 000	16 000
USA	520	69	1.1		7 500
Pyruvaldehyde (937)					
Europe	810	120	2	3100	38
USA	22	3	0.05		140
Ethyl pyruvate (938)					
Europe	5	1	0.02	210	42
USA	150	20	0.3		1.4
Isoamyl pyruvate (939)					
Europe	0	0	0	–	
USA	0	0	0		
3-Oxohexanoic acid glyceride (910)					
Europe	0	0	0	–	
USA	2000	270	4.5		
3-Oxooctanoic acid glyceride (911)					
Europe	240	34	0.6	–	
USA	0	0	0		
Heptanal glyceryl acetal (mixed 1,2 and 1,3 acetals) (912)					
Europe	27	4	0.07	–	
USA	0.05	0	0		
3-Oxodecanoic acid glyceride (914)					
Europe	0	0	0	–	
USA	2000	270	4.5		
3-Oxododecanoic acid glyceride (915)					
Europe	510	73	1.2	–	
USA	0	0	0		
3-Oxotetradecanoic acid glyceride (916)					

Europe	0	0	0	–	
USA	2000	270	5		
4-Methyl-2-pentyl-1,3-dioxolane (928)					
Europe	0.1	0	0	–	
USA	1.4	0.2	0.003		
2,2,4-Trimethyl-1,3-oxyacylopentane (929)					
Europe	2	0.3	0.005	2300	1200
USA	1.8	0.2	0.003		1300

NA, not applicable; NR, not reported; +, reported to occur naturally in foods (Maarse et al., 1999), but quantitative data were not available; –, not reported to occur naturally in foods

[a] Intake expressed as µg/person per day calculated as follows: [(annual volume, kg) x (1×10^9 µg/kg)/ (population x survey correction factor x 365 days)], where population (10%, 'eaters only') = 32×10^6 for Europe and 26×10^6 for the USA. The correction factor = 0.6 for Europe and 0.8 for the USA, representing the assumption that only 60% and 80% of the annual volume of the flavour, respectively, was reported in the poundage surveys (International Organization of the Flavor Industry, 1995; Lucas et al., 1999). Intake expressed as µg/kg bw per day calculated as follows: [(µg/person per day)/body weight], where body weight = 60 kg. Slight variations may occur from rounding.

[b] Quantitative data from Stofberg & Grundschober (1987)

[c] Calculated as follows: (annual consumption in food, kg)/(most recently reported volume as a flavouring agent, kg)

1.3 Metabolic considerations

The aliphatic esters of propylene glycol, lactic acid and pyruvic acid and their parent compounds would all be expected to be readily absorbed from the gastrointestinal tract. Hydrolysis of the aliphatic esters is catalysed largely by hepatic esterases to give the component alcohol and carboxylic acid or aldehyde. After hydrolysis of glycerol esters in the intestine, glycerol is also readily absorbed. Glycerol, pyruvic acid, and lactic acid are endogenous in humans. Glycerol and pyruvic acid are metabolized completely and are not excreted. Lactic acid is also mainly metabolized, although urinary excretion may occur if the blood concentration is high. Propylene glycol can be metabolized, but high doses are likely to be excreted largely unchanged in the urine.

Glycerol is metabolized via the glycolytic pathway after it has been converted in the liver to glycerol-3-phosphate. Glycerol-3-phosphate is then oxidized to yield dihydroxyacetone phosphate, which is isomerized to glyceraldehyde-3-phosphate, eventually yielding pyruvic acid.

Pyruvic acid follows two primary routes of metabolism. Under aerobic conditions, it is converted to acetyl coenzyme A and enters the citric acid cycle. Under anaerobic conditions, primarily in muscles as a result of strenuous physical activity, pyruvic acid is reduced by lactic dehydrogenase to lactic acid.

Lactic acid diffuses through muscle tissue and is transported to the liver in the bloodstream. In the liver, it is converted to glucose by gluconeogenesis. Lactic acid can also be further catabolized in the lactic acid cycle (also known as the Cori cycle).

Propylene gycol can be oxidized to lactic acid via two biochemical pathways. If propylene glycol is phosphorylated, it can be converted to acetol phosphate, lactaldehyde phosphate, lactyl phosphate, and then lactic

acid. If it is not phosphorylated, propylene glycol is successively oxidized to lactaldehyde, methylgloyoxal, and lactic acid.

1.4 Application of the Procedure for the Safety Evaluation of Flavouring Agents

Step 1 Twenty-eight of the 31 flavouring agents in this group are linear, simple branched aliphatic compounds. Twenty-two of these are in structural class I (Cramer et al., 1978) because they contain fewer than three different types of functional group (Nos 909, 913, 918–927, and 930–939). Six of these 28 substances are in structural class III because they contain three or more different types of functional group (Nos 910, 911, 914–917). The three remaining substances in the group are in structural class III because they are cyclic acetals and ketals (Nos 912, 928, and 929).

Step 2 The data on the metabolism of individual members of the group were sufficient to allow conclusions about their probable metabolic fate. The aliphatic esters of propylene glycol (Nos 926, 927, 928, and 929), lactic acid (Nos 931, 932, 934, and 935), and pyruvic acid (Nos 938 and 939) are expected to be hydrolysed to their component alcohol and carboxylic acid. Glycerol esters (Nos 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, and 924) are expected to be hydrolysed to glycerol and carboxylic acids. Esters of propylene glycol are expected to be hydrolysed to propylene glycol and component acid. Esters of lactic acid and pyruvic acid are expected to be hydrolysed to lactic acid and pyruvic acid, respectively, and the corresponding alcohol. Acetals (Nos 927 and 933) are expected to be hydrolysed to their component alcohols and aldehydes, while ketals (Nos 928 and 929) are expected to be hydrolysed to their component ketones and alcohols. Glycerol (No. 909), lactic acid (No. 930), and pyruvic acid (No. 936) are endogeneous and are metabolized through the glycolytic and citric acid pathways. Propylene glycol (No. 925) is oxidized to lactic acid. For all substances in this group, therefore, the evaluation proceeded via the A side of the scheme.

Step A3 The daily *per capita* intakes of 22 of the substances in this group are below the threshold of concern for their respective structural classes (class I, 1800 μg; class III, 90 μg). These substances would not be expected to be of safety concern. The daily *per capita* intakes of the remaining nine substances (Nos 909, 910, 914, 916, 920, 925, 926, 930, and 931) exceed the threshold of concern for their respective structural classes. Evaluation of these substances therefore proceeds to step A4.

Step A4 Glycerol (No. 909), lactic acid (No. 930), and ethyl lactate (No. 931) are endogenous in humans and are therefore not expected to be a safety concern. Triacetin (No. 920), 3-oxohexanoic acid glyceride (No. 910), 3-oxodecanoic acid glyceride (No. 914), and 3-oxotetradecanoic acid glyceride (No. 916) are glycerol esters and are hydrolysed to glycerol. Propylene glycol (No. 925) and propylene glycol stearate (No. 926) are not endogenous in humans; however, the ester is expected to be hydrolysed to propylene glycol and stearic acid. Propylene glycol is known to be oxidized to lactic acid in mammals. These substances would therefore not be expected to be a safety concern.

1.5 Consideration of combined intakes

In the unlikely event that all 23 substances in structural class I were to be consumed concurrently on a daily basis, the estimated *per capita* consumption in Europe and the USA would exceed the human intake threshold for class I. The estimated *per capita* consumption in Europe and the USA for combined intake of the eight flavouring agents in structural class III would also exceed the human intake threshold for class III. Given that the substances are expected to be efficiently metabolized by known metabolic pathways, the Committee considered that the combined intake would not give rise to concerns about safety.

1.6 Conclusions

On the basis of the predicted metabolism, the Committee concluded that the 31 aliphatic acyclic diols, triols, and related substances in this group would not raise safety concerns at the current levels of intake when used as

flavouring agents. In applying the Procedure, the Committee noted that all of the available data on toxicity are consistent with the results of the safety evaluation.

2. RELEVANT BACKGROUND INFORMATION

2.1 Explanation

This monograph summarizes the key data relevant to the evaluation of the 31 flavouring agents in this group. All members of this group are aliphatic acyclic primary alcohols, aldehydes, acids, or related esters with one or more additional oxygenated functional groups. The group consists of four subgroups: glycerol (No. 909) and 15 related glycerol esters and acetals (Nos 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, and 924); propylene glycol (No. 925) and four related esters, acetals, and ketals (Nos 926, 927, 928, and 929); lactic acid (No. 930) and four lactate esters (Nos 931, 932, 934, and 935); and pyruvic acid (No. 936), its corresponding aldehyde (No. 937), two pyruvate esters (Nos 938 and 939) and one acetal of pyruvic acid (No. 933).

2.2 Additional considerations on intake

Quantitative data on natural occurrence and consumption ratios have been reported for seven flavouring agents in the group, which indicate that they are consumed predominantly from traditional foods (i.e., consumption ratio > 1) (Stofberg & Kirschman, 1985; Stofberg & Grundschober, 1987) (Table 2).

The daily *per capita* intake of this group of flavouring substances is 20 000 µg/day in Europe (330 µg/kg bw per day) and 2 500 000 µg/day in the USA (14 000 µg/kg bw per day). Glycerol accounted for approximately 85% (17 000 µg/day) of the total *per capita* intake in Europe; in the USA, propylene glycol accounted for 96% (2 400 000 µg/day) of the total *per capita* intake.

2.3 Biological data

2.3.1 Biochemical data

(a) Absorption and transformation

Little specific information was available on the absorption and transformation of individual members of this group of flavouring substances. The esters, acetals, and ketals of glycerol, lactic acid, and pyruvic acid would be expected to be readily absorbed, as would the parent compounds. After hydrolysis of glycerol esters in the intestine, glycerol is readily absorbed. Glycerol and pyruvic acid are metabolized completely and are not excreted. Lactic acid is also largely metabolized, although urinary excretion may occur if the blood concentration is high. Propylene glycol can be metabolized, but at high concentrations is likely to be largely excreted unchanged in the urine.

Propylene glycol given orally to three persons at a dose of 1038 mg (0.017 g/kg bw) was rapidly absorbed and eliminated in the urine and saliva (Hanzlik et al., 1939). In a study of the pharmacokinetics of propylene glycol in humans, multiple oral doses were rapidly absorbed, and its rate of clearance from blood was dose-dependent (Yu et al., 1985).

In studies of the minor pathways of metabolism of propylene glycol, administration to rats in drinking-water resulted in excretion unchanged in the urine (Van Winkle, 1941). Propylene glycol given orally to rabbits was conjugated with glucuronic acid and excreted in the urine (Miura, 1911; Fellows et al., 1947).

(b) Metabolism

(i) Hydrolysis of linear and branched-chain esters

In general, aliphatic esters of propylene glycol, lactic acid, and pyruvic acid are expected to be hydrolysed to their component alcohol and carboxylic acids. The hydrolysis is catalysed by classes of enzymes recognized as carboxylesterases or esterases (Heymann, 1980), the most important of which are the B-esterases, which, in mammals, predominate in hepatocytes (Heymann, 1980; Anders, 1989). The rates of hydrolysis follow first-order kinetics, with hydrolysis of the straight-chain esters occurring approximately 100 times more rapidly than that of branched-chain esters (Butterworth et al., 1975; Longland et al., 1977; Grundschober, 1977; Leegwater & van Straten, 1979).

Glycerol esters are hydrolysed to glycerol and the corresponding carboxylic acids (see Figure 1). The hydrolysis is catalysed by intestinal lipase (Tietz, 1986), which attacks the ester bonds at carbons 1 and 3. The ester bond at carbon 2 is more resistant to hydrolysis, possibly because of its stereochemistry and steric hindrance. The *beta*-monoglyceride can, however, spontaneously isomerise to the *alpha*-form (3-acylglycerol), permitting further hydrolysis to yield glycerol.

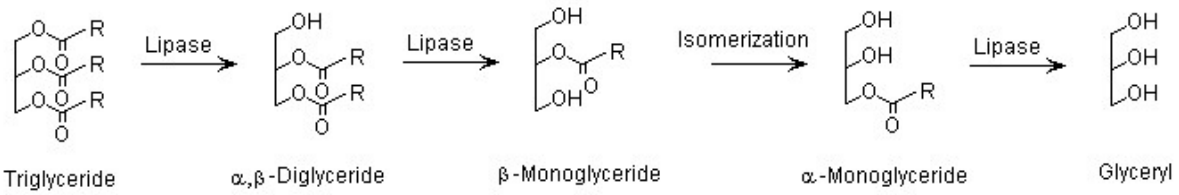


Figure 1. Hydrolysis of glycerol esters in humans

The rate of hydrolysis of glycerol esters depends on the surface area of the lipid–water interfaces, which increases greatly with the churning peristaltic movements of the intestine and the emulsifying action of bile acids. Lipase is rapidly denatured at these interfaces; however, colipase, a pancreatic protein that forms a 1:1 complex with lipase, inhibits the surface denaturation of lipase and anchors it to the lipid–water interface (Voet & Voet, 1990).

Studies of the hydrolysis of the glycerol fatty acid esters (tributyrin (No. 922) (Pilz, 1959; Pilz & Johann, 1967), glycerol 5-hydroxydecanoate (No. 923) (Als, 1975), and glycerol 5-hydroxydodecanoate (No. 924) (Als, 1975) showed complete hydrolysis to glycerol and the corresponding fatty acids, butyric acid, 5-hydroxy-decanoic acid, and 5-hydroxydodecanoic acid, respectively.

Hydroxylated and keto acids formed by hydrolysis of glycerol esters such as 5-hydroxydecanoic acid and 5-hydroxydodecanoic acid may form lactones by acid-catalysed intramolecular cyclization to yield five-member rings (see Figure 2). In aqueous media, equilibrium is established between the open-chain hydroxy-carboxylic acid and the lactone. At basic pH, the equilibrium favours the open-chain hydroxycarboxylate anion, but the lactone predominates at acidic pH. 5-Hydroxy-decanoic acid and 5-hydroxydodecanoic acid may form the *delta*-lactones *delta*-decalactone and *delta*-dodecalactone, respectively. Their metabolic fate can be predicted on the basis of an analogy with the known biotransformation of structurally related aliphatic lactones previously considered by the Committee (Annex 1, reference *132*). Linear saturated 5-hydroxycarboxylic acids, which are formed from *delta*-lactones, are converted, via acetyl coenzyme A (CoA) to hydroxythioesters, which then undergo *beta*-oxidation and cleavage to yield an acetyl CoA fragment and a new *beta*-hydroxy-thioester reduced by two carbons. Even-numbered carbon acids continue to be oxidized and cleaved to yield acetyl CoA, while odd-numbered carbon acids yield acetyl CoA and propinyl CoA. Acetyl CoA enters the citric acid cycle directly, while propionyl CoA is transformed into succinyl CoA, which then enters the citric acid cycle.

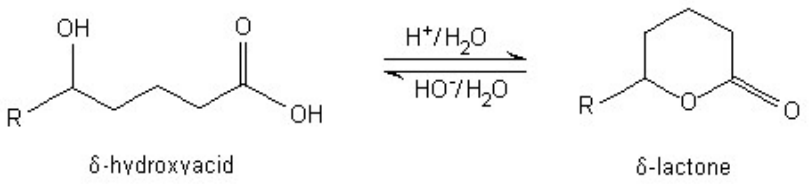


Figure 2. Equilibrium between *delta*-lactones and their corresponding hydroxycarboxylic acids

Esters of propylene glycol are hydrolysed to propylene glycol and their component acid. In the presence of pancreatic lipase, propylene glycol stearate (No. 926) was hydrolysed to propylene glycol and stearic acid (Balls & Matlock, 1938).

Esters of lactic acid are hydrolysed to lactic acid and the corresponding alcohol. In rat plasma, ethyl lactate (No. 931) was hydrolysed to ethyl alcohol and lactic acid (Falke et al., 1981).

Esters of pyruvic acid are expected to be hydrolysed to pyruvic acid and the corresponding alcohol.

(ii) Hydrolysis of acetals and ketals

In general, acetals are hydrolysed to their component alcohols and aldehydes. Studies on the hydrolysis of 1,2,3-tris[(1′-ethoxy)ethoxy] propane (No. 913), which is readily hydrolysed to yield acetaldehyde and glycerol (DeSimone, 1976), support this conclusion.

Acetals of propylene glycol have also been shown to be hydrolysed to their component alcohol and aldehyde. *In vitro*, 1,2-di[(1′-ethoxy)ethoxy]propane (No. 927) was completely hydrolysed to acetaldehyde and propylene glycol (DeSimone, 1976). Potassium 2-(1′-ethoxy) ethoxypropanoate (No. 933), an acetal of lactic acid, was completely hydrolysed to lactic acid, acetaldehyde, and ethanol in simulated stomach fluids (Moreno et al., 1984). Aldehydes are oxidized to their corresponding carboxylic acids, which are subsequently metabolized through known biochemical pathways (Voet & Voet, 1990). For example, pyruvaldehyde (No. 937), the aldehyde of pyruvic acid, was metabolized to pyruvic acid when incubated with rat liver homogenate (Bonsignore et al., 1968).

Ketals are hydrolysed to their component ketones and alcohols. The related compound, benzaldehyde propylene glycol acetal, was hydrolysed in simulated gastric fluid and, to a lesser extent, in intestinal fluid (Morgareidge, 1962). Similarly, 2,2,4-trimethyl-1,3-oxacyclopentane (No. 929) would be expected to be hydrolysed in humans to yield acetone and propylene glycol.

(iii) Metabolism of glycerol (No. 909)

Glycerol is endogenous in the human body. It enters the glycolytic pathway after its conversion in the liver to glycerol-3-phosphate by glycerol kinase. Glycerol-3-phosphate is then oxidized by glycerol-3-phosphate dehydrogenase to yield dihydroxyacetone phosphate (see Figure 3), which is then isomerized to glyceral-dehyde-3-phosphate, eventually yielding pyruvic acid.

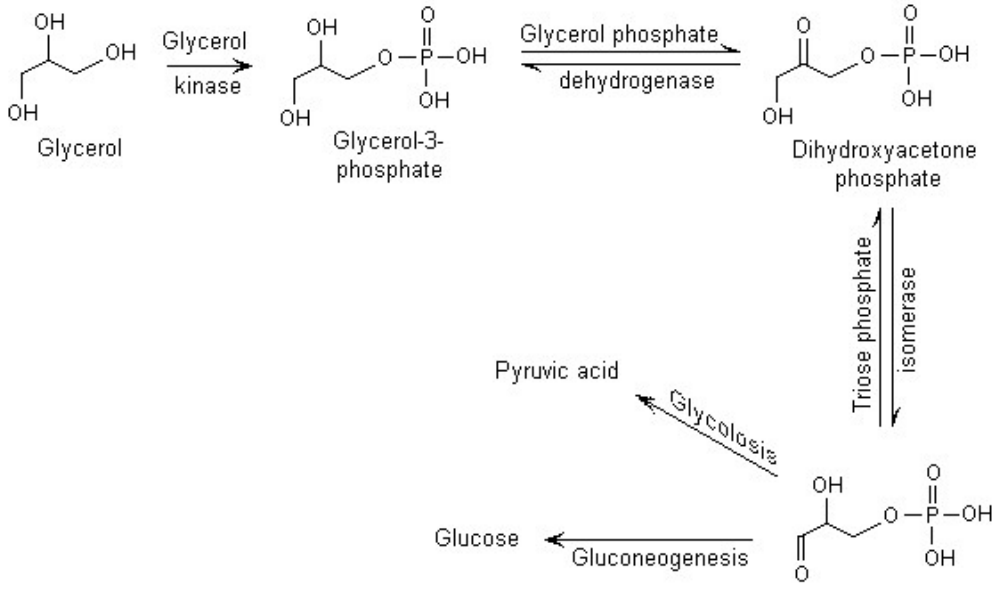
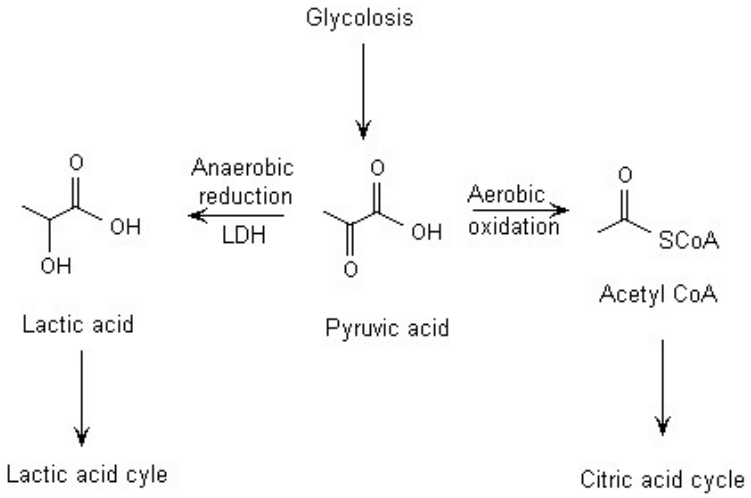


Figure 3. Metabolism of glycerol in humans

(iv) Metabolism of pyruvic acid (No. 936) and lactic acid (930)

Pyruvic acid is endogenous in the human body. It is a critical metabolic intermediate, and its fate depends on the oxidation state of the cell (see Figure 4). Under aerobic conditions, pyruvic acid is converted to acetyl CoA and enters the citric acid cycle, where it is completely metabolized. Under anaerobic conditions, lactate dehydrogenase catalyses the reduction of pyruvic acid to lactic acid and the oxidation of NADH to NAD^+, primarily in muscles.



CoA, coenzyme A

Figure 4. Metabolism of pyruvic acid in humans

Lactic acid diffuses from the muscles and is transported through the bloodstream to oxygen-rich tissues such as the heart and liver, where it is catabolized further through the lactic acid cycle (also known as the Cori cycle) (see

Figure 5), or converted to glucose *via* gluconeogenesis. Even in fully oxygenated muscle tissue, as much as 50% of the metabolized glucose is converted to lactic acid by way of pyruvic acid (Voet & Voet, 1990).

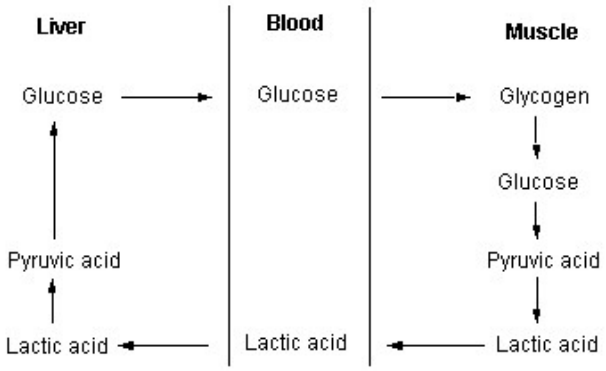


Figure 5. Lactic acid cycle (Cori cycle)

In resting women who received intravenous injections of [2-^{14}C]pyruvate, analysis of blood glucose 1 h later showed 96% conversion of pyruvic acid to glucose (Hostetler et al., 1969). When [2-^{14}C]pyruvate was incubated with liver slices from fasted normal rats, 86% had been used after 90 min of incubation. Of the radiolabel associated with metabolized pyruvic acid, 23% was associated with glycogen and glucose, 16% with CO_2, and 16% with lactic acid. In the presence of glycerol, the use of pyruvic acid was increased to 95%, accompanied by a decrease in conversion to glycogen (16%) and CO_2 (8.6%) and an increase in the production of lactic acid (Teng et al., 1953).

(v) Metabolism of propylene glycol (No. 925)

Propylene glycol can be oxidized to lactic acid *via* one of two pathways, depending on whether the glycol is phosphorylated (Rudney, 1954; Miller & Bazzano, 1965). In studies *in vitro* with rat liver, the free glycol was successively oxidized to lactaldehyde, methylglyoxal (pyuvaldehyde), and lactic acid (see pathway 1, Figure 6) (Ting et al., 1964; Miller & Bazzano, 1965), while the phosphorylated glycol followed the pathway of acetyl phosphate, lactaldehyde phosphate, lactyl phosphate, and lactic acid (Ruddick, 1972; see pathway 2, Figure 6). Lactate is subsequently converted to pyruvate, which enters the citric acid cycle and/or the gluconeogenesis pathway (Ruddick, 1972; Wittman & Bawin, 1974).

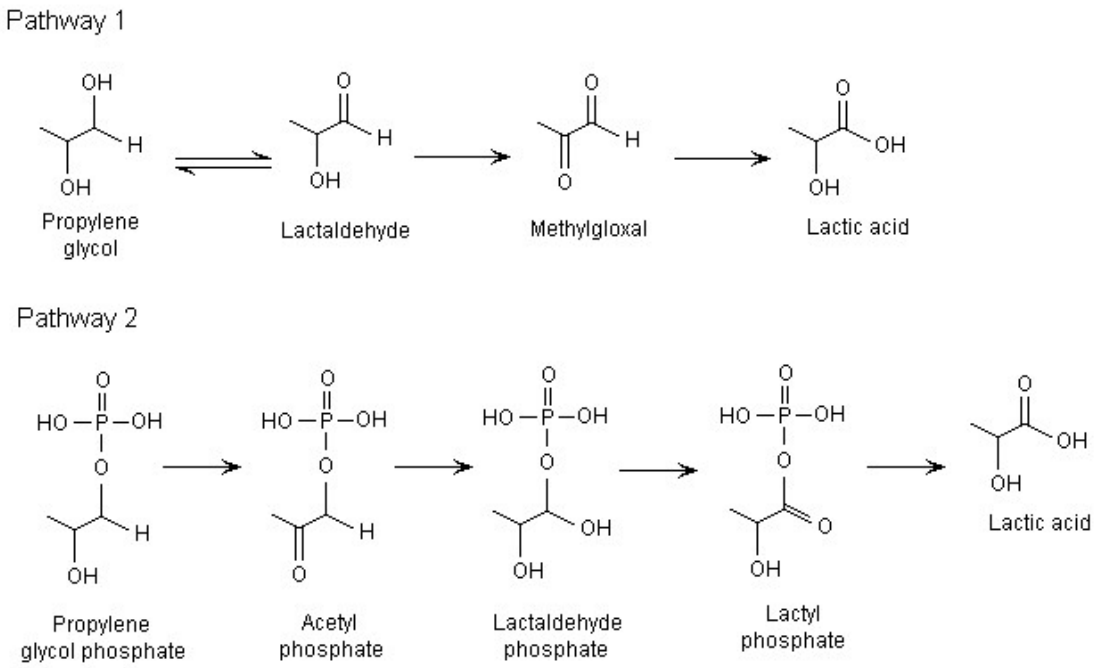


Figure 6. Metabolism of propylene glycol in mammals

2.3.2 Toxicological studies

(a) Acute toxicity

LD_{50} values after oral administration were available for 12 of the 31 substances in this group. In rats, the values ranged from 2000 to 31 000 mg/kg bw (Nos 909, 920, 922, 925, 930–933, 912, and 929), indicating little acute toxicity of this group by the oral route (Smyth et al., 1941; Fassett & Roudabush, 1952; Dominguez-Gil & Cadorniga, 1971; deGroot et al., 1974; Bailey, 1976; Bartsch et al., 1976; Moreno, 1976, 1977, 1978; Moreno et al., 1984; Clary et al., 1998). The available values for mice ranged from 1100 to 5000 mg/kg bw (Nos 922, 935, and 928) (Gast, 1963; Moran et al., 1980; Moreno, 1980).

(b) Short-term studies of toxicity

The results of short-term and long-term studies of toxicity conducted with substances in this group are summarized in Table 3.

Table 3. Results of short-term studies of toxicity with aliphatic acyclic diols, triols and related substances

Flavouring agent (No.)	Species, sex	No. of test groups[a]/ no. per group[b]	Route	Length (days)	NOEL (mg/kg bw per day)	Reference
Glycerol (909)	Rat, M,F	10/10	Diet	140	5000	Guerrant et al. (1947)
	Mouse, M,F	1/81	Oral	365	No tumours at 5000 mg/kg bw	Witschi et al. (1989)
		1/14	Oral	50		

	Human, M,F				No adverse effects reported at 24 000 mg/kg bw	Johnson et al. (1933)
	Rat, M,F	3/18	Diet	350	20 000	Annex 1, reference 41
	Rat, M,F	3/48	Diet	730	10 000	Annex 1, reference 41
	Rat	3/22	Diet	730	10 000	Annex 1, reference 41
3-Oxooctanoic acid glyceride (911)	Rat, M,F	5/10	Diet	14	10	Gill & van Miller (1987)
3-Oxotetradecanoic acid glyceride (916)	Rat, M,F	5/10	Diet	14	10	Gill & van Miller (1987)
Tributyrin (922)	Rat,	NR1/66	Diet	245	Marked hyperplasia and papillomatous growth in fore stomach at 7500 mg/kg bw	Salmon & Copeland (1949)
Glycerol 5-hydroxydecanoate[c] (923)	Rat, M,F	2/8-17	Diet	343	150	Wilson (1961
Glycerol 5-hydroxydodecanoate[c] (924)	Rat, M,F	2/8-17	Diet	343	300	Wilson (1961)
Propylene glycol (925)	Rat, M,F	2/10	Diet	730	1800	Morris et al. (1942)
	Rat, M,F	4/60	Diet	730	1300	Gaunt et al. (1972)
	Dog, M,F	2/10	Diet	730	2000	Weil et al. (1971)
2,2,4-Trimethyl-1,3-oxacyclopentane (929)	Rat, M,F	2/5	Gavage	14	38	de Groot et al. (1974)
Lactic acid (930)	Rat, M,F	2/?	Diet	730	No increase in tumour incidence at 5000 mg/kg bw	Maekawa et al. (1991)
Pyruvaldehyde (937)	Rat, M	3/30 2/10	Oral	224	No increase in tumour incidence at 2500 mg/kg bw	Takahashi et al. (1989)

M, male; F, female; NR, not reported

[a] Does not include control animals

[b] Both male and female animals

[c] *delta*-Decalactone and *delta*-dodecalactone are metabolites of glycerol 5-hydroxydecanoate and glycerol 5-hydroxydodecanoate, respectively.

Glycerol (No. 909)

Groups of five young rats of each sex were fed a diet containing glycerol at a concentration of 0, 1, 3, 6, 10, 15, 20, 30, 40, 50, or 60% (equivalent to 0, 1000, 3000, 6000, 10 000, 15 000, 20 000, 30 000, 40 000, 50 000, or 60 000 mg/kg bw per day) for 20 weeks. There was no significant difference in the body-weight gain at concentrations of glycerol 30%, but reduced body-weight gain was observed at $\geq$ 40%. Histological examination revealed no treatment-related changes at < 10%. The pathological changes observed at concentrations $\geq$ 10% were marked hydropic and fatty degeneration of liver parenchymal cells. The NOEL was 5% glycerol in the diet, equivalent to 5000 mg/kg bw per day (Guerrant et al., 1947).

Ten men and four women were given glycerol orally at a dose calculated to result in an average daily intake of 24 000 mg/kg bw per day, for 50 days. No toxic effects were reported. The only effect was a slight tendency towards an increase in body weight (Johnson et al., 1933).

3-Oxooctanoic acid glyceride (No. 911) and 3-oxotetradecanoic acid glyceride (No. 916)

Groups of five male and five female Fischer 344 rats were given diets containing either 3-oxooctanoic acid or 3-oxotetradecanoic acid as esters of hydrogenated palm oil at a concentration calculated to provide a dose of 10 mg/kg bw per day, for 14 days. Detailed clinical examinations were conducted daily, and food consumption was measured on days 7 and 14. No physical signs of toxicity, abnormal body-weight gain, abnormal food consumption, or treatment-related effects were observed at necropsy. The absolute and relative weights of the liver and kidney were increased by 10% in female rats, but this effect was not considered to be biologically significant as no histological changes were found in these tissues and there were no other observed toxic effects (Gill & van Miller, 1987).

Glycerol 5-hydoxydecanoic acid (No. 923) and glycerol 5-hydroxydodecanoic acid (No. 924)

Studies were available on the lactones, *delta*-decalactone and *delta*-dodecalactone, which are formed from the hydrolysis of their respective glycerol esters glycerol 5-hydroxydecanoic acid and glycerol 5-hydroxydodecanoic acid. Groups of rats were fed a mixture of 30% *delta*-decalactone, 60% *delta*-dodecalactone, and 10% butyric acid at a concentration of 0.01% or 1% *delta*-decalactone or *delta*-dodecalactone in the diet for 49 weeks. These concentrations were calculated to result in average daily intakes of 1.5 or 150 mg/kg bw *delta*-decalactone and 3 or 300 mg/kg bw *delta*-dodecalactone. Histological examination revealed no adverse effects in any group. Haematology, blood chemistry, and urinary analysis showed no significant difference between test and control groups (Wilson, 1961).

2,2,4-Trimethyl-1,3-oxacyclopentane (No. 929)

In rats given 2,2,4-trimethyl-1,3-oxacyclopentane at a dose of 3.8 or 38 mg/kg bw per day for 14 days, there were no signs of toxicity at either dose (deGroot et al., 1974).

(c) Long-term studies of toxicity and carcinogenicity

Glycerol (No. 909)

In a study of the tumour promoting potential of glycerol, groups of male and female C3H mice, 6–8 weeks old, were given various carcinogens followed by 0, 0.5, or 1% (v/v) glycerol solution until they were 1 year old. Animals in the control group received either 5% (v/v) glycerol (equivalent to 5000 mg/kg bw per day) or water. The animals were killed, and the incidences of liver and lung tumours were recorded. Among males, the incidence of liver tumours was 23% in those given glycerol and 39% in those given water. The tumour incidence in the lung was 21% with glycerol abd 41% with water. Similar results were obtained for female mice. Thus, lower incidences of liver and lung tumours were seen after glycerol treatment. No treatment-related adverse effects were reported (Witschi et al., 1989).

A study in which Sprague-Dawley rats were given glycerol in the diet at a concentration of 0, 5, 10, or 20% (equivalent to 0, 5000, 10 000 or 20 000 mg/kg bw per day) for 50 weeks was evaluated previously by the

Committee (Annex 1, reference *41*). No significant treatment-related effects were found on growth rate or gross or histological appearance. The NOEL was 20 000 mg/kg bw per day (Atlas Chemical Co., 1969).

A study in which Sprague-Dawley rats were given glycerol in the diet at a concentration of 0, 5, 10, or 20% (equivalent to 0, 2500, 5000, or 10 000 mg/kg bw per day) for 2 years was evaluated previously by the Committee (Annex 1, reference *41*). No significant treatment-related effects were found on growth rate or gross or histological appearance. Changes observed in relative kidney weights were not accompanied by histopathological changes. The NOEL was 10 000 mg/kg bw per day (Atlas Chemical Co., 1969).

A study in which Long-Evan rats were given glycerol in the diet at a concentration of 0, 5, 10, or 20% glycerol (equivalent to 0, 2500, 5000, or 10 000 mg/kg bw per day) for 2 years was evaluated previously by the Committee (Annex 1, reference *41*). There were no significant treatment-related effects. The NOEL was 10 000 mg/kg bw per day (Hine et al., 1953).

Tributyrin (No. 922)

Groups of rats were fed a diet containing tributyrin, butyric acid, or ethyl butyrate to examine the occurrence of gastric lesions. Tributyrin was given at a concentration of 15 or 25% (equivalent to 7500 and 12 500 mg/kg bw per day) for 3–35 weeks. The animals has severely reduced body-weight gain, which represented approximately one-third of that of the control group. The 66 rats receiving tributyrin that were necropsied showed greatly enlarged stomachs with numerous irregular protuberances on the external surface. Microscopic examination revealed hyperplasia, hyperkeratosis, and occasional ulceration. The mucosa of the forestomach was covered in papillomas, resulting in a significant thickening of the forestomach wall (Salmon & Copeland, 1949).

Propylene glycol (No. 925)

A study in which rats were given propylene glycol in the diet at a concentration of 2.45% or 4.9% (equivalent to 900 and 1800 mg/kg bw per day) for 2 years was evaluated previously by the Committee (Annex 1, reference *33*). No treatment-related adverse effects were found on growth, and histological examination revealed no treatment-related effects (Morris et al., 1942).

A study in which rats received propylene glycol in the diet at a concentration of 0, 310, 630, 1300, or 2500 mg/kg bw per day for 2 years was evaluated previously by the Committee (Annex 1, reference *33*). No treatment-related adverse effects on body-weight gain, haematological, urinary, or clinical chemical end-points, or organ weights were found. The NOEL was 1300 mg/kg bw per day (Gaunt et al., 1972).

A study in which dogs received propylene glycol in the diet at a concentration of 0, 2000, or 5000 mg/kg bw per day for 2 years was evaluated previously by the Committee (Annex 1, reference *33*). Increased erythrocyte destruction was found at the higher dose. No significant treatment-related effects on haematological, clinical chemical, or urinary end-points, or on gross or histological appearance were found (Weil et al., 1971).

Lactic acid (No. 930) and pyruvic acid (No. 936)

As pyruvic acid is reduced to lactic acid *in vivo*, data on lactic acid can be used to evaluate the safety of pyruvic acid.

Groups of male and female Fischer 344 rats were fed diets containing the calcium salt of lactic acid at a concentration of 0, 2.5, or 5% for 2 years, calculated to provide a dose of 0, 2500, or 5000 mg/kg bw per day, respectively. No adverse effects were observed, and no evidence was found of a significant dose-related increase in the incidence of tumours in any organ or tissue of treated animals. No specific dose-related changes were observed in any of the haematological and biochemical parameters measured (Maekawa et al., 1991).

Pyruvaldehyde (No. 937)

In a study to examine the tumour promoting potential of pyruvaldehyde in a two-stage model of stomach carcinogenesis, groups of male Wistar rats were given drinking-water containing 0.25% pyruvaldehyde for 32 weeks, alone or after 8 weeks' treatment with a known tumour initiator, *N*-methyl-*N*-nitro-*N*-nitrosoguanidine

(MNNG). Pyruvaldehyde alone caused no increase in the incidence of stomach hyperplasia or tumours. In rats pretreated with MNNG, pyruvaldehyde did not enhance the development of adenocarcinomas in the pylorus of the glandular stomach, but it significantly increased the incidence of hyperplasia (Takahashi et al., 1989).

(d) Genotoxicity

The results of studies of genotoxicity with these substances are shown in Table 4.

Table 4. Results of studies of the genotoxicity of aliphatic acyclic diols, triols and related substances

No.	Flavouring agent	End-point	Test system	Concentration	Results	Reference
In vitro						
909	Glycerol	Reverse mutation	*S. typhimurium*	11 780 ppm	Negative[a]	Cortruvo et at. (1977)
		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	1000 µg/plate	Negative[b]	Doolittle et al. (1988)
		Reverse mutation	*S. typhimurium* TA97, TA102	0–10 000 µg/plate	Negative[c]	Fujita et al. (1994)
		Reverse mutation	*S. typhimurium* TA98, TA100	0.05–1000 µg/plate	Negative[d]	Haresaku et al. (1985)
		Reverse mutation	*S. typhimurium* TA98, TA100, TA1537, TA1538	10 000 µg/plate	Negative[b]	Haworth et al. (1983)
		Reverse mutation	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	50 000 µg/plate[a]	Negative[b]	Ishidate et al. (1984)
		Reverse mutation	*S. typhimurium* TA98, TA100. TA1535, TA1537, TA1538	1000 µg/plate	Negative[b]	Lee et al. (1988)
		Reverse mutation	*S. typhimurium*	NR	Negative	McCann & Ames (1976)
		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5-5000 µg/plate	Negative[b]	Shimizu et al. (1985)
		Reverse mutation	*S. typhimurium* TA100	1000 µmol/plate	Negative	Stolzenberg & Hine (1979)
		Reverse mutation	*S. typhimurium* TA100	500 µg/ml	Negative[b]	Yamaguchi (1982)
		Reverse mutation	*E. coli* WP2*uvr*A	5-5000 µg/plate	Negative[b]	Shimizu et al. (1985)
		Reverse mutation	*Saccharomyces cerevisiae* D3	12 000 ppm	Negative[a]	Cortruvo et at. (1977)
			E. coli Sd-4-73	12–31 µg/plate	Negative	

		Modified reverse mutation				Szybalski (1958)
		Gene mutation	Chinese hamster ovary cells K1-BH4, *hprt* locus	0–1000 µg/ml	Positive[b]	Doolittle et al. (1988)
		Sister chromatid exchange	Chinese hamster ovary cell line	100-1000 µg/ml	Negative[b]	Doolittle et al. (1988)
		Sister chromatid exchange	Chinese hamster ovary cells	1000 µg/ml	Negative[b]	Lee et al. (1988)
		Chromosomal aberration	Chinese hamster ovary cell line	1000 µg/ml	Negative	Doolittle et al. (1988)
		Chromosomal aberration	Chinese hamster lung fibroblasts	1000 µg/ml	Negative	Ishidate et al. (1984)
		Chromosomal aberration	Chinese hamster ovary cells	1000 µg/ml	Negative[b]	Lee et al. (1988)
		Mutation	Chinese hamster ovary cells	1000 µg/ml	Negative[b]	Lee et al. (1988)
		Unscheduled DNA synthesis	Rat hepatocytes	1000 µg/ml	Negative	Doolittle et al. (1988)
		Unscheduled DNA synthesis	Rat hepatocytes	10–100 000 µg/ml	Negative	Fautz et al. (1991)
		Unscheduled DNA synthesis	Rat hepatocytes	1000 µg/ml	Negative	Lee et al. (1988)
918	Glycerol mono-stearate	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	50 µg/plate	Negative[b]	Blevins & Taylor (1982)
		Reverse mutation	*S. typhimurium* TA97, TA98, TA100	0–400 µg/plate	Positive[b]	Kuroda et al. (1985)
925	Propylene glycol	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	1–10 000 µg/plate	Negative	Clark et al. (1979)
		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	230 µg/plate	Negative[b]	Florin et al. (1980)
		Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	100–10 000 µg/plate	Negative[b]	Haworth et al. (1983)
		Reverse mutation	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	10 000 µg/plate	Negative[b]	Ishidate et al. (1984)
				NR	Negative[b]	

		Reverse mutation	*S. typhimurium* TA98, TA100			Kawachi et al. (1981)
		Reverse mutation	*S. typhimurium*	NR	Negative	McCann & Ames (1976)
		Reverse mutation	*S. typhimurium* TA100	1000 µmol/plate	Negative	Stolzenberg & Hine (1979)
		Host-mediated mutation	*S. typhimurium* TA1530 and G46	0.01–0.25 ml	Negative	Weir (1974)
		Host-mediated mutation	*Saccharomyces cerevisiae*	0.01–0.25 ml	Positive	Weir (1974)
		Mutation	*Bacillus subtilis rec*	NR	Negative[d]	Kawachi et al. (1981)
		Chromosomal aberration	Human embryonic lung cells	0.001-0.1 µg/ml	Negative	Weir (1974)
		Chromosomal aberration	Hamster lung fibroblasts	32 000 µg/ml	Positive[d]	Ishidate et al. (1984)
		Chromosomal aberration	Hamster lung fibroblasts	NR	Positive[d]	Kawachi et al. (1981)
		Micronucleus formation	Chinese hamster ovary Don-6 cell line	3800–23 000 µg/ml	Negative	Sasaki et al. (1980)
		Micronucleus formation	Human fibroblastic cell line HE2144	3800–23 000 µg/ml	Negative	Sasaki et al. (1980)
		Sister chromatid exchange	Hamster lung fibroblasts	NR	Negative[d]	Kawachi et al. (1981)
		Sister chromatid exchange	Hamster lung fibroblasts	NR	Negative	Kawachi et al. (1981)
		Sister chromatid exchange	Chinese hamster ovary Don-6 cell line	3800–23 000 µg/ml	Positive	Sasaki et al. (1980)
		Sister chromatid exchange	Human fibroblastic cell line HE2144	7600 µg/ml	Negative	Sasaki et al. (1980
		Mutation	Mice	2700 mg/kg bw	Negative	Solt & Neale (1980)
		Chromosomal aberration	Mice	0.6–24 mg/kg bw	Negative	Vargova et al. (1980)
		Chromosomal aberration	Rat	30–5000 mg/kg bw	Negative	Weir (1974)
		Micronucleus formation	Mice	0–20 000 mg/kg bw	Negative	Hayashi et al. (1988)
930	Lactic acid	Reverse mutation		0.5–2.0 µl/plate	Negative[b]	Al-Ani & Al-Lami (1988)

			S. typhimurium TA97, TA98, TA100, TA104			
		Chromosomal aberration	Chinese hamster ovary K1 cells	900–1400 µg/ml	Positive[b]	Morita et al. (1990)
931	Ethyl lactate	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	NR	Negative[b]	Clary et al. (1998)
935	Butyl butyryl lactate	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	0–3600 µg/plate	Negative[b]	Wild et al. (1983)
		Micronucleus formation	Mice	1500 mg/kg bw	Negative	Wild et al. (1983)
		Sex-linked recessive lethal mutation	*Drosophila melanogaster*	5400 µg/ml	Negative	Wild et al. (1983)
936	Pyruvic acid	Reverse mutation	*S. typhimurium* TA100	200 µg/plate	Negative[b]	Yamaguchi (1982)
		Reverse mutation	*S. typhimurium* TA98, TA100	10–10 000 µg/plate	Negative[b]	Bjeldanes & Chew (1979)
937	Pyruvaldehyde	Reverse mutation	*S. typhimurium* TA98	30 µg/plate	Positive[b]	Yamaguchi (1982)
		Reverse mutation	*S. typhimurium* TA98, TA100, TA104	NR	Positive[d]	Kato et al. (1989)
		Reverse mutation	*S. typhimurium*	76 µg/plate	Positive	Kim et al. (1987)
937	Pyruvaldehyde	Reverse mutation	*S. typhimurium* TA100, TA102, TA104	5–500 µg/plate	Positive[b]	Shane et al. (1988)
		Reverse mutation	*S. typhimurium* TA102, TA104	0–72 µg/plate	Positive[b]	Migliore et al. (1990)
		Reverse mutation	*S. typhimurium* TA98, TA100, TA102	0.29-29 µg/plate	Positive[b]	Aeschbacher et al. (1989)
		Reverse mutation	*S. typhimurium* TA100	1000 µg/plate	Positive[d]	Nagao et al. (1986)
		Reverse mutation	*S. typhimurium* TA100	220-500 µg/plate	Positive[d]	Dorado et al. (1992)
		Reverse mutation	*E. coli* WP2*uvr*A/pKM101	NR	Positive[d]	Kato et al. (1989)
		Chromosomal aberration	Chinese hamster ovary cells	10–50 µg/ml	Positive	Nishi et al. (1989)
			Human lymphocytes	320 µg/ml	Positive[b]	

		Chromosomal aberration				Migliore et al. (1990)
		Sister chromatid exchange	Chinese hamster ovary cells	7.2 µg/ml	Negative	Tucker et al. (1989)
		Sister chromatid exchange	Chinese hamster ovary cells	14–36 µg/ml	Positive	Tucker et al. (1989)
		Sister chromatid exchange	Chinese hamster ovary cells	7.2–54 µg/ml	Positive	Faggin et al. (1985)
		Sister chromatid exchange	Human lymphocytes	320 µg/ml	Positive[b]	Migliore et al. (1990)
		Micronucleus formation	Human lymphocytes	320 µg/ml	Positive[b]	Migliore et al. (1990)
		DNA strand breaks	Calf thymus DNA	NR	Positive	Rahman et al. (1990)
		Micronucleus formation	Rat	400 mg/kg bw[e]	Negative	Martelli et al. (1989)
		Micronucleus formation	Rat	800 mg/kg bw[f]	Weakly positive	Martelli et al. (1989)
		Sister chromatid exchange	Mice duodenal cells	400 mg/kg bw	Negative	Migliore et al. (1990)
		Sister chromatid exchange	Mice duodenal cells	600 mg/kg bw	Weakly positive	Migliore et al. (1990)
		Unscheduled DNA synthesis	Rat pyloric mucosa cells	50 mg/kg bw	Negative	Furihata et al. (1985)
		Unscheduled DNA synthesis	Rat pyloric mucosa cells	200–600 mg/kg bw	Positive	Furihata et al. (1985)
		Chromosomal aberration	Mice duodenal cells	400–600 mg/kg bw	Negative	Migliore et al. (1990)
938	Ethyl pyruvate	Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	32–20 000 µg/plate	Negative[b]	Anderson & Jensen (1984)

a With and without ozonation

b With and without metabolic activation

c With metabolic activation

d Without metabolic activation

e Administered in drinking-water

f Administered by gavage

The only consistently positive results both *in vitro* and *in vivo* were found with pyruvaldehyde (No. 937). This substance caused reverse mutation in bacteria and chromosomal aberrations in Chinese hamster ovary and human cells, sister chromatid exchange in Chinese hamster ovary cells, micronuclei in human lymphocytes and in rat cells, and unscheduled DNA synthesis in rat cells. Pyruvaldehyde is a natural component of some foods and is readily oxidized to the endogenous substance, pyruvate, *in vivo*. The estimated intake from its use as a flavouring agent is well below the estimated intake from natural sources.

(e) Reproductive toxicity

Glycerol (No. 909)

A seven-generation study of reproductive toxicity in rats given glycerol at a concentration of 0 or 30% (equivalent to 15 000 mg/kg bw per day) was evaluated previously by the Committee (Annex 1, reference *41*). On average, the pups of treated dams weighed 20% less than those of the control group (Guerrant et al., 1947).

Propylene glycol (No. 925)

In a study to examine the potential of di(2-ethylhexyl) phthalate and its metabolites to cause testicular damage in rats after oral administration, a control group of six male Sprague Dawley rats were given propylene glycol orally at a dose of 2000 mg/kg bw per day for 5 days. On day 6, the animals were killed, and the testis, the ventral lobes of the prostate, and the liver were removed and studied. The testes of animals given propylene glycol were reported to contain occasional degenerated cells most of which were in early meiotic prophase or undergoing meiotic division (Sjoberg et al., 1986).

The effects of 15 chemicals, including propylene glycol, on differential ovarian follicle counts and reproductive performance were compared. Propylene glycol had no effect on reproductive function (Bolon et al., 1997).

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ENDNOTES

[1] When evaluating these flavouring agents, the Committee questioned whether some substances in this group (see footnote to Table 1) were used as flavouring agents and therefore appropriate to be evaluated using this Procedure. Information to address this question will be sought from relevant manufacturers.

[2] ADI 'not specified' is used to refer to a food substance of very low toxicity, which, on the basis of the available data (chemical, biochemical, toxicological, and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e., it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.

See Also:
Toxicological Abbreviations

I U C L I D

D a t a s e t

Existing Chemical	Substance ID: 102-76-1
CAS No.	102-76-1
EINECS Name	triacetin
EINECS No.	203-051-9
Molecular Formula	C9H14O6

Dataset created by: EUROPEAN COMMISSION - European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non-confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

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European Chemicals Bureau

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Country: Netherlands
Phone: 010-4555566
Telefax: 010-4553367

1.0.2 Location of Production Site

-

1.0.3 Identity of Recipients

-

1.1 General Substance Information

Substance type: organic
Physical status: liquid

1.1.1 Spectra

-

1.2 Synonyms

"ESTROBOND" B Plasticizer
Source: Eastman Chemical AG Zug
Eastman Chemical (UK) Limited Hemel Hempstead
Eastman Chemical (Deutschland) GmbH Koln

1,2,3-PROPANETRIOL TRIACETATE
Source: SOCIETE CHIMIQUE DE LA COURNEUVE AULNAY SOUS BOIS

1,2,3-Propanetriol, triacetate
Source: COURTAULDS CHEMICALS LEEK,Staffordshire

1,2,3-PROPANTRIOL, TRIACETATE
Source: Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

1,2,3-Triacetoxypropane
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

Acetic acid,glycerol triester
Source: COURTAULDS CHEMICALS LEEK,Staffordshire

Acetic, 1,2,3-Propanetriyl ester
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

Acetin, Tri-
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

Glycerin triacetate
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

GLYCERINE TRIACETATE
Source: SOCIETE CHIMIQUE DE LA COURNEUVE AULNAY SOUS BOIS

Glycerol triacatate
Source: Vat Chemicals BV Rotterdam

Glycerol triacetate
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
COURTAULDS CHEMICALS LEEK,Staffordshire
Unichema Chemicals Ltd Bebington
Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

GLYCEROL TRIACETATE
Source: SOCIETE CHIMIQUE DE LA COURNEUVE AULNAY SOUS BOIS
CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

glycerol triacetate
Source: Bayer AG Leverkusen

Glycerol,triester with acetic acid
Source: COURTAULDS CHEMICALS LEEK,Staffordshire

Glyceryl triacetate
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
COURTAULDS CHEMICALS LEEK,Staffordshire
Unichema Chemicals Ltd Bebington

glyceryl triacetate
Source: Eastman Chemical AG Zug
Eastman Chemical (UK) Limited Hemel Hempstead
Eastman Chemical (Deutschland) GmbH Koln

Glyceryl Triacetate
Source: Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

Triacetin
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

triacetin
Source: Eastman Chemical AG Zug
Eastman Chemical (UK) Limited Hemel Hempstead
Bayer AG Leverkusen
Eastman Chemical (Deutschland) GmbH Koln

TRIACETINE
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

TRIACETYL GLYCERIN
Source: SOCIETE CHIMIQUE DE LA COURNEUVE AULNAY SOUS BOIS

Triacetyl glycerine
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

1.3 Impurities

-

1.4 Additives

-

1.5 Quantity

Quantity 10 000 - 50 000 tonnes

1.6.1 Labelling

-

1.6.2 Classification

-

1.7 Use Pattern

Type: type
Category: Non dispersive use

Type: type
Category: Use resulting in inclusion into or onto matrix

Type: type
Category: Wide dispersive use

Type: industrial
Category: Basic industry: basic chemicals

Type: industrial
Category: Chemical industry: used in synthesis

Type: industrial
Category: Metal extraction, refining and processing of metals

Type: industrial
Category: Paints, lacquers and varnishes industry

Type: industrial
Category: Paper, pulp and board industry

Type: industrial
Category: Personal and domestic use

Type: industrial
Category: Photographic industry

Type: industrial
Category: Polymers industry

Type: industrial
Category: Public domain

Type: industrial
Category: other: cigaret industry

Type: industrial
Category: other: cigarette industry

Type: industrial
Category: other

Type: use
Category: Absorbents and adsorbents

Type: use
Category: Adhesive, binding agents

Type: use
Category: Cosmetics

Type: use
Category: Flux agents for casting

Type: use
Category: Food/foodstuff additives

Type: use
Category: Impregnation agents

Type: use
Category: Softeners

Type: use
Category: Solvents

Type: use
Category: other: Plasticisers

Type: use
Category: other: use as additive in cigarette filters

Type: use
Category: other

1.7.1 Technology Production/Use

-

1.8 Occupational Exposure Limit Values

Type of limit:
Limit value:
Remark: Not established
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

Type of limit:
Limit value:
Remark: Aucune donnée disponible.
Source: SOCIETE CHIMIQUE DE LA COURNEUVE AULNAY SOUS BOIS

Type of limit:
Limit value:
Remark: Low hazard substance. No occupational exposure limit values have been set. However,it is recommended that liquid droplet concentrations should not exceed 10 mg/cu.m.
Source: COURTAULDS CHEMICALS LEEK,Staffordshire

1.9 Source of Exposure

Remark: Aucune donnée disponible.
Source: SOCIETE CHIMIQUE DE LA COURNEUVE AULNAY SOUS BOIS

Remark: Due to its uses Triacetin soon becomes diffused into small quanties and there is little possibility of large scale human contact or environmental effect after it leaves the manufacturers first line customers' premises.
Its use in adhesives may give skin contact.As a carrier and solvent for food soft drinks flavouring materials ingestion will occur.Very small amounts can be found in cigarette smoke drawn through a filter tip using triacetin as the plasticiser.
The production process consists of the batchwise controlled reaction of glycerol,acetic acid and acetic anhydride in a closed reaction system with adequate cooling facilities.this is followed by purification using vacuum distillation.The pungent nature of the raw materials demands a totally enclosed plant.The process is operated at one site in the UK.
Source: COURTAULDS CHEMICALS LEEK,Staffordshire

1.10.1 Recommendations/Precautionary Measures

-

1.10.2 Emergency Measures

-

1.11 Packaging

-

1.12 Possib. of Rendering Subst. Harmless

-

1.13 Statements Concerning Waste

-

1.14.1 Water Pollution

Classified by: KBwS (DE)
Labelled by: KBwS (DE)
Class of danger: 1 (weakly water polluting)
Source: Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

(1)

1.14.2 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: no
Source: Henkel KGaA Duesseldorf
Henkel KGaA Duesseldorf

1.14.3 Air Pollution

-

1.15 Additional Remarks

Remark: WATER POLLUTION
==========

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of Danger : 1 (weakly water polluting)
Reference: Katalog wassergefährdender Stoffe, Datenblatt Nr. 761.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

Remark: MAJOR ACCIDENT HAZARDS
==========

Legislation : Störfallverordnung (DE)
Substances listed : No
Source: Unichema Chemie B.V. Gouda

Remark: 1,2,3-Propanetriol, triacetate is shipped in 238 Kg, steel drums.
Source: Eastman Chemical AG Zug

Remark: WATER POLLUTION
==========

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of Danger : 1 (weakly water polluting)
Reference: Katalog wassergefährdender Stoffe, Datenblatt Nr.761.
Source: Unichema Chemicals Ltd. Merseyside

Remark: MAJOR ACCIDENT HAZARDS
==========

Legislation : Störfallverordnung (DE)
Substances listed : No
Source: Unichema Chemicals Ltd. Merseyside

Remark: DISPOSAL.
Triacetin is fully and easily biodegradable.In both the environment and the human system the ester tends to hydrolyse to acetic acid and glycerol.
Triacetin is 6.1% soluble in water and of low toxicity allowing it to be disposed of in a controlled manner via the sewage undertaker.
STORAGE & HANDLING.
Triacetin is best stored and transported in bulk in 316 Stainless steel.However it may be transported and stored for up to 2 years in mild steel drums provided they remain sealed.
TRANSPORT.
Triacetin is not classified as hazardous by any method of transport and thus there are no special transport rules.
Source: COURTAULDS CHEMICALS LEEK,Staffordshire

Remark: 1,2,3-Propanetriol, triacetate is shipped in 238 Kg, steel drums.
Source: Eastman Chemical (UK) Limited Hemel Hempstead

Remark: MAJOR ACCIDENT HAZARDS
==========

Legislation : Störfallverordnung (DE)
Substances listed : No
Source: Unichema Chemicals Ltd Bebington

Remark: 1,2,3-Propanetriol, triacetate is shipped in 238 Kg, steel drums.
Source: Eastman Chemical (Deutschland) GmbH Koln

1.16 Last Literature Search

-

1.17 Reviews

-

1.18 Listings e.g. Chemical Inventories

-

2.1 Melting Point

Value: = -78 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(2) (3) (4) (5)

Value: = -60 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(6)

Value: = -3.2 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(4)

Value: = 3 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(4)

Value: 3.2 - 4.1 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(6)

Value: = 4.1 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(7)

Value: = 4.1 degree C
Decomposition: no
Sublimation: no
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

2.2 Boiling Point

Value: 258 - 259 degree C at 1013 hPa
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(6)

Value: 258 - 260 degree C at 1013 hPa
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(2) (3) (8) (5)

Value: = 258 degree C at 1013 hPa
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(4)

Value: = 258 degree C at 1000 hPa
Decomposition: no
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

Value: = 259 degree C at 1013 hPa
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(7) (9)

2.3 Density

Type: density
Value: 1.156 - 1.172 g/cm3 at 20 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(6) (10)

Type: density
Value: = 1.1569 g/cm3 at 20 degree C
Remark: Reference temperature: 4 degr. C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(3)

Type: density
Value: = 1.159 g/cm3 at 20 degree C
Remark: Reference temperature: 4 degr. C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(4)

Type: density
Value: = 1.1596 g/cm3 at 20 degree C
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

Type: density
Value: = 1.16 g/cm3 at 20 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(9) (8)

Type: density
Value: 1.16 g/cm3 at 24 degree C
GLP: no
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(11)

Type: density
Value: 1.111 g/cm3 at 70 degree C
Remark: Reference temperature: 4 degr. C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(4)

2.3.1 Granulometry

-

2.4 Vapour Pressure

Value: < .01 hPa at 20 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington
(12)

Value: < .01 hPa at 20 degree C
Source: Unichema Chemicals Ltd. Merseyside
(13)

Value: = .1013 hPa at 20 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington
(14)

Value: = .1013 hPa at 20 degree C
Source: Unichema Chemicals Ltd. Merseyside
(15)

Value: .0033 hPa at 25 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington
(16)

Value: .0033 hPa at 25 degree C
Source: Unichema Chemicals Ltd. Merseyside
(17)

Value: = .067 hPa at 60 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(4)

Value: .07 hPa at 60 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(18)

Value: = 1.33 hPa at 100 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(2)

Value: 5.2 hPa at 125 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(18)

Value: = 13.1 hPa at 140 degree C
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

2.5 Partition Coefficient

log Pow: ca. .1
Method: other (calculated): No information about method: "Log pow octanol/water estimated".
Year:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington
(19)

log Pow: ca. .1
Method: other (calculated): No information about method: "Log pow octanol/water estimated".
Year:
Source: Unichema Chemicals Ltd. Merseyside
(20)

log Pow: = .368
Method: other (calculated): version CLOGP 3.3 (Medchem)
Year:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(21)

2.6.1 Water Solubility

Value: = 7.17 vol% at 15 degree C
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

Value: = 80 g/l at 20 degree C
pH: 7
Remark: pH refers to 10 g/l solution
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(9)

Value: 58 g/l at 25 degree C
Qualitative: soluble
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington
(22)

Value: 58 g/l at 25 degree C
Qualitative: soluble
Source: Unichema Chemicals Ltd. Merseyside
(23)

Value: 5.8 vol%
Qualitative: soluble
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(24)

Qualitative: slightly soluble
Remark: soluble in 14 parts water
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(3)

Qualitative: slightly soluble
Source: Unichema Chemie B.V. Gouda
(4) (8)

Qualitative: slightly soluble
Source: Unichema Chemicals Ltd. Merseyside
(4) (8)

Qualitative: slightly soluble
Source: Unichema Chemicals Ltd Bebington
(4) (8)

2.6.2 Surface Tension

-

2.7 Flash Point

Value: = 137.8 degree C
Type: other
Method: other: Method not mentioned
Year:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(7)

Value: = 138 degree C
Type: other
Method: other: Closed cup
Year:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(4)

Value: 138 degree C
Type: open cup
Method:
Year:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(25)

Value: > 145 degree C
Type: closed cup
Method: other: DIN 51758
Year:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(9)

Value: 145 degree C
Type: open cup
Method:
Year:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(26)

Value: = 149 degree C
Type: other
Method: other: Method not mentioned
Year:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(8)

Value: 151 degree C
Type: closed cup
Method:
Year:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(27)

Value: 153 degree C
Type: open cup
Method: other
Year:
GLP: no
Remark: The study was performed according to ASTM D92
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(11)

Value: = 153 degree C
Type: open cup
Method: other
Year:
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

2.8 Auto Flammability

Value: = 430 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(4)

Value: 432 degree C
Method: other
Remark: The study was performed according to ASTM D2155
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(11)

Value: 433 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(28)

2.9 Flammability

Result: non flammable
Method: other
GLP: no
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(29)

Result: non flammable
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

Result:
Remark: The test was performed according to ASTM E681 and resulted in a lower flammable limit of 1.05% at 189 degree C and an upper flammable limit of 7.75% at 215 degree C.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(11)

2.10 Explosive Properties

Result: not explosive
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

Result: other
Method: other
GLP: no
Remark: Method: ASTM E537
Result: no exothermic activity to boiling
Test type: Differential thermal analysis
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(11)

2.11 Oxidizing Properties

-

2.12 Additional Remarks

Remark: sets to a glass at -37 degr. C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(8)

Remark: solidification point: < -30 degr. C
Source: Unichema Chemie B.V. Gouda
(9)

Remark: solubility: Soluble in acetone, ethanol, benzene and chloroform.
Source: Unichema Chemie B.V. Gouda
(30)

Remark: Viscosity (25 °C) : ca. 17 mPa.s
Source: Unichema Chemie B.V. Gouda
(30)

Remark: NOT COMPATIBLE WITH STRONG OXIDIZING AGENTS
STABLE IN USUAL INDUSTRIAL CONDITIONS
POLYMERIZATION: NOT OCCURRING
COMBUSTIBLE LIQUID WHEN EXPOSED TO FLAME OR HEAT
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

Remark: solidification point: < -30 degr. C
Source: Unichema Chemicals Ltd. Merseyside
(9)

Remark: solubility: Soluble in acetone, ethanol, benzene and chloroform.
Source: Unichema Chemicals Ltd. Merseyside
(30)

Remark: Viscosity (25 °C) : ca. 17 mPa.s
Source: Unichema Chemicals Ltd. Merseyside
(30)

Remark: solidification point: < -30 degr. C
Source: Unichema Chemicals Ltd Bebington
(9)

Remark: solubility: Soluble in acetone, ethanol, benzene and chloroform.
Source: Unichema Chemicals Ltd Bebington
(30)

Remark: Viscosity (25 °C) : ca. 17 mPa.s
Source: Unichema Chemicals Ltd Bebington
(30)

3.1.1 Photodegradation

Type: water
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm3
Rate constant: ca. .00000000000781 cm3/(molecule * sec)
Degradation: ca. 50 % after 2 day
Method: other (calculated)
Year: **GLP:**
Test substance: no data
Remark: temperature used in the calculation: 25 degree C
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(31)

3.1.2 Stability in Water

Type: abiotic
t1/2 pH7: ca. 130 day
t1/2 pH9: ca. 1.3 day
t1/2 pH 8 : ca. 13 day
Method: other
Year: **GLP:**
Test substance: no data
Remark: Method: estimation
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(32)

3.1.3 Stability in Soil

-

3.2 Monitoring Data (Environment)

Type of measurement: other
Medium: surface water
Remark: Measurement: other (not known)
Triacetin was detected in a sample of Tennessee River water collected in April 1973 (concentration not reported)
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(33)

Type of measurement: other
Medium: surface water
Remark: Measurement: other (not known)
Triacetin was detected in a sample of Tennessee River water collected in April 1973 (concentration not reported)
Source: Unichema Chemicals Ltd. Merseyside

(33)

3.3.1 Transport between Environmental Compartments

-

3.3.2 Distribution

Media: water - air
Method: other (calculation)
Year:
Result: Based on a water solubility of 58 g/l and a vapour pressure of 0.00248 mm Hg (at 25 degree C), a Henry's law constant of 1.23 * 10-8 atm*m3/mol is estimated. This value indicates that the compound is essentially non-volatile from water.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(34)

Media: water - air
Method: other (calculation)
Year:
Result: Based on a water solubility of 58 g/l and a vapour pressure of 0.00248 mm Hg (at 25 degree C), a Henry's law constant of 1.23 * 10-8 atm*m3/mol is estimated. This value indicates that the compound is essentially non-volatile from water.
Source: Unichema Chemicals Ltd. Merseyside

(34)

Media: water - soil
Method: other (calculation)
Year:
Result: Based upon a measured water solubility of 58 g/l at 25 °C, the Koc-value can be estimated to be 10.5 from a regression derived equation (reference 1). This Koc-value indicates very high soil mobility (reference 2).
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(35)

Media: water - soil
Method: other (calculation)
Year:
Result: Based upon a measured water solubility of 58 g/l at 25 °C, the Koc-value can be estimated to be 10.5 from a regression derived equation (reference 1). This Koc-value indicates very high soil mobility (reference 2).
Source: Unichema Chemicals Ltd. Merseyside

(35)

3.4 Mode of Degradation in Actual Use

-

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 10 mg/l related to Test substance
Degradation: 64 % after 28 day
Result: readily biodegradable
Method: Directive 84/449/EEC, C.5 "Biotic degradation - modified Sturm test"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: The study was also in accordance with OECD guideline 301B (published 1981).
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(36)

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 20 mg/l related to Test substance
Degradation: 93 % after 28 day
Result: readily biodegradable
Method: Directive 84/449/EEC, C.5 "Biotic degradation - modified Sturm test"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: The study was also in accordance with OECD guideline 301B (published 1981).
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(37)

Type: aerobic
Inoculum: other: municipal sewage treatment plant effluent
Concentration: 5 mg/l related to Test substance
Degradation: = 79 % after 30 day
Result: readily biodegradable
Method: OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year: 1981 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(38)

Type: aerobic
Inoculum: predominantly domestic sewage
Concentration: 3 mg/l related to Test substance
Degradation: 70 % after 30 day
Method: other: DEV, H5 modif.
Year: **GLP:** no
Test substance:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(39)

3.6 BOD5, COD or BOD5/COD Ratio

-

3.7 Bioaccumulation

Species:
Exposure period:
Concentration:
BCF: ca. 1.3
Elimination:
Method: other
Year: **GLP:**
Test substance: no data
Remark: Method: other (estimation)
The BCF was estimated from a recommended regression-derived equation using a water solubility of 58 g/l at 25 °C.
This estimated BCF indicates that bioconcentration in fish is not important environmentally.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(40)

Species:
Exposure period:
Concentration:
BCF: ca. 1.3
Elimination:
Method: other
Year: **GLP:**
Test substance: no data
Remark: Method: other (estimation)
The BCF was estimated from a recommended regression-derived equation using a water solubility of 58 g/l at 25 °C.
This estimated BCF indicates that bioconcentration in fish is not important environmentally.
Source: Unichema Chemicals Ltd. Merseyside

(40)

3.8 Additional Remarks

-

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC0: 100
LC50: 174
LC100: 320
Method: other
Year: 1979 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Bewertung wassergefährdender Stoffe, Bestimmung der akuten Fischtoxizität, Ad-hoc-Arbeitsgruppe 1 (Obmann Dr. Niemitz), LTwS, Nr. 10, September 1979.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(41)

Type: static
Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC0: 100
LC50: 174
LC100: 320
Method: other
Year: 1979 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Bewertung wassergefährdender Stoffe, Bestimmung der akuten Fischtoxizität, Ad-hoc-Arbeitsgruppe 1 (Obmann Dr. Niemitz), LTwS, Nr. 10, September 1979.
Source: Unichema Chemicals Ltd. Merseyside

(41)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC0: = 100
LC50: = 170
LC100: = 300
Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN38412 Teil15
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
Test condition: Test substance directly weighed into test vessel followed by treatment with Ultraturrax.

(42)

Type:
Species: Cyprinus carpio (Fish, fresh water)
Exposure period:
Unit: **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: Carp (Cyprinus carpio) force-fed with triacetin were killed at concentrations between 122 and 184 mg/kg
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
Test condition: exposure time: 66 h, pH 6.7, 18.3 degr. C

(43)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: 65
EC50: 380
EC100: 1000
Method: other: Daphnien-Kurzzeittest, DIN 38412 Teil 11, Bestimmung der Wirkung von Wasserinhaltsstoffen auf Kleinkrebse
Year: **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: Test method conforms with OECD Guideline 202A.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(44)

4.3 Toxicity to Aquatic Plants e.g. Algae

-

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 18 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: > 541.6
Method: other
Year: 1979 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(45) (46)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 18 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: > 541.6
Method: other
Year: 1979 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemicals Ltd. Merseyside

(47) (46)

Type:
Species: Pseudomonas putida (Bacteria)
Exposure period: 30
Unit: mg/l **Analytical monitoring:**
EC0: > 10000
Method: other: Pseudomonas-Atmungs-Hemmtest, DIN 38412 Teil 27, in Vorber.,Bestimmung der Hemmwirkung von Abwasser auf die Sauerstoffzehrung von Pseudomonas putida
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: 10000 mg/l was highest concentration tested.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(48)

Type:
Species: Pseudomonas putida (Bacteria)
Exposure period: 16
Unit: mg/l **Analytical monitoring:**
EC0: = 3000
EC10: = 10000
Method: other: Pseudomonas-Zellvermehrungs-Hemmtest, DIN 38412 Teil 8, zum Gelbdruck verabschiedet, Bestimmung der Hemmwirkung vonWasserinhaltsstoffen auf Bakterien
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
Test condition: 10 min. treatment of stock solution with Ultraturrax; test solution was taken from water phase.

(48)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

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4.5.2 Chronic Toxicity to Aquatic Invertebrates

-

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

-

4.6.2 Toxicity to Terrestrial Plants

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4.6.3 Toxicity to other Non–Mamm. Terrestrial Species

-

4.7 Biological Effects Monitoring

-

4.8 Biotransformation and Kinetics

-

4.9 Additional Remarks

Remark: Toxicity towards tadpoles (Rana temporaria):
Threshold concentration for complete narcosis: 5000 mg/l

Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(49)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: 6400 - 12800 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: The reference gives an overview of acute oral toxicity tests conducted: depending on test conditions, in rats LD50 values from 6400 to 12800 mg/kg bw. were observed.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(50)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: 6400 - 12800 mg/kg bw
Method: other
Year: 1955 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose levels, 1 animal per dose level, 14 day observation, no necropsy. Weakness and ataxia were observed.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(51)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: > 2000 mg/kg bw
Method: other
Year: 1979 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: OECD, EEC and Bewertung Wassergefährdender Stoffe, II Bestimmung der akuten oralen Saugetiertoxizität, Ad-hoc-Arbeitsgruppe I (Obmann: Dr. Niemitz), LTWS, Nr. 10 September 1979.
Year: 1987, 1984, 1979
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(52)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: 3000 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(53)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: 3000 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(54)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: 6400 - 12800 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: The reference gives an overview of acute oral toxicity testsconducted: depending on test conditions, in rats LD50 valuesfrom 6400 to 12800 mg/kg bw. were observed.
Source: Unichema Chemicals Ltd. Merseyside

(50)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: ca. 9300 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: The LD50 value was calculated from the given literature value of 8.0 ml/kg and the density of 1.16 g/cm3.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(55)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: = 1100 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: strain: Swiss
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(56)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: 3200 - 6400 mg/kg bw
Method: other
Year: 1955 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose levels, 1 animal per dose level, 14 day observation period, no necropsy. Weakness and ataxia were observed.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(51)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: 3200 - 6100 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(57)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: 3200 - 6400 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(58)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: 1100 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Peripheral nerve and sensation (spastic paralysis with/without sensory change). Behavioral (altered sleep time; stiffness).
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(59)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Value: = 3000 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: > 2000 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(60)

Type: LDLo
Species: other: frog
Sex:
Number of Animals:
Vehicle:
Value: 150 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(61)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 4 hour(s)
Value: > 1.721 mg/l
Method: other
Year: 1985 **GLP:** no
Test substance: no data
Remark: Value: analytical concentration
Method: an aerosol of triacetin was tested
Effect: 0/5 males died, 0/5 females died
No clinical symptoms
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(62)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: > 5000 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(63)

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: > 2000 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(64)

Type: LD50
Species: guinea pig
Sex:
Number of Animals:
Vehicle:
Value: > 20
Method: other
Year: 1955 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 3 dose groups, resp. 3, 3 and 2 animals per group, 14 days observation.
Unit : ml/kg
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(65)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 800 - 1600 mg/kg bw
Method: other
Year: 1955 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose groups, 1 animal per group, 14 days observation, no necropsy. Weakness, incoordination, gasping and unconsciousness were observed.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(51)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 800 - 1600 mg/kg bw
Method:
Year: 1967 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 6 dose groups, 2 animals per group, 14 days observation, necropsy at termination; necropsy results were negative. Death occured within 15 minutes of dosing at the higher dose levels. Weakness and gasping were observed.

Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington
(66)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 1600 mg/kg bw
Method: other
Year: 1968 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose groups, 2 animals per group, 14 days observation, necropsy at termination.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(67)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 2100 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(61)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 800 - 1600 mg/kg bw
Method: other
Year: 1955 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose groups, 1 animal per group, 14 days observation, no necropsy. Weakness, incoordination, gasping and unconsciousness were observed.
Source: Unichema Chemicals Ltd. Merseyside
(51)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 800 - 1600 mg/kg bw
Method:
Year: 1967 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 6 dose groups, 2 animals per group, 14 days observation, necropsy at termination; necropsy results were negative. Death occured within 15 minutes of dosing atthe higher dose levels. Weakness and gasping were observed.
Source: Unichema Chemicals Ltd. Merseyside

(66)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 800 - 1600 mg/kg bw
Method: other
Year: 1955 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 5 dose groups, 1 animal per group, 14 days observation, no necropsy.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(68)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 1400 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: Periferal nerve and sensation (Spastic paralysis 13), with/without sensory change. Behavioral (Altered sleeptime; stiffness).
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(69) (70)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: 1400 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: Periferal nerve and sensation (Spastic paralysis 13), with/without sensory change. Behavioral (Altered sleeptime; stiffness).
Source: Unichema Chemicals Ltd. Merseyside

(69) (70)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: 2800 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(71)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: 2800 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Behavioral (Somnolence) Lungs, Thorax or respiration (Dyspnea).
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(72)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: 2.3 other: ml/kg
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(73)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: 2300 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Behavioral (Somnolence) Lungs, Thorax or respiration (Dyspnea).
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(72)

Type: LDLo
Species: guinea pig
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.m.
Value: 1740 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Remark: Lungs, Thorax or respiration (Dyspnea).
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(74)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 1600 mg/kg bw
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: Behavioral (Convulsions or effect on seizure threshold), NGS, Thorax or respiration (respiratory depression).
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(75) (76)

Type: LD50
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.v.
Value: 750 mg/kg bw
Method:
Year: **GLP:**
Test substance:
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(61)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(77)

Species: guinea pig
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method: other
Year: 1955 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 3 dose groups, resp. 3, 3 and 2 animals per dose group, 14 days observation for signs of irritation. Findings erythema, slight edema, alopecia and desquamation under the conditions of the test.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(65)

Species: guinea pig
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.: not irritating
Method:
Year: 1978 **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(78) (79)

Species: guinea pig
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method: other
Year: 1955 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 3 dose groups, resp. 3, 3 and 2 animals per dose group, 14 days observation for signs of irritation. Findingserythema, slight edema, alopecia and desquamation under the conditions of the test.

Source: Unichema Chemicals Ltd. Merseyside
(80)

Species: guinea pig
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.: not irritating
Method:
Year: 1978 **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemicals Ltd. Merseyside
(78) (81)

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: not irritating
EC classificat.:
Method: other: Patch Test (geschlossener Epicutan-Test)
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(82)

5.2.2 Eye Irritation

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: not irritating
EC classificat.:
Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(83)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: slightly irritating
EC classificat.:
Method: other
Year: 1967 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 2 rabbits received 1 drop of test substance in one eye. The eye of 1 rabbit was washed. Signs of irritation were evaluated 1, 24 and 48 hours after administration of the test substance.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(66)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: moderately irritating
EC classificat.:
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(84)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: No injury when tested on rabbits eyes.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(85)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: slightly irritating
EC classificat.:
Method: other
Year: 1967 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 2 rabbits received 1 drop of test substance in one eye. The eye of 1 rabbit was washed. Signs of irritation were evaluated 1, 24 and 48 hours after administration of the test substance.
Source: Unichema Chemicals Ltd. Merseyside

(66)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: No injury when tested on rabbits eyes.
Source: Unichema Chemicals Ltd. Merseyside

(86)

Species:
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: irritating
EC classificat.: irritating
Method:
Year: **GLP:**
Test substance:
Source: CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA''

5.3 Sensitization

Type: other: maximation test
Species: human
Number of Animals:
Vehicle:
Result: not sensitizing
Classification:
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: Substance concentration: 20 % in petrolatum; group size: 33 volunteers.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(87)

Type:
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification: not sensitizing
Method: other
Year: 1955 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 0.05 ml of 0.1M solution of test material in solvent composed of acetone, dioxane and guinea pig fat (7:2:1), dosing 3 times in 5 days, challenges at 1, 2 or 3 weeks after initial exposure. Vehicle control and a positive control (phenyl hydrazine) included.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(51)

Type:
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification: not sensitizing
Method: other
Year: 1955 **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, 0.05 ml of 0.1M solution of test materialin solvent composed of acetone, dioxane and guinea pig fat (7:2:1), dosing 3 times in 5 days, challenges at 1, 2 or 3 weeks after initial exposure. Vehicle control and a positivecontrol (phenyl hydrazine) included.
Source: Unichema Chemicals Ltd. Merseyside

(51)

Type:
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: A contact eczema in humans caused by triacetin is reported.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(88)

Type:
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification: not sensitizing
Method:
Year: 1978 **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(84) (79)

Type:
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification: not sensitizing
Method:
Year: 1978 **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemicals Ltd. Merseyside

(84) (81)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** no data
Strain: no data
Route of admin.: inhalation
Exposure period: 64 days
Frequency of treatment: 6 hours per day, 5 days per week
Post. obs. period:
Doses: 250 ppm, 3 rats
Control Group: no
NOAEL: 250 ppm
Method: other
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, whole body exposure to vaporized (heated) test substance.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(89)

Species: rat **Sex:** no data
Strain: no data
Route of admin.: inhalation
Exposure period: 64 days
Frequency of treatment: 6 hours per day
Post. obs. period:
Doses: 8271 ppm, 3 rats
Control Group: no
NOAEL: 8271 ppm
Method: other
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, whole body exposure to vaporized (heated) test substance. Autopsy on 1 rat only.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington

(90)

Species: rat **Sex:** no data
Strain: no data
Route of admin.: inhalation
Exposure period: 6 hours/day for 5 days
Frequency of treatment:
Post. obs. period:
Doses: saturated vapour (plus some mist)
Control Group: other
Method:
Year: **GLP:**
Test substance:
Remark: No symtoms or histopathology.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(91)

Species: rat **Sex:** no data
Strain: no data
Route of admin.: inhalation
Exposure period: 64 days
Frequency of treatment: 6 hours per day, 5 days per week
Post. obs. period:
Doses: 250 ppm, 3 rats
Control Group: no
NOAEL: 250 ppm
Method: other
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, whole body exposure to vaporized (heated)test substance.
Source: Unichema Chemicals Ltd. Merseyside

(89)

Species: rat **Sex:** no data
Strain: no data
Route of admin.: inhalation
Exposure period: 64 days
Frequency of treatment: 6 hours per day
Post. obs. period:
Doses: 8271 ppm, 3 rats
Control Group: no
NOAEL: 8271 ppm
Method: other
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol, whole body exposure to vaporized (heated)test substance. Autopsy on 1 rat only.
Source: Unichema Chemicals Ltd. Merseyside

(90)

Species: rat **Sex:** male
Strain: Sprague-Dawley
Route of admin.: oral feed
Exposure period: 90 day
Frequency of treatment: daily
Post. obs. period: no data
Doses: 20 %
Control Group: yes
Method:
Year: **GLP:**
Test substance:
Remark: Concentration of 60 % triacetin in the diet caused weight reduction and increased mortality.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington

(92)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium, strain TA1535, TA1537, TA98, TA100
Concentration: 5000, 1500, 500, 150 and 50 ug/plate
Metabolic activation: with and without
Result: negative
Method: other
Year: 1983 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: According Ames et al. (1975), Mutation Research, 31 347-364, and modifications according Maron et al. (1983), Mutation Research, 88 343-350 and Maron et al. (1983), Mutation Research, 113 173-215.

Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington
(93)

Type: Ames test
System of testing: Salmonella typhimurium, strain TA1535, TA1537, TA98, TA100
Concentration: 5000, 1500, 500, 150 and 50 ug/plate
Metabolic activation: with and without
Result: negative
Method: other
Year: 1983 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Remark: Method: According Ames et al. (1975), Mutation Research, 31 347-364, and modifications according Maron et al. (1983), Mutation Research, 88 343-350 and Maron et al. (1983), Mutation Research, 113 173-215.
Source: Unichema Chemicals Ltd. Merseyside
(93)

Type: Ames test
System of testing: Salmonella typhimurium
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(94)

Type: Salmonella typhimurium reverse mutation assay
System of testing: Salmonella typhirium TA1535
Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(95)

5.6 Genetic Toxicity 'in Vivo'

-

5.7 Carcinogenicity

-

5.8 Toxicity to Reproduction

-

5.9 Developmental Toxicity/Teratogenicity

-

5.10 Other Relevant Information

Type: Chemobiokinetics general studies
Remark: In a 175 day feeding study with sheep 62 % of metabolic energy were utilized. Concentration of triacetin in food was 10 %. No data on toxicity are reported.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(96)

Type: other
Remark: Triacetin is classified as GRAS-substance.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd. Merseyside
Unichema Chemicals Ltd Bebington
(97)

Type: other
Remark: Pharmacological effect: decrease in blood pressure after i.v. application in cats.
Source: Unichema Chemie B.V. Gouda
(98)

Type: other
Remark: i.v. study in dogs, lowest lethal value 1.5-2.0 cm3/kg
i.v. study in rabbits, lowest lethal value 0.75 cm3/kg, no effect dose 0.5 cm3/kg
Source: Unichema Chemie B.V. Gouda
(70)

Type: other
Remark: Laboratory rats have tolerated diets consisting of 50% triacetin. If hydrolized, systematic acidosos is a possible consequence.
Source: Unichema Chemie B.V. Gouda
(99)

Type: other
Remark: Neurotoxic effects of triacetin include tremors and convulsions.
Source: Unichema Chemie B.V. Gouda
(100)

Type: other
Remark: Minimal tissue irritation in chicken pectoral musle
Source: Unichema Chemie B.V. Gouda
(101)

Type: other
Remark: Triacetin will produce slight hemolysis in vitro.
Source: Unichema Chemie B.V. Gouda
(102)

Type: other
Remark: Pharmacological effect: decrease in blood pressure after i.v. application in cats.
Source: Unichema Chemicals Ltd. Merseyside
(98)

Type: other
Remark: i.v. study in dogs, lowest lethal value 1.5-2.0 cm3/kg
i.v. study in rabbits, lowest lethal value 0.75 cm3/kg, no effect dose 0.5 cm3/kg
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Type: other
Remark: Triacetin will produce slight hemolysis in vitro.
Source: Unichema Chemicals Ltd Bebington
(102)

5.11 Experience with Human Exposure

Remark: Commercial triacetin may contain diacetin, as well as monoacetin, and when applied to human eyes causes severe burning, pain and much redness of the conjunctiva, but no injury. Diacetin causes considerably more discomfort than pure triacetin.
Source: Unichema Chemie B.V. Gouda
Unichema Chemicals Ltd Bebington
(104)

Remark: Glycerol triacetate appears to be innocuous when swallowed, inhaled or in contact with the skin, but may cause slight irritation to sensitive individuals.
Source: Unichema Chemie B.V. Gouda
(105)

Remark: A Duhring-chamber test was conducted on 20 healthy volunteers. The test substance was applied as 50% dilution for 24 hours. Result: only very mild skin reactions were observed. The substance has a good skin compartibility.
Source: Unichema Chemie B.V. Gouda
(106)

Remark: Commercial triacetin may contain diacetin, as well as monoacetin, and when applied to human eyes causes severe burning, pain and much redness of the conjunctiva, but no injury. Diacetin causes considerably more discomfort than pure triacetin.
Source: Unichema Chemicals Ltd. Merseyside
(107)

Remark: Glycerol triacetate appears to be innocuous when swallowed, inhaled or in contact with the skin, but may cause slight irritation to sensitive individuals.
Source: Unichema Chemicals Ltd. Merseyside
(105)

Remark: A Duhring-chamber test was conducted on 20 healthy volunteers. The test substance was applied as 50% dilution for 24 hours. Result: only very mild skin reactions were observed. The substance has a good skin compartibility.
Source: Unichema Chemicals Ltd. Merseyside
(106)

Remark: Glycerol triacetate appears to be innocuous when swallowed, inhaled or in contact with the skin, but may cause slight irritation to sensitive individuals.
Source: Unichema Chemicals Ltd Bebington
(105)

Remark: A Duhring-chamber test was conducted on 20 healthy volunteers. The test substance was applied as 50% dilution for 24 hours. Result: only very mild skin reactions were observed. The substance has a good skin compartibility.
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7.1 Risk Assessment

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DANISH MINISTRY
OF THE ENVIRONMENT
Environmental
Protection Agency

Identification and assessment of alternatives to selected phthalates

Jacob Maag, Carsten Lassen, Ulla Kristine Brandt,
Jesper Kjølholt, Lise Molander og Sonja Hagen Mikkelsen

COWI A/S, Denmark

Environmental Project No. 1341 2010
Miljøprojekt

The Danish Environmental Protection Agency will, when opportunity offers, publish reports and contributions relating to environmental research and development projects financed via the Danish EPA.

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Preface

Since spring 2007, three phthalates, DEHP, DBP and BBP, have been prohibited for use in toys and childcare articles. Further three phthalates, DINP, DIDP and DNOP, are prohibited in toys and childcare articles which can be placed in the mouth by children.

On the basis of their classification as toxic to reproduction, DEHP, DBP and BBP have been identified as presenting properties of very high concern, and have been placed on the candidate list for consideration for inclusion in Annex XIV of the REACH Regulation.

Substances included in Annex XIV are subject to authorisation. Authorisation should according to the REACH Regulation be granted where it is demonstrated that the risks to human health and the environment arising from the use of the substance are adequately controlled. Otherwise, uses may still be authorised if it can be shown that the socio-economic benefits from the use of the substance outweigh the risks connected with its use and there are no suitable alternative substances or technologies that are economically and technically viable.

As consequence of the prohibition of the three classified phthalates in toys and childcare articles, alternative substances and alternative materials have been introduced for such products.

In order to establish an overview of the risks to human health and the environment arising from the use of the alternative substances and to evaluate to what extent alternative substances or technologies are economically and technically viable as substitutes for DEHP, DBP and BBP in the different applications, the Danish Environmental Protection Agency has initiated this study.

The results of the study are intended to feed in to the discussion regarding the inclusion of the three phthalates in Annex XIV and the conditions for the authorisation if the substances are included in the Annex.

The objectives of the study are:

- To survey possible alternatives to DEHP, BBP and DBP with particular emphasis on alternatives to restricted phthalates used in toys and childcare articles,
- To assess health and environmental properties of the alternatives;
- To assess the technical and economic feasibility of the use of the alternatives for the main applications of DEHP, BBP and DBP;
- To disseminate information on alternatives and the feasibility of substitution to relevant stakeholders in Denmark.

The study has been guided by a Steering Group consisting of Shima Dobel and Lotte Kau Andersen, Danish Environmental Protection Agency, and Carsten Lassen and Sonja Hagen Mikkelsen, COWI A/S.

This report has been prepared by Carsten Lassen (Project Manager), Ulla Kristine Brandt, Jakob Maag, Jesper Kjølholt, Lise Molander and Sonja Hagen Mikkelsen, COWI A/S, Denmark.

Summary

In this study a number of alternative plasticisers to the phthalates DEHP, DBP and BBP are described and assessed. Suitable alternative plasticisers have been identified for most applications of the phthalates, and 10 of these have been assessed in detail. Some of the assessed alternative plasticisers have a broad application scope, others are more specialised. Plasticiser alternatives to DEHP, first of all the plasticisers DINA, DINCH, DEHT, ATBC and ASE are marketed at somewhat higher to significantly higher prices than the price of DEHP. The results of the assessment further indicate that alternatives to DBP and BBP are available for the major applications of the substances, at prices quite similar to the prices of the phthalates.

All 10 assessed substances are expected to have low acute toxicity based on animal studies. For three of the assessed alternatives data exists demonstrating that they cannot be considered CMR substances (carcinogenic, mutagenic, reprotoxic); for the other alternatives data for at least one critical parameter are missing. The toxicological data for DEGD and DGD, two of the available alternatives to DBP and BBP in polymeric applications (plastics), indicate that the substances might be some effect on reproduction, but the results are not statistically significant and more data are necessary for a clear conclusion. With regard to the environmental properties, none of the 10 studied alternatives meet the criteria for being PBT substances (persistent, bioaccumulative and toxic in the aquatic environment) or vPvB substances (very persistent and very bioaccumulative), although all substances except GTA show one or two of these properties.

Ortho-phthalates are a group of substances which have together proven to be widely applicable for plasticising purposes. Especially the general plasticisers DEHP, DINP and DIDP have had high importance due to their very wide applicability in PVC. DBP and BBP are specialty plasticisers which in polymer applications typically have been used together with other plasticisers in order to obtain specific processing conditions or material properties. The wide range of applications combined with comparatively low prices have made the ortho-phthalates the preferred choice of plasticiser for the PVC industry for many years and phthalates account today for about 90% of the total plasticiser use for PVC in Europe. This percentage has been quite stable for the last ten years only the distribution between the different phthalates has changed. The consumption of DBP and BBP has decreased markedly the last 15 years and the manufactured volume of each of the substances is today approximately 1% of the total manufactured phthalates.

DINP and DIDP have become dominating alternatives to DEHP due to their closeness in performance to DEHP and only moderately higher costs. DINP or DIDP can replace DEHP for practically all applications and the price is approximately 10% higher than the price of the DEHP. DINP and DIDP have not been further assessed in this study because they are already well described and finished EU risk assessments are available for these substances.

Information on alternatives to DEHP, DBP and BBP, actually applied today, has been collected from the following data sources:

- Danish manufacturers and importers of toys and childcare articles;
- Surveys of plasticisers in toys and childcare articles marketed in the Netherlands, Germany, Austria and Switzerland;
- Direct contact to major manufacturers of plasticisers.

These data sources have been supplemented with information from the literature and manufacturers' web sites.

As consequence of the prohibition of DEHP, DBP and BBP in toys and childcare articles and the prohibition of DINP, DIDP and DNOP in toys and childcare articles which can be placed in the mouth by children, experience exist in substitution of the phthalates for these products. Dutch surveys of plasticisers in toys demonstrate that DEHP and DBP a few years ago could be found in a significant percentage of all samples. In accordance with the fact that the major uses of BBP are in flooring and non-polymer applications (e.g. adhesives) BBP was only found in a few of the toy samples and the surveys of plasticisers used in toys would not give any indication of which plasticisers are applied as alternatives to BBP.

Table 0.1 lists plasticisers used in toys and childcare products. The substances reported by Danish manufacturers have specifically been used by the manufacturers as substitutes for phthalates, whereas some of the plasticisers reported in the surveys of plasticisers in toys and childcare products from other EU countries may in fact not have substituted a former use of phthalates.

Three of non-phthalate plasticisers were found in a significant percentage of the samples in both surveys and are reported by all responding Danish manufacturers of toys as used as alternatives to phthalates: DINCH, DEHT and ATBC. All three are marketed as general plasticiser alternatives to DEHP. Among the non-phthalate plasticisers there seems not to be one substance that can make a one-to-one substitution for all applications of each phthalate. Which substitutes are suitable depends on the actual processing conditions and the desired properties of the final product. Finding the right plasticiser for a given application is often a complex process, as many technical criteria have to be met simultaneously. Comprehensive testing of the performance of the polymer/plasticiser system is often required. By way of example one Danish manufacturer reports that the development led to the use of a mixture of ATBC, DINCH and DEHT, which could be blended in a variety of combinations to achieve softened PVC that performed to the required standards with the existing production setup.

On request a number of manufacturers of plasticisers have provided information on their market experience with possible alternatives to DEHP, BBP and DBP. Unfortunately the manufacturers of DINCH and DEHT, widely used in toys, did not provide detailed information, and the assessment of these substances has mainly been based on information from the manufacturers' websites and the literature. Both substances are marketed as general plasticisers for PVC.

Based on information on the plasticisers found in toys and childcare articles and initial information from manufacturers, a gross list of 25 potential non-phthalate alternatives was compiled and from this list 10 plasticisers were selected for further assessment.

Benzoates (represented in Table 0.2 by DGD and "Mix of DGD, DEGD, TGD") have been the main alternative to BBP, because they provide both suitable processing conditions and properties of the final products and have quite similar price. BBP is mentioned as a critical component in seals for insulating double glazing and it cannot be ruled out that niche applications of BBP and DBP exist where alternatives are not suitable.

Table 0.1
Plasticisers found in toys and childcare articles

Group of plasticiser	Chemical name	Abbreviation	CAS no.	Occurrence in toys and childcare articles		
				Reported by Danish manufacturers /suppliers *2	Survey in the Netherlands 2007, % of samples	Survey in Germany, Austria and Switzerland 2007, % of samples
Phthalates	Diisononyl phthalate	DINP	28553-12-0 68515-48-0	Only non-phthalates reported	49%	10%
	Diisodecyl phthalate	DIDP	26761-40-0 271-091-4	_"_	15%	2%
	Diisodecyl phthalate	DIBP	84-69-5	_"_	2%	2%
Cyclohexanes	Di-isononyl-cyclohexane-1,2dicarboxylate	DINCH	166412-78-8	X	25%	48%
Terephthalates	Di (2-ethyl-hexyl) terephthalate	DEHT, DOTP	6422-86-2	X	7%	10%
Sulphonates	Sulfonic acids, C10 – C18-alkane, phenylesters	ASE	91082-17-6	X	*3	*3
Other alkyl esters	Trimethyl pentanyl diisobutyrate	TXIB	6846-50-0		14%	11%
Citrates	Acetyl tributyl citrate	ATBC	77-90-7	X	9%	10%
Aliphatic dibasic esters	Diisononyl adipate	DINA	33703-08-1	x	6%	4%
	Bis(2-ethylhexyl) adipate	DEHA	103-23-1		4%	2%
	Diisobutyl adipate	DiBA	141-04-8		0.6%	
	Dioctyl sebacate	DEHS	122-62-3		0.6%	
Mixed alkyl aryl esters	Mixed diesters neopentylglycol-benzoate/2-ethylhexanoate	NPG-EHA-BA				7%
	Mixed triesters 1,1,1-trimethylol-propane-benzoate/2-ethylhexanoate	TPG-EHA-BA				2%
	Hexanoic acid, 2-ethyl, mixed triesters with benzoic acid and trimethylopropane	LG-flex BET	610787-76-3	x	*3	*3
Polyesters	Polyadipate	PA				3%
Epoxy esters and epoxidized oils	Epoxidized soy bean oil	ESBO	8013-07-8			1%
Alkyl acetyl esters	Tert-butyl acetate *1	TBAC	540-88-5		11%	
Alkylphenols	Nonylphenol *1		25154-52-3		18%	
Trimellates	Tri-(2-ethylhexyl)-trimellitate	TEHTM (TOTM)	3319-31-1			1%

*1 These substances are usually not mentioned as plasticisers in plastics, but may serve other purposes in the plastics. It has not been confirmed that the substances are actually used as plasticiser in the plastics.

*2 "X" indicates that the substance is reported by all manufactures. "x" indicates that the substance is reported by one manufacturer only.

*3 It is not clear from the report whether the surveys have screened for these alternatives.

Experience in the use of alternative plasticiser exists for all major applications of DEHP, DBP, and BBP. Experience for 6 of the selected plasticisers, for which detailed information was obtained is shown in Table 0.2. Note that the alternatives typically do not substitute for the phthalates 1:1; often are more substances used in combination.

Table 0.2
Alternatives to DEHP, BBP and DBP proposed by contacted manufactures, by application and with indication of market experience

Application	Market experience (1 to 4) *1					
	ASE	GTA	DGD	Mix of DGD, DEGD, TGD	ATBC	COMGHA
As substitute for DEHP						
Polymer applications:						
Calendering of film, sheet and coated products	2	2	4	4	3	3
Calendering of flooring, roofing, wall covering	4	2	3	3		3
Extrusion of hose and profile	2	2	3	3	3	3
Extrusion of wire and cable	2	2	3	3		3
Extrusion of miscellaneous products	2	2	2	2	2	3
Injection moulding	?	2	2	2		3
Spread coating of flooring	2	2	2	2		2
Spread coating	2	2	2	2		3
Car undercoating	2		3	3		
PVC medical articles		2			2	
Toy and childcare articles		2			1	
Non polymer applications:	0					
Adhesives/sealant, rubber	2	2	1	1	2	4
Lacquers and paint	2	2	2	2		4
Printing ink	2	2	2	2	2	3
Production of ceramics						
As substitute for DBP						
Plasticiser in PVC	2		1	1	2	2
Plasticiser in other polymers	2					2
Adhesives	2	2		1	3	4
Printing inks	2	3			2	3
Miscellaneous:						
Sealants	2				3	4
PU foam sealants	2				4	
Nitrocellulose paints	2	3	2	2	2	
Film coatings	3				3	
Glass fibre production						4
Cosmetics						2
As substitute for BBP						
Polymer applications:						
General PVC (e.g. for moulded plastic parts)	2					4
Plastisol coating, for flooring	2		1	1		3
Extrusion or spread coating	2			2		2
Films, calendering	2		4	4		3
Non polymer applications:						
Sealants	2		1	1		
Coatings and inks)		2	1		3	
Adhesives	2			1		
Nail polish					1	

*1: Market experience categories interpretation: 1) Main alternative on market.
2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience

The non-phthalate alternatives to DBP and DEHP have until now primarily been used for particular applications. DBP is in polymers typically used in relatively low concentration in combination with DEHP and the whole plasticiser system is replaced by other plasticiser systems.

A summary of the technical suitability of the 10 alternatives and their prices relative to DEHP, DBP and BBP is provided in Table 0.3.

Table 0.3
summary of the technical assessment of alternative plasticisers (in alphabetical order), and their prices relative to DEHP; DBP and BBP *1

Substance	Overall technical assessment	Price relative to DEHP *1
ASE	ASE is a general plasticiser alternative to DEHP. The producer has indicated significant market experience for most traditional DEHP, DBP and BBP uses.	+
ATBC	The performance of ATBC on some parameters seems similar to DEHP, indicating technical suitability for substitution of DEHP for some applications. The higher extractability in aqueous solutions and the higher volatility may reduce the performance of ATBC as a plasticiser in PVC. The data available does not allow a closer assessment of ATBC's technical suitability as alternative to DEHP, DBP and BBP	++
Benxoflex 2088 (with DEGD)	The producer has indicated significant market experience in several of the traditional DBP and BBP specialty plasticiser applications and certain DEHP applications, notably in the non-polymer (adhesives, sealants, etc.) and PVC spread coating (plastisol) application fields. According to the producer, Benzoflex 2088 (with DEGD) has become the main non-phthalate alternative to DBP or BBP in vinyl flooring production in Europe. The higher extractability in water may limit its use for some applications.	≈
COMGHA	According to the producer, COMGHA still has relative moderate market experience, albeit with many examples of full scale usage and pilot/lab scale tests, and significant market experience in some plastisol application and cosmetics. The producer found good performance on key technical parameters indicating a potential for substituting for DEHP and perhaps for DBP and BBP in some traditional uses of these substances.	++
DEHT	DEHT is a general plasticiser alternative to DEHP. Today, terephthalates like DEHT are more commonly used in the USA than elsewhere.	≈
DINA	DINA has mostly been used for low temperature PVC applications and in PVC film/wrapping . The data available for this study does not allow clear-cut conclusions as regards DINA's suitability as alternative to DEHP	+
DINCH	The producer's sales appraisal indicates a relatively wide usage of DINCH for general plasticiser purposes. DINCH was the most frequently found plasticiser in two European surveys of plasticisers in toys and childcare articles. The data available does not allow a closer assessment of DINCH's technical suitability as alternative to DEHP, DBP and BBP.	+
DGD	The fact that DGD for many years has been a well known and much used competitor to BBP, especially in PVC flooring and in PVA adhesives, indicates a clear potential for substituting DGD for BBP, from a technical point of view. DGD may probably also substitute for some traditional uses of DEHP and DBP.	≈
GTA	According to a producer, GTA can substitute for DBP and BBP in adhesives, inks and coatings. The data available does not allow a closer assessment of GTA's technical suitability as alternative to DEHP, DBP and BBP.	+
TXIB	TXIB was found in more than 10% of the samples in surveys of plasticisers in toys and childcare articles. However, the producer does not consider TXIB an alternative to DEHP, DBP or BBP, and the usage of TXIB in vinyl flooring has declined in the 1990's due to high emissions from end products. Consequently, TXIB seems not to be a suitable alternative to DEHP, DBP or BBP.	NA

Notes: *1: Based on comparison with DEHP, but DBP and BBP are reported to have similar price and the notation therefore serves as indicating price relative to DBP and BBP as well. "≈" means similar price or slightly lower or higher than DEHP; "+" means somewhat higher price (10-50% higher) than DEHP and "++" means significantly higher price than DEHP. The report provides actual price examples.

Price of alternatives

As shown in the table above, the price of the non-phthalate alternatives DEHT, DGD and Benzoflex 2088 were in the same price range as the price of DEHP, DBP and BBP, (as well as the ortho-phthalate alternatives DINP

and DIDP), whereas ASE, DINA , DINCH and GTA were somewhat more expensive and ATBC and COMGHA were considerably more expensive. The content of DEHP in plasticised PVC is typically 30% of the plastics and an increase in the price of the plasticiser of e.g. 30% will result in a material price increase of 10% for the plastic material.

Prices of chemicals (and other industrial products) tend to decrease as production capacity and competition is increased. Different chemicals are however based on different raw materials and more or less complex and resource demanding chemical synthesis technologies. This of course sets limits to the minimum prices attainable even in a mature market, and some of the alternative plasticisers described may likely remain at higher price levels. It should be noted that the prices of DEHP have dropped significantly over the last ten year or more; probably due to the reduced demand driven by the regulation.

Besides the price of the plasticisers, the substitution of the phthalates may imply some costs of research and development and process changes which have not been assessed in this study.

Assessment of alternative flexible polymers

A number of flexible polymers are available which can substitute for many traditional uses of flexible PVC. Polyethylene (PE), polyolefin elastomers, different polyurethane (PU) qualities, ethylene vinyl acetate (EVA) and different rubber types are examples among others. For many flexible PVC uses, also other substitute materials than flexible polymers exist. The existing LCA-based, application-focused assessments are few, and often the studies could not make clear-cut conclusions. But many materials exist with seemingly equal or better environmental, health and safety, performance and cost profiles. The assessment made here does not allow for a more detailed analysis of possibilities and limitations in the use of alternative flexible polymers.

Environmental and health assessment

A summary of the inherent properties for the investigated alternative plasticisers is shown in Table 0.4 using key parameters: acute and local effects, sensitisation, carcinogenicity, mutagenicity, reproductive toxicity, persistence, bioaccumulation and aquatic toxicity.

From the overview it can be seen that all ten substances are expected to have low acute toxicity based on animal studies. With regard to local effects most substances are non-irritating to skin and eyes or only produce slight irritation which would not lead to classification. None of the tested substances are sensitising.

Effects from repeated dose toxicity studies mainly include reduced body weight gain, increased organ weights (liver and/or kidney) and for some substance also changes in clinical chemistry or clinical pathology parameters. However, more serious pathological effects were not observed.

Studies to evaluate the potential for reproductive/developmental toxicity primarily show toxic effects on parents and offspring. For TXIB statistically significant reproductive and developmental toxicity is observed.

Table 0.4
Overview of main toxicological and ecotoxicological properties

Name of substance	CAS No.	Health					Environment			Data quality / data completeness (CMR and PBT)
		Acute, local and sens. effects (A/L/S)	Carcinogenic (C)	Mutagenic (M)	Repro-toxic (R)	Subchronic toxicity	Persistence	Bioaccumulation	Aquatic Toxicity	
							*1	*2	*3	*4
ASE	91082-17-6	○/○/○	-	○	○	●	● (not readily)	● P_{ow}	○	2 / 2
ATBC	77-90-7	○/(○)/○	○	○	○	[●]	○	● BCF	●	1 / 2
COMGHA	330198-91-9	○/○/○	-	○	-	(●)	○	● P_{ow}	●	1 / 2
DEGD	120-55-8	○/(○)/○	-	○	(●)	●	○	(○) BCF	●	1 / 2
DGD	27138-31-4	○/(○)/○	-	○	(●)	●	○	● P_{ow}	●	1 / 2
DEHT / DOPT	6422-86-2	○/(○)/○	○	○	○	●	● (inherently)	● P_{ow}	(●)	1 / 2
DINA	33703-08-1	○/○/○	-	○	-	●	○	(●) (conflicting)	○	1 / 2
DINCH	166412-78-8	○/(○)/○	○	○	○	●	● (not readily)	● P_{ow}	○	1 / 2
GTA	102-76-1	○/○/○	-	○	○	○	○	○	○	1 / 2
TXIB	6846-50-0	○/(○)/○	-	○	●	●	● (inherently)	○ BCF	●	1 / 2

Notes:

The inherent properties for the investigated substances are summarised using key parameters: acute and local effects, sensitisation, carcinogenicity(C), mutagenic toxicity (M), reproductive toxicity (R), persistence, bioaccumulation and aquatic toxicity. If data are not available for all parameters or only from non standard test results a tentative assessment is given (shown in parentheses). The symbols: ● identified potential hazard, ○ no identified potential hazard, and – no data available. [] indicate the effects are considered of minor significance.

*1 The terms refer to different biodegradability tests:

Inherently biodegradable: Not meeting the criteria in an "inherent biodegradability" test

Not readily biodegradable: Not meeting the criteria in "ready biodegradability" tests.

*2 ● is based on BCF > 100 or Pow > 3 (BCF prevails over Pow where both values exist).

*3 ●● is used for very toxic and toxic < 10 mg/L.

*4 The following notation is used:

Data quality (first number):

1 Data summaries from recognised, peer reviewed sources (e.g. EU HVP programme, SIDS, SCHENIR, NICNAS) or reliable test data.

2 Data summaries from not peer reviewed sources, considered reliable with restrictions (e.g. IUCLID).

3 Data summaries which do not give sufficient experimental details for the evaluation of the quality.

Data completeness (second number):

1 Data considered sufficient for classification of CMR effects and according to PBT criteria.

2 Data available about the endpoint, but not considered sufficient for classification.

3 Data not available or relevant for classification of the endpoint.

An average score is assigned based on the sum of scores for C, M, R, P, B and T properties as follows: Sum 6-8=1, Sum 9-14=2 and Sum 14-18=3

Carcinogenicity has only been evaluated for three substances in combined studies. For all three substances the outcome was negative (no carcinogenicity effect). However, the studies cannot be considered sufficient to exclude possible carcinogenic effects.

The assessment in this study of the toxic properties of ATCB, COMGHA, DINCH and DEHT is in line with the recent assessment from the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR).

All substances have been tested for acute toxicity for at least one exposure route, sensitisation (except ASE), subchronic toxicity and mutagenicity. All substances except ASE, COMGHA and DINA have been tested for both reproductive and developmental toxicity.

With regard to carcinogenicity only ATBC, DEHT and DINCH have been tested in combined chronic toxicity and carcinogenicity studies. For DEGD, DGD and DEHT estrogenic activity has been tested in a uterotrophic assay without positive response.

Most data used for the evaluation are considered of good quality, i.e. studies following accepted guidelines (OECD or US EPA) or studies considered acceptable at the time they were carried out. For some of the studies little information is available to evaluate the quality. However, key information is obtained from IUCLID data sheets, USEPA or OECD HPV robust summaries.).

With regard to environmental properties, none of the 10 studied alternatives meet the criteria for being a PBT or vPvB substance, although all substances except GTA show one or two of these properties. GTA (triacetin) appears to be easily biodegradable, it does not bioaccumulate and has very moderate toxicity in the aquatic environment.

DEGD, DGD and DINA also come out rather favourable, while ATBC and COMGHA come out negatively despite their degradability because of their aquatic toxicities and bioaccumulative properties. ASE and DINCH both have low acute toxicities to aquatic organisms, but are not easily degradable and have high log K_{OW} values. DEHT is also not easily biodegradable and is bioaccumulative but its aquatic toxicity cannot be fully evaluated based on the data available.

Useful fate data regarding biodegradability (in water) and bioaccumulative properties (either as BCF or log K_{OW}) are available for all alternatives while other fate data are incomplete for some substances. With regard to ecotoxicological effect data, results from short-term tests with the base-set of organisms - fish, crustaceans and algae - exist for all 10 substances although the duration of some studies deviate from the current OECD standard.

Overall, the data indentified are of good quality i.e. they are mostly based on studies performed according to accepted guideline procedures, and the studies have been evaluated to be reliable without restrictions or reliable with restrictions (e.g. in the USEPA HPV robust summaries).

Dansk sammenfatning

I denne undersøgelse er en række blødgørere, som kan anvendes som alternativer til ftalaterne DEHP, DBP and BBP, blevet beskrevet og vurderet. Til de fleste anvendelser af ftalaterne er der blevet fundet brugbare alternative blødgørere og 10 af disse er blevet vurderet i detaljer. Nogle af de vurderede alternativer har et bredt anvendelsesområde mens andre er mere specialiserede. Alternative blødgørere, der kan erstatte DEHP, først og fremmest blødgørerne DINA, DINCH, DEHT, ATBC og ASE markedsføres til priser der varierer fra lidt højere til væsentligt højere end prisen på DEHP. Resultatet af vurderingen viser endvidere at alternativer til DBP og BBP er til rådighed for de fleste af anvendelserne af stofferne til priser, som er meget lig prisen på ftalaterne.

Alle 10 vurderede stoffer forventes, på basis af undersøgelser på dyr, at have en lav akut toksicitet. For tre af de vurderede alternativer er der data, som viser at stofferne ikke kan betragtes at være CMR stoffer (at kunne fremkalde kræft, skader på arveanlæg, eller skader på fostre eller forplantningsevnen). For de øvrige alternativer mangler der data for mindst én af de kritiske parametre. De toksikologiske data for DEGD og DGD, to af de tilgængelige alternativer til DBP og BBP anvendt i polymerer (plastmaterialer) indikerer, at stofferne måske kan have en effekt på forplantningsevnen, men resultaterne er ikke statistisk signifikante, og der er brug for flere data for at kunne lave en klar konklusion. Med hensyn til miljøegenskaberne er der ingen af de 10 undersøgte alternativer der opfylder kriterierne for at være PBT stoffer (persistente, bioakkumulerbare og giftige i vandmiljøet) eller vPvB stoffer (meget persistente og meget bioakkumulerbare), selv om alle stofferne på nær GTA udviser én eller to af disse egenskaber.

Ortho-ftalater er en gruppe af stoffer som sammen har vist sig at have en bred anvendelse som blødgørere. Især har almen-blødgørerne DEHP, DINP and DIDP har haft stor betydning på grund af deres brede anvendelighed i PVC. DBP og BBP er special-blødgørere som i polymeranvendelser typisk har været brugt sammen med andre blødgørere for at opnå bestemte procesbetingelser eller materialeegenskaber. Det brede anvendelsesområde kombineret med forholdsvis lave priser har gjort ftalaterne til det foretrukne valg af blødgørere i PVC industrien, og ftalaterne udgør i dag 90% af det totale forbrug af blødgørere til PVC in Europa. Denne andel har været ret stabil i de eneste 10 år, hvor kun fordelingen mellem de enkelte ftalater har forandret sig. Forbruget af DBP og BBP har faldet markant de seneste 15 år og den producerede mængde udgør i dag - for hvert af stofferne - kun omkring 1% af den totale mængde ftalater, som produceres

DINP og DIDP er blevet de dominerende alternativer til DEHP på grund af deres lighed med DEHP og kun lidt højere pris. DINP og DIDP kan erstatte DEHP til stort set alle anvendelser og prisen er omkring 10% højere end prisen på DEHP. DINP og DIDP er ikke blevet nærmere vurderet i denne undersøgelse, fordi de allerede er velbeskrevne og der er færdiggjorte EU risikovurderinger omhandlende disse stoffer.

Information om alternativer til DEHP, DBP and BBP, som faktisk anvendes i dag, er blevet indsamlet fra følgende datakilder:

- Danske producenter og importører af legetøj og småbørnsartikler;
- Kortlægninger af blødgørere i legetøj og småbørnsartikler markedsført i Holland, Tyskland, Østrig og Schweiz;
- Direkte kontakt til større producenter af blødgørere.

Disse datakilder er blevet suppleret med information fra litteraturen og producenternes internetsteder.

Som følge af forbuddet mod DEHP, DBP og BBP i legetøj og småbørnsartikler og forbuddet mod DINP, DIDP and DNOP i legetøj og småbørnsartikler, der kan puttes i munden, er der erfaring med at erstatte brugen af ftalaterne i disse produkter. Hollandske kortlægninger af blødgørere i legetøj viser, at DEHP og DBP for få år siden kunne findes i en væsentlig del af alle prøver. I overensstemmelse med det faktum at de væsentligste anvendelser af BBP er i gulvbelægninger og ikke-polymer anvendelser (f.eks. lime) blev der kun fundet BBP i få af legetøjsprøverne, og kortlægninger af blødgørere i legetøj kan derfor ikke bruges til at vise, hvilke blødgørere der anvendes som alternativer til BBP.

Tabel 0.1 oplister blødgørere, som anvendes i legetøj og småbørnsartikler. De stoffer, som er oplyst af danske producenter, er specifikt anvendt af producenterne som erstatning for ftalater, hvorimod nogle af de blødgørere, der er blevet fundet i kortlægningerne af blødgørere i legetøj og småbørnsartikler i andre EU lande, måske ikke har erstattet en tidligere anvendelse af ftalater.

Tre af ikke-ftalat blødgørerne blev fundet i en væsentlig del af alle prøver i begge undersøgelser og alle de danske legetøjsproducenter, der har svaret, har oplyst at disse bliver brugt som alternativer til ftalater: DINCH, DEHT og ATBC. All tre markedsføres som almen-blødgører alternativer til DEHP. Blandt ikke-ftalat alternativer synes der ikke at være ét stof, der kan lave en en-til-en erstatning for alle anvendelser af hver af ftalaterne. Det afhænger af procesbetingelser og de ønskede egenskaber af det færdige produkt, hvilket alternativ der er brugbart. At finde den rette blødgører til en given anvendelse er ofte en kompleks proces da der er mange tekniske kriterier, der skal opfyldes på samme tid. Der kræves ofte omfattende tests af de tekniske egenskaber af polymer/blødgører systemet. Eksempelvis oplyser en dansk producent at udviklingen ledte til en kombination af ATBC, DINCH and DEHT, som kunne blandes i forskellige blandingsforhold, for at opnå en blødgjort PVC der levede op til de krævede standarder med brug af det eksisterende produktionsapparat.

På anmodning har et antal producenter af blødgørere leveret information om deres markedserfaringer med mulige alternativer til DEHP, BBP og DBP. Desværre har producenterne af DINCH og DEHP, som har en stor anvendelse i legetøj, ikke leveret detaljeret information, og vurderingen af disse stoffer er derfor overvejende baseret på information fra producenternes Internetsteder. Begge stoffer markedsføres som almen-blødgørere til PVC.

Baseret på informationen om blødgørere fundet i legetøj og småbørnsartikler og indledende oplysninger fra producenter, blev der opstillet en bruttoliste på 25 potentielle ikke-ftalat alternativer, og fra denne liste blev der udvalgt 10 blødgørere til den videre vurdering.

Benzoater (repræsenteret i tabel 0.2 af DGD og "Blanding af DGD, DEGD, TGD") har været de vigtigste alternativer til BBP, fordi de giver tilfredsstillende procesbetingelser og egenskaber af det færdige produkt og har næsten samme pris som BBP. BBP er omtalt som en kritisk komponent i forseglinger til termoglasruder, og det kan ikke udelukkes, at der findes nogle niche-anvendelser, hvor alternativerne ikke er anvendelige.

Tabel 0.1
Blødgørere fundet i legetøj og småbørnsartikler

Gruppe af blødgørere	Kemisk navn	Forkortelse	CAS nr.	Forekomst i legetøj og småbørnsartikler		
				Oplyst af danske producenter og leverandører *2	Kortlægning i Holland i 2007, % af prøver	Kortlægning i Tyskland, Østrig og Schweiz i 2007, % af prøver
Ftalater	Diisononyl ftalat	DINP	28553-12-0 68515-48-0	Kun oplysninger om ikke-ftalater	49%	10%
	Diisodecyl ftalat	DIDP	26761-40-0 271-091-4	_"_	15%	2%
	Diisodecyl ftalat	DIBP	84-69-5	_"_	2%	2%
Cyclohexaner	Di-isononyl-cyclohexane-1,2dicarboxylat	DINCH	166412-78-8	X	25%	48%
Tereftalater	Di (2-ethyl-hexyl) tereftalat	DEHT, DOTP	6422-86-2	X	7%	10%
Sulfonater	Sulfoniske syrer, C10 – C18-alkaner, phenylestere	ASE	91082-17-6	X	*3	*3
Andre alkyl estere	Trimethyl pentanyl diisobutyrat	TXIB	6846-50-0		14%	11%
Citrater	Acetyl tributyl citrat	ATBC	77-90-7	X	9%	10%
Alifatiske dibasiske estere	Diisononyl adipat	DINA	33703-08-1	x	6%	4%
	Bis(2-ethylhexyl) adipat	DEHA	103-23-1		4%	2%
	Diisobutyl adipat	DiBA	141-04-8		0.6%	
	Dioctyl sebacat	DEHS	122-62-3		0.6%	
Blandede alkyl aryl estere	Mixed diestere neopentylglycol-benzoat/2-ethylhexanoat	NPG-EHA-BA				7%
	Mixed triesters 1,1,1-trimethylol-propan-benzoat/2-ethylhexanoat	TPG-EHA-BA				2%
	Hexan syre, 2-ethyl, blanded triestere with benzon syre og trimethylopropan	LG-flex BET	610787-76-3	x		
Polyestere	Polyadipat	PA				3%
Epoxy estere og epoxiderede olier	Epoxideret sojabønne olie	ESBO	8013-07-8			1%
Alkyl acetyl estere	Tert-butyl acetat *1	TBAC	540-88-5		11%	
Alkylphenoler	Nonylphenol *1		25154-52-3		18%	
Trimellater	Tri-(2-ethylhexyl)-trimellitat	TEHTM (TOTM)	3319-31-1			1%

*1 Disse stoffer omtales normalt ikke som værende blødgørere i plastik, men tjener eventuelt andre formål i plastikmaterialerne. Det er ikke blevet bekræftet, at stofferne faktisk bruges som blødgørere i plastikmaterialerne.

*2 "X" indikerer at stoffet er oplyst af alle producenter "x" indikerer at stoffet er oplyst af kun én producent.

*3 Det fremgår ikke klart af rapporterne, om der ved screeningerne er undersøgt for disse alternativer.

Der findes erfaring i brug af alternativer til alle større anvendelser af DEHP, DBP, og BBP. Erfaring for 6 af de udvalgte blødgørere, for hvilke detaljeret information blev tilvejebragt, er vist i tabel 0.2. Bemærk at alternativerne typisk ikke kan erstatte ftalaterne 1:1, men at de ofte bruges i en kombination af flere stoffer.

Tabel 0.2
Alternativer til DEHP, BBP og DBP, som er foreslået af de kontaktede producenter af blødgørere, fordelt på anvendelsesområder med en indikation af markedserfaringer.

Anvendelse	Markedserfaringer (1 til 4) *1					
	ASE	GTA	DGD	Blanding af DGD, DEGD, TGD	ATBC	COMGHA
Som alternativ til DEHP						
Anvendelser i polymerer:						
Kalendrering af film, plader og overfladebehandlede produkter	2	2	4	4	3	3
Kalendrering af gulvbelægning, loft- og vægbeklædnin g	4	2	3	3		3
Extrudering af slanger og profiler	2	2	3	3	3	3
Extrudering af ledninger og kabler	2	2	3	3		3
Extrudering af diverse produkter	2	2	2	2	2	3
Sprøjtestøbning	?	2	2	2		3
Plastisol belægning af gulvbelægning	2	2	2	2		2
Anden plastisol belægning	2	2	2	2		3
Undervognsbehandling	2		3	3		
Medicinske artikler af PVC		2			2	
Legetøj og småbørnsartikler		2			1	
Anvendelser i ikke-polymerer:	0					
Lime/fugemasser, gummi	2	2	1	1	2	4
Lak og maling	2	2	2	2		4
Trykfarver	2	2	2	2	2	3
Produktion af keramik						
Som alternativ til DBP						
Anvendelser i polymerer:						
Blødgører i PVC	2		1	1	2	2
Blødgører i andre polymerer	2					2
Anvendelser i ikke-polymerer:						
Lime	2	2		1	3	4
Trykfarver	2	3			2	3
Fugemasser	2				3	4
Fugemasser af PU skum	2				4	
Nitrocellulose maling	2	3	2	2	2	
Overfladefilm	3				3	
Glasfiber produktion						4
Kosmetik						2
Som alternativ til BBP						
Anvendelser i polymerer:						
Generel PVC (f.eks. støbte plastikdele)	2					4
Plastisol overfladebelægning af gulvbelægninger	2		1	1		3
Extrudering eller plastisol overfladebelægning	2			2		2
Kalendrering af film	2		4	4		3
Anvendelser i ikke-polymerer:						
Fugemasser	2		1	1		
Overfladebelægninger og trykfarver		2	1		3	
Lime	2			1		
Neglelak					1	

Note til tabel på

*1: Forklaring af kategorierne for markedserfaring: 1) Vigtigste alternativ på markedet 2) Væsentlig markedserfaring. 3) Eksempler på erfaring i fuldskala. 4) Erfaring på pilot- eller laboratorieskala.

Ikke-ftalat alternativer til DBP og DEHP har indtil nu primært været brugt til særlige anvendelser. DBP er i polymerer typisk blevet brugt i relativt lav koncentration i kombination med DEHP og hele blødgørersystemet erstattes af andre blødgørersystemer. En sammenfatning af de 10 alternativers tekniske egnethed og deres pris sammenlignet med DEHP, DBP and BBP er vist i Tabel 0.3.

Tabel 0.3
Sammenfatning af den tekniske vurdering af alternative blødgører (i alfabetisk orden) og deres pris i forhold til DEHP; DBP of BBP *1

Stof	Overordnet teknisk vurdering	Pris sammenlignet med DEHP *1
ASE	ASE er en almen-blødgører, som kan anvendes som alternativ til DEHP. Producenten har indikeret en væsentlig erfaring i forhold til de fleste traditionelle anvendelser af DEHP, DBP og BBP.	+
ATBC	ATBC opfører sig i forhold til nogle parametre ligesom DEHP, hvilket indikerer at stoffet teknisk set egner sig til at erstatte DEHP til nogle anvendelser. Den højere ekstraherbarhed i vandige opløsninger og stoffets større flygtighed begrænser muligvis ATBCs egnethed som blødgører i PVC. De data, der har været til rådighed, tillader ikke en nærmere vurdering af ATBCs tekniske egnethed som alternativ til DEHP, DBP og BBP.	++
Benxoflex 2088 (med DEGD)	Producenten har indikeret væsentlig markedserfaring inden for flere af de traditionelle anvendelser af DBP og BBP som special-blødgørere og visse anvendelser af DEHP, navnlig i ikke-polymer anvendelser (lime, fugemasser og andet) og PVC plastisol overfladebehandling. I følge producenten er Benzoflex 2088 (med DEGD) det væsentligste ikke-ftalat alternativ til DBP og BBP i produktionen af vinylgulve i Europa. Den højere ekstraherbarhed i vand begrænser muligvis stoffets brug til nogle anvendelser.	≈
COMGHA	I følge producenten har COMGHA stadig en relativ lille markedserfaring, omend der er mange eksempler på fuldskala-brug og pilot- eller laboratorieskala forsøg og en væsentlig markedserfaring i nogle plastisol anvendelser og i kosmetik. Producenten fandt at stoffet havde gode egenskaber i relation til en række væsentlige tekniske parametre, hvilket indikerer et potentiale for at kunne erstatte DEHP og eventuelt DBP og BBP til nogle af disse blødgøreres traditionelle anvendelser.	++
DEHT	DEHT er en almen-blødgører, som kan anvendes som alternativ til DEHP. DEHT er for øjeblikket mere almindeligt brugt i USA end andre steder.	≈
DINA	DINA har mest været brugt til lav-temperatur anvendelser i PVC og i PVC film/indpakning. De data, som har været til rådighed for denne undersøgelse, tillader ikke en klar vurdering af DINAs egnethed som alternativ til DEHP.	+
DINCH	Producentens salgsmateriale indikerer en relativt udbredt brug af DINCH som almen-blødgører. DINCH var den mest hyppigt fundne blødgører i to europæiske undersøgelser af blødgørere i legetøj og småbørnsartikler. De data, der har været til rådighed, tillader ikke en nærmere vurdering af DINCHs tekniske egnethed som alternativ til DEHP, DBP og BBP.	+
DGD	Det faktum at DGD i mange år har været en velkendt og meget anvendt konkurrent til BBP, især i PVC gulvbelægning of PVA lime, indikerer, at DGD fra en teknisk synsvinkel har et klart potentiale for at kunne erstatte BBP. DGD kan formentlig også erstatte DEHP og DBP til nogle af disse blødgøreres traditionelle anvendelser.	≈
GTA	I følge en producent kan GTA erstatte DBP og BBP i lime, trykfarver og overfladebehandlinger. De data, der har været til rådighed, tillader ikke en nærmere vurdering af GTAs tekniske egnethed som alternativ til DEHP, DBP og BBP.	+
TXIB	TXIB blev fundet i mere end 10% af prøverne i kortlægninger af blødgørere i legetøj og småbørnsartikler. Producenten betragter dog ikke TXIB som alternativ til DEHP, DBP og BBP, og brugen af TXIB i vinylgulvbelægninger har været faldende i 1990-erne på grund af høje emissionsrater fra produkterne. TXIB synes derfor ikke at være et egnet alternativ til DEHP, DBP og BBP.	NA

Noter: *1: Baseret på en sammenligning med DEHP, men DBP og BBP er oplyst at have den samme pris og notationen kan derfor også bruges til at indikere prisen relativt til DBP og BBP.. "≈" betyder samme pris eller en smule højere eller lavere end DEHP; "+" betyder en del højere

pris (10-50% højere)end DEHP og "++" betyder betydeligt højere pris end DEHP. Rapporten giver eksempler på de faktiske priser.

Alternativernes pris

Som det er vist i tabellen ovenfor var prisen på alternativerne DEHT, DGD og Benzoflex 2088 på det samme niveau som prisen på DEHP, DBP and BBP (såvel som på ortho-ftalat alternativerne), hvorimod ASE, DINA, DINCH og GTA var en del dyrere og ATBC og COMGHA var væsentligt dyrere. Indholdet af DEHP i blødgjort PVC er typisk 30% af plastikmaterialet, og en stigning i prisen på eksempelvis 30% vil resultere i en prisstigning på 10% på plastikmaterialet.

Prisen på kemikalier (og andre industriprodukter) har en tendens til at falde når produktionskapaciteten og konkurrencen stiger. Forskellige kemikalier er dog baseret på forskellige råmaterialer og mere eller mindre komplekse og ressourcekrævende kemiske synteseteknologier. Dette sætter naturligvis en grænse for den laveste pris, som kan opnås selv i et modent marked, og nogle af de beskrevne alternative blødgørere vil formentlig forblive på et højere prisniveau end ftalaterne. Det skal bemærkes, at prisen på DEHP er faldet væsentligt over de seneste ti år, formentlig på grund af en mindsket efterspørgsel, som konsekvens af reguleringen.

Udover prisen på blødgørerne, kan erstatningen af ftalaterne indebære nogle omkostninger til forskning og udvikling og til procesændringer, som ikke er blevet vurderet i denne undersøgelse.

Vurdering af alternative fleksible polymerer

Der er en række fleksible polymerer til rådighed, som kan erstatte blødgjort PVC til mange anvendelser. Polyethylen (PE), polyolefin elastomerer, forskellige typer af polyuretan (PU), ethylen vinyl acetat (EVA) and forskellige gummityper er eksempler.

For mange anvendelser af blødgjort PVC eksisterer der også andre erstatningsmaterialer end fleksible polymerer. Der er kun få eksisterende LCA-baserede, anvendelsesfokuserede vurderinger, og oftest har der ikke kunnet laves entydige konklusioner i undersøgelserne. Men der findes mange materialer, som synes at have lige så gode eller bedre profiler med hensyn til miljø, sundhed og sikkerhed. Vurderingerne, som er lavet i denne undersøgelse, tillader ikke en mere detaljeret analyse af muligheder og begrænsninger i brugen af alternative fleksible polymerer.

Miljø- og sundhedsvurdering

I tabel 4 er de iboende egenskaber af de undersøgte alternativer sammenfattet ved at angive en række nøgleparametre: akutte og lokale effekter, sensibilisering, kræftfremkaldende effekter, skader på arveanlæg, skader på fostre eller forplantningsevnen, persistens, bioakkumulering, og giftighed i vandmiljøet.

Af sammenfatningen ses, at alle ti stoffer - baseret på undersøgelser på dyr - forventes at have en lav akut toksicitet. Med hensyn til lokale effekter virker de fleste af stofferne ikke irriterende på hud og øjne eller giver kun anledning til en svag irritation, som ikke vil medføre en klassificering af stofferne. Ingen af de testede stoffer er sensibiliserende.

Effekter fra toksicitetsstudier med gentagne doser omfatter overvejende reduceret kropsvægt, forøget organvægt (lever og/eller nyre) og for nogle stoffer også ændringer i kliniske kemiske eller patologiske parametre. Der er dog ikke observeret væsentlige patologiske effekter.

Studier med henblik på at evaluere stoffernes potentiale for at indvirke på forplantningsevnen eller afkommets udvikling viser toksiske effekter på forældre og afkom. Der er blevet observeret en statistisk signifikant toksicitet af TXIB på forplantning og udvikling.

Tabel 0.4
Overblik over de væsentligste toksikologiske og økotoksikologiske egenskaber af alternativer.

Stofnavn	CAS N Nr.	Sundhed					Miljø			Data kvalitet / data fuldstændighed (CMR and PBT)
		Akutte, lokale og sensibiliserende effekter (A/L/S)	Kræftfremkaldende eff. (C)	Skader på arveanlæg (M)	Skader på fostre eller forplantningsevnen (R)	Subkronisk toksicitet	Persistens	Bioakkumulering	Giftighed i vandmiljøet	
							*1	*2	*3	*4
ASE	91082-17-6	○/○/○	-	○	○	●	● (Not readily)	● P_{ow}	○	2 / 2
ATBC	77-90-7	○/(○)/○	○	○	○	[●]	○	● BCF	●	1 / 2
COMGHA	330198-91-9	○/○/○	-	○	-	(●)	○	● P_{ow}	●	1 / 2
DEGD	120-55-8	○/(○)/○	-	○	(●)	●	○	(○) BCF	●	1 / 2
DGD	27138-31-4	○/(○)/○	-	○	(●)	●	○	● P_{ow}	●	1 / 2
DEHT / DOPT	6422-86-2	○/(○)/○	○	○	○	●	● (Inherently)	● P_{ow}	(●)	1 / 2
DINA	33703-08-1	○/○/○	-	○	-	●	○	(●) (modstridende)	○	1 / 2
DINCH	166412-78-8	○/(○)/○	○	○	○	●	● (Not readily)	● P_{ow}	○	1 / 2
GTA	102-76-1	○/○/○	-	○	○	○	○	○	○	1 / 2
TXIB	6846-50-0	○/(○)/○	-	○	●	●	● (Inherently)	○ BCF	●	1 / 2

Noter:

De iboende egenskaber af de undersøgte stoffer er sammenfattet med brug af følgende nøgleparametre: akutte og lokale effekter, sensibilisering, kræftfremkaldende effekter (C), skader på arveanlæg (M), skader på fostre eller forplantningsevnen (R), persistens, bioakkumulering og giftighed i vandmiljøet. Hvis der ikke er data til rådighed for alle parametre, eller der kun er resultater fra ikke-standard forsøg, er der givet en foreløbig vurdering (vist i parenteser). Symboler: ● potentiel fare fundet, ○ ingen potentiel fare fundet, og – ingen tilgængelige data. [] angiver at effekterne anses for at være af mindre betydning.

*1 Betegnelserne henviser til forskellige bionedbrydelighedstests:
"Inherently biodegradable": Opfylder ikke kriterierne i en "inherent biodegradability" test
"Not readily biodegradable": Opfylder ikke kriterierne i en "ready biodegradability" tests.

*2 ● er baseret på BCF > 100 eller Pow > 3 (BCF foretrækkes frem for Pow, hvor begge værdier findes).

*3 ●● anvendes for "meget toksisk" og toksisk < 10 mg/L.

*4 Den følgende notation anvendes:
Data kvalitet (første tal):
1 Data-sammenfatninger fra anerkendte, "peer reviewede" kilder (f.eks. EU HVP program, SIDS, SCHENIR, NICNAS) eller pålidelige test data.
2 Data-sammenfatninger fra kilder som ikke er "peer reviewede", som anses for at være pålidelige med visse begrænsninger (f.eks. IUCLID).

3 Data-sammenfatninger, som ikke giver tilstrækkelige eksperimentelle detaljer til at man kan evaluere kvaliteten.

Data fuldstændighed (andet tal):

1 Data betragtes at være tilstrækkelige til, at der kan foretages en klassifikation i relation til CMR effekter og i henhold til PBT kriterier.

2 Data i relation til den enkelte effekt er til rådighed, men betragtes ikke at være tilstrækkelige til at der kan foretages en klassificering.

3 Date er ikke til rådighed eller ikke relevante i relation til at kunne foretage en klassifikation

En gennemsnitlig score er tildelt på basis af scoren for de forskellige egenskaber: C, M, R, P, B og T på denne måde: Samlet score 6-8=1, Samlet score 9-14=2 og Samlet score 14-18=3

Muligheden for kræftfremkaldende effekter er kun blevet undersøgt for tre af stofferne i kombinerede undersøgelser. For alle tre stoffer var udfaldet negativt dvs. der sås ikke nogen kræftfremkaldende effekt. Undersøgelserne kan dog ikke anses for tilstrækkelige til at udelukke eventuelle kræftfremkaldende effekter.

Vurderingen af de toksiske egenskaber af ATCB, COMGHA, DINCH og DEHT i denne undersøgelse er i overensstemmelse med en vurdering som for nyligt er lavet af de samme stoffer af EUs videnskabelige komité for nye og nyligt identificerede sundhedsricici (SCENIHR).

Alle stofferne er blevet testet for akut toksicitet for mindst én eksponeringsvej, sensibilisering (pånær ASE), subkronisk toksicitet og skader på arveanlæg. Alle stofferne, på nær ASE, COMGHA og DINA, er testet for både skader på arveanlæg og skader på fostre eller forplantningsevnen.

Med hensyn til kræftfremkaldende effekt er kun ATBC, DEHT og DINCH blevet testet i undersøgelser for kombineret kronisk toksicitet og kræft. For DEGD, DGD og DEHT er den østrogene aktivitet blevet testet i en uterustest uden positiv respons

De fleste af dataene brugt til evalueringen anses for at være af god kvalitet dvs. undersøgelserne følger accepterede guidelines (OECD og US EPA) eller undersøgelserne betragtes som acceptable på det tidspunkt de blev udført. For nogle af studierne er det vanskeligt at vurdere kvaliteten da der kun er begrænset information til rådighed. Nøgleinformation er dog hentet fra IUCLID data ark, USEPA eller OECD "HPV robust study summaries".

Med hensyn til miljøegenskaber, er der ingen af de 10 undersøgte alternativer, som opfylder kriterierne for at være PBT stoffer (persistente, bioakkumulerbare eller toksiske i vandmiljøet) eller vPvB stoffer (meget persistente og meget bioakkumulerbare), selv om alle stofferne bortset fra GTA udviste én eller to af disse egenskaber. GTA (triacetin) synes at være let bionedbrydeligt, det bioakkumuleres ikke og det har en meget begrænset giftighed i vandmiljøet.

DEGD, DGD og DINA kommer også ud ganske gunstigt, hvorimod ATBC og COMGHA kommer negativt ud - på trods af deres nedbrydelighed - på grund af deres giftighed i vandmiljøet og bioakkumulerbarhed. Både ASE og DINCH har lav akut giftighed i vandmiljøet, men er ikke let nedbrydeligt og har en høj log K_{OW} værdi. DEHT nedbrydes heller ikke let og er bioakkumulerbart, men dets giftighed i vandmiljøet kan på basis af de tilgængelige data ikke blive fuldt ud vurderet.

Anvendelige data vedrørende bionedbrydelighed (enten som BCF eller log K_{OW}) er tilgængelige for alle alternativer, mens andre data vedrørende stoffernes skæbne i miljøet er mere ukomplette for nogle af stofferne. Med hensyn til

data vedrørende økotoksikologiske effekter findes der for alle stoffer resultater fra kort-tids tests med basis-sættet af organismer: fisk, krebsdyr, og alger. Varigheden af nogle af undersøgelserne afviger dog fra den nuværende OECD standard.

Alt i alt er de fundne data af god kvalitet, dvs. de er hovedsageligt baseret på undersøgelser, som er udført i overensstemmelse med accepterede guideline-procedurer og undersøgelserne er blevet evalueret til at være pålidelige med forbehold (f.eks. i USEPA "HPV robust summaries").

Abbreviations and acronyms

ASE	Sulfonic acids, C10 – C18-alkane, phenylesters
ASTM	American Society for Testing and Materials
ATBC	Acetyl tributyl citrate
BBP	Butyl benzyl phthalate
BCF	Bioconcentration factor
BOA	Benzyl octyl adipate
CEPE	European Council of producers and importers of paints, printing inks and artists' colours
COMGHA	Mixture of COMGHA 1 and COMGHA 2
COMGHA 1	12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester
COMGHA 2	Octadecanoic acid, 2,3-(bis(acetoxy)propyl ester.
CMR	Carcinogenic, mutagenic, reprotoxic
CSTEE	Scientific Committee on Toxicity, Ecotoxicity and the Environment
DBA	Dibutyl adipate
DBP	Di-n-butyl phthalate
DBT	Di-butyl terephthalate
DEGD	Diethylene glycol dibenzoate
DEHA	Bis(2-ethylhexyl) adipate
DEHP	Di(2-ethylhexyl) phthalate (also designates DOP)
DEHS	Dioctyl sebacate
DEHT	Di (2-ethyl-hexyl) terephthalate (same as DOTP)
DGD	Dipropylene glycol dibenzoate
DPHP	Di- (2-Propyl Heptyl) Phthalate
DiBA	Diisobutyl adipate
DIBP	Diisobutyl phthalate
DIDP	Diisodecyl phthalate
DINA	Diisononyl adipate
DINCH	Di-isononyl-cyclohexane-1,2dicarboxylate
DINP	Diisononyl phthalate
DNA	Deoxyribo Nucleic Acid
DNOP	Di-n-octyl phthalate
DOP	Di-octyl phthalate (same as DEHP)
DOTP	Di(2-ethylhexyl) terephthalate (same as DEHT)
DPHP	Di-(2-propyl heptyl) phthalate
DTDP	Ditridecyl Phthalate
ECHA	European Chemicals Agency
ECOSAR	Ecological Structure Activity Relationships
ECPI	European Council for Plasticisers and Intermediates
EPA	Environmental Protection Agency (here used for US EPA)
ESBO	Epoxidized soy bean oil
EU	European Union
GLP	Good Laboratory Practice
GTA	Glycerol Triacetate
HPV	High Production Volume
IC_{50}	Median Inhibitory Concentration. The concentration of a substance which reduces the effect by 50%

LC_{50}	Median Lethal Concentration. The concentration of a substance which causes the death of 50% of a group of test animals
LD_{50}	Median Lethal Dose 50. The dose of a substance which causes the death of 50% of a group of test animals
LG-flex BET	Hexanoic acid, 2-ethyl, mixed triesters with benzoic acid and trimethylopropane
LOAEL	Lowest Observed Adverse Effect Level
Log K_{ow}	The logarithm to the octanol/water partition coefficient
K_{oc}	Organic carbon normalised distribution coefficient
K_{ow}	Octanol/water partition coefficient
NPG-EHA-BA	2,2-Dimethyl-1,3-propanediol -benzoate 2-ethylhexanoate
OECD	Organisation for Economic Cooperation and Development
PA	Polyadipate
PBT	Persistent, bioaccumulative, toxic
PVA	Polyvinyl acetate
PVC	Polyvinyl chloride
P/vP	Persistent/very persistent
RAR	Risk Assessment Report
SCENIHR	EU Scientific Committee on Emerging and Newly Identified Health Risks
TBAC	Tert-butyl acetate
TBG-EHA-BA	Mixed triesters 1,1,1-trimethylol-propane-benzoate/2-ethylhexanoate
TEHTM	Tri-(2-ethylhexyl)-trimellitate (same as TOTM)
TGD	Triethylene glycol dibenzoate
ThOD	Theoritical Oxygen Demand
TOTM	Tris- (2-ethyhexyl) trimellitate (same as TEHTM)
TXIB	Trimethyl pentanyl diisobutyrate
UK	United Kingdom
USEPA	United States Environmental Protection Agency

1 Introduction

1.1 Data collection

Besides collection of information from the literature basic information has been collected from three major groups of data sources:

- **Manufacturers and suppliers of toys and childcare articles**
  In cooperation with the Nordic Association of Toy Manufacturers, manufacturers of toys and childcare articles in Denmark was identified and contacted by e-mail and telephone in order to collect information on applied plasticisers. This survey was supplemented with enquiries to major importers of toys in Denmark identified via the Internet and business databases.

- **Manufacturers of alternative plasticisers and materials**
  Manufacturers of alternative plasticisers and materials were indentified via the Internet and the literature. Information on technical properties and the substances' ability to substitute for the phthalates concerned, the price in comparison to the phthalates and the human and environmental properties were collected by direct queries to the manufacturers, by use of email or/and telephone interview.

- **Databases**
  A number of databases were consulted in order to collect information on physico-chemical properties and human health and environmental effects of selected substances. Data has been searched for in among others the European Chemical Substances Information System database (ESIS), OECD's e-ChemPortal, CHEM ID, IPCS InChem database, SRC Chemfate, HSDB, IRIS, CCRIS, TOXLINE, NTP – National Toxicology Program, Chemical Health & Safety Data, ECOTOX and RTECS.

Contacted companies and organisations are listed in Annex 1

2 Application of DEHP, DBP and BBP in products and articles

2.1 The phthalates

The term "phthalates" is here (and commonly) used for esters of ortho-phthalic acid and are the most commonly used plasticisers in the world.

The general structural formula of phthalates is shown in Figure 2.1. The functional groups (indicated as R) can either be linear aryl groups or alkyl groups with an aromatic ring. The properties of the phthalates are determined by the functional groups.

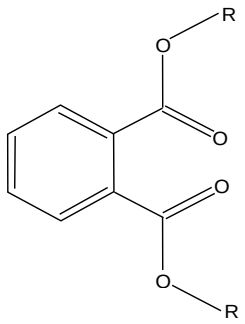


Figure 2.1
General structural formula of ortho-phthalates. R can be linear alkyl groups or aryl groups with an aromatic ring.

Examples of two of the phthalates are shown below, DEHP with symmetric linear functional groups and BBP with asymmetric aryl and alkyl functional groups.

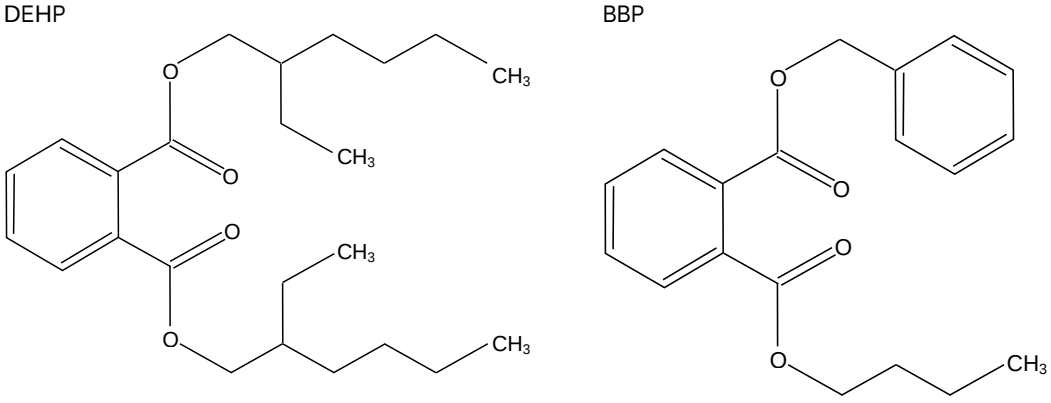


Figure 2.2
Examples of structural formula of phthalates

The softening effects of the phthalates decrease with increasing length of the functional groups (Hoffmann, 1996): DBP > BBP > DEHP > DINP > DIDP > DTDP. Consequently higher loading are necessary to obtain a certain level of softness for the phthalates with longer functional groups.

One property of importance for the application of the phthalates concerned in this study is the gelling ability of the plasticiser i.e. the ability of the plasticiser

to mix with the resin by processing. The ability decrease in the following order: BBP > DBP > DIHP > DEHP > DINP > DIDP > DTDP (Hoffman, 1996).

The most common phthalates are di-isononyl phthalate (DINP); di-isodecyl phthalate (DIDP); and di-2-ethyl hexyl phthalate (DEHP).

Phthalates are widely used as general-purpose plasticisers because they offer the advantage of lower costs and increased production efficiency. When added to plastics, phthalates allow the long polyvinyl molecules to slide against one another. The phthalates show low water solubility, high oil solubility, and low volatility.

This is achieved through improved melt viscosity and production speeds of heated PVC with phthalates added. Increased flow characteristics give better workability and reduced out-of service breaks in equipment.

Table 2.1
Classification of and use restrictions on phthalates included in this study

Chemical name	Abb.	CAS No	Classification cf. 1272/2008 (GHS)	Use restrictions
Di(2-ethylhexyl) phthalate	DEHP, DOP	117-81-7	Repr. 1B (Repr. Cat. 2; R60-61)	Shall not be used as substances or as constituents of preparations, at concentrations of greater than 0,1% by mass of the plasticised material, in toys and child-care articles (Regulation No 552/2009) Not permitted for use in cosmetics (Directive 2004/93/EC)
Di-n-butyl phthalate	DBP	84-74-2	Repr. 1B Aquatic Acute 1 (Repr. Cat. 2;R61 Repr. Cat. 3; R62 N; R50)	
Butyl benzyl phthalate	BBP	85-68-7	Repr. 1B Aquatic Acute 1 Aquatic Chronic 1 (Repr. Cat. 2; R61 Repr. Cat. 3; R62 N; R50-53)	
Diisononyl phthalate	DINP	28553-12-0 68515-48-0	No harmonised classification	Shall not be used as substances or as constituents of preparations, at concentrations of greater than 0,1% by mass of the plasticised material, in toys and child-care articles which can be placed in the mouth by children (Regulation No 552/2009)
Diisodecyl phthalate	DIDP	26761-40-0 271-091-4	No harmonised classification	
Di-n-octyl phthalate	DNOP	117-84-0	No harmonised classification	
Diisobutyl phthalate	DIBP	84-69-5	Repr. 1B (Repr. Cat. 2; R61 Repr. Cat. 3; R62)	Not permitted for use in cosmetics (Directive 2004/93/EC)

Table 2.2
Summary on application and technical properties of concerned phthalates

Chemical name	Abb.	Use and technical properties
Di(2-ethylhexyl) phthalate	DEHP	Offers a good all-round performance and is therefore used for a great many cost-effective, general purpose products including building material such as flooring, cables, profiles and roofs, as well as medical products such as blood bags and dialysis equipment The content of DEHP in flexible polymer materials varies, but is often around 30% (w/w).
Di-n-butyl phthalate	DBP	Is a specialist plasticiser often used in combination with other high molecular weight phthalates. It is a fast fusing plasticiser which by itself it is too volatile for PVC applications. It is frequently used as a gelling aid in combination with other plasticisers. DBP is used extensively in the adhesives industry to plasticise polyvinyl acetate (PVA) emulsions and used solvent for many oil-soluble dyes, insecticides, peroxides and other organic compounds. It is used as an antifoam agent and as a fibre lubricant in textile manufacturing.
Butyl benzyl phthalate	BBP	Butyl benzyl phthalate is an unusual plasticiser because of its chemical asymmetry which results in unique performance properties. One of the manufacturing benefits of using BBP is that it allows PVC transformers to operate with less energy input than with many similar plasticisers. It is used widely by the flooring industry because it adds surface properties to flooring materials that minimise maintenance and give it a prolonged life. More than 90% of BBP is used for plasticising PVC or other polymers. Butyl benzyl phthalate is also used in seals for insulating double glazing
Diisononyl phthalate	DINP	General, all-purpose plasticiser. Wide range of indoor and outdoor applications. 95 per cent of DINP is used as a plasticiser for flexible PVC used for construction and industrial applications, and durable goods (wire and cable, film and sheet, flooring, industrial hoses and tubing, footwear, toys, food contact plastics). Heat resistance, low temperature resistance and volatility resistance are some of its main properties that make it suitable for a wide range of applications (ECPI, 2009)
Diisodecyl phthalate	DIDP	Diisodecyl phthalate (DIDP) is a common phthalate plasticiser, used primarily to soften Polyvinyl chloride (PVC). The typical content of DIDP in flexible PVC products is between 25 and 50% (w/w). It has properties of volatility resistance, heat stability and electric insulation and is typically used as a plasticiser for heat-resistant electrical cords, leather for car interiors, and PVC flooring (ECPI, 2009).
Di-n-octyl phthalate	DNOP	The principal use of DNOP is as a plasticiser in the production of PVC resins and other polymers, such as cellulose esters and polystyrene resins, as a dye carrier in plastic production (primarily PVC), and as a chemical intermediate in the manufacture of adhesives, plastisols, and nitrocellulose lacquer coatings (ATSDR, 2005) DNOP may represent 5 to 60% of the total weight of the plastics and resins (ATSDR, 2005) No actual confirmation of the use of DNOP in the EU today has been identified
Diisobutyl phthalate	DIBP	Diisobutyl phthalate (DIBP) is a specialist plasticiser often used in combination with other high molecular weight phthalates. It is a fast fusing plasticiser which by itself it is too volatile for PVC applications. It is frequently used as a gelling aid in combination with other plasticisers. A plasticiser for nitrocellulose, cellulose ether, and polyacrylate and polyacetate dispersions. Has very similar application properties to DBP and may therefore be used to substitute for DBP in most, if not all, of its applications.

The main alternatives to DEHP have been the two phthalates di-isononyl phthalate (DINP) and di-isodecyl phthalate (DIDP). As illustrated in Figure 2.3 in Sweden the shift from DEHP to first of all DINP took mainly place in the period 1999 to 2002.

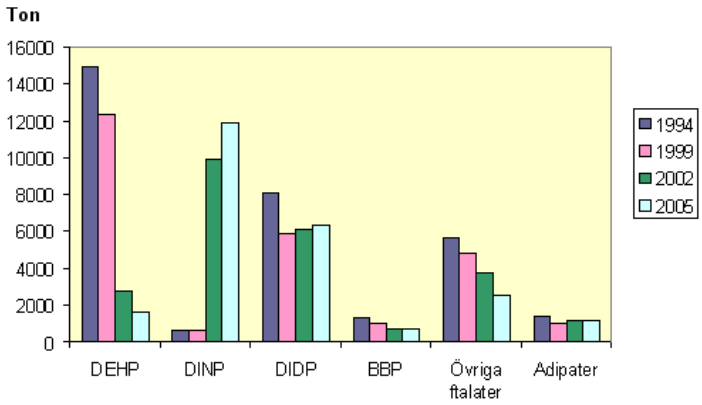


Figure 2.3
Use of plasticisers for PVC in Sweden. Kemi (2008) quoting the Swedish Productregister as source. 2005 figures are indicated as "preliminary". "Övrige ftaalter" = "Other phthalates", "Adipater" = "Adipates".

The evolution in the EU use of plasticisers shows that the consumption of DEHP deceased from 1999 to 2005 from 42% of the market to 21% (Figure 2.4). The DEHP was replaced by DINP/DIDP, while the non-phthalate plasticisers remained a market share of around 7-8%.

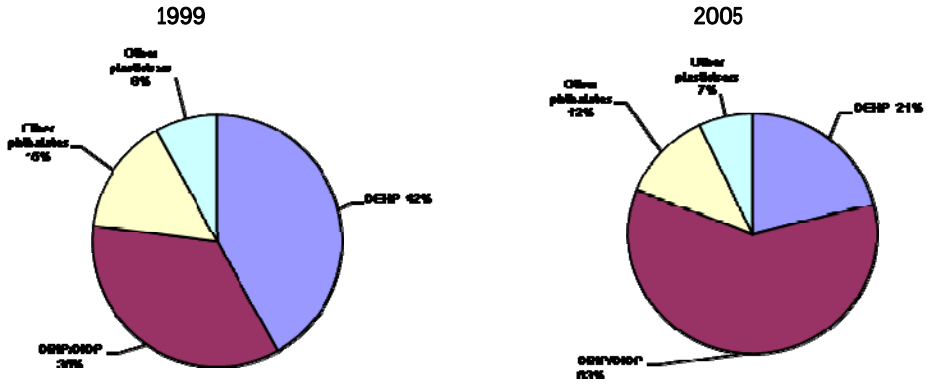


Figure 2.4
Evolution of PVC plasticisers' sales between 1999 and 2005 (based on Cadogan, 2006)

Technical key parameters of some ortho-phthalates

For comparison with other plasticisers described in this report, some technical key parameters for selected phthalates are shown in Table 2.3. Note that for these related substances, the larger the molecule, the lower is the volatility, the extractability and the softness (efficiency), whereas the gelling temperature increases with higher molecule weight.

Table 2.3
Technical key parameters of selected phthalate plasticisers' performance in PVC (from Wilson, 1995, citing BP Chemicals)

Plasticiser in PVC, conc. phr 50, except for plastisol viscosity *1	Gelling temperature, °C	Shore A hardness*2	Elongation at break,%	Volatility (loss on heating),%	Extracted in mineral oil, g/m^2	Extracted in 1% soap in water, g/m^2	Plastisol viscosity, at phr 60, after 1 day, Pa s
DBP	72	75	285	8.6	16	25	11.8
BBP	88	76	290	1.6	10	27	65.0
DEHP	109	80	325	0.8	10	19	6.9
DINP	118	84	325	0.5	7	12	6.9
DIDP	112	86	320	0.4	10	9	8.0

Notes: *1: phr = parts per hard resin, meaning parts per weight of hard PVC. *2: A measure for the plasticiser's efficiency in making PVC flexible; the lower the number, the softer the PVC and the more efficient plasticiser.

2.2 Application of DEHP

The following information is, if nothing else is mentioned, extracted from an assessment of the manufacturing and use of di(2-ethylhexyl) phthalate (DEHP) recently published by the European Chemicals Agency (COWI, 2009a).

DEHP is widely used as a plasticiser in polymer products, mainly PVC. It offers a good all-round performance and is therefore used for a many general purpose products. The content of DEHP in flexible polymer materials varies, but is often around 30% (w/w).

The main end-product uses of DEHP are as follows:

- Flooring:
  - PVC flooring (with PVC surface);
  - Carpets with PVC back-coating;
  - Cork with PVC top-coating or back-coating ;
- Wall covering;
- Roofing;
- Film/sheet and coated products:
  - Curtains, blinds, table linen, etc.;
  - Packaging;
  - Tape and self-adhesive foils;
  - Office supplies (ring binders, files, slip cases, etc.);
  - Medical bag/sheet devices;
  - Bottom sheets for hospitals.
- Wires and cables;
- Hoses and profiles;
  - Garden hoses and tubes;
  - Hoses and tubes in industry;
  - Profiles of windows and electrical products;
  - Medical tubing.

- Coated fabric;
  - Upholstery and car seats (synthetic leather);
  - Luggage;
  - Rainwear;
  - Tarpaulins;
  - Water beds.

- Moulded product;
  - Footwear;
  - Adult toys; (DEHP is not permitted in toys for children)

- Car undercoating;

Non-polymer applications:

- Adhesives;

- Lacquers and paints;

- Printing inks (see comment below);

- Sealants (glass insulation, construction);

- Ceramics.

The main part of DEHP is added to PVC in different formulation and processing steps including calendering, extrusion, spread coating, and moulding.

At EU level in total 341,000 tonnes was produced in 2007. A part of this was exported and around 291,000 tonnes DEHP was used for manufacturing processes in the EU in 2007. DEHP accounted for around 18% of all plasticiser usage in Western Europe (data for the entire EU plasticiser use is not available). The consumption of DEHP has decreased markedly the last decade. Of the 341,000 tonnes produced in the EU in 2007, 187,000 tonnes were produced in Western Europe corresponding to 31% of the 1997 level of 595,000 t/y. In the early 1990s, DEHP represented about 51% of the total phthalate plasticiser market in Western Europe.

Investigations of the historic use of phthalates in Denmark in different products shows that DEHP represented a major part of the phthalate use in the 1990's and was to a large extent replaced by DINP around 2000. Today DEHP seems to have been replaced by DINP or non-phthalate plasticisers in Danish produced PVC products (Christensen ***et al.***, 2007; Brandt ***et al.***, 2009).

Quantitative information is available on the approximate split between the different processes. In combination with information on which products are produced by different processes it is possible to indicate the main and uses of DEHP as illustrated in Figure 2.5.

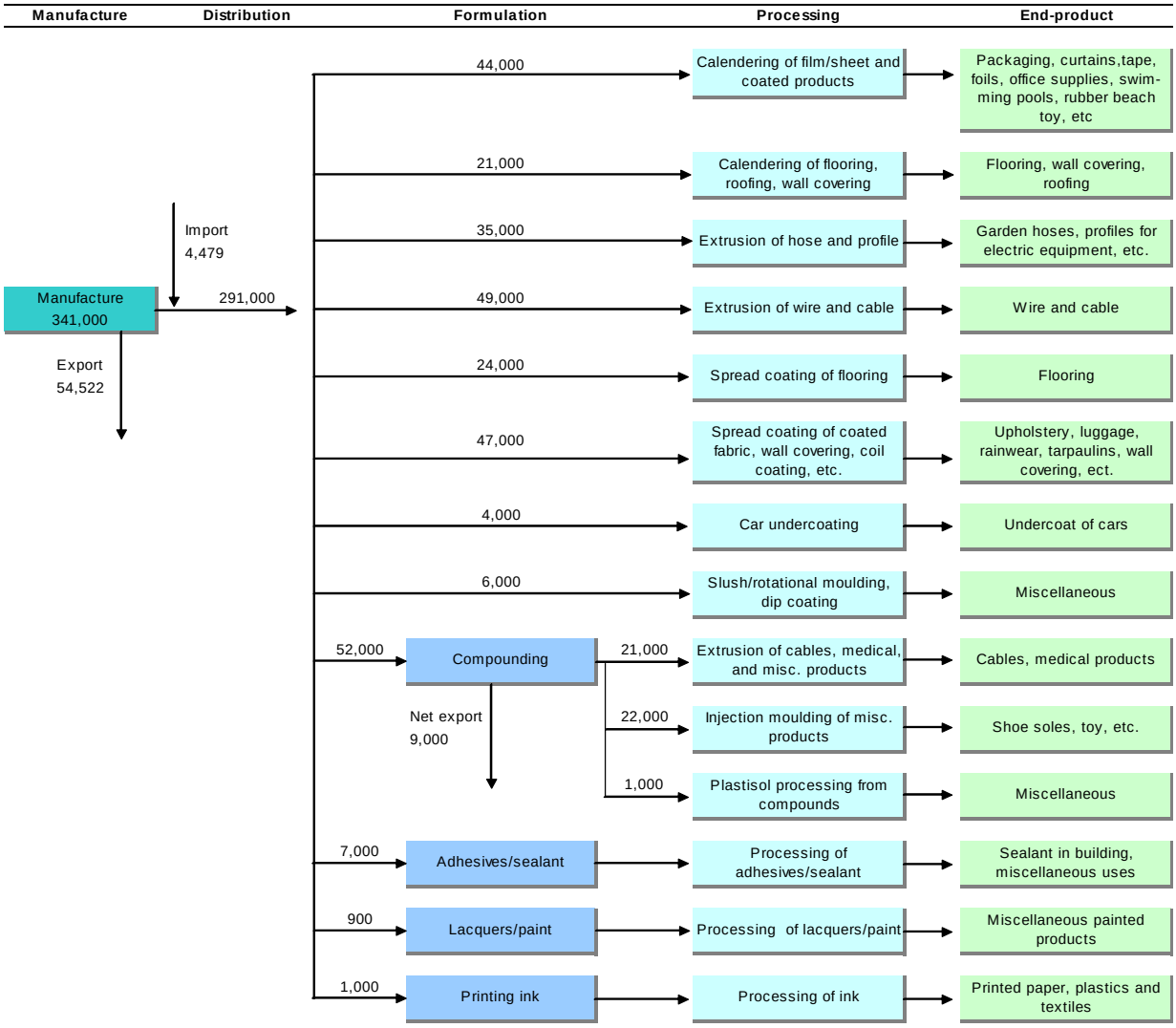


Figure 2.5
Overall flow of DEHP through manufacturing processes in 2007. For processing steps without prior formulation step, the formulation and processing are integrated in one step. All figures in tonnes DEHP/year. (COWI, 2009a)

DEHP is to some extent imported and exported with finished products. Table 2.4 shows the estimated extra-EU import and export for some of the main product groups, for which information can be estimated on the basis of the trade statistics (please see COWI, 2009a for details regarding the calculation method). For most product groups the net import is relatively small compared to the production within the EU, and the end-use distribution follows in broad outline the distribution of EU production.

Table 2.4
Estimated DEHP tonnage in end-products marketed in the EU based on EU manufacture and EU-extra import and export data (based on COWI, 2009a)

End-product use area	Tonnage, t/y				% of total use
	EU Manufac-ture	Import	Export	End-product use	
Polymeric applications:					
Flooring	33,000	2,000	4,800	30,200	10.6
Wall covering	11,000	700	1,600	10,100	3.5
Roofing material	3,600	n.d.	n.d.	3,600	1.3
Film/sheet and coated products made by calendering	44,000	13,600	16,400	41,200	14.5
Wires and cables	64,100	6,200	5,600	64,700	22.3
Hoses and profiles	34,700	1,600	3,000	33,300	12.7
Coated fabric and other products from plastisol	43,800	2,200	1,400	44,600	15.1
Shoe soles	19,400	n.d.	n.d.	19,400	6.8
Other moulded products	3,000	2,700	700	5,000	1.8
Car undercoating	4000	n.d.	n.d.	4000	1.4
Other polymer applications	12,300	10,900	3,100	20,100	7.1
Non polymer applications:					0.0
Adhesives and sealant	4,000	n.d.	n.d.	4,000	1.4
Lacquers and paints	900	n.d.	n.d.	900	0.3
Adhesives and sealant	3300	n.d.	n.d.	3300	1.2
Printing ink	1,000	n.d.	n.d.	1,000	0.4
Other non-polymeric	20	n.d.	n.d.	20	0.0
Total end-product use (round)	282,000	40,000	37,000	285,000	100

2.3 Application of DBP

The following information is, if nothing else is mentioned, extracted from an assessment of the manufacturing and use of dibutyl phthalate (DBP) recently published by European Chemicals Agency (COWI, 2009b).

DBP is a specialist, fast fusing plasticiser. By itself it is too volatile for PVC applications and it is used in PVC as a gelling aid in combination with other high molecular weight plasticisers. The gelling agent is the agent which reacts fastest with the PVC.

The total manufactured tonnage in 2007 in the EU is confidential, but it was less than 10,000 tonnes. A significant part of the manufactured tonnage is exported to countries outside the EU. DBP seems to represent less than 1% of the production of phthalates in Europe. As DBP is used in relatively small concentrations it may however be present in higher share of products. Dutch surveys of phthalates and other plasticisers in toys and childcare products demonstrate that 30% of 24 analysed products in 2004 contained DBP (FCPSA, 2008a). The share had decreased to 13% of the products in 2007 and 1% in 2008 (FCPSA, 2008b).

The market for DBP has been decreasing over recent decades: In 1994 the production volume of DBP in the EU was 49,000 tonnes and in 1998 it was 26,000 tonnes, with an export of 8,000 tonnes.

Current uses of DBP, according to actual information obtained from industry or product registers, are listed below:

- Gelling aid in combination with other plasticisers in plastics. In general, limited information is available on the actual uses of DBP in polymers. DBP is used in PVC (manufacturer information). It has not been possible to obtain very specific information on the uses, but the following applications are mentioned by different sources: floor coverings, automotive uses (manufacturer information) and garden hoses. The European Plastic Converters (EuPC), has in a survey by their members not indentified any use of DBP, and assume that DBP today is used by relatively few companies for different niche purposes. The results of the Dutch surveys show that DBP was formerly used at a relatively high frequency in many different types of toys (FCPSA, 2008a).

- Rubbers (manufacturer information). The Risk Assessment for DBP (ECB, 2004) specifies that DBP is used in some polychloroprene rubber and nitrile rubber, but not in all polychloroprene (neoprene) or nitrile rubbers. New information on actual uses is not available.

- DBP is used extensively in the adhesives industry to plasticise polyvinyl acetate (PVA) emulsions. The low viscosity and compatibility of DBP make it suited for PVA-based adhesives for bonding cellulosic materials. According to the Risk Assessment for DBP (ECB, 2004) the most important uses of the adhesives are for paper and packaging, wood building and automobile industry.

- Epoxy resins. Probably same application that in the Risk Assessment for DBP (ECB, 2004) is mentioned as "solvent in the production of fiber glass". More specific information on this application has not been available.

- In the coatings industry as a primary plasticiser-solvent for nitrocellulose lacquers.

- Grouting agents, used to reduce water leakages in tunnels, sewer systems, buildings etc. DBP contents as high as 30-60% were found in polyurethane foams used in grouting applications for water control in tunnels, sewer systems, buildings etc. No actual confirmation of this application has been obtained.

- Other applications:

    - Solvent for many oil-soluble dyes, insecticides, peroxides and other organic compounds;
    - Antifoam agent and as a fibre lubricant in textile manufacturing;
    - Used in compounding flavours;
    - Printing inks, polishing agents, corrosion inhibitor materials;
    - Use in PP (polypropylene) catalytic systems;
    - One application described in the confidential part of the ECHA report.

According to CEPE (European Council of producers and importers of paints, printing inks and artists' colours), DEHP, BBP and DBP are no longer used

in printing inks by CEPE/EuPIA (European Printing Ink Association) members following its classification as reprotoxic.

The flow chart below illustrates the "best estimate scenario" for the flow of DBP through the different process and the resulting end-products. It was for the ECHA report (COWI, 2009b) not possible to obtain comprehensive quantitative updated information on the use of DBP for the different uses from manufacturers and suppliers and the available information did not allow real estimates of the distribution between the different use areas to be made. It is, however, deemed that the distribution between applications most likely is different from the 1997 distribution used in the RAR, but the updated distribution is highly uncertain. The figures are for confidentiality reasons rounded and somewhat higher than the actual figures.

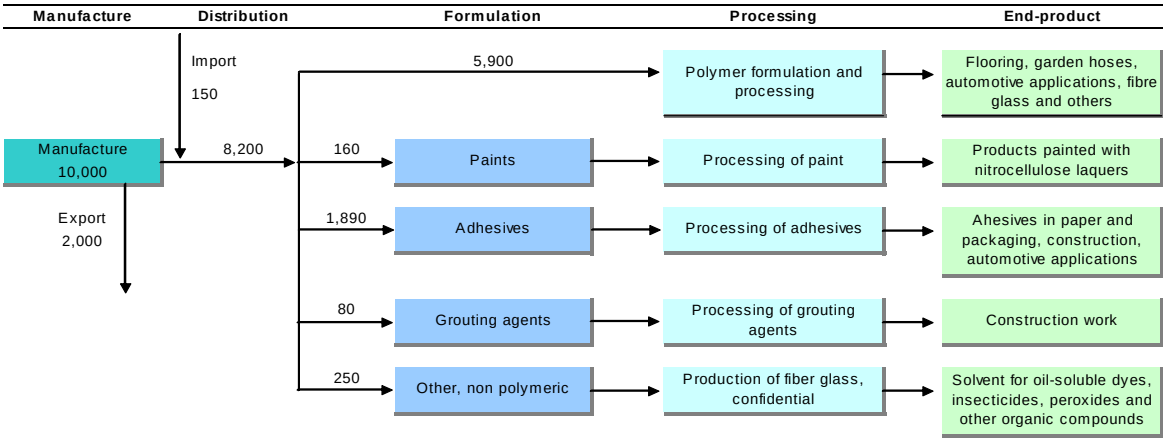


Figure 2.6
"Best estimate scenario" of the overall flow of DBP through manufacturing processes. Tonnes DBP/year. Figures are rounded and higher than actual figures. (COWI, 2009b)

DBP may be exported and imported in preparations and articles, but no statistical information allowing an estimate of this import/export is available.

Use in Denmark

No detailed assessment of the use of DBP in Denmark exists. The use of DBP in chemical products (preparations) registered in the Danish product register is shown in Table 2.5. The total consumption of DBP in declared preparations has decreased from 320 tonnes/year in 2000 to 71 tonnes/year in 2004. In the period from 2004 to 2006 the registered consumption was stable at a level of 70-80 tonnes. The main use category was paint, lacquers and varnishes and in total 56 different products within this use category in was registered in 2006. Other preparations representing significant uses of DBP were binding agents (may be used as synonymous for adhesives) and corrosion inhibitors/under seal materials.

The declaration of the substances to the product register is mandatory for preparations containing one or more substances listed in Annex 1 of Directive 67/548/EEC (now the Annex VI to Regulation 1272/2008). All preparations containing DBP should consequently be declared. However, there is no systematic updating of quantities of products. The companies are obliged to send in any new information regarding their products whenever changes occur. If companies fail to fulfil their obligations, a result might be that products that have been discontinued still remain on the lists. The relatively high consumption of DBP in paint, lacquers and varnishes may reflect that DBP is used for production of some specific paints by Danish paint manufacturers.

The data shows a steep decrease i the use of DBP in "flooring materials", "casting materials", " printing inks", "adhesives" and "other".

Table 2.5
Uses of DBP registered in the Danish product register (SPIN, 2009)

Product group	Registered consumption, tonnes DBP/year						
	2006	2005	2004	2003	2002	2001	2000
Paint, lacquers and varnishes	64.7	69.4	67.0	29.0	27.8	27.9	63.4
Binding agents	9.1	1.4	0.8	21.1	13.3	21.4	21.7
Filling materials	0.2	0.2	0.2	2.7	51.1	49.1	50.2
Hardeners, curing agents	1.7	2.0	2.0	5.9	9.8	10.3	28.6
Flooring materials (joint-less floors)	0.0	0.1	0.1	18.3	18.9	19.0	19.0
Corrosion inhibitors, anticorrosive paints, underseal materials, incl. cavity seals	3.9	0.1	0.1	0.2	0.3	0.3	0.7
Casting materials	0.5	0.1	0.1	3.3	4.2	4.3	6.1
Surface treatment for non-metals	0.0	0.1	0.1	1.7	1.7	1.7	1.7
Polishing agents	0.2	0.2	0.2	0.6	0.0	0.0	1.2
Printing inks	0.7	0.9	0.1	0.7	0.3	0.3	102.0
Adhesives	0.0	0.0	0.0	4.4	0.2	0.2	16.8
Other	0.0	0.0	0.0	8.7	22.4	29.5	8.7
Total	81	75	71	97	150	164	320

2.4 Application of BBP

The following information is, if nothing else is mentioned, extracted from an assessment of the manufacturing and use of butyl benzyl phthalate (BBP) recently published by European Chemicals Agency (COWI, 2009c).

The total manufactured tonnage in 2007 in the EU was below 18,000 tonnes. A significant part of the manufactured tonnage is exported to countries outside the EU. BBP seems to represent less than 1% of the production. The market for BBP has been decreasing over the last decade. In the period 1994-1997, the total reported Western European manufacture of BBP was 45,000 tonnes/year whereas for 2004 a production volume of 19,500 tonnes/year was reported.

More than 70% of the BBP was in 2007 used as a plasticiser in polymer products, mainly PVC for flooring. BBP is, according to industry, an unusual plasticiser because of its chemical asymmetry which results in unique performance properties.

BBP is typically used together with other plasticisers e.g. DEHP or DINP. It has not been possible to identify information on typical concentration of BBP in the final materials, but examples of formulations indicate that the concentration may be in the range of 5-20%. As an example Eastman (2001) compares two different BBP/DINP plastisol formulations with other formulation. One of the formulations has 12 parts BBP and 28 parts DINP (together with other additives) to 100 parts PVC whereas the other has 24 parts BBP and 56 parts DINP to 100 parts PVC.

BBP is used widely by the flooring industry because it speeds up production and adds surface properties to flooring materials that minimise maintenance and give it a prolonged life.

The end-product uses of BBP are as follows:

- Flooring (both calendered and spread coated flooring);
- Wall covering;
- Coating of leather and textiles (upholstery, shoe uppers, wallets/bags, luggage);
- Packaging films;
- Sealants (polysulphide based, polyurethane based or acrylic-based) for insulating double glazing and other applications;
- Paints for car care and construction (acrylic lacquers and other);
- Inks for paper and board;
- Adhesives (polyvinyl acetate and other);
- Miscellaneous (hard PVC, nitrile rubber and other).

The main part of BBP is added to PVC in different formulation and processing steps including calendering and plastisol spread coating. The following flow diagram illustrates the relationship between the different processes and the end-product uses. The major application area is flooring accounting for about 50% of the total while the second larges application area, polysulphide sealants account for about 19% of the total.

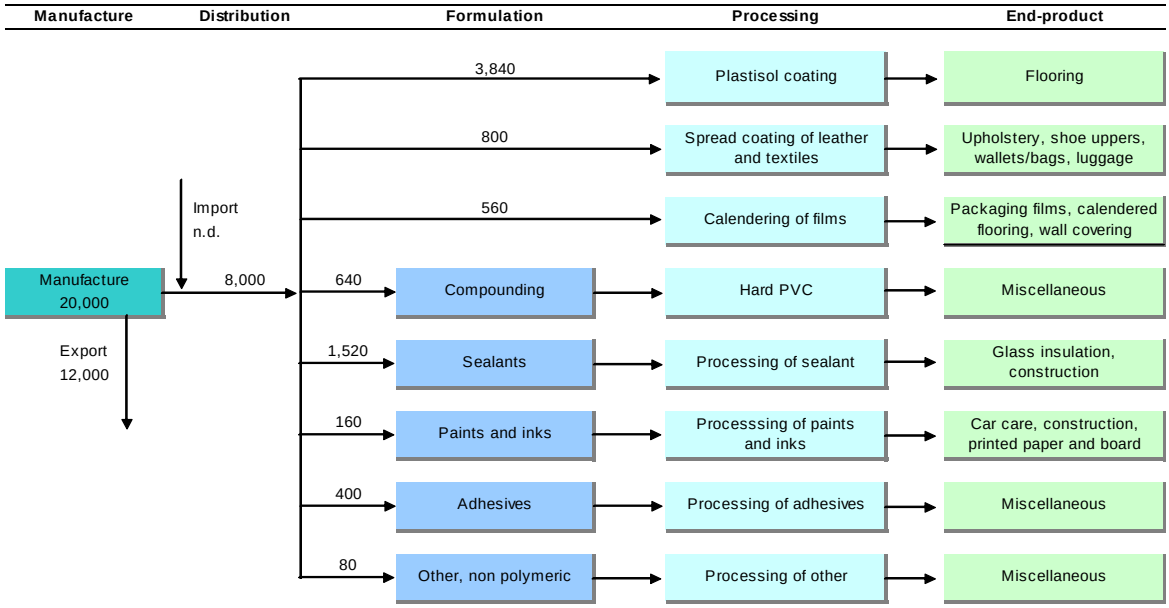


Figure 2.7
Overall flow of BBP through manufacturing processes in 2007. Tonnes BBP/year (COWI, 2009c)

BBP may be exported and imported in preparations and articles, but no statistical information allowing an estimate of this import/export is available.

Use in Denmark

No detailed assessment of the use of DBP in Denmark exists. The use of

DBP in chemical products (preparations) registered in the Danish product register is shown in Table 2.6. The total consumption of DBP in declared preparations has decreased from 233 tonnes/year in 2000 to 75 tonnes/year in 2004. In the period from 2004 to 2006 the registered consumption was fairly stable at a level of 60-75 tonnes.

The main use categories were filling materials (may be used synonymous with sealants), paint, lacquers and varnishes and adhesives. The increase in the use of DBP from a level below 1 tonnes/year in 2000-2005 to 11 tonnes in 2006 may be due to an error in the registration.

The declaration of the substances to the product register is mandatory for preparations containing one or more substances listed in Annex I to Directive 67/548/EEC (now Annex VI to Regulation 1272/2008) . All preparations containing BBP should consequently be declared. However, there is no systematic updating of quantities of products. The companies are obliged to send in any new information regarding their products whenever changes occur. If companies fail to fulfil their obligations, a result might be that products that have been discontinued still remain on the lists. This may explain the relatively high registered consumption of DBP in preparations in Denmark compared to the EU consumption for non-polymeric applications as shown in Table 2.5.

Table 2.6
Consumption of BBP registered in the Danish product register (SPIN, 2009)

Product group	Registered consumption, tonnes BBP/year						
	2006	2005	2004	2003	2002	2001	2000
Filling materials	47.8	46.7	46.7	65.0	19.2	8.4	79.3
Paint, lacquers and varnishes	14.9	8.7	25.5	18.4	9.3	14.2	45.8
Adhesives	10.9	0.1	0.2	0.5	0.1	0.1	0.3
Casting materials	0.2	2.7	2.7	0.0	7.0	7.0	0.0
Binding agents - for binding together the individual constituents in the product	0.4	0.0	0.0	1.1	2.9	2.9	3.9
Padding materials	0.0	0.0	0.0	0.0	40.1	40.1	0.0
Tightening materials (putty)	0.0	0.0	0.0	0.0	28.5	28.6	0.0
Other and unknown function	0.3	0.3	0.3	0.5	164.8	110.9	103.3
Total	75	59	75	86	272	212	233

3 Identified alternatives to DEHP, DBP and BBP

Information on alternatives to DEHP, DBP and BBP, actually applied today, has been collected from the following data sources:

- Danish manufacturers and importers of toys and childcare articles;
- Surveys of plasticisers in marketed toys and childcare articles;
- Direct contact to major suppliers of plasticisers.

These data sources have been supplemented with information from the literature and manufacturers' web sites.

The first section gives a general introduction to the way plasticisers work and to the different available plasticiser substance families, followed by a description of information collected directly from the above mentioned data sources.

3.1 Functional mode of external plasticisers

To get an impression of the many possibilities for plasticising polymers, we give an introduction to the basic functions of plasticisers, the variability in these functions, and which properties govern the functions. The description is used as basis for the later discussion of the technical feasibility of replacing phthalate plasticisers with alternatives.

We describe here the basics of external plasticisation of PVC, the major use of plasticisers. The word "external" denotes plasticisers that are not bound chemically in the polymer matrix, and can therefore migrate out of the polymer at certain conditions. Polymers can also be plasticised "internally" by incorporation of functional groups into the polymer itself, which imparts flexibility. Phthalates are external plasticisers, as are their direct substitutes, and external plasticisation is described in this section.

PVC consists of long chains of the basic vinyl building block. The polymer is bound together in three dimensions by two overall types of forces. In some points the polymer is crystallised into a fixed geometric pattern with strong chemical bonds. In the rest of the polymer matrix, the polymer chains are somewhat more randomly organised and bound together by weaker forces based on attraction between polar parts of the polymer chain with different polarity. The ideal plasticiser works in these less strictly organised parts of the polymer.

In the hard polymer, the chains are packed closely together, also in the randomly organised parts, and the weak attraction forces bind the polymer together to a rigid structure with no flexibility. The (external) plasticiser has solvent capabilities and penetrates the less strongly bound parts of the polymer in the so-called swelling, where plasticiser and polymer resin is mixed. In the polymer, the plasticiser acts as a kind of sophisticated lubricant, as it cre-

ates distance between the freely organised polymer chain parts, and shields the attraction forces between polar parts of the chain, and thereby weakens the attraction between the chain parts. This allows for more free movement amongst the weakly bound chain parts, which means that the material becomes flexible.

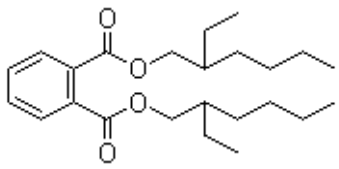
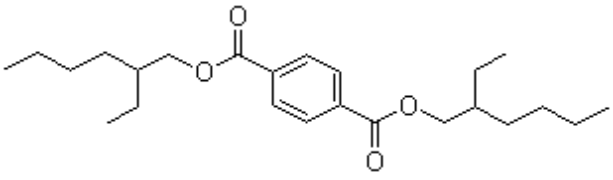
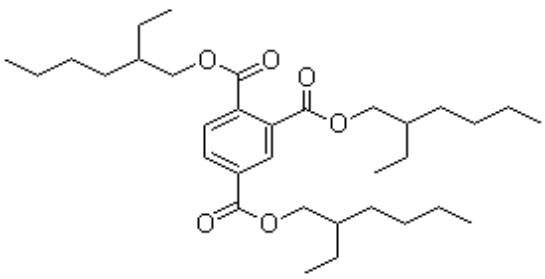
The properties of the plasticiser have immense influence of how well it plasticises the polymer, and on the performance characteristics of the plasticised material. It is however important to understand that the plasticiser (with a few exceptions) does not form specific chemical bonds with the polymer, and there is therefore in principle a flexibility in which type and configuration of plasticisers that actually can be used to obtain the desired plasticising performance characteristics.

External plasticisers may be separated from the PVC matrix due to extraction by solvents, oils, water, surface rubbing, volatility, migration into adjacent media, or degradation mechanisms.

Structure of some plasticiser families

As mentioned, many families of plasticisers are available. Most of them have however certain chemical functionalities in common with the phthalates family. This can be seen in Figure 3.1, which shows representatives of some different plasticiser families. They are typically branched, quite "voluminous" molecules, with many oxygen bonds (= carbonyl groups). Many have benzyl rings or the hydrogenated counterpart, cyclohexane.

Even so, many similar plasticisers have distinctly different impacts on health and environment, and are therefore relevant alternatives to phthalates. This is probably primarily due to the fact that many types of interactions with biological systems are substance specific, and even shape-specific (structurally specific), meaning that substances with identical chemical composition may work differently, if just a part of the molecule has shifted position from one place to another.

Phthalate (DEHP, DOP; di 2-ethylhexylphthalat)	
Terephthalate, (DEHT, DOT DOTP; di 2-ethylhexyl terephthalate)	
Trimellitates (TOTM; tri (2-ethylhexyl) trimellitate)	

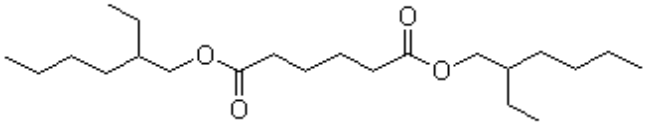
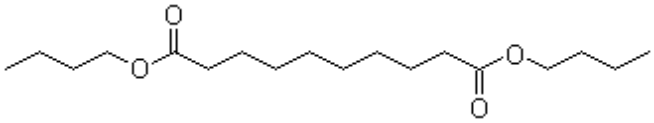
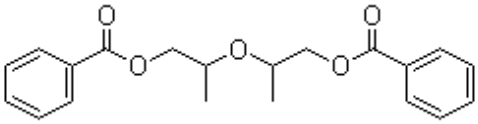
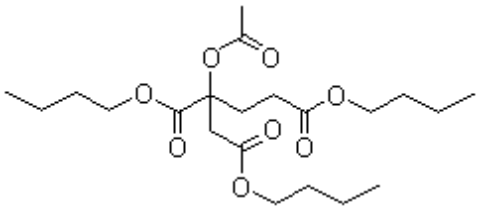
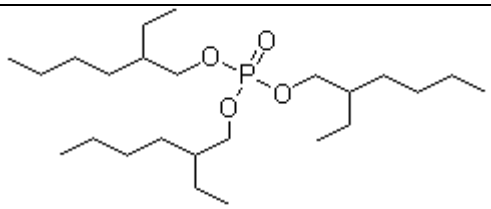
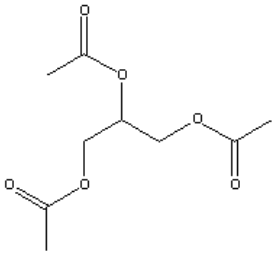
Aliphatic dibasic esters, adipates (DEHA, DOA = di (2-ethylhexyl) adipate)	
(DBS = Dibutyl sebacate)	
Benzoates (DGD; dipro-pylene glycol dibenzoate)	
Citrates (ATBC; acetyl tributyl citrate)	
Phosphates (tri(2-ethylhexyl) phosphate)	
Glyceryl triacetate (GTA, Triacetin)	

Figure 3.1
Structural diagrams of different plasticiser (Source: www.chemblink.com)

The substance family of the plasticiser influences its performance significantly, but some functional groups in the molecules also influence the performance across families, and plasticisers can thus to a certain extend be tailor-made to suit different performance needs. In addition, plasticisers can be mixed to achieve desired properties. Some of the important performance parameters of plasticisers are shown in Table 3.1 with some general chemical features influencing a plasticiser's performance for each parameter. All these parameters influence the performance of a plasticiser, and they are not independent, because one change in the plasticiser molecule may affect most or all of the parameters. Finding the good plasticiser is therefore not a distinct theoretical science, but rather an empiric process supported by a large number of measuring methods designed for this purpose.

Table 3.1
Selected parameters used to characterise plasticisers, and examples of decisive factors influencing these parameters (primarily based on Krauskopf and Godwin, 2005)

Parameter	Plasticiser characteristics influencing parameter
Solvency in polymer resin (also called compatibility or miscibility)	The good plasticiser for PVC has, within its molecule, a suitable mix of polar and apolar functional groups. Oxygen (carbonyl groups) and aromatic rings impart higher solvency. Plain hydrocarbon chain parts add apolarity, and thus lower solvency. Good solubility is required for a plasticiser, but too high solubility dissolves the crystalline parts of the polymer and thereby breaks the polymer apart. Lower molecular weight phthalates such as BBP, and other high aromaticity substances such as benzoate esters and tri(cresyl) phosphate, or more polar structures such as sulfonates, are examples of high solvency plasticisers.
Efficiency (defined as flexibility in polymer compared to DEHP)	Branched hydrocarbon chains in the plasticiser increase flexibility amongst the polymer chains, and thus the overall flexibility of the resulting material. Too many hydrocarbon branches decrease solubility and resistance to hydrolysis (degradation in contact with water).
Volatility	Smaller, lower weight molecules tend to have higher volatility than larger, heavier molecules. For example DBP is deemed to be too volatile for many polymer applications, while a large molecule like ditridecyl phthalate has low volatility and can therefore be used in polymers exposed to elevated temperatures. Large molecules like trimellitates and polyesters have typically even lower volatility. In some cases high volatility is desired. BBP is an example of as plasticiser which can contribute to volatile fuming during processing and volatilization in end use applications, and thus give a hardened, stain resistant surface, due to volatilization. The same is the case for certain benzoates. Volatile losses of plasticiser are influenced by vapour pressure, solvency strength for the polymer and oxidative degradation.
Diffusivity	Movements of the plasticisers within the polymer matrix are ruled by diffusion. Low diffusivity is contributed by high molecular weight and highly branched isomeric structures. For example, DIDP and the polyester family impart improved resistance to diffusion-controlled plasticiser losses. Plasticiser losses due to extraction by oily media (in which plasticisers are highly soluble) are controlled by diffusivity rates.
Low temperature performance	Higher share of linear hydrocarbons (versus branched hydrocarbons) in the plasticiser increase flexibility at low temperatures. The entire family of aliphatic dibasic esters contributes exceptional low temperature properties. Di-2-ethylhexyl adipate (DEHA, DOA) is the standard and most widely used plasticiser in this class. Di-2-ethylhexyl azelate (DOZ), di-2-ethylhexyl sebacate (DOS), and diisononyl adipate (DINA) are used for low temperature applications requiring lower plasticiser volatility.

Another important factor for plasticiser selection is the ease of processing of the resin-plasticiser system in the various steps involved in flexible polymer manufacture. Both the polymer and the plasticiser characteristics influence the processability. For a given polymer resin, the choice of plasticiser influences the temperatures needed for gelling (absorption of the plasticiser in the resin) and fusing (settling of the mixture in its final state), and the viscosity of the hot PVC melt or the plastisol blend, etc. Solvency for the PVC resin plays a role, and strong solvating plasticisers may be mixed into the general plasticiser to enhance processability. The volatility of the plasticiser, on the other hand, is typically the limiting factor on levels of strong solvating plasticisers used. Higher molecular weight plasticisers typically decrease volatility, but also viscosity, etc., with resulting constraints in processability (Krauskopf and Godwin, 2005). BBP is an example of a plasticiser which can reduce the operating temperatures in PVC processing.

3.2 Introduction to plasticiser substance families

This section focuses on the alternative plasticisers. The phthalates are described in more detail in Chapter 2.

Hundreds of substances have plasticising properties in PVC and other polymers. According to Krauskopf and Goodwin (2005), about 70 different plasticisers are available today, even though the consumption has so far been dominated by phthalates. DEHP, DINP and DIDP together comprise around 80% of global plasticiser consumption.

The main families of available plasticisers are shown in a generalised overview in Table 3.2 along with an indication of their performance characteristics. It shall be noted, however, that a number of plasticisers on the market are not member of any of the listed substance families. Each substance family has many members with different performance characteristics, and the table may not include all performance options for all families. The table also shows a traditional grouping of plasticisers in "general purpose" plasticisers with a vide application field and currently low prices (such as DEHP), "performance plasticisers" which provide special performance possibilities and are currently more expensive (such as DBP and BBP), and last "speciality plasticisers" which also provide other functionalities than flexibility and have generally currently even higher prices (Krauskopf and Goodwin, 2005).

A general description of the plasticiser substance families is given in Annex 2. Technical aspects for selected plasticisers are described in more detail in Chapter 6.

Table 3.2
Plasticiser families and traditional application characteristics (according to Krauskopf and Goodwin, 2005)

Substance family	General purpose	Performance plasticisers			Specialty plasticisers		
		Strong solvent	Low temperature	Low volatility	Low diffusion	Thermal & UV stability	Flame resistance
Phthalates (ortho-phthalates)	X	x	x	x	x		x
Trimellitates			x	X	x		
Aliphatic dibasic esters *4			X				
Meta- and terephthalates; DINCH *1,2		X		X	X		
Benzoates *1		X		X	X		
Sulfonates *1		X		X	X		
Citrates *1		X		X	X		
Polyesters				X	X		
Epoxides			x	x		X	
Phosphates							X
Extenders (chlorinated paraffins, etc.) *3	X						

X denotes primary performance function; x denotes other performance functions (as used in Krauskopf and Goodwin, 2005).

*1: In Krauskopf and Goodwin (2005) these plasticisers were pooled in one group in a similar table, and primary/secondary function distinction may be imprecise here.

*2: Designated as "phthalate-like esters" in Krauskopf and Goodwin (2005). Include substances such as DEHT (terephthalate), DEHIP (metaphthalate) and DINCH (cyclohexane counterpart to DINP).

*3: Extenders are low price oils which are used to extend the effect of other plasticisers, but cannot work as plasticisers alone; e.g. chlorinated paraffins.

*4: Includes adipates.

Table 3.3
Technical key parameters of some plasticisers' performance in PVC (from Sears and Darby, 1982; Monsanto research work; unless noted)

Plasticiser in PVC, conc. 40% =67 phr in same PVC resin *1	Shore A hardness *2	Volatility,% lost, 1 day at 87 °C over activated carbon	Extracted in water, %	Extracted in kerosene (jet fuel, etc.), %
Phthalates:				
DEHP	69	4.5	0.01	44
DEHP (PVC2)*3	73	3.6	0.02	54.7
DBP	62	45.4	0.25	9.1
BBP	68	7.7	0.07	3.4
DIDP	71	1.8	0.03	74
DINP	73	2.1	0.07	76.7
Non-phthalates:				
ASE	72	5.3	0.03	4.8
ATBC	73	17.8	0.09	
DEGD (as single substance)	69	5.5	0.75	3.4
DGD	71	7.9	0.45	2.9
DEHT (PVC2)*3	76	1.9	0.09	70.8
DINA	72	4.1	0.14	80.4
TXIB	76	23.7	2.83	5.2
COMGHA*4	88.0	NA	NA	NA
DEHP *4	90.0	NA	NA	NA

*1: phr = parts per hard resin, meaning parts per weight of hard PVC.

*2: A measure for the plasticiser's efficiency in making PVC flexible; the lower the number, the softer the PVC and the more efficient plasticiser.

*3 Measured performance in another PVC resin (the same for DEHP and EHT).

*4 Data from Danisco; at concentration 40 phr; PVC resin type not specified.

3.3 Alternative plasticisers and polymers used in toys and childcare articles

3.3.1 Toys and childcare articles on the Danish Market

Data on alternative plasticisers and polymers have been obtained by direct contact to Danish manufacturers and larger suppliers of toys and childcare articles. A list of contacted companies can be found in Annex 1. Five out of eleven contacted manufacturers/suppliers have responded with information on alternative plasticisers, whereas four report that they do not have any experience with PVC, DEHP, DBP, BBP or alternatives. All manufacturers have been asked to provide examples of own polymer products containing plasticisers and to specify the applied polymers and plasticisers. Furthermore they were requested information on the technical and economical applicability of the alternative plasticisers.

The results are based on statements by three large companies on the Danish marked for toys and childcare articles. Table 3.4 shows the plasticisers used in PVC products by these three companies.

Table 3.4
Non-phthalate plasticisers used in PVC products by major manufacturers and suppliers of toys and childcare articles in Denmark

Plasticiser	CAS No	Company I	Company II	Company III
DINA	33703-08-1	X		
TMP	77-99-6	X		
ATBC	77-90-7	X	X	X
DEHT	6422-86-2	X	X	X
DINCH	166412-78-8	X	X	X
LG-Flex BET	610787-76-3		X	
Mesamoll (ASE)	91082-17-6		X	

Chemical name of plasticiser:
DINA: diisononyl adipate,
TMP (trimethylolpropane): 2,2-dihydroxymethybutanol, 2-ethyl-2-hydroxyl-1,3-propanediol,
ATBC: acetyl tributyl citrate,
DEHT: 1,4-benzenedicarboxylic acid, di(2-ethylhexyl) ester,
DINCH: di(isononyl) cyclohexane-1,2-dicarboxylate,
LG-Flex BET: trimethylolpropane, mixed triesters and diesters with benzoic acid and 2-ethylhexanoic acid,
Mesamoll: alkyl sulfonic acid ester of phenol (ASE).

Table 3.5 shows examples of product types and currently applied plasticisers from one of the large toy companies on the Danish marked.

Table 3.5
Alternative plasticisers in toys and childcare articles used by one major toy company on the Danish market

Product	Part	Alternative plasticiser in PVC	Substituted plasticiser
Dolls	Head	DINA	DEHP or DINP
Dolls	Head	ATBC	
Inflatable toys	All	DEHT	
Inflatable toys	All	TMP	
Inflatable toys	All	DINCH	
Small vehicles	No information	DINCH	

Chemical name and CAS No: DINA: diisononyl adipate, CAS No 33703-08-1, ATBC: acetyl tributyl citrate, CAS No 77-90-7, DEHT: 1,4-benzenedicarboxylic acid, di(2-ethylhexyl) ester CAS No 6422-86-2, TMP: 2,2-dihydroxymethybutanol, CAS No 77-99-6, DINCH: di(isononyl) cyclohexane-1,2-dicarboxylate, CAS No 166412-78-8.

Experiences with alternative plasticisers

The restriction of the use of DEHP, DBP, BBP, DINP, DIDP and DnOP in toys and childcare articles has challenged the companies on the Danish marked on toys and childcare articles to find alternative solutions for product manufacturing. The companies contacted in this study have various experiences with substitution and some of these are described in the following.

In 2005, a company switched to the alternative ATBC (Citroflex A-4) for all toys for children under 3 years and those of any age which are designed to go to the mouth. This particular plasticiser had been given a favourable opinion by the CSTEE for use in toys. However it suffered from a variety of technical drawbacks when compared with DINP. For instance ATBC would not take decoration and it had high migration into adjacent materials leading to swelling and splitting. There was consequently a need for changes of tools and it had a relatively high cost. The work on alternatives to ATBC suffered technical set backs as the company discovered that alternatives could give rise to mal-odours and poor colour matching in the final PVC. Three potential re-

placements for DINP were identified: ATBC, DINCH and DEHT. These could be blended in a variety of combinations to achieve softened PVC that performed to the required standards of safety and reliability. These blends could be used in many cases as one-to-one replacements for DINP so major changes to designs and tooling were not necessary.

According to a Danish manufacturer, when the Danish ban came into force, the price of products for the company raised by approximately 50% because the international manufacturers had to produce special deliverances to the Danish marked without phthalates. After the restrictions comprised the entire EU, the prices dropped again. The company estimates that the ban has resulted in a remaining increase in prises of approximately 10-20% because the alternative substances generally are more expensive even after the preliminarily reduced costs related to changing the production.

3.3.2 Toys and childcare articles on the Dutch market

In addition to the information obtained from manufacturers and suppliers of toys and childcare articles in Denmark, data on plasticisers and polymers in toys have been provided by the Dutch Food and Consumer Product Safety Authority, under the Dutch Ministry of Agriculture. The Dutch Food and Consumer Product Safety Authority has investigated plastic softeners in toys and childcare articles for several years.

During May 2007 in total 200 samples of soft plastic toys and 12 samples of soft childcare articles were acquired by The Dutch Food and Consumer Product Safety Authority from the local retail market. These included bath toys, bouncy balls and inflatable aquatic toys as well as bibs, changing table pillows and seats of high chairs. At least 96 brands were represented. Regulated phthalates were analysed quantitatively, whereas other plasticisers, phthalates as well as alternatives, were analysed qualitatively only. The surveys conducted the other years included analyses on regulated phthalates only.

Most examined samples (67%) were made of PVC. Of the examined samples, toys as well as childcare articles, 41% exceeded the legislative limit for DEHP, DBP, BBP, DINP, DIDP and DnOP.

Statistics of the occurrence of non-phthalate plasticisers ranked the alternatives according to the number of products in which they were used as follows (clearly identified substances): DINCH, nonylphenol, TXIB, TBAC, ATBC, DEHTP, DINA, DEHA (see Table 3.6). It is not clear whether the nonylphenol serves as a plasticiser in the plastics. In the literature other applications of nonylphenol in plastics are described, e.g. as an antioxidant.

Table 3.6
Indentified non-phthalate plasticisers in toys and childcare articles on the Dutch market in 2007 (FCPSA, 2008a)

Abbreviation	Chemical name	CAS No	Percentage of samples
DINCH	Di(isononyl) cyclohex-ane-1,2-dicarboxylate	166412-78-8	25
	Nonylphenol	25154-52-3	18
TXIB	Trimethyl pentanyl diisobutyrate	6846-50-0	14
TBAC	Tert-butyl acetate	540-88-5	11
ATBC	Acetyl tributyl citrate	77-90-7	9
DEHTP (same as DEHT)	Di(2-ethyl-hexyl)terephthalate	6422-86-2	7
DINA	diisononyl adipate ester	33703-08-1	6
DEHA	Bis(2-ethylhexyl) adipate	103-23-1	4
DEHS	Dioctyl sebacate	122-62-3	0,6
	Bis(2-ethylhexyl)ester	-	0,6
DiBA	Diisobutyl adipate	141-04-8	0,6
	Other non-specified plas-ticisers		0,6 each

The plasticisers and polymers by product type are shown in Table 3.7. The table includes only the product types for which both phthalate plasticisers and alternatives were found.

Table 3.7
plasticisers in toys and childcare articles on the Dutch market in 2007 (Based on FCPSA, 2008a)

Product	Regulated phthalate	Non-phthalate plasticiser	Polymer
Duck bath toys	DEHP, DINP, DBP	ATBC, DINCH, nonylphenol, TBAC, DINA, TXIB, esters	PVC, PET
Other bath toys	DINP, DEHP, DBP	DEHTP, DEP, DIBP, ACTB, DINCH, DEHA, TXIB, nonylphenol, DINA	PVC, TPE, PET, PMMA
Balls	DINP, DIDP, DEHP	DEHS, TXIB,	PVC, TPU, PE
Dices	DEHP, DINP	DINCH, nonylphenol	PVC
Inflatable toys	DINP, DIDP, DEHP	ATBC, DINCH, TXIB, TBAC	PVC
Dolls	DEHP, BBP, DINP, DiBA	ATBC, DINCH, DiBA	PVC
Puppetry	DINP	DINCH	PVC
Strings for making bracelets or key chains	DEHP, BBP, DINP, DBP	ATBC, non-classified phthalates	PVC
Toy dinosaurs	DEHP, DINP, DIDP, DBP	TXIB, TBAC, DEP	PMMA, PE/PP, SEBS
Toy pig	DINP	Nonylphenol	PVC
Swimming bracelets	DEHP, DINP	ATBC, DEHA, DEHT, DINCH, Non-ylphenol	PVC, TPE, PET
Baby change pad	DEHP, DIDP, DINP	DINCH	PVC

Compared to similar surveys in 2001, 2004 and 2005 there seems to be only a slight reduction in the use of the six phthalates during the period as shown in Figure 3.2. Notably DBP were found in 30% of the samples in 2004. The percentage had decreased to about 10% in 2007 and further to 1% in 2008 (FCPSA 2008b). BBP is found in only a few percentages of the samples all the year.

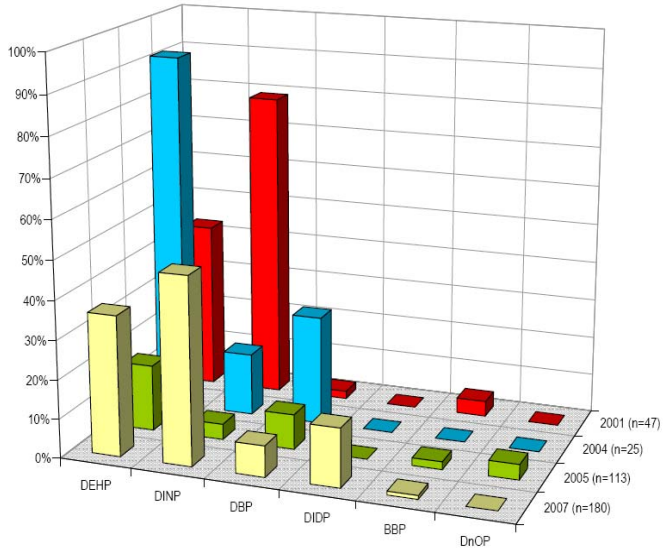


Figure 3.2
Percentage of samples of toys and childcare products from the Dutch retail market that contain 6 specified phthalates (n = number of samples) (FCPSA, 2008a)

3.3.3 Toy s and childcare products on the market in Germany, Austria and Switzerland

A joint study performed in Germany, Austria and Switzerland screened and analysed for all possible plasticisers in 252 samples from 172 toy and child-care products collected in these countries in 2007 (Biedermann-Brem ***et al.***, 2008). The study identified the substances shown in Table 3.8 and made detailed statistics of the occurrence, concentrations and mixtures of the identified plasticisers across product groups enabling a ranking of the phthalates as well as the alternatives.

Table 3.8
Plasticisers identified in 172 toy and child care products in Austria, Germany and Switzerland in 2007; with abbreviations used in that study (Biedermann-Brem et al., 2008)

Abbreviation *	Chemical name
ATBC	Acetyl-tributyl-citrate (Citroflex A)
DBP	Dibutyl-phthalate
DEHA	Di-(2-ethylhexyl)-adipate
DEHP	Di-(2-ethylhexyl)-phthalate
DEHTP (DEHT)	Di-(2-ethylhexyl)-terephthalate
DIBP	Diisobutyl-phthalate
DIDP	Diisodecyl-phthalate
DINA	Diisononyl-adipate
DINCH	Diisononyl-cyclohexane-1,2-dicarboxylate
DINP	Diisononyl-phthalate
DNOP	Di-(n-octyl)-phthalate
ESBO	Epoxidized soy bean oil
NPG-EHA-BA	Mixed diesters neopentylglycol-benzoate/2-ethylhexanoate
PA	Polyadipate
TEHTM	Tri-(2-ethylhexyl)-trimellitate
TMP-EHA-BA	Mixed triesters 1,1,1-trimethylol-propane-benzoate/2-ethylhexanoate
TXIB	2,2,4-Trimethyl-1,3-pentanediol-diisobutyrate

* Abbreviation used in this study in brackets.

The results for each products group involved are shown in Table 3.9, for all plasticiser with occurrence above 4% (main plasticisers in each product). Across all product categories examined, the most important non-phthalate plasticisers used in these products were DINCH, ATBC, DEHT, TXIB and NPG-EHA-BA; see chemicals names in Table 3.8.

Phthalates were detected in 27% of the samples. The phthalates DEHP, DINP, DBP, DIBP, DIDP and DnOP were found. In most cases, the PVC products contained more than one plasticiser; the number of plasticisers in the same product varied between 1 and 5.

Table 3.9
Main plasticisers (>4% conc.), their occurrence and concentrations in 5 products groups (table reproduced from Biedermann-Brem et al., 2008)

	All samples (252)		Baby articles (49)		Dolls (105)		Pinafores, shoes (17)		Water toys (56)		Various toys (25)	
	Number of uses	Mean conc. (%)	Number of uses	Mean conc. (%)	Number of uses	Mean conc. (%)	Number of uses	Mean conc. (%)	Number of uses	Mean conc. (%)	Number of uses	Mean conc. (%)
DINCH	120	29	34	29	42	28	1	19	33	32	10	24
DEHP	28	29	1	21	1	41	11	31	12	23	4	28
TXIB	27	8.4	4	13	22	8	0		1	5	0	
ATBC	24	21	6	18	16	18	1	30	1	29	3	14
DEHTP	24	25	0		18	20	0		6	37	0	
DINP	23	29	3	25	15	31	1	17	2	28	2	25
NPG-EHA-BA	18	35	1	35	14	32	0		1	52	2	43
DINA	9	20	3	21	5	18	0		1	25	0	
PA	8	11	2	11	1	14	0		3	14	2	7
DEHA	6	19	1	45	2	7	0		1	41	2	7
DIBP	6	22	0		0		2	24	1	5	3	27
DIDP	4	24	0		3	29	0		1	9	0	
TMP-EHA-BA	4	15	0		4	15	0		0		0	
TEHTM	3	20	0		2	15	0		0		1	30
ESBO	2	13	0		1	18	0		0		1	7
DBP	2	13	0		0		2	13	0		0	
DNOP	1	38	0		0		1	38	0		0	

3.4 Alternatives recommended by plasticiser producers

In view of the wide spectre of alternative plasticisers available, and in order to get more detailed information on the experience gained on the market with alternatives plasticisers, a number of plasticiser producers were contacted directly with detailed questions on the following issues:

- Proposals for alternative plasticisers for specified traditional DEHP, DBP and BBP applications;
- Level of experience gained on the market with proposed alternatives, according to the manufacturers' own judgement (4 simplified categories);
- Important processing adjustments, if any, compared to DEHP, DBP and BBP, respectively;
- Limitations in use of alternatives for specified applications;
- Prices of alternatives.

The following plasticiser producers have been contacted based on an initial literature and Internet identification, and asked for this detailed information on their alternatives with focus on non-phthalate alternatives:

- BASF
- Lanxess (formerly Bayer)
- Genovique
- Vertellus (formerly Morflex)
- Eastman Chemicals
- Danisco
- Indo-Nippon Chemicals
- Exxon Mobil

The responses provide an improved indication of, which alternatives are important on the market, and which are emerging or more peripheral. Some producers have not adhered strictly to the market categorisation texts suggested, and here an interpretation was needed to allow for a uniform presentation. Some of the responding companies have not mentioned all their products that otherwise appear to be relevant alternatives to the phthalates judging from their websites. The reasons for this are unknown.

3.4.1 Phthalate alternatives

A number of phthalates are marketed as alternatives to the regulated phthalates and as mentioned above several of the alternatives have a significant market share.

It is highly dependent on the specific application which phthalates are recommended as alternatives. Table 3.10 lists the alternatives recommended by one major manufacturer for five different layers in flooring applications; the main application area for DEHP and BBP.

Table 3.10
Examples of replacement of BBP and DEHP for flooring application (Exxon Mobil, 2009)

Application	Recommended Plasticiser(s)	Advantages
Top wear layer	Jayflex 77 *1 (replacing BBP/DEHP) *2	- Lover plastisol viscosity - Improved viscosity stability - Lower cost - Comparable (or better) stain resistance
Chemical foam layers	Jayflex DINP or 77 (replacing BBP/DEHP)	- Lower volatility (end use and process) - Lower migration - Lover cost - Equal expansion - Comparable foam structure
Impregnation layer	Jayflex DINP (replacing DEHP)	- Lover viscosity - Lover plastisol viscosity - Lower migration - Lower volatility
Mechanical foam layer	Jayflex DINP (replacing DEHP at lower BBP concentrations)	- Lower migration - Lower volatility - Lower cost - Equivalent foam ratio at lower emulsifier concentrations
Solid PVC layer	Jayflex DINP (replacing DEHP)	- Lower migration - Lower volability - Lower cost

*1 Diisoheptyl phthalate (DIHP). CAS No. 71888-89-6

*2 DEHP is designated DOP at the webpage.

According to ECPI (2009) 21 different phthalates are in common use. It has been beyond the limits of this study to make a comprehensive assessment of all phthalates that may be used as alternatives to the classified substances. Selected alternatives marketed as alternatives for major applications of the three classified substances are shown in Table 3.11.

Table 3.11
Non-classified phthalates marketed as alternatives to classified phthalates.

Substances	Abb.	CAS No	recommended alternative to:	Remark
Diisononyl phthalate	DINP	28553-12-0 68515-48-0	DEHP; DEHP/DBB	Main all-round alternative to DEHP
Diisodecyl phthalate	DIDP	26761-40-0 271-091-4	DEHP	Diisodecyl phthalate (DIDP) is a common phthalate plasticiser, used primarily to soften polyvinyl chloride (PVC). It has properties of volatility resistance, heat stability and electric insulation and is typically used as a plasticiser for heat-resistant electrical cords, leather for car interiors, and PVC flooring. (ECPI, 2009)
Diisoheptyl phthalate	DIHP	71888-89-6	DEHP/BBP	Marketed as alternative to DEHP/BBP blends in flooring.

3.4.2 Non-phthalate alternatives

The received responses as regards identification of non-phthalate alternatives to DEHP, DBP and BBP, their application, as well as the level of market experience are presented in Table 3.12, Table 3.13 and Table 3.14 below as recommended by contacted manufacturers.

Besides the results presented in the tables, BASF has reported, that it is their understanding of their customers' experiences that in most, if not all, PVC polymer applications the DEHP functionality may be substituted by applying other plasticisers such as DINP, DPHP (Di- (2-propyl heptyl)phthalate), Hexamoll DINCH or others.

Danisco has further reported that Soft-n-safe (consisting of two substances here designated as COMGHA 1 and COMGHA 2) can be used as alternative to DEHP for various applications.

Table 3.12
Alternatives to DEHP proposed by contacted producers, by application and with indication of market experience

Substances	Market experience *1							
	ASE	Mixture of glycerine acetates	BOA	DEHT	DGD	Mix of DGD, DEGD, TGD	ATBC	COMGHA
Product names	Mesamoll	Unimoll AGF	Adimoll BO	Eastman 168	Benzoflex 9-88	Benzoflex 2088	Citroflex A-4	Soft-N-Safe
CAS No.	91082-17-6	mixture	58394-64-2	6422-86-2	27138-31-4	Mix of 120-55-8, 27138-31-4, 120-56-9	77-90-7	Mix of 330198-91-9 and 33599-07-4
Producers	Lanxess	Lanxess	Lanxess	Eastman	Genovique	Genovique	Vertellus	Danisco
Application/ Market experience 1,2,3,4 *1								
Polymer applications:								
Calendering of film, sheet and coated products	2			2	4	4	3	3
Calendering of flooring, roofing, wall covering	4			2	3	3		3
Extrusion of hose and profile	2			2	3	3	3	3
Extrusion of wire and cable	2			2	3	3		3
Extrusion of miscellaneous products from compounds	2	?		2	2	2	2	3
Injection moulding of footwear and miscellaneous	?			2	2	2		3
Spread coating of flooring	2			2	2	2		2
Spread coating of coated fabric, wall covering, coil coating, etc.	2			2	2	2		3
Car undercoating	2				3	3		
PVC medical articles				2			2	
Toy and childcare articles				2			1	
Non polymer applications:	0							
Adhesives/sealant, rubber	2	3	3	2	1	1	2	4
Lacquers and paint	2			2	2	2		4
Printing ink	2			2	2	2	2	3
Production of ceramics								

*1: Market experience categories interpretation: 1) Main alternative on market. 2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience.

Table 3.13
Alternatives to DBP proposed by contacted producers, by application and with indication of market experience

Substances	Market experience *1								
	ASE	GTA	DBA	DBT	ATBC	COMGHA	DGD	Mix of DGD, DEGD, TGD	Mix of proprietary substance and DGD
Product names	Mesamoll	Triacetin	Adimoll DB	Eastman DBT	Citroflex A-4	Soft-N-Safe	Benzoflex 9-88	Benzoflex 2088	Benzoflex LA-705
CAS No.	70775 -94-10	102-76-1	105-99-7	1962-75-0	77-90-7	Mix of 330198-91-9 and 33599-07-4	27138-31-4	Mix of 120-55-8, 27138-31-4, 120-56-9	Mix of proprietary substance and 27138-31-4
Producers	Lanxess	Lanxess	Lanxess	Eastman	Vertellus	Danisco	Genovique	Genovique	Genovique
Application/ Market experience 1,2,3,4									
Plasticiser in PVC	2			4	2	2	1	1	
Plasticiser in other polymers	2			4		2			
Adhesives	2	2		3	3	4		1	1
Printing inks	2	3		4	2	3			
Miscellaneous:									
Sealants	2			4	3	4			
PU foam sealants	2		3		4				
Nitrocellulose paints	2	3	3	4	2		2	2	
Film coatings	3			4	3				
Glass fibre production				4		4			
Cosmetics						2			
Other processes (fill in):									
Polyurethane				3					

*1: Market experience categories interpretation: 1) Main alternative on market.
2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience.

Table 3.14
Alternatives to BBP proposed by contacted producers, by application and with indication of market experience

Substances	Market experience *1										
	ASE	GTA	DBT	ATBC	COM-GHA	DGD	Mix of DGD, DEGD, TGD	Mix of proprietary substance and DGD	Mix of proprietary substance and DGD	Mix of DEGD and DGD	Proprietary mixture
Product names	Mesamoll	Triacetin	Eastman DBT	Citroflex A-4	Soft-N-Safe	Benzoflex 9-88	Benzoflex 2088	Benzoflex LA-705	Velate 375	Benzoflex 50	LC-531
CAS No.	70775-94-10	102-76-1	1962-75-0	77-90-7	Mix of 330198-91-9 and 33599-07-4	27138-31-4	Mix of 120-55-8, 27138-31-4, 120-56-9	Mix of proprietary substance and 27138-31-4	Mix of proprietary substance and 27138-31-4	Mix of 120-55-8, 27138-31-4	Proprietary mixture
Producers	Lanxess	Lanxess	Eastman	Vertellus	Danisco	Genovique	Genovique	Genovique	Genovique	Genovique	Genovique
Application/ Market experience 1,2,3,4											
Polymer applications:											
General PVC (e.g. for moulded plastic parts)	2		4		4						
Plastisol coating, for flooring	2		4		3	1	1				
Extrusion or spreadcoating: Leather and cloth coating (e.g. for furniture, shoes, bags, suitcases)	2		4		2		2			2	
Films, calendering (e.g. for packaging, calendered flooring, wall covering, etc.)	2				3	4	4				
Non polymer applications:											
Sealants (polysulfide based, polyurethane foam sealants, acrylic based; e.g. for windows, construction etc.)	2		4			1	1				1
Coatings and inks (e.g. for car care products, construction, paper, board)		2	4	3		1			1		
Adhesives (polymer based, e.g. for construction, paper)	2						1	1			
Nail polish				1							

*1: Market experience categories interpretation: 1) Main alternative on market.
2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience

3.5 Alternative plasticisers applied with processing adjustments

As indicated in the sections above, a large spectre of plasticisers are available, which can influence the final product quality in a number of ways, and additional variety can be obtained by mixing different plasticisers. Besides this, the possibility exists, of accepting that the production conditions or the specifications of the final product are slightly altered, as compared to the present situation. For some products, this may not be critical, whereas for applications requiring specific technical functionalities, such as low temperature flexibility, specific migration thresholds, etc. such deviations may be critical. A closer evaluation of possibilities for substitution of plasticisers with resulting altered performance must be taken in each case.

3.6 Alternatives plasticisers selected for further assessment

Table 3.15 below lists the identified plasticisers and indicates the plasticisers selected for further evaluation in this study (marked in gray).

The selection was based on the following factors:

- Experience with the substances on the marked, based on data collected from suppliers of alternative plasticisers.
- Occurrence as plasticisers in toys and child care articles, based on the studies of plasticisers in these products described above.
- The list should cover the main alternatives for each of the three phthalates DEHP, DBP, and BBP.
- Representation of major substance groups used as plasticisers based on description above.
- Substances with identified significant environment and health effects (CMR or PBT, based on reviews in COWI, 2009 a) were not suggested for further assessment.

Table 3.15
Identified plasticisers and reason for selection for environmental and health assessment

Group of plasticiser	Chemical name	Abbreviation	CAS no.	Occurrence in toys and childcare articles			Proposed by manufacturers of plasticisers as alternatives for: *2,3	Previously evaluated by *4	Reason for selection
				Reported by Danish manufacturers/suppliers *7	Survey in the Netherlands 2007,% of samples,	Survey in Germany, Austria and Switzerland 2007,% of samples,			
Phthalates	Diisononyl phthalate	DINP	28553-12-0 68515-48-0	Only non-phthalates reported	49%	10%	DEHP *6	E	
	Diisodecyl phthalate	DIDP	26761-40-0 271-091-4	_"_	15%	2%	DEHP *6		
	Diisoheptyl phthalate	DIHP	71888-89-6	_"_			DEHP/DBB blends *6		
	Diisodecyl phthalate	DIBP	84-69-5	_"_	2%	2%	DBP *6	E	
Benzoates	Diethylene glycol dibenzoate	DEGD	120-55-8				DEHP, BBP, DBP (M)		Significant market experience as alternatives for some BBP applications, according to producer. Indicated as important substitute for BBP and DBP in ECHA study
	Dipropylene glycol dibenzoate	DGD	27138-31-4				DEHP, BBP, DBP	E,C,T,K	Significant market experience as alternatives for some BBP applications, according to producer. Indicated as important substitute for BBP and DBP in ECHA study
	Triethylene glycol dibenzoate	TGD	120-56-9				DEHP, BBP, DBP (M)		
Cyclohexanes	Di-isononyl-cyclohexane-1,2dicarboxylate	DINCH	166412-78-8	X	25%	48%		E,T,S	Most used alternative in toys, according to surveys
Terephthalates	Di (2-ethyl-hexyl) terephthalate	DEHT, DOTP	6422-86-2	X	7%	10%	DEHP	E, T, S	Significant market experience as alternatives for some applications, according to producer.. Much used alternative in toys, according to surveys
	Di-butyl terephthalate	DBT	1962-75-0				DBP, BBP		
Sulphonates	Sulfonic acids, C10 – C18-alkane, phenylesters	ASE	91082-17-6	x			DEHP, BBP, DBP	E,N	Significant market experience as alternatives for some applications, according to producer.
Glycorol acetyl esters	Glycerol Triacetate	GTA	102-76-1				BBP, DBP	E	Significant market experience among alternatives for some applications, according to producer.
Other alkyl esters	Trimethyl pentanyl diisobutyrate	TXIB	6846-50-0		14%	11%		C	Frequently used alternative in toys, according to surveys

Group of plasticiser	Chemical name	Abbreviation	CAS no.	Occurrence in toys and childcare articles			Proposed by manufacturers of plasticisers as alternatives for: *2,3	Previously evaluated by *4	Reason for selection
				Reported by Danish manufacturers/suppliers *7	Survey in the Netherlands 2007,% of samples,	Survey in Germany, Austria and Switzerland 2007,% of samples,			
Citrates	Acetyl tributyl citrate	ATBC	77-90-7	X	9%	10%	DEHP, BBP, DBP	C,P,K,S	Much used alternative in toys, according to toy studies; significant market experince among alternatives for some applications, according to producer
Aliphatic dibasic esters	Diisononyl adipate	DINA	33703-08-1	x	6%	4%			Frequently used alternative in toys, according to surveys; adipate representative of DEHP substitutes
	Dibutyl adipate	DBA	105-99-7				DBP		
	Bis(2-ethylhexyl) adipate	DEHA	103-23-1		4%	2%		C,P,K,T,S	Reported by SCENIHR(2008) to have reproductive toxicity
	Benzyl octyl adipate	BOA	58394-64-2				DEHP		
	Diisobutyl adipate	DiBA	141-04-8		0.6%				
	Dioctyl sebacate	DEHS	122-62-3		0.6%			C,K	
Mixed alkyl aryl esters	Mixed diesters neopentylglycol-benzoate/2-ethylhexanoate	NPG-EHA-BA				7%			
	Mixed triesters 1,1,1-trimethylol-propane-benzoate/2-ethylhexanoate	TPG-EHA-BA				2%			
	Hexanoic acid, 2-ethyl, mixed triesters with benzoic acid and trimethylopropane	LG-flex BET	610787-76-3	x					
Polyesters	Polyadipate	PA				3%		C	
Castor oil derivatives	12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester)	COMGHA 1	330198-91-9				DEHP, BBP, DBP	S *5	Significant market experience, expected low toxicity (food ingredient)
	Octadecanoic acid, 2,3-(bis(acetoxy)propyl ester.	COMGHA 2	33599-07-4				DEHP, BBP, DBP	S *5	
Epoxy esters and epoxidized oils	Epoxidized soy bean oil	ESBO	8013-07-8			1%		S, K	
Alkyl acetyl esters	Mixture of glycerine acetates (Unimoll AGF)		-				DEHP		
	Tert-butyl acetate *1	TBAC	540-88-5		11%				
Alkylphenols	Nonylphenol *1		25154-52-3		18%				
Glycerols	Trimethylolpropane (hexaglycerine) *1	TMP	77-99-6	x					

Group of plasti-ciser	Chemical name	Abbre-viation	CAS no.	Occurrence in toys and childcare articles			Proposed by manufacturers of plasticisers as alternatives for: *2,3	Previously evaluated by *4	Reason for selection
				Reported by Danish manu-factur-ers/suppliers *7	Survey in the Nether-lands 2007,% of samples,	Survey in Ger-many, Austria and Switzerland 2007,% of sam-ples,			
Trimellates	Tri-(2-ethylhexyl)-trimellitate	TEHTM (TOTM)	3319-31-1			1%		S, T,K,S	Reported by SCENIHR(2008) to have reproductive toxicity

*1 These substances are usually not mentioned as plasticisers in plastics. It has not been confirmed that the substances are actually used as plasticiser in the plastics.

*2 (M): In mixtures with other substances.

*3 As proposed for this study. Information has not been obtained for all substances. An empty cell in this column does not necessary mean that the substances are not suitable substitutes.

*4: Sources: E: COWI, 2009 (a,b,c) for ECHA; C: Stuer-Lauridsen et al., 2001 ;T: TURI, 2006; K: Karbæk, 2003; P: Postle et al., 2000; S: SCENIHR, 2008. N: Nilsson et al., 2002.

*5 The evaluated CAS No is "acetylated monoglycerides of fully hydrogenated castor oil", CAS No 736150-63-3 which consist of a mixture of the above mentioned substances.

*6 As recommended at manufacturers' web pages.

*7 "X" indicates that the substance is reported by all manufactures. "x" indicates that the substance is reported by one manufacturer only.

3.7 Alternative flexible polymers

Besides the direct alternatives to DEHP, DBP and BBP used as chemicals in various applications, a large number of materials can substitute for flexible PVC in the production of the products.

These alternative materials include, among others, such diverse examples as linoleum and wood for flooring, woven glass fibre and paper for wall coverings, and glass for medical appliances.

The ECHA study on DEHP (COWI, 2009a) concludes that available studies demonstrate that for many applications of DEHP/PVC, alternative materials exist at similar price. Many of the materials seem to have equal or better environment, safety and health performance and cost profiles, but clear conclusions are complicated by the fact that not all aspects of the materials' lifecycles have been included in the assessments.

Due to the wide spectre of products and applications covered, it was decided in this study to limit the considerations for assessment of alternative materials to alternative flexible polymers with characteristics similar to the characteristics of flexible PVC. Based on the information in previous studies, the following flexible polymers are among the principal alternatives to flexible PVC:

- Ethylene vinyl acetate, EVA;
- Low density polyethylene, LDPE;
- Polyolefin elastomers (polyethylene and polypropylene elastomers);
- Several types of polyurethanes (may in some cases be plasticised with phthalates);
- Isobutyl rubber;
- EPDM rubber (may in some cases be plasticised with phthalates);
- Silicone rubber.

3.7.1 Alternative materials suggested for further assessment

A number of studies have been undertaken on replacing PVC with other materials for different applications. For example, an environmental and health assessment of two alternative materials has been conducted by Stuer Lauridsen ***et al.*** (2001): PU (polyurethane) and LDPE (low density polyethylene). On the basis of the available data it was not possible to make a full assessment of the materials. This has been the case for several other studies on the subject.

To focus the efforts in this study, it was decided to include an assessment of polyolefin (polyethylene/polypropylene) elastomers as alternatives to flexible PVC - on an overall screening level - of its lifecycle impacts, supplemented by brief description of other flexible polymers mentioned above based on available aggregated reviews.

4 Human health and environmental assessment of alternative plasticisers

Background data for the environmental and human health assessment of the selected alternative plasticisers are presented in Annex 3, which also includes the references to data sources.

4.1 ASE (alkylsulphonic phenylester)

4.1.1 Physico-chemical properties

ASE, a mixture of similar esters of sulfonic acids, phenyl and C10 – C18 alkanes, is a liquid at ambient temperatures. It has low solubility in water (2 mg/L) and low volatility (Vp = 0.01 Pa). It is lipophilic with a log K_{OW} >6.

4.1.2 Human health assessment

Results from pharmacokinetic studies show that a single oral application by gavage of 1000 mg sulfonic acid, C10-21-alkane, Ph esters/kg bw leads to a concentration of 65 µg sulfonic acid, C10-21-alkane, Ph esters/g fat tissue. After 34 days 4µg sulfonic acid, C10-21-alkane, Ph esters/g was still found in the fat tissue. An elimination half-life of 8 days was calculated for the fat tissue. No accumulation was observed in the liver. 20-30% of the dose was excreted in the faeces within 24 hours. When 100 mg of the substance was administered by gavage, the concentration in fat tissue was 22 µg sulfonic acid, C10-21-alkane, Ph esters/g fat tissue after 3 days and 1 µg/g fat tissue after 14 days. No accumulation was observed in the liver.

ASE has low acute toxicity by the oral route with LD_{50} reported in the range of 26,380 - 31,650 mg/kg bw in the rat. LD_{50} by the dermal route was found to be > 1,055 mg/kg bw in a rat in a study with no indication of toxicity. ASE was not irritating to rabbit skin when applied to the ears for 24 hours and also not to humans exposed to a saturated patch for 8 hours and followed by a 7 days observation period. Rabbit eyes did not show signs of irritation when exposed to ASE and observed for 7 days.

Subchronic toxicity is studied in a repeated dose 90-day oral toxicity study in the rat. Rats were dosed at 750, 3.000 and 12.000 ppm and a NOAEL was reported at 3,000 ppm corresponding to 228 mg/kg bw in males and 282.6 mg/kg bw in females in spite of significantly dose related absolute and relative liver weights at all dose levels. Effects at the highest dose level included reduced body weight gain, increased feed (females), increased water consumption (males) and increased kidney weight. No accumulation in the liver was observed in repeated dose toxicity studies of shorter duration (28 to 49 days). Elimination half-life for fat tissue was calculated at 15 days.

ASE was negative in Ames test, In vitro Mammalian Cytogenetic Test (OECD 473) and in a HGPRT gene mutation assay, all with and without metabolic activation.

No effects on fertility were seen in what appears to be a three generation reproductive toxicity (fertility) study in rats dosed at 530 mg/kg bw for 6 weeks and observed for 3 months. For the F_0-generation, no effects on fertility are reported. The F_1-generation is reported to have normal weight gain, normal weight of endocrine organs and normal first oestrus. For the F_2 and F_3-generation, no effects on fertility and body weight gain are reported. The study dates back to 1956 and details are not available. It is also not clear if a control group has been included in the study. However, due to the limited information about the study and the high degree of uncertainty, it is not possible to draw any conclusions regarding reproductive toxicity from these data.

No other health data was found.

In summary the following profile was identified:

Acute toxicity			Local effects and sensitisation		
LD_{50}, oral mg/kg bw	LD_{50}, dermal mg/kg bw	LC_{50}, inhal.. mg/m^3	Skin irritation	Eye irritation	Sensitisation
26,380 - 31,650	> 1,055	ND	No irritation	No irritation	ND

Repeat dose, genotoxicity, carcinogenicity				Reproductive toxicity		
Repeat dose, NOAEL mg/kg bw/day	Genotoxicity	Carcinogenicity	Maternal toxicity mg/kg bw/day	NOAEL mg/kg bw/day	Reproductive toxicity	Critical endpoint
228 (m) 282.6 (f)	Negative	ND	-	530	No reliable data	None

4.1.3 Environmental assessment

Aerobic biodegradation of ASE is found to be 31% in 28 days. Thus, ASE is not readily biodegradable and its log K_{OW} (>6) is indicative of significant potential for bioaccumulation.

Data on effects of ASE on aquatic organisms are few, however, the data in IUCLID indicate low toxicity to fish in OECD acute test with zebrafish (LC_0 ≥100 mg/L and LC_{50} >10,000 mg/L) and similarly a very low toxicity to crustaceans (***D. magna***); EC >1,000 mg/L and >10,000 mg/L in the two reported tests (OECD acute method). A test with algae (***S. suspicatus***) gave the same result. It is noted that these test and effect concentrations are far above the reported water solubility of ASE (2 mg/L).

No inhibition of the bacteria ***Photobacterium phosphoreum*** was observed at 500 mg/L in one test while in another <20% inhibition occurred at 1.2 g/L. The EC_{50} for inhibition of activated sludge was >10,000 mg/L (all reported in IUCLID).

The main constituents of sulphonic acids, C10-21-alkane, Ph esters are not considered as PBT. They do not meet the P/vP criteria based on

screening data but they meet the screening B criteria. Assessment of ecotoxicity (T) was not carried out during this assessment by the PBT Working Group, PBT List No. 82.

No other environmental effect data have been found.

Table 4.1
Summary of environmental fate and ecotoxicity data on ASE

Environmental fate			Ecotoxicity				
Biodegradation	Bioaccumulation	Mobility	Fish	Daphnia	Algae	Micro-organisms	Terrestrial
Not readily biodegradable (31% in 28 d)	Log K_{OW} >6	ND (Log K_{OW} indicates low mobility)	LC_{50} (96 h) >100 mg/L	EC_{50} (48 h) >1,000 mg/L	EC_{50} (72 h) >10 mg/l	<20% inhib. at 1.2 mg/l (activated sludge)	ND

ND = No Data

4.2 ATBC (acetyl, tri-N-butyl citrate)

4.2.1 Physico-chemical properties

ATBC (CAS No. 77-90-7) consists of citrate with three ester bonded butyl groups and one acetyl group bonded to the fourth available oxygen atom. ATBC is a liquid at ambient temperatures and it has a moderate vapour pressure (6.9 Pa at 20 °C). It is sparingly soluble in water (5 mg/L / < 100 mg/L) and quite lipophilic (log K_{OW} = 4.29).

4.2.2 Human health assessment

ATBC is easily absorbed and rapidly metabolised and excreted in the rat. In an absorption study radiolabelled material was recovered at 59 - 70% in urine and cage rinse, 25 - 36% in faeces, 2% expired and 0.36 - 1.26 in tissues and carcass. At least 9 radiolabelled metabolites were found in urine and at least 3 in faeces.

ATBC has low acute toxicity by the oral route in rats with LD_{50} reported to exceed 30 g/kg bw. No data on acute toxicity by other routes have been found.

ATCB was not irritating to rabbit skin (OECD 404). A study from 1978 in guinea pigs did also not produce irritation, but in an older study from 1955, ATCB produced slight oedema. Patch tests in humans did not produce irritation. ATBC was not irritating to rabbit eyes in a test according to OECD 405. Older studies show slight to moderate irritation. ATCB was not sensitising in guinea pigs or in human volunteers exposed to the substance.

Subchronic toxicity has been studied in several repeated dose toxicity studies of varying quality. In a 90 days study (according to OECD 408) in rats exposed to doses of 100, 300 and 1,000 mg/kg/day, NOAEL was reported at 300 mg/kg bw. All rats survived to scheduled necropsy and no treatment related clinical signs were noted throughout the study. Mean body weights were slightly reduced in both sexes in the high dose group and females in the 300 mg/kg dose group beginning at day 28. These findings were however not statistically significant. Increased liver relative weights for both sexes in the 1,000 mg/kg bw dose group and in the males in the 300 mg/kg bw dose group were

not associated with any evidence of hepatotoxicity as evaluated by histopathological examination or clinical chemistry. The only other organ weight change was a slightly increased relative kidney weight for males in the high dose group. NOAEL was based on a few statistically significant differences between the control group and animals administered 1,000 mg/kg bw.

Chronic toxicity was studied in a two-year oral feeding study in rats administered 200, 2000 or 20000 ppm in the diet. Transient reduction in body weight gain was observed in all dose groups from week 5 to 15. Because of this unexplained depression in growth rate, two additional groups of 10 rats received ATCB in concentrations of 200 and 2,000 ppm in the diet for one year. As the findings could not be reproduced it was considered to be an artifact. Most other findings were not statistically significant or not considered treatment related. NOAEL was concluded to be 2,000 ppm (100 mg/kg/day) using a conservative approach as the study lacks in detail and is without GLP.

In a 13-week toxicity study with an In Utero Exposure phase, sensitive reproductive and developmental endpoints were examined. Wistar rats received ATBC in the diet in concentration levels of 100, 300 and 1,000 mg/kg/day. F0 males and females were treated for four weeks prior to mating. F1 male and female offspring were exposed in utero and from birth until start of the 13 week study. F1 offspring selected for the study were then treated for 13 weeks. Based on the results a NOAEL for males was established at 100 mg/kg/day and the NOAEL for females at 300 mg/kg/day. At the highest dose level a slight reduction in body weight gain was seen in both sexes, liver weights were increased and hepatic hypertrophy (common finding at high doses of xenobiotics) was seen in males and females. Weak peroxisome proliferase was measured in males at 300 mg/kg/day and in both sexes at 1,000 mg/kg/day. Slight, reversible variations in urinary composition and plasma electrolyte concentration were considered to be due to adaptation to excretion of high levels of test material and and/or metabolites and were not considered toxicologically significant.

ATBC showed no evidence of mutagenic activity in several Bacterial Reverse Mutation tests (Ames) with and without metabolic activation and also not in Mammalian Cell Gene mutation assays with and without activation. In vitro cytotoxicity was observed in mouse lymphoma cells and less pronounced in HeLa cells. ATCB was not genotoxic in ***in vivo/in vitro*** unscheduled DNA synthesis study.

ATBC was administered to rats with the diet in a 2-generation reproductive toxicity study in the following doses: 100, 300 and 1,000 mg/kg/day. NOAEL for both parental animals and offspring was found to be 100 mg/kg/day. No treatment-related clinical observations were noted throughout the study in either F0 or F1 parental animals. Body weights the F1 parental males in the 300 and 1,000 mg/kg/day groups were lower that controls and appeared to be related to treatment. Body weights of the F0 females in the 1,000 mg/kg/day group at the end of pregnancy (gestation days 21 or 22) was significantly lower than control values. No reproductive effects were observed in the F0 and F1 generation and no treatment related abnormalities. Slightly lower body weight and slightly higher mortality was observed among pups in the 300 and 1,000 dose groups, which could be a consequence of reduced water consumption.

No significant treatment related effects on development and embryotoxic effects were observed in a 12 month study in rats.

ATBC showed some signs of neurotoxicity when applied in a 3% acacia to the sciatic nerve in rats and in a 5% suspension of ATBC in 3% gum acacia to the conjunctival sac of the eye of a rabbit. The substance was found to have local anaesthetic action in rabbits and to block neural transmission in rats when placed in contact with a nerve trunk.

In summary the following profile was identified:

Acute toxicity			Local effects and sensitisation		
LD_{50}, oral mg/kg bw	LD_{50}, dermal mg/kg bw	LC_{50}, inhal.. mg/m^3	Skin irritation	Eye irritation	Sensitisation
> 30,000	> 1,055	ND	No irritation	No / slight irritation	Not sensitising

Repeat dose, genotoxicity, carcinogenicity				Reproductive toxicity		
Repeat dose, NOAEL mg/kg bw/day	Genotoxicity	Carcinogenicity	Maternal toxicity mg/kg bw/day	NOAEL mg/kg bw/day	Reproductive toxicity	Critical endpoint
100	Negative	Negative	NOAEL 100	100 (rat)	R and D: No	Decreased bw

R: Reproductive toxicity; D: Developmental toxicity

4.2.3 Environmental assessment

A number of studies have been conducted to determine the aerobic biodegradability of ATBC. In the modified MITI test with activated sludge inoculum, 80% of the theoretical BOD was reached in 4 weeks. In the static biometer EPA test (EPA 835.3300), ATBC was characterised as readily biodegradable based >60% ThCO2 observed within a 10-14 day window following the lag period. Also in the ASTM D 5338 test, ATBC was found to readily biodegradable as well as ultimately biodedegradable.

A BCF = 250 and a K_{OC} = 1,800 have been calculated for ATBC based on water solubility = 5 mg/L. These values indicate some bioaccumulation potential as well as strong sorption properties i.e. low mobility in soil.

The acute toxicity to fish has been studied using a number of species. The most sensitive end point was found for ***Pimephales promelas*** larvae (18 hr) in a 7 day static-renewal test (USPEA Method 1000.0). The LC_{50} (48 h) was 2.8 mg/L and the LC_{50} (168 hr) was 1.9 mg/L. In an older (1974) non-guideline flow-through study, the 96 h LC_{50} for ***Lepomis macrochirus*** was estimated at 38-60 mg/L and for the mummichog, ***Fundalus heteroclitus***, to 59 mg/L (both nominal). ECOSAR modelling using ***P. promelas*** as model species gave LC_{50} = 1.67 mg/L.

The water flea ***Cerodaphnia dubia*** was used for testing acute toxicity to daphnia using the USEPA 850.1010 method. The 48 h EC_{50} was determined to be 7.82 mg/L. ECOSAR modelling using ***D. magna*** as the model species gave an LC_{50} = 0.704 mg/L (48 h). The toxicity to algae has not been tested for ATBC, only estimated by ECOSAR with the green alga ***Selenastrum capricornutum***. The 96 hour EC50 was 0.148 mg/L by this method.

Table 4.2
Summary of environmental fate and ecotoxicity data on ATBC

Environmental fate			Ecotoxicity				
Biodegradation	Bioaccumulation	Mobility	Fish	Daphnia	Algae	Micro-organisms	Terrestrial
Ready	BCF = 250 (calculated)	K_{OC} = 1,800 (estimated)	LC_{50} (48 h) = 2.8 mg/L LC_{50} (168h) = 1.9 mg/L	EC_{50} (48 h) = 7.82 mg/L	EC_{50} (96 h) = 0.148 mg/L (calculated)	ND	ND

4.3 COMGHA

4.3.1 Physico-chemical properties

12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester is the main constituent (ca. 84%) in a plasticiser consisting of two castor oil derivatives and commonly known as COMGHA (Soft-n-safe). The other main component (ca. 10%) is octadecanoic acid, 2,3-(bis(acetoxy)propyl ester. The CAS number of the mixture, which is a greasy substance, is 736150-63-3. It has a very low volatility (Vp = 0.00000011 Pa at 25 °C), low water solubility (<0.33 mg/L / 7 mg/L) and is highly lipophilic (log K_{OW} = 6.4).

4.3.2 Human health assessment

Toxicokinetic studies on COMGHA show that there is no significant absorption of the material across gastrointestinal epithelium. Based on the results from a 90-days oral toxicity study, it was concluded that there were no marked effects on peroxisomal enzyme activities in liver samples at concentration levels of 0.4%, 1.2% and 3.6% in the diet.

Acute toxicity (OECD 402) of COMGHA by the dermal route has been studied in rat and LD_{50} found to be > 2,000 mg/kg bw. Other acute toxicity data are not available. COMGHA was not irritating to rabbit skin (OECD 404) and rabbit eyes (OECD 405) and also not a skin sensitizer when studied in a local lymph node assay in mice (OECD 429).

No signs of toxicity were observed in a 28-day repeated dose oral toxicity study (OECD 407) in rats when administered at 3% and 7.5% of the diet/gavage. No effect on the palatability of the diet was observed during the study.

In a 90-day oral toxicity study (OECD 408) with extreme doses: 3, 8.5, 20 ml/kg/day administered by gavage, NOAEL was found to be < 3 ml/kg/day. In a 90-day oral toxicity study (OECD 408) with adequate doses: NOAEL was found to be 5,000 mg/kg/day.

COMGHA was not found mutagenic in Ames test (OECD 471) and no clastogenic activity was seen in the ***In vitro*** Mammalian Chromosome Aberration Test (OECD 473). COMGHA was also not mutagenic in ***In vitro*** Mammalian Cell Gene Mutation Test (OECD 476).

More studies are planned to investigate genotoxic effects ***in vivo*** as well as chronic toxicity, teratogenicity and reproductive toxicity.

In summary the following profile was identified:

Acute toxicity			Local effects and sensitisation		
LD_{50}, oral mg/kg bw	LD_{50}, dermal mg/kg bw	LC_{50}, inhal.. mg/m^3	Skin irritation	Eye irritation	Sensitisation
> 2,000	ND	ND	No irritation	No irritation	Not sensitising

Repeat dose, genotoxicity, carcinogenicity				Reproductive toxicity		
Repeat dose, NOAEL mg/kg bw/day	Genotoxicity	Carcinogenicity	Maternal toxicity mg/kg bw/day	NOAEL mg/kg bw/day	Reproductive toxicity	Critical endpoint
< 3042 (3 ml)	Negative	ND	ND	ND	ND	-

4.3.3 Environmental assessment

COMGHA was found to be readily biodegradable when tested by OECD method 301: 98% degradation occurred in 28 days. The log K_{OW} of 6.4 indicates significant bioaccumulation potential and very low mobility in soil.

Acute toxicity to zebrafish was tested using OECD 203 but the LC_{50} (96 h) could not be determined as it was higher than the solubility of COMGHA. A no observed effect concentration (LC_{10}) after 96 h is stated to be 0.28 mg/L (presumably the highest concentration tested but no detailed information is given).

The acute toxicity to daphnia was EC_{50} = 0.92 mg/L in the OECD 202 test but COMGHA is, according to the manufacturer, not considered to be acutely toxic at the solubility concentration (<0.33 mg/L). The 72 hour growth inhibition EC_{50} for algae was 106 mg/L, however a 70-95% loss in test concentration over the test period was observed.

Regarding inhibition of activated sludge respiration (OECD 209), the EC_{20} (and EC_{50}) was >143 mg/L. No further data on the ecotoxicity of COMGHA is available.

Table 4.3
Summary of environmental fate and ecotoxicity data on COMGHA

Environmental fate			Ecotoxicity				
Biodegradation	Bioaccumulation	Mobility	Fish	Daphnia	Algae	Micro-organisms	Terrestrial
Ready	log K_{OW} = 6.4	"Immobile in soil"	NOEC(LC_{10}) (96h) = 0.28 mg/L	EC_{50} (48 h) = 0.92 mg/L	EC_{50} (72h) = 106 mg/L	EC_{50} >143 mg/L, activated sludge	ND

4.4 DEGD (diethylene glycol dibenzoate)

4.4.1 Physico-chemical properties

DEGD is the esterification product of two benzoate groups with diethylene glycol. It has CAS No. 120-55-8. DEGD becomes liquid at temperatures in the range 24-33 °C and has a very low volatility (Vp = 0,000017 Pa at 25 °C).

It has a rather low water solubility of 38.3 mg/L and it is moderately lipophilic with a log K_{OW} of 3.0-3.2.

4.4.2 Human health assessment

Metabolism of DEGD was studied in Sprague-Dawley CD rats after single oral doses of 50 mg/kg (low level) and 750 mg/kg (high level). Almost all of single oral doses of 50 and 750 mg/kg of DEGD administered to the rats were adsorbed, metabolized and excreted in the urine within 24 hours of administration. DEGD was metabolized via hydrolysis of the ester bonds to benzoic acid. The free acid was then conjugated with either glycine (major pathway) or glucuronic acid (minor pathway) prior to excretion.

DEGD has low acute toxicity by the oral route in rats with LD_{50} reported at 4,198 mg/kg bw (OECD 401). Dermal LD_{50} in rats was found to be > 2,000 mg/kg bw (OECD 402). An acute inhalation toxicity study in the rat was conducted with DEGD resulting in an LC_{50} > 200 mg/L (4 h).

No dermal reaction was reported following a single semi-occlusive application of DEGD to intact rabbit skin for 4 hours. A single instillation of DEGD into the eye of the rabbit elicited transient very slight conjunctival irritation only. No allergic skin reaction was reported in guinea pigs after repeated skin contact (intradermal and topical) using the Magnusson and Kligman method.

Subchronic toxicity was studied in a repeated dose 13 week oral toxicity study in the rat (OECD 408). Animals received DEGD in the diet in concentration levels of 250, 1000, 1750 or 2500 mg/kg/day. A NOAEL of 1,000 mg/kg bw was established based on the results of the study. There were no findings of toxicological importance at a dosage of 1,000 mg/kg/day or below. In animals receiving 1,750 or 2,500 mg/kg/day, there was an adverse effect on body-weight gain, changes in clinical pathology parameters and an increased incidence/degree of haemosiderosis in the spleen. In addition, at 2,500 mg/kg/day, a few treatment-related clinical signs were evident, minimal periportal hepatocyte hypertrophy was noted in both sexes. When selected animals previously receiving 2,500 mg/kg/day were maintained off-dose for 4-weeks, all treatment related changes showed evidence of recovery or recovered completely.

No effects were reported in dogs administered up to 300 mg/kg/day of DEGD in their diet for 90 days.

DEGD did not demonstrate mutagenic potential in bacterial (Ames test, OECD 471/2) or mammalian cell (mouse lymphoma cells, OECD 476) systems with and without metabolic activation. No reponse considered to be indicative of clastogenic activity was observed in a ***In-vitro*** Mammalian Chromosome Aberration Test in CHL cells (OECD 473).

Prenatal developmental toxicity of DEGD (purity 97.67%) in rats was studied in a test according to US EPA 870.3700 Harmonized Guideline (corresponding to OECD 414). Animals were administered doses of 250, 500 and 1,000 mg/kg/day in the diet. NOEL for maternal toxicity was found to be 1,000 mg/kg/day. At 1,000 mg/kg/day, there were no detectable signs of maternal toxicity; there were no maternal deaths and all females had a live litter at sacrifice. NOAEL for prenatal development was found to be 500 mg/kg/day. A small number of foetuses with cervical ribs was seen at 1,000 mg/kg/day, but not considered indicative of substantial disturbance of morphological development. NOEL for foetal growth and development was 250 mg/kg/day. At

1,000 mg/kg/day mean foetal weights, and consequently litter weight were slightly lower than the control, combined with foetal weight and female foetal weight attaining statistical significance. At 1,000 mg/kg/day 4 foetuses showed cervical ribs, this incidence being higher than the concurrent control and marginally outside the current background control data. Although the incidence of this finding was relatively low, it is considered that a treatment relationship could not be ruled out.

Reproductive toxicity of DEGD (purity 97.67%) in rats was studied in a 2-generation test according to OECD 416 and at dose levels of 1000, 3300 or 10000 ppm in the diet. corresponding to 50, 165 and 500 mg/kg bw/day based on standard conversion factors. There were no obvious toxicological effects of treatment for the two generations on the general condition of the parental animals although a slight disturbance in the pattern of maternal weight change was noted at 10,000 ppm in both generations and at 3,300 ppm in the F_1 generation. There was no effect on fertility and reproductive performance at any of the dietary inclusion levels in either generation. Litter parameters at birth of the F_1 and F_2 progeny and their survival to weaning showed no apparent detrimental effects of treatment. However, for the F2 offspring at 10,000 ppm there was a reduction in weight gain from birth to weaning. No abnormal findings were apparent at necropsy of the F_O or F_1 parental animals, the post weaned unselected F_1 offspring or the F_2 offspring. Organ weight assessment of the F_O and F_1 parent animals did not suggest any adverse effects on any organs. Assessment of spermatogenesis and histopathology in both parental generations showed that there were no injurious effects on the testes or other reproductive organs. Furthermore, detailed histopathological examination of the tissues from both sexes in both generations did not reveal any adverse effects of treatment. The only possible effect of treatment detected at assessment of organ weights from Fl and F2 offspring was lower absolute and bodyweight relative spleen weights among F2 males and females compared with controls. The evidence from this study suggested that a dietary concentration of 10,000 ppm (500 mg/kg bw/day) should be considered as the NOAEL for the F_O and F_1 parent animals. The NOAEL for the developing offspring is considered to be 3,300 ppm (165 mg/kg bw/day). The NOEL for reproductive parameters is considered to be 10,000 ppm (500 mg/kg bw/day).

Evaluation of estrogenic activity at doses of 500, 1000, 1500 or 2000 mg/kg/day for 7 days by oral gavage in ovariectomized adult Spraque-Dawley (CD) rats using vaginal cornification and the uterotrophic response as the endpoints demonstrated that DEGD did not exhibit estrogenic activity up to and including the maximally tolerated dose.

In summary the following profile was identified:

Acute toxicity			Local effects and sensitisation		
LD_{50}, oral mg/kg bw	LD_{50}, dermal mg/kg bw	LC_{50}, inhal.. mg/m^3	Skin irritation	Eye irritation	Sensitisation
4,198	> 2,000	> 200mg/L	No irritation	Slight irritation	Not sensitising

Repeat dose, genotoxicity, carcinogenicity				Reproductive toxicity		
Repeat dose, NOAEL mg/kg bw/day	Genotox-icity	Carcino genicity	Maternal toxicity mg/kg bw/day	NOAEL mg/kg bw/day	Reproduc-tive toxicity	Critical endpoint
1,000	Negative	ND	1,000	500 250 (NOEL)	R: No D: Yes	Foetal bw Cervical ribs

4.4.3 Environmental assessment

DEGD is found to be readily biodegradable (93% of ThOD in 28 days) in the modified Sturm test (OECD 301B) while in the Closed Bottle Test (OECD 301D) the BOD5/COD ratio was only 0.32 (>0.5 required for ready biodegradability). A K_{OC} of 540 indicates rather low mobility of DEGD in soil, and a moderately high calculated BCF of 120 indicates some bioaccumulation potential.

The aquatic toxicity of DEGD is quite uniform in short term/acute OECD tests between the three main standard groups of test organisms; fish, crustaceans and algae. Thus, the acute (96 h) LC50 to fish (***Pimephales promelas***) is 3.9 mg/L, while the EC50 (48 h) for daphnia is 6.7 mg/L and the 72 hours growth rate-based EC50 for algae (***Seleneastrum capricornutum***, now known as ***Pseudokirchneriella subcapitata***) is 11 mg/L. This could indicate a non-specific mode-of-action of DEGD.

The acute toxicity to earthworm (***Eisenia foetida***) (14 days) was found to be >1,000 ppm while the inhibitory effect (IC50) on the bacterium ***Pseudomonas putida*** could not be determined specifically but only be stated as higher than the highest testable concentration of 10 mg/L. Activated sludge respiration was not inhibited at 100 mg/L.

Table 4.4
Summary of environmental fate and ecotoxicity data on DEGD

Environmental fate			Ecotoxicity				
Biodegradation	Bioaccumu-lation	Mobility	Fish	Daphnia	Algae	Micro-organisms	Terrestrial
Ready	BCF = 120 (calculated)	K_{OC} = 540 (calculated)	LC_{50} (96 h) = 3.9 mg/L	EC_{50} (48 h) = 6.7 mg/L	EC_{50} (72 h) = 11 mg/L	EC_{50} >10 mg/L (P. putida) NOEC ≥100 mg/L, activated sludge	LC_{50} (14 d) >1,000 mg/kg (earthworm)

4.5 DGD (dipropylene glycol dibenzoate)

4.5.1 Physico-chemical properties

DGD, CAS No. 27138-31-4, is the esterification product of two benzoate groups with dipropylene glycol. DGD is a liquid and is quite similar to DEGD except for two extra methyl groups. It is a substance with low volatility (Vp = 0.00016 Pa at 25 °C), a quite low water solubility of 8.9-15 mg/L and relatively lipophilic character with a log K_{OW} of 3.9.

4.5.2 Human health assessment

Studies show that DGD is rapidly metabolised and excreted from the body and not accumulated in rats. 70% was excreted in the urine within 48 hours of administration as hippuric acid and about 10% was observed in faeces. Half-life of radiocarbon in the blood was 3 hours and for other organs 2-15 hours.

DGD has low acute toxicity by the oral route in rats with LD_{50} reported at 3,914 mg/kg bw (OECD 401). Dermal LD_{50} in rats was found to be > 2,000 mg/kg bw (OECD 402). An acute inhalation toxicity study in the rat was conducted with DGD resulting in an LC_{50} > 200 mg/L (4 h).

No dermal irritation was reported following a single semi-occlusive application of DGD to intact rabbit skin for 4 hours (OECD 404). A single instillation of DGD into the eye of the rabbit elicited transient very slight conjunctival irritation only (OECD 405). No allergic skin reaction was reported in guinea pigs after repeated skin contact (intradermal and topical) using the Magnusson and Kligman method (OECD 406).

Subchronic toxicity was studied in a repeated dose 13 week oral toxicity study in the rat (OECD 408). Animals received DGD in the diet in concentration levels of 250, 1000, 1750 or 2500 mg/kg/day. A NOAEL of 1,000 mg/kg bw (or below) was established based on the results of the study. A few minor intergroup differences were noted at 1,000 mg/kg/day but were insufficient to be of toxicological importance. Higher dosages of 1,750 or 2,500 mg/kg/day were tolerated but the adverse effect on bodyweight was more pronounced, there were increases in circulating enzyme activities, low grade hepatocyte hypertrophy and an increased incidence and degree of hemosiderosis in the spleen in one or both sexes. At 2,500 mg/kg/day, an increased incidence of minimal epithelial hyperplasia was noted in the caecum. When selected animals previously receiving 2,500 mg/kg/day were maintained off dose for 4 weeks, all treatment related effects showed evidence of recovery or recovered completely.

DGD did not demonstrate mutagenic potential in bacterial (Ames test, OECD 471/2) or mammalian cell (mouse lymphoma cells, OECD 476) systems with and without metabolic activation. No response considered to be indicative of clastogenic activity was observed in a ***In-vitro*** Mammalian Chromosome Aberration Test in CHL cells (OECD 473) with and without activation.

Prenatal developmental toxicity of DGD (purity 94.84%) in rats was studied in a test according to US EPA 870.3700 (corresponding to OECD 414). Animals were administered doses of 250, 500 and 1,000 mg/kg/day in the diet. NOEL for maternal toxicity was found to be 1,000 mg/kg/day. At 1,000 mg/kg/day, there were no detectable signs of maternal toxicity; there were no maternal deaths and all females had a live litter at sacrifice. NOAEL for prenatal development was found to be 500 mg/kg/day. A small number of foetuses with cervical ribs was seen at 1,000 mg/kg/day. NOEL for foetal growth and development was 250 mg/kg/day. There were no effects of treatment on prenatal survival or growth. At 1,000 mg/kg/day, treatment was associated with a small but definite increase in the number of foetuses with cervical ribs.

Reproductive toxicity of DGD (purity 94.84%) in rats was studied in a 2-generation test according to OECD 416 and at dose levels of 1000, 3300 or 10000 ppm in the diet corresponding to 50, 165 and 500 mg/kg bw/day based

on standard conversion factors. There were no obvious toxicological effects of treatment for the two generations on the general condition of the parental animals or on their fertility and reproductive performance.

Litter parameters at birth of the F_1 and F_2 progeny and their survival to weaning showed no apparent detrimental effects of treatment. However, in both the F_1 and F_2 offspring at 10,000 ppm there was a slight reduction in weight gain during days 14-21 of age and this finding may be linked to the transition to direct exposure to the test material as the offspring weaned onto solid diet at the same dietary inclusion levels as their parents.

No abnormal findings were apparent at necropsy of the F_O or F_1 parental animals, the post weaned unselected F_1 offspring or the F_2 offspring. Organ weight assessment of the F_O and F_1 parent animals did not suggest any adverse effects on any organs. Assessment of spermatogenesis and histopathology in both parental generations showed that there were no injurious effects on these testes or other reproductive organs. Furthermore, detailed histopathological examination of the tissues from both sexes in both generations did not reveal any adverse effects of treatment. Regarding survival and growth of the offspring, there were no unequivocal adverse effects. However, a slight reduction in bodyweight gain during days 14 to 21 (F_1 and F_2), likely due to the neonatal consumption of the dam's treated diet, and a slight reduction in spleen weights only observed in the F_2 generation are of questionable toxicological relevance. The evidence from this study suggested that a dietary concentration of 10,000 ppm (500 mg/kg bw/day) should be considered as the NOEL for the F_0 and F_1 parent animals. The NOAEL for survival and growth of the offspring is considered to be 10,000 ppm (500 mg/kg bw/day).

Evaluation of estrogenic activity in a uterotrophic Assay at doses of 500, 1000, 1500 or 2000 mg/kg/day for 7 days by oral gavage in ovariectomized (ovaries removed and no natural source of oestrogen) adult Spraque-Dawley (CD) rats using vaginal cornification and the uterotrophic response as the endpoints demonstrated that DGD did not exhibit estrogenic activity up to and including the maximally tolerated dose.

In summary the following profile was identified:

Acute toxicity			Local effects and sensitisation		
LD_{50}, oral mg/kg bw	LD_{50}, dermal mg/kg bw	LC_{50}, inhal.. mg/m^3	Skin irritation	Eye irritation	Sensitisation
3,914	> 2,000	> 200mg/L	No irritation	Slight irritation	Not sensitising

Repeat dose, genotoxicity, carcinogenicity				Reproductive toxicity		
Repeat dose, NOAEL mg/kg bw/day	Genotoxicity	Carcino genicity	Maternal toxicity mg/kg bw/day	NOAEL mg/kg bw/day	Reproductive toxicity	Critical endpoint
< 1,000	Negative	ND	1,000 (NOEL)	500 250 (NOEL)	R: No D: Yes	Foetal bw Cervical ribs

D: Developmental

4.5.3 Environmental assessment

DGD is found to be readily biodegradable (85% of ThOD in 28 days) in the modified Sturm test (OECD 301B) while in the Closed Bottle Test (OECD 301D) the BOD5/COD ratio was only 0.29 (>0.5 required for ready biodegradability). 75% was degraded after 120 days in an anaerobic biodegradation test with a pass level of 60% (US EPA 796.3140, corresponding to OECD 311) and therefore considered to be ultimately biodegradable under anaerobic conditions. The log K_{OW} of 3.9 indicates some bioaccumulation potential and, at the same time, a likely low mobility in soil.

The LC_{50} of fish (***P. promelas***) exposed to DGD for 96 hours was found to be 3.7 mg/L (OECD 203), the 48 hour EC_{50} for daphnia 19.3 mg/L (OECD 202), and the 72 hours growth rate-based EC_{50} for algae (***Seleneastrum capricornutum***, now known as ***Pseudokirchneriella subcapitata***) is 11 mg/L. The corresponding 72 h NOEC was 1.0 mg/L. These quite uniform values across three main taxonomic groups could indicate a non-specific mode-of-action of DGD.

The acute toxicity of DGD to earthworm (***Eisenia foetida***) (14 days) was found to be >1,000 ppm while the inhibitory effect (IC_{50}) on the bacterium ***Pseudomonas putida*** could not be determined specifically but only be stated as higher than the highest testable concentration of 10 mg/L. Activated sludge respiration was not inhibited at 100 mg/L.

Table 4.5
Summary of environmental fate and ecotoxicity data on DGD

Environmental fate			Ecotoxicity				
Biodegradation	Bioaccumulation	Mobility	Fish	Daphnia	Algae	Micro-organisms	Terrestrial
Ready Ultimately biodegradable under anaerobic conditions	Log K_{OW} = 3.9	ND	LC_{50} (96 h) = 3.7 mg/L	EC_{50} (48 h) = 19.3 mg/L	EC_{50} (72 h) = 4.9 mg/L NOEC (72 h) = 1.0 mg/L	EC_{50} >10 mg/L (*P. putida*) NOEC ≥100 mg/L, activated sludge	LC_{50} (14 d) >1,000 mg/kg (earthworm)

4.6 DEHT (di-ethylhexyl-terephthalate)

4.6.1 Physico-chemical properties

DEHT, CAS No. 6422-86-2, is a phthalate ester stoekiometrically equal to DEHP, i.e. phthalate ester bound to two ethylhexyl groups, but with a different spatial structure, because one of the carboxylic groups is placed differently on the benzyl ring ("tere" means tertiary, or third, because the carboxylic group is placed on the third carbon atom counted from the first carboxyl group).

DEHT is a liquid with low volatility (Vp = 0.0029 Pa) and a very low solubility in water; determined to be 0.4 µg/L in a recent (2002) GLP study using the slow-stir method. Previously reported, higher solubilities (in the low or sub-mg/L range) are now believed to be incorrectly determined. The log K_{OW} of DEHT is as high as 8.39.

4.6.2 Human health assessment

DEHT has been shown in both ***in vitro*** and ***in vivo*** studies to have the potential to undergo complete hydrolysis to yield terephthalic acid and 2-ethylhexanol (2-EH), which are rapidly eliminated. Results of these metabolism studies also indicate DEHT was not well absorbed within the gastrointestinal tract, with 36% of it recovered in the faeces still intact. A study to assess dermal absorption rate indicated that DEHT has a very low potential to penetrate the skin (0.103 µg/cm^2/hr), which further limits systemic exposure potential.

DEHT has low acute toxicity by the oral route in rats with LD_{50} reported at >3,200 mg/kg bw (male rat, no guideline) and >5,000 mg/kg bw (TSCA FHSA Regulations (1979): 16 CFR Part 1500.40). Dermal LD_{50} in male guinea pigs was found to be > 19,670 mg/kg bw. No deaths occurred following inhalation exposure of mice for 4 hr to "saturated" vapours; however, mucosal irritation, loss of coordination and decreased mobility were noted. Recovery occurred in 24 hours.

DEHT was concluded to be a slight dermal irritant in male guinea pigs with no evidence of percutaneous absorption following a single-dose occlusive dermal application and 24 hours exposure. DEHT produces slight irritation to rabbit eyes in a study using a procedure similar to OECD 405.

In studies with some limitations, no skin sensitization was observed in humans or guinea pigs.

Subchronic toxicity was evaluated in a 90-days repeated dose toxicity study where rats were fed diets containing DEHT in concentrations of 0.1, 0.5 or 1%. Study was conducted in a manner similar to the one described in the U.S. EPA guideline, 799.9310 TSCA. The only significant treatment related difference between controls and treated animals was increased relative liver weight in the 1.0% dose group. NOEL was 0.5% corresponding to approximately 500 mg/kg/day. In a 21-days repeated oral toxicity study in rats NOEL was also 0.5% (≈ 500 mg/kg/day) based on increased relative liver weight in females at 1.0%.

DEHT did not produce mutagenicity in Ames tests (procedure similar to OECD 471) and also no response considered to be indicative of clastogenic activity in doses up to 1,000 nL/mL in a ***In-vitro*** Mammalian Chromosome Aberration assays in CHO cells (procedure similar to OECD 473) with and without activation.

DEHT was evaluated for combined chronic toxicity and carcinogenicity. The test substance was administered in the diets of male and female Fischer-344 inbred rats at concentrations of 20, 142, and 1,000 mg/kg/day. Clinical evaluations revealed no treatment-related signs, however, eye opacities (cataracts) occurred frequently in all groups. At 1,000 mg/kg/day, body weights and female liver weights were reduced. There were no consistent reductions in food consumption. There were no treatment-related effects evident from the gross and histopathologic examinations conducted at 6 and 12 months. At 18 months, two basic lesions of the females in the 1,000 mg/kg/day level appear to be associated with treatment. These were hyperplasia and/or transitional cell adenomas of the urinary bladder and adenomas or adenocarcinomas of the uterus.

In another combined chronic toxicity and carcinogenicity study (industry study) in F-344 rats DEHT was administered in doses of 1,500, 6,000 and 12,000 ppm (79, 324 and 666 mg/kg bw/day (m) and 102, 418 and 901 mg/kg bw/day) in the diet. It was concluded that the oral administration of DEHT via the diet was well tolerated at all dose levels. There was no effect upon tumour incidence and therefore the NOEL for tumorigenicity was at least 666 mg/kg bw/day in males and 901 mg bw/day in females. Toxic responses were confined to low weight gain and food conversion efficiency in males and females receiving 6,000 and 12,000 ppm. Consequently the NOEL for chronic toxicity in the study was 1,500 ppm (79 mg bw/day (m) and 102 mg bw/day (f)).

Reproductive toxicity of DEHT in Sprague-Dawley rats was studied in a 2-generation test according to OECD 416 and at dose levels of 3000, 6000 or 10000 ppm in the diet. The NOAEL for reproductive toxicity was 1.0% in the diet (500-700 mg/kg bw/day for males and 800-1,000 mg/kg bw/day for females; highest dose tested), and the NOAEL for parental and offspring toxicity based on reduced body weight gains was 0.3% (150-200 mg/kg bw/day for males and 250-300 mg/kg bw/day for females). Mean maternal body weights and body weight gains were reduced for F_0 and F_1 females in the 1.0% group throughout pregnancy and decreased mean terminal body weights were noted in F_1 males and females given 0.6% or 1.0% test material. The results of this study, in conjunction with the 90-day study which also showed no effect of DEHT on histology of reproductive organs indicate that DEHT has a low potential to induce reproductive toxicity.

Developmental toxicity was evaluated in a dietary study following OECD Test Guideline 414 and at dose levels of 3000, 6000 or 10000 ppm in the diet. The NOEL for maternal toxicity was 0.6% (458 mg/kg/day) and the NOEL for developmental toxicity was 1.0% (747 mg/kg/day; highest dose tested).

The ability of DEHT to induce anti-androgenic like effects in male offspring was assessed by giving pregnant rats 750 mg/kg DEHT by gavage on gestation day 14 until postnatal day (PND) 3. No changes indicative of a feminization effect were induced in male pups. NOEL for maternal toxicity and teratogenicity was 750 mg/kg.

Results of an uterotrophic assay in which immature females were given up to 2,000 mg/kg/day DEHT by gavage on PND 19-21 also indicate that DEHT does not possess estrogenic activity.

In summary the following profile was identified:

Acute toxicity			Local effects and sensitisation		
LD_{50}, oral mg/kg bw	LD_{50}, dermal mg/kg bw	LC_{50}, inhal.. mg/m^3	Skin irritation	Eye irritation	Sensitisation
> 5000	> 19,670	No deaths, saturated vapour (mice)	Slight irritation	Slight irritation	Not sensitising

Repeat dose, genotoxicity, carcinogenicity				Reproductive toxicity		
Repeat dose, NOAEL mg/kg bw/day	Genotox-icity	Carcino genicity	Maternal toxicity mg/kg bw/day	NOAEL mg/kg bw/day	Reproduc-tive toxicity	Critical endpoint
500	Negative	Nega-tive	458 (rat)	747 (high-est dose tested)	R: Low potential D: No	-

D: Developmental

4.6.3 Environmental assessment

In a study from 1986, performed according to the EPA aerobic biodegradation guideline, the biodegradability of DEHT was found to be 56% in 28 days, corresponding to a classification as inherently biodegradable. The BCF of 393 (in oysters, determined in an EPA protocol study) indicates a medium potential to bioaccumulate, and the K_{OC} of 2,000 a high sorptivity to soil organic matter.

A 7 days flow-through study with ***Salmo gairdneri*** using acetone to enhance solubility of DEHT resulted in an LC_{50} of $\geq$ 0.25 mg/L (measured), and a 71 days early life-stage study with the same species gave a NOEC $\geq$ 0.28 mg/L (measured). The acute toxicity (immobilization) to Daphnia magna was determined in a standard 48 hour static test and found to be $EC_{50} \geq 1.4$ mg/L while the 21 days NOEC (reproduction) for D. magna in a flow-through test was 0.76 mg/L (both measured). Inhibition of growth of ***Seleneastrum capricornutum*** (now known as ***Pseudokirchneriella subcapitata***) in the standard 72 hours static test did not occur at the possible test concentrations and the EC_{50} was therefore just stated to be $\geq$ 0.86 mg/L.

In the OECD 218 test on sediment- dwelling organisms (larvae of ***Chironomus riparius***), the EC_{50} after 28 days was determined to $\geq$ 950 mg/kg while the NOEC for emergence was 180 mg/kg. In a 3 hour activated sludge inhibition test according to OECD 209 the EC_{50} was found to be higher than 10 mg/L.

Table 4.6
Summary of environmental fate and ecotoxicity data on DEHT

Environmental fate			Ecotoxicity				
Biodegradation	Bioaccumu-lation	Mobility	Fish	Daphnia	Algae	Micro-organisms	Terrestrial
Inherent	BCF = 393	K_{OC} = 2,000	LC_{50} (7 d) > 0.25 mg/L NOEC (71d) $\geq$ 0.28 mg/L	EC_{50} (48 h) > 1.4 mg/L NOEC (21d) $\geq$ 0.76 mg/L	EC_{50} (72 h) > 0.86 mg/L	EC_{50} >10 mg/L, acti-vated sludge	ND

4.7 DINA (diisononyl adipate)

4.7.1 Physico-chemical properties

DINA is formed by an adipate (hexanoic acid) ester bound with two C-9 alkanes. The CAS No. is 33703-08-1. It is a liquid at room temperature and it appears to be moderately volatile (Vp < 10 Pa at 20 °C). It has a low water solubility of < 1 mg/L and is extremely lipophilic with a log K_{OW} = 9.24.

4.7.2 Human health assessment

No data on toxicokinetics have been identified.

DINA has low acute toxicity by the oral and dermal route with oral LD_{50} in rats reported at > 5,000 mg/kg bw and dermal LD_{50} in rabbits reported at > 3,160 mg/kg bw.

DINA was not irritating to rabbit skin (OECD 404) or rabbit eyes (OECD 405). No allergic skin reaction was reported in guinea pigs after repeated skin contact (intradermal and topical) using the Magnusson and Kligman method (OECD 406).

Subchronic toxicity was evaluated in a repeated dose 13 week oral toxicity study in the rat at dose levels up to 500 mg/kg/day. NOAEL in males was 500 mg/kg/day. Increased relative kidney weight was observed at 500 mg/kg/day but no change in absolute kidney weight and histopathological changes was seen. It was concluded that there were no significant findings at any dose level. In a 13 week oral toxicity study in dogs fed at doses up to 3% for 8 weeks and 6% for 5 weeks, NOAEL was 1% in the diet corresponding to approximately 274 mg/kg/day. Adverse effects at the high dose included decreased body weight and food consumption, increased liver weight, elevated enzyme levels, liver and kidney discoloration, and histopathological changes in the liver and kidneys.

DINA did not produce mutagenicity in Ames tests or mammalian cell (mouse lymphoma cells) systems with and without metabolic activation. No other data on health effects was found. Bridging data gaps and read across to the structural analogue, adipic acid, bis (2-ethylhexyl) ester (C22) (CAS No. 103-23-1) and three other structurally similar alkyl diesters (C12-C32) was suggested in the US EPA HPV programme for reproductive and developmental toxicity. These diesters show no or low potential for reproductive and developmental toxicity.

In summary the following profile was identified:

Acute toxicity			Local effects and sensitisation		
LD_{50}, oral mg/kg bw	LD_{50}, dermal mg/kg bw	LC_{50}, inhal.. mg/m^3	Skin irritation	Eye irritation	Sensitisation
> 5000	> 3,160	ND	No irritation	No irritation	Not sensitising

Repeat dose, genotoxicity, carcinogenicity				Reproductive toxicity		
Repeat dose, NOAEL mg/kg bw/day	Genotoxicity	Carcinogenicity	Maternal toxicity mg/kg bw/day	NOAEL mg/kg bw/day	Reproductive toxicity	Critical endpoint
274	Negative	ND	1000 (rat)	-	No data[1)]	-

1) Data from structurally similar diesters show low potential for reproductive and developmental toxicity.

4.7.3 Environmental assessment

DINA is readily biodegradable, it has been found to degrade by 82% in 28 days in the modified MITI test (OECD 301C) and by > 90% in the EEC

manometric respirometric method. No data on mobility in soil have been found, but the extremely high log K_{OW} of 9.24 indicates a very low mobility. The BCF in a 21 day test with ***D. magna*** was 1,102-2,031 while in a 35 day test with the blue mussel, ***Mytilus edulis***, a BCF = 11,000 was found. No results for BCF in fish have been identified but an estimate from the USEPA gave a BCF = 3.2.

The tests performed with DINA have all been carried out at concentrations exceeding the aqueous solubility i.e. by the use of solubility enhancing solvents such as DMF or acetone. The acute (96 h) toxicity to fish was determined in a test with ***Leuciscus idus*** according to DIN 38412. The LC_{50} was > 500 mg/L (nominal), which corresponded to > 2.6 mg/L (measured). The 79/831/EEC static acute immobilization test was conducted with ***Daphnia magna***, and an EC_{50} > 100 mg/L was determined. A 21days NOEC > 100 mg/L was found for effects on reproduction of ***D. magna*** when using the OECD 202, part 2 test method. The 72 hour EC_{50} for algae was > 100 mg/L.

Table 4.7
Summary of environmental fate and ecotoxicity data on DINA.

Environmental fate			Ecotoxicity				
Biodegradation	Bioaccumulation	Mobility	Fish	Daphnia	Algae	Micro-organisms	Terrestrial
Ready	BCF ≥ 1,100 BCF (estimated) = 3.2	ND	LC_{50} (96 h) > 500 mg/L (nominal) LC_{50} (96 h) > 2.6 mg/L (measured)	EC_{50} (48 h) > 100 mg/L NOEC (21d) > 100 mg/L	EC_{50} (72 h) > 100 mg/L	EC_{50} >10,000 mg/L (*P. putida*) EC_{20} > 1,000 mg/L, activated sludge	ND

4.8 DINCH (di-isononyl- cyclohexane-1,2-dicarboxylate)

4.8.1 Physico-chemical properties

DINCH (CAS No. 166412-78-8) is the hydrogenated parallel to DINP, with the difference that the ring structure is cyclohexane (a cyclic alkane) instead of a benzene ring (an aromate). It is a colourless liquid at 20 °C with a very low water solubility of <0.02 mg/L, low volatily (Vp = 0.000022 Pa) and highly lipophilic character (log K_{OW} >6.2).

4.8.2 Human health assessment

DINCH is rapidly absorbed after oral administration and readily eliminated. After 24 hours approximately 80% of the radioactivity is excreted, after 48 hours more than 90% is excreted via urine and mainly via faeces. There is no indication of bioaccumulation. The characterisation of metabolites after oral and intravenous administration of DINCH indicates two main pathways: the partial hydrolysis of DINCH to the mono-isonyl ester followed by conjugation to glucuronic acid, which is the most abundant metabolite in bile, or the hydrolysis of the remaining ester bond to yield free cyclohexane dicarboxylic acid, the predominant urinary metabolite.

DINCH has low acute toxicity by the oral (OECD 423) with LD_{50} in rats reported at > 5,000 mg/kg bw. Dermal LD_{50} in rabbits (OECD 402) was reported at > 2,000 mg/kg bw.

DINCH was slightly irritating to rabbit skin (OECD 404) with mean scores for erythema of 2.0 in one animal and 1.7 in two animals. DINCH was not irritating to rabbit eyes (OECD 405). There was no evidence of skin sensitisation in guinea pigs in a study according to OECD 406.

DINCH was studied in a 28-days oral repeated dose toxicity study (OECD 407) in rats at concentrations of 600, 3000 and 15000 ppm in the diet. Doses of 15,000 ppm caused changes in clinical chemistry parameters in animals of both sexes. Indications of mild renal function impairment (urinary epithelial cells, elevated serum Na+/K+) were observed in male rats. Female rats showed signs that may be associated with hepatic microsomal enzyme induction, characterised by stimulation of γ-glutamyltransferase synthesis and by increased excretion of bilirubin due to stimulation of phase II reactions. NOAEL was established as 3,000 ppm (318 mg/kg bw/day (males) and 342 mg/kg bw/day (females)) in this study, based on the absence of effects on clinical chemistry parameters at this intake level.

In a 90-days oral repeated dose toxicity study (OECD 408) in rats DINCH was administered in the diet at concentrations of 1500, 4500 and 15000 ppm. NOAEL was established at 107.1 mg/kg bw/day (males) and 389.4 mg/kg bw/day (females) in this study, based on kidney weight changes in both sexes and the appearance of degenerated epithelial cells in the urine of males.

In a combined chronic toxicity/carcinogenicity study (OECD 453) rats were administered doses of 40, 200 or 1,000 mg/kg bw/day in the diet. After 24 months of treatment, dose-related follicular cell hyperplasia and increased number of follicular adenomas were observed in the thyroid glands of male rats administered 200 mg/kg bw/day and in both genders administered 1,000 mg/kg bw/day. The thyroid glands are a target organ for the effects of the notified substance in rats. There was a dose-related increased incidence of follicular adenomas in the thyroid gland of mid and high dose male rats and high dose female rats. However, thyroid effects in rats are potentially secondary effects associated with liver enzyme induction and of limited relevance to humans. Such an indirect mechanism is plausible based on the findings of increased GGT activity and lower serum bilirubin levels in this study, and supported by further studies (see special studies below) on enzyme induction and cell proliferation. NOAEL was established at 40 mg/kg bw/day (males) and 200 mg/kg bw/day (females) based on liver weight changes (both sexes) and kidney weight changes (males).

DINCH did not produce mutagenicity in Ames tests (OECD 471) or in ***in vitro*** mammalian CHO cells with and without metabolic activation. No clastogenic activity was seen in a ***c***hromosome aberration assay (OECD 473) with and without activation. DINCH was also not found to be clastogenic or aneuploidogenic in a ***in vivo*** mouse nucleus test (OECD 474).

Developmental toxicity was examined in rabbits (OECD 414) at doses of 100, 300 or 1,000 mg/kg bw/day in the diet. DINCH did not have any adverse effects on maternal toxicity, gestational parameters or developmental toxicity up to 1,000 mg/kg bw/day. NOAEL was established at 1,000 mg/kg bw/day. In a similar study in rats (OECD 414) with animals dosed at 200, 600 or 1,200 mg/kg bw/day, NOAEL was established at 1,200 mg/kg bw/day due to absence of adverse effects on maternal toxicity and prenatal development. Same conclusions were obtained in a study following elements of OECD 414 and OECD 415 (one-generation reproduction toxicity test) with

rats dosed at 750 and 1,000 mg/kg bw/day. NOAEL for maternal and development toxicity was established at 1,000 mg/kg bw/day.

Toxicity to reproduction was studied in a two-generation study with animals dosed at 100, 300 or 1,000 mg/kg bw/day. Under the conditions of this reproduction study, the NOAEL for fertility and reproductive performance was established at 1,000 mg/kg bw/day for F_0 and F_1 generation rats of both genders. The NOAEL for general toxicity was 1,000 mg/kg bw/day (F_0 rats of both genders) and 100 mg/kg bw/day for the F_1 male and female rats (based on tubular vacuolisation and flaky thyroid follicular colloid). The NOAEL for developmental toxicity (growth and development of offspring) was 1,000 mg/kg bw/day for the F1 and F2 pups.

In summary the following profile was identified:

Acute toxicity			Local effects and sensitisation		
LD_{50}, oral mg/kg bw	LD_{50}, dermal mg/kg bw	LC_{50}, inhal.. mg/m^3	Skin irritation	Eye irritation	Sensitisation
> 5,000	> 2,000	ND	Slight irritation	No irritation	Not sensitising

Repeat dose, genotoxicity, carcinogenicity				Reproductive toxicity		
Repeat dose, NOAEL mg/kg bw/day	Genotoxicity	Carcino genicity	Maternal toxicity mg/kg bw/day	NOAEL mg/kg bw/day	Reproductive toxicity	Critical endpoint
107	Negative	Negative	1000 (rat)	1000	R and D: No	-

4.8.3 Environmental assessment

With only 41% degradation in the CO_2 evolution test (OECD 301B), DINCH cannot be classified as readily biodegradable. The BCF of 189 indicates a moderate bioaccumulation potential but 90% depuration of the substance occurred within 1.6 days. The log K_{OW} of >6.2 indicates high sorption potential.

The acute toxicity to fish was tested with zebrafish using the 96 hour static EC-test method and found to be LC_{50} >100 mg/L. Similarly, the acute EC_{50} for daphnia was found to be higher than the highest test concentration in OECD 202 of 100 mg/L. In a 21 days reproduction test (OECD 211) no effects occurred at the highest test level of 0.021 mg/L (measured) and the NOEC was therefore determined to be ≥0.021 mg/L. The rate based 72 hour EC_{50} for algae (***Scenedesmus subspicatus***) was found to be >100 mg/L and the corresponding NOEC ≥100 mg/L.

DINCH was found to be virtually non-toxic to activated sludge (EC_{50} >1,000 mg/L) and to earthworms in the 14 days acute artificial soil test (LC_{50} >1,000 mg/kg).

Table 4.8
Summary of environmental fate and ecotoxicity data on DINCH

Environmental fate			Ecotoxicity				
Biodegradation	Bioaccumulation	Mobility	Fish	Daphnia	Algae	Micro-organisms	Terrestrial
Not readily biodegradable (41% in 28 d)	BCF = 189	ND	LC_{50} (96 h) >100 mg/L	EC_{50} (48 h) >100 mg/L NOEC (21d) ≥0.021 mg/L	EC_{50} (72 h) >100 mg/L NOEC (72h) ≥100 mg/L	EC_{50} >1,000 mg/L, activated sludge	LC_{50} (14 d) >1,000 mg/kg (earthworm)

4.9 GTA (glycerol triacetate)

4.9.1 Physico-chemical properties

GTA ("Triacetin") is an ester of glycerol and three acetate groups. Its CAS no. is 102-76-1. It is a liquid at room temperature with a relatively low vapour pressure of 0.33 Pa at 25 °C. It has high solubility in water (58,000-70,000 mg/L) and a correspondingly low log K_{OW} of 0.21-0.36.

4.9.2 Human health assessment

GTA is rapidly absorbed following ingestion and metabolised like other shorter-chain triglycerides. Several studies confirmed that GTA is hydrolysed to glycerol and acetic acid by digestive enzymes, particularly lipases, liver or plasma carboesterases. GTA is readily hydrolyzed to free glycerol and acetic acid, when incubated with rat intestine in vitro. The chemical infused in dogs undergoes intravascular hydrolysis and the majority of the resulting acetate is oxidized nearly quantitatively. The substance has been shown to be a source of liver glycogen and when fed in amounts equal in caloric value to 15% glucose it was utilised as efficiently as glucose.

The acute oral and dermal toxicity of GTA is low. In an oral acute toxicity study in rats (OECD 401), a limit dose of 2,000 mg/kg bw caused no mortality and no signs of systemic toxicity during the 14-day observation period. The LD_{50} in rats by gavage is determined to be >2,000 mg/kg bw for both sexes, and dermal LD_{50} in rabbits and guinea pigs were >2,000 mg/kg bw. Acute inhalation toxicity is considered to be very low, since the LC_{50} in an acute inhalation toxicity study in rats was >1,721 mg/m3 for both sexes (OECD 403) and repeated daily exposure of rats to 73,700 mg/m^3 produced no sign of toxicity after 5 days.

GTA was not found irritating to rabbit skin and eyes in studies following OECD 404 and 405. GTA did not induce sensitisation in guinea pigs.

In a combined repeat dose and reproductive/developmental screening toxicity test (OECD 422), rats were exposed to 40, 200 or 1,000 mg/kg/day by oral gavage for 44 days from 2 weeks prior to mating for males and for 41 - 48 days from 14 days before mating to day 3 postpartum for females. GTA had no effects on clinical signs, body weight, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in either sex. There were no abnormalities in haematological or blood chemical parameters in males. The NOAEL for repeated dose oral toxicity is thus considered to be 1,000 mg/kg bw/day for both sexes.

An inhalation study was conducted in rats given GTA for 90 days at a dose of 249 ppm (2,220 mg/m^3). No signs of toxicity were noted during the exposure. The NOAEL is considered to be 249 ppm (2,220 mg/m^3) for 90 days. Although the inhalation study is considered to be useful, it does not fully comply with the current testing protocol.

GTA did not induce gene mutation in Ames test at concentrations up to 5,000 ug /plate (OECD 471 and 472). Induction of chromosome aberrations was observed in the Chinese hamster lung cells at the highest concentration (2.2 mg/mL, 10 mM) in the presence of metabolic activation (OECD 473). Because of high toxicity (75%) that might be caused by low pH (4.9) at the end of the treatment, the chromosomal aberration observed might not be biological relevant. Under un-physiological culture condition, such as low pH, it was reported that the frequency of chromosomal aberrations could be increased. Polyploidy was not induced under any of the conditions tested. Results were equivocal, but taking all data into consideration, GTA could be considered to be non-genotoxic.

The combined repeated dose and reproductive/developmental toxicity study in rats at doses of 40, 200 or 1,000 mg/kg bw/day (OECD 422) showed no statistically significant adverse effects on reproductive parameters (mating index, fertility index, gestation length, numbers of corpora lutea and implantations, implantation index, gestation index, delivery index, parturition and maternal behaviour at delivery and lactation). In addition, there were no significant differences in numbers of offspring or live offspring, the sex ratio, the live birth index, the viability index or body weight. Developmental toxicity, clinical signs of toxicity, and change in necropsy findings were not found in offspring. Therefore, the NOAEL is considered to be 1,000 mg/kg bw/day for parental animals and offspring.

In summary the following profile was identified:

Acute toxicity			Local effects and sensitisation		
LD_{50}, oral mg/kg bw	LD_{50}, dermal mg/kg bw	LC_{50}, inhal.. mg/m^3	Skin irritation	Eye irritation	Sensitisation
> 2,000	> 2,000	> 1,721	No irritation	No irritation	Not sensitising

Repeat dose, genotoxicity, carcinogenicity				Reproductive toxicity		
Repeat dose, NOAEL mg/kg bw/day	Genotoxicity	Carcino genicity	Maternal toxicity mg/kg bw/day	NOAEL mg/kg bw/day	Reproductive toxicity	Critical endpoint
1000	Negative	ND	1000 (rat)	1000	R and D: No	-

4.9.3 Environmental assessment

The bulk of data on aerobic biodegradability of GTA suggests that the substance is readily biodegradable, e.g. 77% degradation after 14 days based on BOD, 93% after 28 days based on $ThCO_2$ and 94% after 28 days based on TOC (OECD methods 301B, 301C and 301 D). The K_{OC} of 10.5 indicates high mobility in soil (corresponds well with high water solubility and low log K_{OW}), and the calculated BCF = 1.3 implies an insignificant bioaccumulation potential.

The acute toxicity of GTA to fish has been studied on a number of species such as ***Pimephales promelas, Oryzias latipes, Cyprinus carpio, Brachydanio rerio and Leuciscus idus***. In the test with ***O. letipes***, the lethal level was not reached at the highest test concentration of 100 mg/L, and among the other species the LC_{50} ranged from 165 to 300 mg/L with ***P. promelas*** being the most sensitive species (tested with OECD 203, DIN38412 or ISO 7346/2 (conforming to OECD 203)). In a prolonged test with ***O. latipes*** the 14 days LC_{50} was > 100 mg/L (nomimal) (OECD 204).

EC_{50}'ies for acute toxicity to ***D. magna*** range from 380 to 811 mg/L with the most sensitive result being obtained with the DIN 39412 Teil 11 test, which conforms to OECD 202. The 21 days NOEC on reproduction of ***D. magna*** was 100 mg/L in the OECD 211 test. Inhibition of growth of ***Seleneastrum capricornutum*** (now known as ***Pseudokirchneriella subcapitata***) in the standard 72 hours static test (OECD 201) could not be determined but was > 1,000 mg/L. The NOEC (72 h) was determined to be 556 mg/L. The toxicity to bacteria, ***Pseudemonas putida***, was determined using the EN ISO 10712 guideline. A 16 hours NOEC = 3,000 mg/L was determined.

Table 4.9
Summary of environmental fate and ecotoxicity data on GTA

Environmental fate			Ecotoxicity				
Biodegradation	Bioaccumulation	Mobility	Fish	Daphnia	Algae	Micro-organisms	Terrestrial
Ready	BCF = 1.3	K_{OC} = 10.5	LC_{50} (96 h) = 165 mg/L LC_{50} (14 d) > 100 mg/L	EC_{50} (48 h) = 380 mg/L NOEC (21d) = 100 mg/L	EC_{50} (72 h) > 940 mg/L NOEC (72h) = 556 mg/L	NOEC (16h) = 3,000 mg/L (*P. putida*)	ND

4.10 TXIB (trimethyl pentanyl diisobutyrate)

4.10.1 Physico-chemical properties

TXIB is an ester of the branched alkane trimethyl pentanyl with two butyrate groups. Its CAS no. is 6846-50-0. The vapour pressure is only 0.089 Pa, the water solubility low (1-2 mg/L; 15 mg/L) and the lipophilicity quite high (log K_{OW} is 4.1 or more).

4.10.2 Human health assessment

TXIB was rapidly adsorped, metabolized and excreted. The major route of elimination was urine (47 – 72% total dose) within 5 - 10 days and the majority of this occurring in the first 72 hours. Radioactivity in faeces accounted for 14 – 31% of the dose with elimination being essentially complete by 7 days with the majority isolated after 48 hours. Radiolabeled CO_2 was not detected. In total, excretions accounted for 95-99% of the dose. Residual radioactivity of treated animals approached control by two weeks. Identification of metabolites showed the faeces to contain both 2,2,4-trimethyl pentanediol (TMPD) and TXIB-3-14C indicating esterase cleavage of the two isobutyrates. A small potion of the absorbed material in the urine was unchanged TXIB-3-14C while the majority consisted of metabolites consistent with complete cleavage to the glycol (TMPD) parent molecule. Although much of the urinary metabolite was unidentified it does, nonetheless, represent rapidly cleared material.

TXIB has low acute toxicity by the oral route with LD_{50} in rats reported at > 3,200 mg/kg bw. Dermal LD_{50} in rabbit (OECD 402) was reported at > 2,000 mg/kg bw. LC_{50} in rats exposed to 0.12 mg/L or 5.3 mg/L for 6 hours was > 5.3 mg/L.

Skin irritation was studied in guinea pigs and rabbits. In guinea pigs TXIB was slightly irritating to the skin and in rabbits (OECD 404) no irritation was observed. TXIB was not found irritating to rabbit eyes (OECD 405).

TXIB was not found sensitising to skin in guinea pigs in a test following a protocol similar to OECD 406. In a study on human volunteers using a modified Draize procedure , TXIB was found non-irritating ad did not induce any evidence of sensitisation.

TXIB was studied in a 103 days oral repeated dose toxicity study in rats receiving concentrations of 1% and 1.0% in the diet. There was a slight, significant increase in the relative liver weights in the 1.0% group and in the absolute liver weights in the 1.0% male group when compared to controls. NOAEL was established at 0.1%. In another study rats were exposed to the same concentrations for 52 or 99 days (I: 52 days TXIB diet, II: 99 days TXIB diet, III: 52 days TXIB + 47 days control diet or 52 days control diet + 47 days TXIB diet). From the study it appeared that high doses of TXIB cause significant adaptive changes in the rat liver, and these changes are reversible if the animal is returned to normal diet. NOAEL was 0.1%. In dogs (beagles) fed a diet with 0.1, 0.35 or 1.0% TXIB for 13 weeks, NOAEL was established at 1.0% because of no toxicological significant findings related to treatment.

In a combined repeat dose and reproductive/developmental screening toxicity test (OECD 422), rats were exposed to 30, 150 or 750 mg/kg/day. A NOEL at 30 mg/kg/day was established based on effects on liver and kidneys in the higher dose groups. When evaluating the reproductive toxicity, NOEL (Parental) and NOEL (F_1 offspring) was established at 750 mg/kg/day, as no effects on reproduction (mating, fertility and oestrus cycle, dams during pregnancy and lactation, pubs after birth) related to treatment were observed.

In another combined study (OECD 421 with additional sperm motility asssessment) TXIB was administered in doses of 91, 276 or 905 mg/kg /day in males and 120, 359 and 1,135 mg/kg/day in females. Statistically significant reproductive effects observed in the high dose group include reduced number of implantation sites, reduced mean litter weights on postnatal (PND) 0, reduced mean number of live pubs on PND 4, decreased mean absolute epididymal sperm counts, and reduced absolute and relative testicular sperm counts. The mean number of live pubs per litter was also reduced on PND 0. NOAEL for reproductive and developmental toxicity was 276 mg/kg/day on males and 359 mg/kg/day in females based on reduced number of implantation sites and reduced mean number of live pubs on PND 0.

TXIB did not produce mutagenicity in Ames tests (Japanese guideline) or in ***in vitro*** mammalian CHL cells (Japanese guideline) with and without metabolic activation.

In summary the following profile was identified:

Acute toxicity			Local effects and sensitisation		
LD_{50}, oral mg/kg bw	LD_{50}, dermal mg/kg bw	LC_{50}, inhal.. mg/m^3	Skin irritation	Eye irritation	Sensitisation
> 3,200	> 2,000	> 5,3 mg/L (6h)	No / slight irritation	No irritation	Not sensitising

Repeat dose, genotoxicity, carcinogenicity				Reproductive toxicity		
Repeat dose, NOAEL mg/kg bw/day	Genotoxicity	Carcinogenicity	Maternal toxicity mg/kg bw/day	NOAEL mg/kg bw/day	Reproductive toxicity	Critical endpoint
1000	Negative	ND	1000 (rat)	276 (m)	R: Yes D: No	Red. no. implantations sites and mean no. of live pubs

4.10.3 Environmental assessment

TXIB was found to be inherently biodegradable in the OECD 301C test and the BCF (carp) determined to be in the range 5.2-31 (OECD 305C), i.e. a low bioaccumulation potential. The BCF of 4.1 (or more) indicates a low mobility of TXIB in soil.

Acute toxicity of TXIB to fish: LC_{50} (96 h) = 18 mg/L (OECD 203; ***Oryzias latipes***). In one test (OECD 202) on ***Daphnia magna*** the EC_{50} was found to be 300 mg/L while in another EC_{50} >1.46 mg/L. The 14 days NOEC (reproduction) for ***D. magna*** was determined to 3.2 mg/L in a test basically performed according to OECD principles but apparently not fulfilling all test requirements. The 72 hours biomass-based EC_{50} for algae (***Seleneastrum capricornutum***, now known as ***Pseudokirchneriella subcapitata***) has been determined to 8.0 mg/L using the OECD 201 method. The corresponding 72 h NOEC was 5.3 mg/L.

Table 4.10
Summary of environmental fate and ecotoxicity data on TXIB

Environmental fate			Ecotoxicity				
Biodegradation	Bioaccumulation	Mobility	Fish	Daphnia	Algae	Micro-organisms	Terrestrial
Inherent	BCF = 5.2-31	ND	LC_{50} (96 h) = 18 mg/L	EC_{50} (48 h) >1.46 mg/L NOEC (14d) = 3.2 mg/L	EC_{50} (72h) = 8.0 mg/L NOEC = 5.3 mg/L	ND	ND

4.11 Summary of human health and environmental assessment of alternative plasticisers

4.11.1 Human health assessment summary

Table 4.11 provides an overview of the toxicological properties of the selected alternatives.

All substances have been tested for acute toxicity for at least one exposure route, sensitisation (except ASE), subchronic toxicity and mutagenicity. All substances except ASE, COMGHA and DINA have been tested for both reproductive and developmental toxicity.

With regard to carcinogenicity only ATBC, DEHT and DINCH have been tested in combined chronic toxicity and carcinogenicity studies. For DEGD, DGD and DEHT estrogenic activity has been tested in a uterotrophic assay without positive response.

Most data used for the evaluation are considered of good quality, i.e. studies following accepted guidelines (OECD or US EPA) or studies considered acceptable at the time they were carried out. For some of the studies little information is available to evaluate the quality. However, key information is obtained from IUCLID data sheets, USEPA or OECD HPV robust summaries. Studies evaluated under the USEPA HPV programme are considered to be reliable without restrictions or reliable with restrictions (Klimisch codes 1 and 2, and restrictions in cat. 2 generally not severe).

From the overview it can be seen that all ten substances have low acute toxicity. With regard to local effects most substances are non-irritating to skin and eyes or only produce slight irritation which would not lead to classification. None of the tested substances show any sensitising potential.

Effects from repeated dose toxicity studies mainly include reduced body weight gain, increased organ weights (liver and/or kidney) and for some substances also changes in clinical chemistry or clinical pathology parameters. However, more serious pathological effects were not observed. Only GTA did not show any adverse effects in repeat dose toxicity studies.

Studies to evaluate the potential for reproductive/developmental toxicity primarily show toxic effects on parents and offspring resulting in effects on body weight or relative organ weights. Effects on foetal growth and development of cervical ribs were observed in prenatal development studies with DEGD and DGD. With regard to DEHT it was concluded that DEHT has a low potential to induce reproductive toxicity. TXIB showed statistically significant reproductive and developmental toxicity in a combined study (repeat dose/reproductive-developmental screening). Effects included reduced number of implantation sites, reduced mean litter weights and reduced mean number of live pubs.

Carcinogenicity has only been evaluated for three substances in combined studies with negative outcome.

Table 4.11
Overview of toxicological properties of selected alternatives

Name of substance	CAS No.	Acute toxicity O: oral LD_{50} D: dermal LD_{50} I: inhalation LC_{50}	Local effects / sensitisation	Subchronic / chronic	Carcinogenicity	Mutagenicity / genotoxicity	Reproductive toxicity	Other
ASE	91082-17-6	O: 26,380-31,650 mg/kg D: > 1,055 mg/kg I: ND	Skin: No irritation Eye: No irritation	NOAEL, 90 days: 228 mg/kg/day (m) 282.6 mg/kg/day (f) (increased kidney weight)	ND	Negative (Ames, mammalian cells) Reliable guideline studies for *in vitro* mammalian mutagenicity/genotoxicity. No i*n vivo* studies available.	No reliable data.	-
ATBC	77-90-7	O: > 30 g/kg D: ND I: ND	Skin: No or slight irritation Eye: No or slight irritation Not sensitising	NOAEL, 90 days: 300 mg/kg/day (increased kidney weight) NOAEL, 2 years: 100 mg/kg/day (conservative) NOAEL, 13 weeks: 100 mg/kg/day (m) 300 mg/kg/day (f) (reduced body weight gain, increased liver weights, hepatic hypertrophy)	(No carcinogenicity observed in 2 year oral repeated dose toxicity study) No guideline study available. Existing study reliable with restrictions (lack of detail).	Negative (Ames, mammalian cells, *in vivo/in vitro* UDS test) Reliable (with some restrictions) guideline studies for *in vitro* mammalian mutagenicity/genotoxicity. No i*n vivo* studies available.	Not considered toxic to reproduction (2-generation study) NOAEL: 100 mg/kg/day (parental, offspring) Reliable data available for both reproductive and developmental toxicity. Data for developmental toxicity lack some details.	Weak signs of neurotoxicity
COMGHA	330198-91-9	D: > 2,000 mg/kg	Skin: No irritation Eye: No irritation Not sensitising	NOAEL, 90 days: < 3 ml/kg/day	ND	Negative (Ames, chromosomal aberration test) Reliable guideline studies for *in vitro* mammalian mutagenicity/genotoxicity. No i*n vivo* studies available.	ND	-

Name of substance	CAS No.	Acute toxicity O: oral LD_{50} D: dermal LD_{50} I: inhalation LC_{50}	Local effects / sensitisation	Subchronic / chronic	Carcinogenicity	Mutagenicity / genotoxicity	Reproductive toxicity	Other
DEGD	120-55-8	O: 4,198 mg/kg D: > 2,000 mg/kg I: > 200 mg/L	Skin: No irritation Eye: Slight irritation Not sensitising	NOAEL, 13 week: 1,000 mg/kg/day (reduced body weight gain, haemosiderosis in spleen, hepatocyte hypertrophy)	ND	Negative (Ames, mammalian cells, chromosomal aberration test) Reliable guideline studies for *in vitro* mammalian mutagenicity/genotoxicity. No i*n vivo* studies available.	Developmental tox: NOEL: 1,000 mg/kg/day (maternal) NOAEL: 500 mg/kg bw/day (prenatal dev.) NOEL: 250 mg/kg bw/day (foetal growth) Reproductive tox.: NOAEL: 10,000 ppm (500 mg/kg bw/day) (F_0 and F_1 parents) NOAEL: 3,300 ppm (165 mg/kg bw/day) (offspring) NOEL: 10,000 ppm (500 mg/kg bw/day) (reproductive) Reliable guideline studies with GLP for both developmental and reproductive toxicity..	No estrogenic activity up to 2,000 mg/kg/day (Endpoints: vaginal cornification and uterotrophic response)
DGD	27138-31-4	O: 3,914 mg/kg D: > 2,000 mg/kg I: > 200 mg/L (4h)	Skin: No irritation Eye: Slight irritation Not sensitising	NOAEL, 13 week: 1,000 mg/kg/day (reduced body weight gain, haemosiderosis in spleen, hepatic hypertrophy)	ND	Negative (Ames, mammalian cells, chromosomal aberration test) Reliable guideline studies for *in vitro* mammalian mutagenicity/genotoxicity. No i*n vivo* studies available.	Developmental tox: NOEL: 1,000 mg/kg/day (maternal) NOAEL: 500 mg/kg/day (prenatal dev.) NOEL: 250 mg/kg/day (foetal growth) Reproductive tox.: NOAEL: 10,000 ppm (F_0 and F_1 parents) NOAEL: 10,000 ppm (offspring) Reliable guideline studies with GLP for both developmental and reproductive toxicity..	No estrogenic activity up to 2,000 mg/kg/day (Endpoints: vaginal cornification and uterotrophic response)

Name of substance	CAS No.	Acute toxicity O: oral LD_{50} D: dermal LD_{50} I: inhalation LC_{50}	Local effects / sensitisation	Subchronic / chronic	Carcinogenicity	Mutagenicity / genotoxicity	Reproductive toxicity	Other
DEHT / DOPT	6422-86-2	O: > 5,000 mg/kg D: > 19,670 mg/kg (guinea pig) I: no deaths in mice exposed to saturated vapour (4h)	Skin: Slight irritation Eye: Slight irritation Not sensitising	NOAEL, 90 days, 21 days 500 mg/kg/day (increased relative liver weight) NOEL, 104 weeks, 1500 ppm (79 mg/kg/day (m) and 102 mg/kg/day (f))	2-year study: No signs of tumorigenicity (unreviwed study, few details) 104 week: NOEL: ≥12000 ppm (666 mg/kg bw/day (m) and 901 mg/kg bw/day (f)) - highest dose tested (industry data) No data on guidelines for the studies. The industry study appears to follow established guidelines.	Negative (Ames, chromosomal aberration test) Reliable studies for *in vitro* mammalian mutagenicity/genotoxicity. No i*n vivo* studies available.	Developmental tox: NOEL: 458 mg/kg/day (maternal) NOEL: 747 mg/kg/day (developmental) Reproductive tox.: NOAEL: 500 - 700 mg/kg/day (m) 800 - 1,000 mg/kg/day (f) NOAEL, tox: 150 - 200 mg/kg/day (m) 250 - 300 mg/kg/day (f) (parental, offspring) Reliable guideline studies with GLP for both developmental and reproductive toxicity..	No estrogenic activity (Uterotrophic assay)
DINA	33703-08-1	O: > 5,000 mg/kg D: > 3,160 mg/kg	Skin: No irritation Eye: No irritation Not sensitising	NOAEL, 13 week (dog): 274 mg/kg/day (reduced body weight gain, increased liver weight, elevated enzyme levels, liver and kidney histopathology)	ND	Negative (Ames, mammalian cells) Reliable studies for *in vitro* mammalian mutagenicity/genotoxicity. No i*n vivo* studies available.	No data	-

Name of substance	CAS No.	Acute toxicity O: oral LD_{50} D: dermal LD_{50} I: inhalation LC_{50}	Local effects / sensitisation	Subchronic / chronic	Carcinogenicity	Mutagenicity / genotoxicity	Reproductive toxicity	Other
DINCH	166412-78-8	O: > 5,000 mg/kg D: > 2,000 mg/kg	Skin: Slight irritation Eye: No irritation Not sensitising	NOAEL, 28 days: 318 mg/kg/day (m) 342 mg/kg/day (f) (liver and kidney clinical chemistry) NOAEL, 90 days: 107.1 mg/kg/day (m) 389.4 mg/kg/day (f) (kidney weight changes, degenerated epithelial cells in urine (m)) NOAEL, 12 months: 40 mg/kg bw/day (m) and 200 mg/kg bw/day (f) - I(iver and kidney weight (m) changes)	No findings of relevance for carcinogenicity in humans in combined chronic tox. and carc. test. Reliable guideline study.	Negative (Ames, signs of chromosomal aberration - but considered non-genotoxic). Not found to be clastogenic or aeuploidogenic in micronucleus test. Reliable guideline studies for *in vitro* mammalian mutagenicity/genotoxicity and in vivo mammalian micronucleus test.	No developmental toxicity at doses up to 1,000 mg/kg/day Not considered toxic to reproduction (2-generation study up to 1,000 mg/kg/day) NOAEL, tox.: 100 mg/kg/day (F_1) Reliable guideline/combined guideline studies for both developmental (rat and rabbit) and reproductive (rat) toxicity. in	-
GTA	102-76-1	O: > 2,000 mg/kg D: > 2,000 mg/kg I: > 1,721 mg/m^3	Skin: No irritation Eye: No irritation Not sensitising	Combined repeat dose /dev. screening: No effects at tested doses up to 1,000 mg/kg/day 90 days, inhalation: No signs of toxicity up to 2,220 mg/m^3	ND	Negative (Ames, mammalian cells, chromosomal aberration test, *in vivo* mouse nucleus) Reliable guideline studies for *in vitro* mammalian mutagenicity/genotoxicity and in vivo mammalian micronucleus test.	Combined repeat dose / dev. screening: No significant adverse effect on reproductive parameters or offspring NOAEL(Dev/Repr.): 1000 mg/kg bw/day. Reliable guideline study.	-

Name of substance	CAS No.	Acute toxicity O: oral LD_{50} D: dermal LD_{50} I: inhalation LC_{50}	Local effects / sensitisation	Subchronic / chronic	Carcinogenicity	Mutagenicity / genotoxicity	Reproductive toxicity	Other
TXIB	6846-50-0	O: > 3,200 mg/kg D: > 2,000 mg/kg I: > 5.3 mg/L (6h)	Skin: Slight irritation (guineas pigs) no irritation (rats and humans) Eye: No irritation Not sensitising	NOAEL, 103 days, rat: 0.1% in diet (slight increase in relative and absolute liver weight)	ND	Negative (Ames, mammalian cells) Reliable guideline studies for *in vitro* mammalian mutagenicity/genotoxicity. No i*n vivo* studies available.	Combined repeat dose / dev. screening: NOEL,parental and F1: 750 mg/kg/day No effects on reproduction Combined study: NOAEL: repr., dev.: 276 mg/kg/day (m) 359 mg/kg/day (f) Reliable guideline studies for both developmental and reproductive toxicity..	-

4.11.2 Environmental assessment summary

Table 4.12 summarises the main data on environmental fate (biodegradation, bioaccumulation and mobility) and ecotoxicological effects (fish, daphnia and algae) of the 10 studied phthalate alternatives. The data on effects on bacteria have been omitted in the summary table because the effects were generally negligible at relevant exposure levels, while terrestrial data were so sparse that a comparative evaluation cannot be made for these organisms anyway.

Useful fate data regarding biodegradability (in water) and bioaccumulative properties (either as BCF or log K_{OW}) are available for all alternatives while other fate data are quite variable and incomplete. With regard to ecotoxicological effect data, results from short-term tests with the base-set of organisms - fish, crustaceans and algae - exist for all 10 substances although the duration of some studies deviate from the current OECD standard. The low solubility of many of the phthalate alternatives has rendered it necessary to enhance solubility by means of organic solvents in order to be able to carry out the tests.

Overall, the data obtained are of good quality i.e. they are mostly based on studies performed according to accepted guideline procedures, and the studies have been evaluated (e.g. in the USEPA HPV robust summaries) to be reliable without restrictions or reliable with restrictions (Klimisch codes 1 and 2, and restrictions in cat. 2 generally not severe).

None of the 10 studied alternatives fulfil the criteria for being PBT or vPvB substances.

Table 4.12
Summary of environmental fate and ecotoxicity data on 10 selected possible alternatives to phthalate ester plasticisers

Substance	Environmental fate			Ecotoxicity		
	Biodegradation	Bioaccumulation	Mobility	Fish	Daphnia	Algae
ASE	Not readily biodegradable (31% in 28 d)	Log K_{OW} >6	ND (log K_{OW} indicates low mobility)	LC_{50} (96 h) >100 mg/L	EC_{50} (48 h) >1,000 mg/L	EC50 (72 h) >10 mg/l
ATBC	Ready	BCF = 250 (calculated)	K_{OC} = 1,800 (estimated)	LC_{50} (48 h) = 2.8 mg/L LC_{50} (168h) = 1.9 mg/L	EC_{50} (48 h) = 7.82 mg/L	EC50 (96 h) = 0.148 mg/L (calculated)
COMGHA	Ready	Log K_{OW} = 6.4	"Immobile in soil"	NOEC(LC_{10}) (96h) = 0.28 mg/L	EC_{50} (48 h) = 0.92 mg/L	EC_{50} (72h) = 106 mg/L
DEGD	Ready	BCF = 120 (calculated)	K_{OC} = 540 (calculated)	LC_{50} (96 h) = 3.9 mg/L	EC_{50} (48 h) = 6.7 mg/L	EC_{50} (72 h) = 11 mg/L
DGD	Ready Ultimately biodegradable under anaerobic conditions	Log K_{OW} = 3.9	ND	LC_{50} (96 h) = 3.7 mg/L	EC_{50} (48 h) = 19.3 mg/L	EC_{50} (72 h) = 4.9 mg/L NOEC (72 h) = 1.0 mg/L
DEHT	Inherent	BCF = 393	K_{OC} = 2,000	LC_{50} (7 d) > 0.25 mg/L NOEC (71d) ≥ 0.28 mg/L	EC_{50} (48 h) > 1.4 mg/L NOEC (21d) ≥ 0.76 mg/L	EC_{50} (72 h) > 0.86 mg/L
DINA	Ready	BCF ≥ 1,100 BCF (estimated) = 3.2	ND	LC_{50} (96 h) > 500 mg/L (nominal) LC_{50} (96 h) > 2.6 mg/L (measured)	EC_{50} (48 h) > 100 mg/L NOEC (21d) > 100 mg/L	EC_{50} (72 h) > 100 mg/L
DINCH	Not readily biodegradable (41% in 28 d)	BCF = 189	ND	LC_{50} (96 h) >100 mg/L	EC_{50} (48 h) >100 mg/L NOEC (21d) ≥0.021 mg/L	EC_{50} (72 h) >100 mg/L NOEC (72h) ≥100 mg/L
GTA	Ready	BCF = 1.3	K_{OC} = 10.5	LC_{50} (96 h) = 165 mg/L LC_{50} (14 d) > 100 mg/L	EC_{50} (48 h) = 380 mg/L NOEC (21d) = 100 mg/L	EC_{50} (72 h) > 940 mg/L NOEC (72h) = 556 mg/L
TXIB	Inherent	BCF = 5.2-31	ND	LC_{50} (96 h) = 18 mg/L	EC_{50} (48 h) >1.46 mg/L NOEC (14d) = 3.2 mg/L	EC_{50} (72h) = 8.0 mg/L NOEC = 5.3 mg/L

GTA (triacetin) appears to be easily biodegradable; it does not have bioaccumulative properties and has very moderate toxicity in the aquatic environment.

DEGD, DGD and DINA also come out rather favourable (if using the estimated BCF of 3.2 for DINA), while ATBC and COMGHA come out negatively despite their degradability because of their aquatic toxicities and bioaccumulative properties. ASE and DINCH both have low acute toxicities to aquatic organisms but are not easily degradable and have high log K_{OW} values. DEHT is also not easily biodegradable and is bioaccumulative but its aquatic toxicity cannot be fully evaluated based on the data available.

4.11.3 Health and environmental assessment overview

A simplified overview of the main toxicological and ecotoxicological properties of the evaluated substances is shown in Table 4.13.

In the table a rough overview of the quality and completeness of data is presented using the scoring system indicated in note 4 to the table.

Table 4.13
Overview of main toxicological and ecotoxicological properties

Name of substance	CAS No.	Health					Environment			Data quality / data completeness (CMR and PBT)
		Acute, local and sens. effects (A/L/S)	Carcinogenic (C)	Mutagenic (M)	Repro-toxic (R)	Subchronic toxicity	Persistence	Bioaccumulation	Aquatic Toxicity	
							*1	*2	*3	*4
ASE	91082-17-6	○/○/○	-	○	○	●	● (Not readily)	● P_{ow}	○	2/2
ATBC	77-90-7	○/(○)/○	○	○	○	[●]	○	● BCF	●	1/2
COMGHA	330198-91-9	○/○/○	-	○	-	(●)	○	● P_{ow}	●	1/2
DEGD	120-55-8	○/(○)/○	-	○	(●)	●	○	(○) BCF	●	1/2
DGD	27138-31-4	○/(○)/○	-	○	(●)	●	○	● P_{ow}	●	1/2
DEHT / DOPT	6422-86-2	○/(○)/○	○	○	○	●	● (inherently)	● P_{ow}	(●)	1/2
DINA	33703-08-1	○/○/○	-	○	-	●	○	(●) (conflicting)	○	1/2
DINCH	166412-78-8	○/(○)/○	○	○	○	●	● (Not readily)	● P_{ow}	○	1/2
GTA	102-76-1	○/○/○	-	○	○	○	○	○	○	1/2
TXIB	6846-50-0	○/(○)/○	-	○	●	●	● (inherently)	○ BCF	●	1/2

Notes:

The inherent properties for the investigated substances are summarised using key parameters: acute and local effects, sensitisation, carcinogenicity(C), genetic toxicity (M), reproductive toxicity (R), persistence, bioaccumulation and aquatic toxicity. If data are not available for all parameters or only from non standard test results a tentative assessment is given (shown in parentheses). The symbols: ● identified potential hazard, ○ no identified potential hazard, and – no data available. [] indicate the effects are considered of minor significance.

*1 The terms refer to different biodegradability tests:

Inherently biodegradable: Not meeting the criteria in an "inherent biodegradability" test

Not readily biodegradable: Not meeting the criteria in "ready biodegradability" tests.

*2 ● is based on BCF > 100 or Pow > 3 (BCF prevails over Pow where both values exist).

*3 ●● is used for very toxic and toxic < 10 mg/L.

*4 The following notation is used:

Data quality (first number):

1 Data summaries from recognised, peer reviewed sources (e.g. EU HVP programme, SIDS, SCHENIR, NICNAS) or reliable test data.

2 Data summaries from not peer reviewed sources, considered reliable with restrictions (e.g. IUCLID).

3 Data summaries which do not give sufficient experimental details to evaluate the quality.

Data completeness (second number):

1 Data considered sufficient for classification of CMR effects and according to PBT criteria.

2 Data available about the endpoint, but not considered sufficient for classification.

3 Data not available or relevant for classification of the endpoint.

An average score is assigned based on the sum of scores for C, M, R, P, B and T properties as follows: Sum 6-8=1, Sum 9-14=2 and Sum 14-18=3

5 Technical and economical assessment of alternative plasticisers

5.1 ASE (Alkylsulfonic phenylester)

ASE is a mixture of similar esters of sulfonic acids, phenyl and C10 – C18 alkanes (mixture CAS 70775–94–10). It is marketed by Lanxess (formerly Bayer) under the product name Mesamoll.

Producer's description (extracts)
The producer Lanxess presents ASE as having the following characteristics (Lanxess, 2009b):

- Outstanding gelling capacity with a large number of polymers including PVC and polyurethanes, resulting in lower processing temperatures and shorter processing times.
- High saponification resistance, especially compared to DEHP, due to ASE's chemical structure; this is especially beneficial for articles which come into contact with water and alkalis.
- Good compatibility with a large number of polymers such as polyurethane (PU), polyvinyl chloride (PVC), natural rubber (NR), styrene-butadiene rubber (SBR), blends of styrene-butadiene rubber and butadiene rubber (SBR/BR), isobutylene-isoprene rubber (IIR), acrylonitrile-butadiene rubber (NBR) and chloroprene rubber (CR)
- Outstanding resistance to weathering and light.
- Good dielectric properties which give plasticised PVC outstanding weldability at high frequencies leading to shorter cycle times than with other plasticisers.

Application and market experience
Lanxess has provided information on application areas for ASE among the traditional DEHP, DBP and BBP applications shown in Table 5.1. The table also indicates the level of market experience in each application area according to Lanxess (2009; interpreted from qualitative text by the report authors). Note that Lanxess has indicated significant market experience for most applications, indicating both general plasticiser characteristics and coverage of several of the special performance characteristics of DBP and BBP.

A Danish study (Nilsson et al., 2002) demonstrated the feasibility of ASE as alternative to phthalates in waterbeds (in the plastisol saturated textile lining), where it is used today.

Table 5.1
Applications of ASE and level of market experience in each application, data from Lanxess provided for this study

Application	Market experience *1
Substituting for DEHP	
Polymer applications:	
Calendering of film, sheet and coated products	2
Calendering of flooring, roofing, wall covering	4
Extrusion of hose and profile	2
Extrusion of wire and cable	2
Extrusion of miscellaneous products from compounds	2
Injection moulding of footwear and miscellaneous	?
Spread coating of flooring	2
Spread coating of coated fabric, wall covering, coil coating, etc.	2
Car undercoating	2
Non polymer applications:	
Adhesives/sealant, rubber	2
Lacquers and paint	2
Printing ink	2
Production of ceramics	
Substituting for DBP	
Plasticiser in PVC	2
Plasticiser in other polymers	2
Adhesives	2
Printing inks	2
Miscellaneous:	
Sealants	2
PU foam sealants	2
Nitrocellulose paints	2
Film coatings	3
Glass fibre production	
Cosmetics	
Substituting for BBP	
Polymer applications:	
General PVC (e.g. for moulded plastic parts)	2
Plastisol coating, for flooring	2
Extrusion or spreadcoating: Leather and cloth coating (e.g. for furniture, shoes, bags, suitcases)	2
Films, calendering (e.g. for packaging, calendered flooring, wall covering, etc.)	2
Non polymer applications:	
Sealants (polysulfide based, polyurethane foam sealants, acrylic based; e.g. for windows, construction etc.)	2
Coatings and inks (e.g. for car care products, construction, paper, board)	
Adhesives (polymer based, e.g. for construction, paper)	2

*1: Market experience categories interpretation: 1) Main alternative on market. 2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience.

Key characteristics

Table 5.2 below describes some key characteristics of ASE as alternative to DEHP, DBP and BBP.

Table 5.2
key characteristics of ASE as alternative to DEHP, DBP and BBP

Parameter	Value	Remarks
Efficiency(as plasticiser in PVC compared to DEHP)*1	NA	
Price (primo 2009)	€1,75/kg	Lanxess (2009)
Price relative to DEHP (≈0.8-1€/kg in 2008/2009; 1€ used for calculations)	175%	
Effective price relative to DEHP	NA	
Compatibility/solubility in PVC		Good (Lanxess, 2009, 2009b)
Permanency (migration, evaporation, extraction)	+	High resistance to extraction by saponification (extraction with soap water), (Lanxess, 2009, 2009b)
Processability (fusing speed and temperature, viscosity, etc.)	+	Low gelling temperature. Faster gellation/fusing speed than DEHP; lower than BBP and DBP (Wilson, 1995; Lanxess, 2009, 2009b)
Limitations in use, if any, noted by supplier		Not suitable for polysulfide based sealants (Lanxess, 2009, 2009b)

Notes: *1: Effectiveness indicator, also called substitution factor, indicating the concentration of plasticiser in PVC needed, compared to DEHP, to achieve a specified flexibility according to a well defined method. DEHP has substitution factor 1 per definition, while plasticisers needing lower concentration (more effective) have lower values, and plasticisers needing higher concentrations have higher effectiveness value. *2: According to Lanxess, 2009, 2009b. NA = not available

Table 5.3 below shows some performance data for ASE compared to DEHP. As shown, performance parameters are quite close to DEHP's, except for a higher resistance to kerosene (jet-fuel, lipophilic solvent).

Table 5.3
Technical key parameters of ASE in PVC compared to DEHP (from Sears and Darby, 1982)

Plasticiser in PVC, conc. 40% =67 phr in same PVC resin	Shore A hardness	Volatility,% lost, 1 day at 87 °C over activated carbon	Extracted in water,%	Extracted in kerosene (jet fuel, etc.),%
DEHP	69	4.5	0.01	44
ASE	72	5.3	0.03	4.8

Wilson (1995) states, that were it not for the higher prices of ASE, it could easily be used as an alternative to the general purpose phthalate plasticisers in a wide range of applications. Its structure gives it some advantages over phthalates for certain processes and aggressive environments. The higher polarity results in faster gelling speed than can be achieved with other plasticisers at similar molecular weight and volatility. ASE has high resistance to degradation from weathering, microorganisms and alkaline media.

Conclusions

Based on the above mentioned, it seems reasonable to conclude that ASE appears - based on technical observations only - to be an actual general plasticiser alternative to DEHP. The producer, Lanxess, has indicated significant market experience for most traditional DEHP, DBP and BBP uses, indicating both general plasticiser characteristics and coverage of several of the special performance characteristics of DBP and BBP.

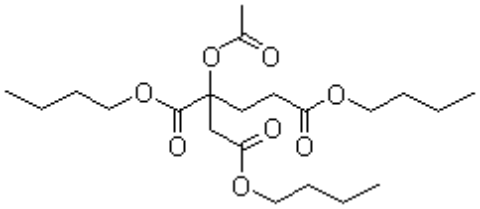
ASE was reported as used for toys by Danish toy manufacturers (with contract production in China), but was not found in the surveys of plasticisers in toys in the Netherlands and Switzerland.

The significantly higher price currently may, however, likely be an impediment to widespread substitution. The potential for attaining reduced prices with increased production volume has not been investigated by the research made for this study.

5.2 ATBC (Acetyl tri-n-butyl Citrate)

ATBC consists of citrate with three ester bonded butyl groups and one acetyl group bonded to the fourth available oxygen atom, see the structure below. The CAS no. is 77-90-7. It is marketed by Vertellus (formerly Morflex), under the product name Citroflex A-4, and by Jungbunzlauer under the products name CITROFOL® BII.

Citrates (ATBC; acetyl tributyl citrate)



Producer's description (extracts)
Vertellus (formerly Morflex) has characterised ATBC as follows in their sales material (Vertellus, 2009b): ATBC is compatible with PVC resin, as well as with a range of other polymers. ATBC has mostly been used in products used for sensitive purposes such as medical products food contact products and children's toys. It is, however, too extractable to be useful in some of the applications in the medical area where contact with lipids is important. For such uses, the larger molecule n-butyryltri-n-hexyl Citrate is recommended by Vertellus. The higher molecular weight citric acid esters, including ATBC, are effective replacements for di-(2-ethylhexyl) phthalate (DEHP) and di-(2-ethylhexyl) adipate (DEHA). ATBC also has similar characteristics to some of the lower molecular weight phthalates in a variety of polymers. ATBC is widely used in food contact polymers. It provides many improvements over DBP in cellulose nitrate films, including lower volatility, better resistance to yellowing, and better adhesion to metals. ATBC is effective in solution coating both paperboard and foil. It is a good plasticizer for vinyl toys. ATBC Special is developed and recommended for medical articles and similar sensitive applications. It is manufactured in a unique, patented process. A special version for use in pharmaceutical coatings is sold as ATBC, PG.

Application and market experience
Vertellus has provided information on application areas for ATBC among the traditional DEHP, DBP and BBP applications shown in Table 5.4. The table also indicates the level of market experience in each application area according to Vertellus (2009).

Table 5.4
Applications of ATBC and level of market experience in each application (data from Vertellus provided for this study)

Application	Market experience *1
Substituting for DEHP	
Polymer applications:	
Calendering of film, sheet and coated products	3
Calendering of flooring, roofing, wall covering	
Extrusion of hose and profile	3
Extrusion of wire and cable	
Extrusion of miscellaneous products from compounds	2
Injection moulding of footwear and miscellaneous	
Spread coating of flooring	
Spread coating of coated fabric, wall covering, coil coating, etc.	
Car undercoating	
Non polymer applications:	
Adhesives/sealant, rubber	2
Lacquers and paint	
Printing ink	2
Production of ceramics	
Other applications (added to list by producer)	
PVC medical articles	2
Toy and childcare articles	1
Substituting for DBP	
Plasticiser in PVC	2
Plasticiser in other polymers	
Adhesives	3
Printing inks	2
Miscellaneous:	
Sealants	3
PU foam sealants	4
Nitrocellulose paints	2
Film coatings	3
Glass fibre production	
Cosmetics	
Substituting for BBP	
Polymer applications:	
General PVC (e.g. for moulded plastic parts)	
Plastisol coating, for flooring	
Extrusion or spreadcoating: Leather and cloth coating	
Films, calendering (e.g. for packaging, calendered flooring, wall covering, etc.)	
Non polymer applications:	
Sealants (polysulfide based, polyurethane foam sealants, acrylic based; e.g. for windows, construction etc.)	
Coatings and inks (e.g. for car care products, construction, paper, board)	3
Adhesives (polymer based, e.g. for construction, paper)	
Nails polish	1

*1: Market experience categories interpretation: 1) Main alternative on market.
2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience.

Note that Vertellus has indicated significant market experience for toys, medical articles, and certain non-polymer applications substituting for both DEHP, DBP and BBP, indicating both general plasticiser characteristics and coverage of some of the special performance characteristics of DBP and BBP.

In a study of alternatives to flexible PVC with phthalates, PVC products plasticised with ATBC were reported to match all of the technical requirements (Postle et al., 2000). Similarly, in a lab test of different alternatives to DEHP for their suitability as plasticisers in PVC for medical uses ATBC was found suitable on all technical parameters tested (Karbæk, 2003).

Key characteristics

According to ECPI, acetyl tributyl citrate is traditionally used in electrical coatings and casings because of its solvating characteristics. It is also used in inks, hair sprays and aerosol bandages (ECPI, 2009).

The table below (from Vertellus, 2009b) compares various characteristics of medical grade PVC with 50 parts by PVC weight plasticiser (= plasticiser concentration in PVC product 33,3% by weight), 2.5 parts by PVC weight stabiliser (Cl/Zn) and 0.25 parts by PVC weight lubricant (stearic acid), milled and pressure died to sheet (mechanical tests by ASTM methods; Vertellus, 2009b). A-4 is ATBC. T4 and Tf are torsion flex indicators at specific conditions (see Vertellus, 2009b).

Table 5.5
Comparison of ATBC (=A-4) with DEHP and DEHA for various parameters, from Vertellus (2009).

	DEHP	DEHA	A-4
Hardness	79	78	78
Tensile Strength, psi	2748	1797	2862
Ultimate Elongation, %	395	414	400
100% Modulus, %	1368	1092	1348
T_4 (10,000 Psi), °C	-8.4	-30.8	-7.6
T, (100,000 psi), °C	-38.8	-66.5	-35.6
Brittle Point, °C	-24.5	-56.5	-18.5
Volatile loss (air), %	4.8	7.1	12.1
Volatile loss (A/C), %	3.4	7.6	7.0
Water extraction, %	0.7	1.5	1.2
Soapy water extraction, %	2.7	11.0	9.5
ASTM Oil #3 extraction, %	11.4	34.7	10.9
Silica gel migration, %	12.2	23.0	17.0

As shown, the mechanical tests and oil extraction for DEHP and A-4 = ATBC are very close, while losses to air and aqueous liquids are a factor 2-3 higher for ATBC. According to the reference, extraction and volatilization

properties can be adjusted by adding another plasticiser, for example the less expensive epoxidized soybean oil (ESO).

Table 5.6 describes some key characteristics of ATBC as alternative to DEHP, DBP and BBP.

Table 5.6
key characteristics of ATBC as alternative to DEHP, DBP and BBP

Parameter	Value	Remarks
Efficiency(as plasticiser in PVC compared to DEHP)*1		Equal to or slightly above 1 judged from Shore A hardness.
Price (primo 2009)	NA	
Price relative to DEHP	300%	ExxonMobil (2009); Karbæk (2003)
Effective price relative to DEHP	NA	
Compatibility/solubility in PVC		Compatible
Permanency (migration, evaporation, extraction)		Extractability in medical appliances with lipid (fat) contact not found optimal, but losses to oil is found similar to DEHP. Losses to air and aqueous liquids are a factor 2-3 higher than for DEHP (Vertellus, 2009b).
Processability (fusing speed and temperature, etc.)		High solvating
Limitations in use, if any, noted by supplier in data for this study		None noted

Notes: *1: Efficiency indicator, also called substitution factor, indicating the concentration of plasticiser in PVC needed, compared to DEHP, to achieve a specified flexibility according to a well defined method. DEHP has substitution factor 1 per definition, while plasticisers needing lower concentration (more effective) have lower values, and plasticisers needing higher concentrations have higher effectiveness value. NA = not available

Table 5.7 below shows some performance data for ATBC compared to DEHP, DBP and BBP. As shown, ATBC results in a similar hardness as DEHP and BBP, and volatility and extractability higher than DEHP and BBP, but lower than DBP (DBP is the smallest, most mobile molecule of these phthalates).

Table 5.7
Technical key parameters of ATBC in PVC compared to DEHP, DBP and BBP (from Sears and Darby, 1982)

Plasticiser in PVC, conc. 40% =67 phr in same PVC resin	Shore A hardness	Volatility,% lost, 1 day at 87 °C over activated carbon	Extracted in water,%	Extracted in kerosene (jet fuel, etc.),%
DEHP	69	4.5	0.01	44
DBP	62	45.4	0.25	9.1
BBP	68	7.7	0.07	3.4
ATBC	73	17.8	0.09	

A Danish toy producing company switched from DINP to ATBC (Citroflex A-4) for all toys for children under 3 years and for toys which are designed to go to the mouth. This particular plasticiser had been given a favourable opinion by the CSTEE for use in toys. However it suffered from a variety of technical drawbacks when compared with DINP. For instance ATBC would not take decoration, it had high migration into adjacent materials leading to swelling and splitting, and there was a need for tooling changes. Development led to the use of a mixture of ATBC, DINCH and DEHT, which could be

blended in a variety of combinations to achieve softened PVC that performed to the required standards of safety and reliability with the existing production setup. These blends could be used in many cases as one-to-one replacements for DINP so that major changes to designs and tooling were not necessary.

Conclusions

The performance of ATBC on some parameters seems similar to DEHP, indicating technical suitability for substitution for some purposes. The producer, Vertellus, has indicated significant market experience for toys, medical articles, and certain non-polymer applications substituting for both DEHP, DBP and BBP, indicating both general plasticiser characteristics and coverage of some of the special performance characteristics of DBP and BBP.

ATBC was found in 9% and 10%, respectively, of products analysed in two European studies of large samples of toys and childcare articles. It was also reported as used for toys by Danish toy manufacturers (with contract production in China); used alone it did however not perform adequately in the established toy production setup due to migration to adjacent materials, print resistance, etc. Used in combination with DINCH and DEHT it could be used with no major processing changes.

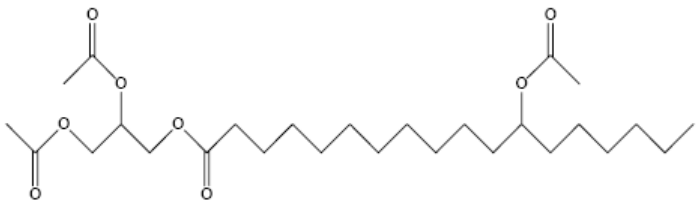
The higher extractability in aqueous solutions and the higher volatility may reduce the performance of ATBC as a plasticiser in PVC, and could perhaps limit its use for certain applications. Similarly, the extractability in medical appliances with lipid (fat) contact may perhaps limit its use for certain medical applications.

The price of ATBC is significantly higher than the price of DEHP, and this may represent a major impediment for its wider use as alternative to DEHP; DBP and BBP.

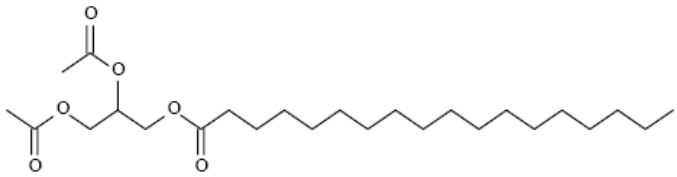
5.3 "COMGHA1" (12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester)

12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester is the main constituent (ca. 84%) in a plasticiser consisting of two castor oil derivatives designated as "COMGHA" (by SCENIHR, 2008) and marketed as Soft-n-Safe by Danisco. The other main component (ca. 10%) is octadecanoic acid, 2,3-(bis(acetoxy)propyl ester. Both main substances are shown below (from, SCENIHR, 2008). The remaining 5% are excess glycerine from the production. In the following technical text, this mixed product is therefore described. The CAS number of the mixture is 736150-63-3.

"COMGHA1" , 12-(Acetoxy)-stearic acid, 2,3-bis (acetoxy)propyl ester; CAS: 330198-91-9



"COMGHA2" ,
Octadecanoic acid, 2,3-(bis(acetoxy)
propyl ester;
CAS: 33599-07-4



Producer's description (extracts)

Danisco characterises COMGHA/Soft-n-safe as follows (Danisco, 2009b):

COMGHA is an efficient, one-to-one replacement for most conventional plasticisers, such as phthalates. In tests, the quality, durability and functional properties achieved have proven equivalent to phthalate-based solutions. Not only that, COMGHA can be directly applied, without any further alteration to the formulation or processing.

COMGHA has been tested against traditional plasticisers in many PVC applications. Compared with plasticisers such as DEHP, DINP and DOA, the efficiency and reliability of COMGHA is consistently on top.

The main application areas for COMGHA are:

- Food contact applications
- Plastisol production
- Medical devices

COMGHA has been compared with DEHP in numerous flexible PVC applications that perform a sensitive medical role, including tubing and medical film. The test results show that COMGHA meets all requirements in the extrusion, calendaring and injection moulding applications where it has been evaluated. In medical applications where plasticiser migration is a particular concern, COMGHA demonstrated high extraction resistance in aqueous and oily solvents.

Compared with traditional plasticisers such as DEHP and DINP, COMGHA performs consistently well in applications such as vinyl flooring, wallpaper, shrink wrap film, textile dyes, ink applications, adhesives and sealants. In application tests with toys for young children, COMGHA provided the same level of efficiency as DEHP, when measured according to the Shore A scale.

While COMGHA has a significantly higher molecular weight than DEHP and a comparable molecular weight to TOTM, its efficiency remains on top. This makes it a viable candidate for applications that demand low volatility. TGA analysis has shown that COMGHA is considerably less volatile than DEHP under all conditions. Although the novel plasticiser is more volatile than a high end permanency plasticiser as TOTM, the lower loading level required means overall volatility is reduced.

Application and market experience

Danisco has provided information on application areas for COMGHA among the traditional DEHP, DBP and BBP applications shown in Table 5.8. The table also indicates the level of market experience in each application area according to Danisco (2009). Note that COMGHA still has relative moderate market experience, albeit with many examples of full scale usage and pilot/lab scale tests, and significant market experience in plastisol applications and cosmetics.

Table 5.8
Applications of COMGHA and level of market experience in each application, data from Danisco provided for this study

Application	Market experience *1
Substituting for DEHP	
Polymer applications:	
Calendering of film, sheet and coated products	3
Calendering of flooring, roofing, wall covering	3
Extrusion of hose and profile	3
Extrusion of wire and cable	3
Extrusion of miscellaneous products from compounds	3
Injection moulding of footwear and miscellaneous	3
Spread coating of flooring	2
Spread coating of coated fabric, wall covering, coil coating, etc.	3
Car undercoating	
Non polymer applications:	
Adhesives/sealant, rubber	4
Lacquers and paint	4
Printing ink	3
Production of ceramics	
Substituting for DBP	
Plasticiser in PVC	2
Plasticiser in other polymers	2
Adhesives	4
Printing inks	3
Miscellaneous:	
Sealants	4
PU foam sealants	
Nitrocellulose paints	
Film coatings	
Glass fibre production	4
Cosmetics	2
Substituting for BBP	
Polymer applications:	
General PVC (e.g. for moulded plastic parts)	4
Plastisol coating, for flooring	3
Extrusion or spreadcoating: Leather and cloth coating (e.g. for furniture, shoes, bags, suitcases)	2
Films, calendering (e.g. for packaging, calendered flooring, wall covering, etc.)	3
Non polymer applications:	
Sealants (polysulfide based, polyurethane foam sealants, acrylic based; e.g. for windows, construction etc.)	
Coatings and inks (e.g. for car care products, construction, paper, board)	
Adhesives (polymer based, e.g. for construction, paper)	

*1: Market experience categories interpretation: 1) Main alternative on market. 2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience.

Key characteristics

Table 5.9 below shows selected comparisons from Danisco (2009b) between COMGHA, DEHP and DINP for selected parameters (more parameters are shown in Danisco, 2009b). Note that COMGHA has very similar characteristics as DEHP and DINP.

Table 5.9 shows comparisons of COMGHA, DEHP and DINP for selected parameters.

Table 5.9
comparison of COMGHA, DEHP and DINP for selected parameters (Danisco, 2009)

Plasticiser (at 40 phr)	Shore A, after 15 sec	Tensile strength, MPa	100% modulus, MPa	Max. elongation,%
COMGHA	88.0	25.0	9.1	367
DEHP	90.0	22.2	8.5	320
DINP	91.5	24.1	9.3	344

Table 5.10 describes some key characteristics of COMGHA as alternative to DEHP, DBP and BBP.

Table 5.10
key characteristics of COMGHA as alternative to DEHP, DBP and BBP

Parameter	Value	Remarks
Efficiency(as plasticiser in PVC compared to DEHP)*1	≈1	(Danisco, 2009b)
Price	3.5 €/kg	Danisco (2009)
Price relative to DEHP (≈0.8-1€/kg in 2008/2009; 1€ used for calculations)	≈350%	
Effective price relative to DEHP	≈350%	
Compatibility/solubility in PVC		Compatible
Permanency (migration, evaporation, extraction)		Much lower extractability than DEHP in acidic water solutions and ethanol/water solutions. Lower extractability in sunflower oil (Danisco, 2009b)
Processability (fusing speed and temperature, viscosity, etc.)		Higher viscosity than DEHP (Danisco, 2009b)
Limitations in use, if any, noted by supplier in data for this study		None noted

Notes: *1: Efficiency indicator, also called substitution factor, indicating the concentration of plasticiser in PVC needed, compared to DEHP, to achieve a specified flexibility according to a well defined method. DEHP has substitution factor 1 per definition, while plasticisers needing lower concentration (more effective) have lower values, and plasticisers needing higher concentrations have higher effectiveness value. NA = not available

Both substances in COMGHA are derived from castor oil produced from castor beans. According to Danisco, the beans must be handpicked which sets limits to production volume and cost reductions (Danisco, 2009). Research is therefore ongoing to produce the substances from other, more abundant, biological substrates (Buck Jensen, 2009).

Conclusions

According to the producer, Danisco, COMGHA still has relative moderate market experience, albeit with many examples of full scale usage and pilot/lab scale tests, and significant market experience in some plastisol application and cosmetics. The producers found technically good performance on key pa-

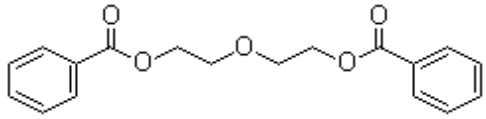
rameters indicating a potential for substituting for DEHP and perhaps for some traditional DBP/BBP uses.

The significantly higher price than DEHP is a major impediment to a wider application of COMGHA. New research initiated needs yet to prove potential for increased production at lower prices.

5.4 DEGD (diethylene glycol dibenzoate)

DEGD is the esterification product of two benzoate groups with diethylene glycol, see structural formula below. Its CAS No. is 120-55-8. It is marketed by Genovique in a mixture with two other dibenzoates under the product name Benzoflex 2088. The two other dibenzoates are dipropylene glycol dibenzoate (DGD; CAS 27138-31-4) and triethylene glycol dibenzoate (CAS 120-56-9). In this section, the mixed product is described. Note that DGD is described separately in the toxicological assessment. DGD is quite similar to DEGD in structure except for two extra methyl groups.

DEGD; diethylene glycol dibenzoate)



(diagram from www.chemblink.com)

Producer's description (extracts)
Benzoflex® 2088 is a high solvating plasticizer primarily known for its exceptional performance in polyvinyl acetate and water-based adhesive systems. It displays good wet tack, set times and open times. It also improves adhesion in acrylic latex caulks (Genovique, 2009b).

In Europe, Benzoflex® 2088 is Genovique's most cost effective replacement for fast fusing phthalate plasticizers used in vinyl applications. It can substitute for phthalates such as BBP, DBP, DIHP and DIBP. It has had its greatest success replacing phthalates in plastisol application, the largest of which is resilient flooring. Over the past five years Benzoflex® 2088 has been established as largest volume non-phthalate, fast fusing plasticizer used in resilient flooring in Europe. Most plastisols were formulated with phthalates in mind, so utilizing an alternative chemistry, like benzoates, requires formulation adjustments (Genovique, 2009).

Application and market experience
Genovique has provided information on application areas for Benzoflex 2088 among the traditional DEHP, DBP and BBP applications shown in Table 5.11. The table also indicates the level of market experience in each application area according to Genovique (2009; interpreted from qualitative text by the report authors). Note the significant market experience in several of the traditional DBP and BBP specialty plasticiser applications and certain DEHP applications, notably in the non-polymer (adhesives, sealants, etc.) and PVC spread coating (plastisol) application fields.

In a study of plasticiser alternatives for non-PVC applications (COWI, 2000), DEGD was proposed by market actors as a substitute for phthalates in adhesives and sealants.

Table 5.11
Applications of Benzoflex 2088 and level of market experience in each application. data from Genovique provided for this study

Application	Market experience *1
Substituting for DEHP	
Polymer applications:	
Calendering of film, sheet and coated products	4
Calendering of flooring, roofing, wall covering	3
Extrusion of hose and profile	3
Extrusion of wire and cable	3
Extrusion of miscellaneous products from compounds	2
Injection moulding of footwear and miscellaneous	2
Spread coating of flooring	2
Spread coating of coated fabric, wall covering, coil coating, etc.	2
Car undercoating	3
Non polymer applications:	
Adhesives/sealant, rubber	1
Lacquers and paint	2
Printing ink	2
Production of ceramics	
Substituting for DBP	
Plasticiser in PVC	1
Plasticiser in other polymers	
Adhesives	1
Printing inks	
Miscellaneous:	
Sealants	
PU foam sealants	
Nitrocellulose paints	2
Film coatings	
Glass fibre production	
Cosmetics	
Substituting for BBP	
Polymer applications:	
General PVC (e.g. for moulded plastic parts)	
Plastisol coating, for flooring	1
Extrusion or spreadcoating: Leather and cloth coating (e.g. for furniture, shoes, bags, suitcases)	2
Films, calendering (e.g. for packaging, calendered flooring, wall covering, etc.)	4
Non polymer applications:	
Sealants (polysulfide based, polyurethane foam sealants, acrylic based; e.g. for windows, construction etc.)	1
Coatings and inks (e.g. for car care products, construction, paper, board)	
Adhesives (polymer based, e.g. for construction, paper)	1

*1: Market experience categories interpretation: 1) Main alternative on market. 2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience.

Key characteristics

DGD is a commonly used benzoate. According to Krauskopf and Godwin (2005), benzoates are generally strong solvates due to the high aromaticity, as are lower molecular weight phthalates such as BBP. Commercial practice includes the use of up to 10–20% of the plasticiser system as "strong solvating" type plasticisers, such as aryl-alkyl phthalates (e.g. BBP), benzoates, etc.

Table 5.12 below describes some key characteristics of Benzoflex 2088 as alternative to DEHP, DBP and BBP.

Table 5.12
key characteristics of Benzoflex 2088 as alternative to DEHP, DBP and BBP

Parameter	Value	Remarks
Efficiency(as plasticiser in PVC compared to DEHP)*1		
Price (primo 2009)		
Price relative to DEHP		"Slightly higher" than DEHP and DBP; equivalent to BBP (Genovique, 2009)
Effective price relative to DEHP		
Compatibility/solubility in PVC		Compatible
Permanency (migration, evaporation, extraction)		App. double volatility as DEHP in plastisols. Three times higher water extraction than DEHP. Much lower organic solvents extraction than DEHP (Genovique, 2009).
Processability (fusing speed and temperature, viscosity, etc.)		Lower gelling/fusing temperature in PVC than with BBP and DEHP. Slightly higher viscosity in plastisols (Genovique, 2009)
Limitations in use, if any, noted by supplier in data for this study		

Notes: *1: Efficiency indicator, also called substitution factor, indicating the concentration of plasticiser in PVC needed, compared to DEHP, to achieve a specified flexibility according to a well defined method. DEHP has substitution factor 1 per definition, while plasticisers needing lower concentration (more effective) have lower values, and plasticisers needing higher concentrations have higher effectiveness value. NA = not available

Table 5.13 below shows some performance data for DEGD (as single substance) compared to DEHP, DBP and BBP. As shown, DEGD has similar characteristics to BBP on these parameters, except for a factor 10 higher extractability in water.

Table 5.13
Technical key parameters of DEGD in PVC compared to DEHP (from Sears and Darby, 1982)

Plasticiser in PVC, conc. 40% =67 phr in same PVC resin	Shore A hardness	Volatility,% lost, 1 day at 87 °C over activated carbon	Extracted in water,%	Extracted in kerosene (jet fuel, etc.),%
DEHP	69	4.5	0.01	44
DBP	62	45.4	0.25	9.1
BBP	68	7.7	0.07	3.4
DEGD (as single substance)	69	5.5	0.75	3.4

Conclusions

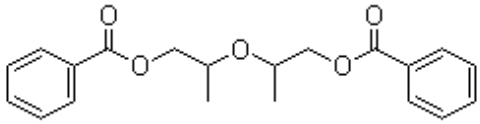
The producer, Genovique, has indicated significant market experience in several of the traditional DBP and BBP specialty plasticiser applications and certain DEHP applications, notably in the non-polymer (adhesives, sealants,

etc.) and PVC spread coating (plastisol) application fields. According to the producer, Benzoflex 2088 has become the main non-phthalate alternative to DBP/BBP in vinyl flooring production in Europe. The higher extractability in water may limit its use for some applications. Prices are indicated as "slightly higher" than DEHP and DBP; equivalent to BBP by Genovique.

5.5 DGD (dipropylene glycol dibenzoate)

DGD is the esterification product of two benzoate groups with dipropylene glycol, see structural formula below. Its CAS No. is 27138-31-4. It is marketed by Genovique under the product name Benzoflex 9-88. DGD is quite similar to DEGD except for two extra methyl groups.

DGD; dipropylene glycol dibenzoate



Producer's description (extracts)
DGD is a high solvating plasticizer that has been used for many years in a wide variety of applications. Its diverse uses include resilient flooring, adhesives, artificial leather cloth and caulk (Genovique, 2009b).

DGD can be used as a replacement for BBP and DBP in vinyl applications. Its gel fusion temperature is identical to BBP and DBP in vinyl plastisol applications allowing it to be as close to a drop-in replacement for BBP and DBP as possible (Genovique, 2009).

Application and market experience
Genovique has provided information on application areas for DGD among the traditional DEHP, DBP and BBP applications shown in Table 5.14. The table also indicates the level of market experience in each application area according to Genovique (2009; interpreted from qualitative text by the report authors). Note the significant market experience in sealants, adhesives, coatings and inks as well as in PVC spread coating (plastisols), extrusion and injection moulding. DGD seems to be capable of substituting for both DEHP, DBP and BBP, indicating coverage of some general plasticiser features as well as some of the special performance characteristics of DBP and BBP.

In a study of plasticiser alternatives for non-PVC applications (COWI, 2000), DGD was proposed by market actors as a substitute for phthalates in adhesives and sealants.

Table 5.14
Applications of DGD and level of market experience in each application, data from Genovique provided for this study

Application	Market experience *1
Substituting for DEHP	
Polymer applications:	
Calendering of film, sheet and coated products	4
Calendering of flooring, roofing, wall covering	3
Extrusion of hose and profile	3
Extrusion of wire and cable	3
Extrusion of miscellaneous products from compounds	2
Injection moulding of footwear and miscellaneous	2
Spread coating of flooring	2
Spread coating of coated fabric, wall covering, coil coating, etc.	2
Car undercoating	3
Non polymer applications:	
Adhesives/sealant, rubber	1
Lacquers and paint	2
Printing ink	2
Production of ceramics	
Substituting for DBP	
Plasticiser in PVC	1
Plasticiser in other polymers	
Adhesives	
Printing inks	
Miscellaneous:	
Sealants	
PU foam sealants	
Nitrocellulose paints	2
Film coatings	
Glass fibre production	
Cosmetics	
Substituting for BBP	
Polymer applications:	
General PVC (e.g. for moulded plastic parts)	
Plastisol coating, for flooring	1
Extrusion or spreadcoating: Leather and cloth coating (e.g. for furniture, shoes, bags, suitcases)	
Films, calendering (e.g. for packaging, calendered flooring, wall covering, etc.)	4
Non polymer applications:	
Sealants (polysulfide based, polyurethane foam sealants, acrylic based; e.g. for windows, construction etc.)	1
Coatings and inks (e.g. for car care products, construction, paper, board)	1
Adhesives (polymer based, e.g. for construction, paper)	

*1: Market experience categories interpretation: 1) Main alternative on market. 2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience.

Key characteristics

DGD is a commonly used benzoate. According to Krauskopf and Godwin (2005), it's preferred use is in PVC flooring products, owing to its strong solvating strength, and it reportedly controls plasticiser bleeding into asphalt adhesives. In vinyl sheet flooring, the benzoate enhances processing, while the low molecular weight contributes a hardened, stain resistant surface, due to volatilization, similar to the effect of BBP in flooring. Benzoates are generally strong solvents due to the high aromaticity, as are lower molecular weight phthalates such as BBP. Commercial practice includes the use of up to 10–20% of the plasticiser system as "strong solvating" type plasticisers, such as aryl-alkyl phthalates (e.g. BBP), benzoates, etc.

Table 5.15 describes some key characteristics of DGD as alternative to DEHP, DBP and BBP.

Table 5.15
key characteristics of DGD as alternative to DEHP, DBP and BBP

Parameter	Value	Remarks
Efficiency(as plasticiser in PVC compared to DEHP)*1	0.98	TURI (2006, citing industry)
Price	0.73 USD/Lb	TURI (2006, citing industry)
Price relative to DEHP (2006: 0.70 USD/Lb)	2009: "Slightly higher" 2006: 104%	2009: "Slightly higher" according to Genovique (2009); also compared to DBP prices. Equivalent to BBP prices. 2006: Calculated from (TURI, 2006, citing industry); Same price relative to BBP.
Effective price relative to DEHP	102%	
Compatibility/solubility in PVC		Compatible
Permanency (migration, evaporation, extraction)		Lover volatility than its competitor BBP (Wilson, 1995).
Processability (fusing speed and temperature, viscosity, etc.)		High solvating, fast fusing; competing with BBP (Wilson, 1995, and others). TURI (2006): Compounding easier than with DEHP; calendering: no issues identified. Some general plasticiser like applications will require blends with slower fusing plasticizers (Genovique, 2009).
Limitations in use, if any, noted by supplier in data for this study		None noted

Notes: *1: Efficiency indicator, also called substitution factor, indicating the concentration of plasticiser in PVC needed, compared to DEHP, to achieve a specified flexibility according to a well defined method. DEHP has substitution factor 1 per definition, while plasticisers needing lower concentration (more effective) have lower values, and plasticisers needing higher concentrations have higher effectiveness value. NA = not available

Table 5.16 below shows some performance data for DGD compared to DEHP, DBP and BBP. As shown, DGD has very similar characteristics to BBP on these parameters, except for a higher extractability in water.

Table 5.16
Technical key parameters of DGD compared to DEHP, DBP and BBP (from Sears and Darby, 1982)

Plasticiser in PVC, conc. 40% =67 phr in same PVC resin	Shore A hardness	Volatility,% lost, 1 day at 87 °C over activated carbon	Extracted in water,%	Extracted in kerosene (jet fuel, etc.),%
DEHP	69	4.5	0.01	44
DBP	62	45.4	0.25	9.1
BBP	68	7.7	0.07	3.4
DGD	71	7.9	0.45	2.9

Wilson (1995) states that the consumption of benzoates had so far been minor in Europe although they were well known in the USA, where they were established plasticisers in the PVC flooring industry. Here they were used as fast fusing stain resistant plasticisers. Wilson states the most commercially important benzoate as DGD, which is broadly competitive with BBP, had the advantage of somewhat lower volatility.

Wilson (1995) also emphasises that DGD had replaced much of the previous C4 phthalate use (i.e. DBP, BBP) in PVA adhesives in the USA. In the mid 1990s this substitution had not yet happened in Europe, partly due to higher benzoate prices in Europe, partly due to less regulatory (health and environment) pressure at that time.

Karbæk (2003), who tested DGD and other plasticisers in PVC for medical purposes, found its poor resistance to extraction by water a major drawback for its use in medical applications. Otherwise DGD performed technically well compared to DEHP on all tested parameters, except for tensile strain at break and flexibility at low temperatures.

BBP is mentioned as a critical component in seals for insulating double glazing (BBP Information Centre, 2009), but it has not been specifically investigated whether DGD or other benzoates can substitute for BBP for this particular application.

Conclusions

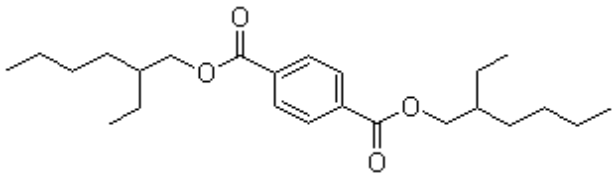
Genovique, the producer of DGD, has indicated significant market experience in sealants, adhesives, coatings and inks as well as in PVC spread coating (plastisols), extrusion and injection moulding. The qualities of DGD seem especially suitable for substitution of BBP, while it may also substitute for some traditional uses of DEHP and DBP. The fact that DGD has for many years been a well known and much used competitor to BBP in USA, especially in the flooring industry and in PVA adhesives, indicates a clear potential for substituting DGD for BBP, from a technical point of view. DGD and benzoates may already have played a part in the observed reductions (COWI, 2009c) of BBP usage in Europe.

The price of DGD seems also to be largely competitive with low molecular weight phthalates such as BBP. Currently the effective price is only slightly higher than the price of BBP. As with many other substitution processes, a price decrease may occur if the market increases in open competition between producers.

5.6 DEHT (di-ethyl-hexyl-terephthalate)

DEHT is a phthalate ester stoekiometrically equal to DEHP, i.e. phthalate ester bound to two ethylhexyl groups, but with a different spatial structure, because one of the carboxylic groups is placed differently on the benzyl ring; see diagram of the structure below ("tere" means tertiary, or third, because the carboxylic group is placed on the third carbon atom counted from the first carboxyl group). DEHT is marketed by Eastman Chemical Company under the product name Eastman 168. It is also marketed by LG Chem under the name LGflex GL300. There are several other producers world wide.

Terephthalate, (DEHT; di 2-ethylhexyl terephthalate); CAS no. 6422-86-2



Producer's description (extracts)

Eastman Chemicals has given the following short presentation of DEHT (Eastman, 2009b): DEHT is a good general purpose plasticizer for PVC, with performance equal or better than most orthophthalate plasticizers (Eds.: "ortho" is the form for most common phthalate plasticisers, such as in DEHP). It offers good performance properties, good low temperature flexibility, resistance to extraction by soapy water and good non-migration properties. In plastisols, DEHT results in low initial viscosity and good keeping viscosity.

Applications/Uses according to Eastman (2009b):

- Bottle caps and closures
- Coatings
- Coatings for cloth
- Electric connectors
- Flexible film
- Pavement striping compounds
- Sheet vinyl flooring
- Toys
- Traffic cones
- Vinyl compounding
- Vinyl gloves
- Vinyl products
- Vinyl water stops
- Walk-off mats

Application and market experience

Eastman Chemicals has provided information on application areas for DEHT among the traditional DEHP, DBP and BBP applications shown in Table 5.17. The table also indicates the level of market experience in each application area according to Eastman (2009; interpreted from qualitative text by the report authors). Note that Eastman has indicated significant market experience for all traditional DEHP uses, except car undercoating and production of ceramics. No traditional DBP and BBP applications have been indicated by Eastman, signalling that they consider DEHT as general plasticiser (such as DEHP, DINP and DIDP).

Table 5.17
Applications of DEHT and level of market experience in each application, data from Eastman Chemicals provided for this study

Application	Market experience *1
Substituting for DEHP	
Polymer applications:	
Calendering of film, sheet and coated products	2
Calendering of flooring, roofing, wall covering	2
Extrusion of hose and profile	2
Extrusion of wire and cable	2
Extrusion of miscellaneous products from compounds	2
Injection moulding of footwear and miscellaneous	2
Spread coating of flooring	2
Spread coating of coated fabric, wall covering, coil coating, etc.	2
Car undercoating	
Non polymer applications:	
Adhesives/sealant, rubber	2
Lacquers and paint	2
Printing ink	2
Production of ceramics	
PVC medical articles	2
Toy and childcare articles	2

*1: Market experience categories interpretation: 1) Main alternative on market. 2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience.

Key characteristics

Table 5.18 below shows selected comparisons from Eastman (2009c) between DEHT ("168"), DEHP ("DOP"), TXIB and other plasticisers of interest for selected parameters (more parameters are shown in Eastman 2009c). Note that DEHT has similar extraction values to DEHP in oil and hexane, and a factor two lower in soapy water. Volatility at elevated temperatures (expressed as activated carbon extraction) is 50%-67% of the volatility of DEHP. The low temperature flexibility of DEHT in PVC is equal to that of DEHP, whereas 100% modulus is app. 20% higher than for DEHP indicating slightly lower efficiency of DEHT (substitution factor 1.03) than DEHP. DEHT has about half the viscosity of DEHP in plastisols.

Table 5.18
Comparison between DEHT ("168"), DEHP ("DOP"), TXIB and other plasticisers (from Eastman, 2009c)

Soapy Water Extraction (% wt loss)			Oil Extraction (% wt loss)			Hexane Extraction (% wt loss)		
Eastman Plasticizer	Plastisols	Milled	*Eastman* Plasticizer	Plastisols	Milled	*Eastman* Plasticizer	Plastisols	Milled
TOTM	0.2	0.1	*TXIB*[f]	14	6.3	*TXIB*[f]	31	24
168	0.5	0.4	DOP	15	8.3	168	31	26
DOP	1.1	0.3	168	16	10	DOP	34	26
TXIB[f]	1.7	1.2	TOTM	24	10	TOTM	35	26
DOA	1.9	0.9	DOA	31	18	DOA	35	29

Activated Carbon Extraction (% wt loss)[c]		
Eastman Plasticizer	Plastisols	Milled
TOTM	0.8	0.5
168	1.2	1.0
DOP	2.5	1.5
DOA	3.7	2.8
TXIB[f]	7.0	6.0

s

Plastisol Viscosity P (Pa·s)[d]		
Eastman Plasticizer	1 Day	21 Days
DOA	45 (4.5)	90 (9.0)
168	75 (7.5)	110 (11.0)
TXIB[f]	95 (9.5)	180 (18.0)
DOP	120 (12.0)	220 (22.0)
TOTM	190 (19.0)	265 (26.5)

Notes: Plastisols contain 60 phr plasticiser; milled and calendered PVC contains 50 phr plasticiser; phr meaning parts per 100 parts hard PVC by weight.
a) Stress at which PVC is elongated 100%. Lower value indicates higher efficiency of plasticiser (ASTM D638). b) Temperature at which the shown stiffness (torsion) is reached (ASTM D1043). c) Indication of volatility at elevated temperatures (ASTM D1203). d) Brookfield viscosity, determined with a number 4 spindle at 6rpm and 23 C.

Table 5.19 shows another performance data set for DEHT compared to DEHP. As shown, DEHT results in quite similar hardness as DEHP on these parameters. The volatility of DEHT is somewhat lower, and the extractability in water and kerosene is somewhat higher.

Table 5.19
Technical key parameters of DEHT compared to DEHP (from Sears and Darby, 1982)

Plasticiser in PVC, conc. 40% =67 phr in same PVC resin*1	Shore A hardness*2	Volatility,% lost, 1 day at 87 °C over activated carbon	Extracted in water,%	Extracted in kerosene (jet fuel, etc.),%
DEHP (PVC2)	73	3.6	0.02	54.7
DEHT (PVC2)	76	1.9	0.09	70.8

Table 5.20 below describes some generalised key characteristics of DEHT as alternative to DEHP.

Table 5.20
key characteristics of DEHT as alternative to DEHP

Parameter	Value	Remarks
Efficiency(as plasticiser in PVC compared to DEHP)*1	1.03	TURI (2006)
Price	0.74 USD/Lb	TURI (2006)
Price relative to DEHP (2006: 0.70 USD/Lb)	106%	TURI (2006) Also according to Krauskopf and Godwin (2005), DEHT is commercially available at similar price as DEHP.
Effective price relative to DEHP	109%	TURI (2006)
Compatibility/solubility in PVC		Compatible
Permanency (migration, evaporation, extraction)		Similar to DEHP, slightly higher permanence on some parameters, slightly lower on others, see above (Eastman, 2009c).
Processability (fusing speed and temperature, viscosity, etc.)	See some values in Table 5.18 above	Overall very similar to DEHP and DINP (Eastman, 2009; TURI, 2006). Half the viscosity in plastisols as DEHP (advantage of DEHT); slightly higher gelling temperatures than DEHP (Eastman, 2009c).
Limitations in use, if any, noted by supplier in data for this study		Poor weatherability properties for external applications such as roofing and coil coating (Eastman, 2009)

Notes: *1: Efficiency indicator, also called substitution factor, indicating the concentration of plasticiser in PVC needed, compared to DEHP, to achieve a specified flexibility according to a well defined method. DEHP has substitution factor 1 per definition, while plasticisers needing lower concentration (more effective) have lower values, and plasticisers needing higher concentrations have higher effectiveness value. NA = not available.

In practice, terephthalates are more commonly used in the USA than elsewhere (TURI, 2006).

Conclusions

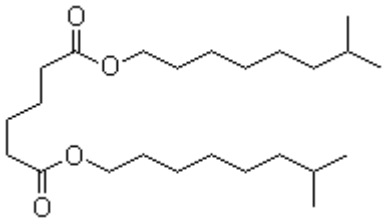
All available information indicates that, technically, DEHT may be a good substitute for most or all traditional DEHP uses. In practice, terephthalates are more commonly used in the USA than elsewhere. DEHT was found in 7% and 10%, respectively, of products analysed in two European surveys of large samples of toys and childcare articles. It was also reported as used for toys by Danish toy manufacturers (with contract production in China).

According to 2006 information, DEHT is slightly more expensive than DEHP. As with many other substitution processes, a price decrease may occur if the market increases in open competition between producers.

5.7 DINA (diisononyl adipate)

DINA is formed by an adipate (hexanoic acid) ester bound with two C-9 alkanes, see diagram. It is marketed by ExxonMobil under the product name Jayflex-DINA, by BASF under the product name Plastomoll DNA, and formerly by Lanxess under the product name Adimoll® DN.

DINA = di isononyl adipate; CAS 33703-08-1



www.chemblink.com

Producers' descriptions (extracts)

BASF has given the following short presentation of DINA (BASF, 2009): DINA is a nearly colourless, clear and practically anhydrous liquid with a hardly noticeable odour. It is soluble in the usual organic solvents and is miscible and compatible with all of the monomeric plasticizers commonly used in PVC. In water DINA is soluble only in very small amounts. Owing to its chemical structure, DINA permits – preferably, in combination with phthalates and polymeric plasticizers – the production of plasticized PVC products with exceptionally good low temperature properties. PVC plasticized with DINA has far less volatility than, for example, PVC plasticized with DOA.

ExxonMobil has given the following short presentation of DINA (ExxonMobil, 2009b):

Improved permanent adipate widely used in a variety of end-uses.

- Low temperature flexibility, low freezing point
- Lower volatility/higher permanence than DOA
- Enhanced viscosity stability and air release properties in plastisols
- Partial replacement for phthalates to improve low temperature flexibility

Applications:

- Films
- Shrink wrap
- Electrical wire jacket

Application and market experience

Neither BASF nor ExxonMobil has wished to provide detailed feedback for this project on DINA's suitability for substituting for DEHP, DBP and BBP.

In a study of plasticiser alternatives for non-PVC applications (COWI, 2000), DINA was proposed by market actors as a substitute for phthalates in adhesives, printing inks, paint and lacquer, and rubber.

Key characteristics

The family of adipic acid esters used in PVC applications improves low temperature performance relative to phthalates and give significantly lower plastisol viscosities in plastisol applications, due to the lower inherent viscosities of the plasticisers themselves (ECPI, 2009).

Table 5.21 shows some performance data for DINA compared to DEHP, DBP and BBP. As shown, DINA has similar hardness and volatility as DEHP, but higher extractability in water and kerosene.

Table 5.21
Technical key parameters of DINA compared to DEHP, DBP and BBP (from Sears and Darby, 1982)

Plasticiser in PVC, conc. 40% =67 phr in same PVC resin	Shore A hardness	Volatility,% lost, 1 day at 87 °C over activated carbon	Extracted in water,%	Extracted in kerosene (jet fuel, etc.),%
DEHP	69	4.5	0.01	44
DBP	62	45.4	0.25	9.1
BBP	68	7.7	0.07	3.4
DINA	72	4.1	0.14	80.4

Table 5.22 describes some generic characteristics of DINA as alternative to DEHP, DBP and BBP.

Table 5.22
key characteristics of DINA as alternative to DEHP, DBP and BBP

Parameter	Value	Remarks
Efficiency(as plasticiser in PVC compared to DEHP)*1	0.98	
Price (primo 2009)	NA	
Price relative to DEHP	150-200% ≈130%	ExxonMobil (2009) Arbeitsgemeinschaft PVC und Umwelt e.V. (2006; statement for adipates in general)
Effective price relative to DEHP	NA	
Compatibility/solubility in PVC		Compatible
Permanency (migration, evaporation, extraction)		Far less volatility in PVC than DOA (BASF, 2009); DOA is slightly more volatile than DEHP (Eastman, 2009c)
Processability (fusing speed and temperature, viscosity, etc.)		Enhanced viscosity stability and air release properties in plastisols
Limitations in use, if any, noted by supplier in data for this study		NA

Notes: *1: Efficiency indicator, also called substitution factor, indicating the concentration of plasticiser in PVC needed, compared to DEHP, to achieve a specified flexibility according to a well defined method. DEHP has substitution factor 1 per definition, while plasticisers needing lower concentration (more effective) have lower values, and plasticisers needing higher concentrations have higher effectiveness value. NA = not available

Conclusions

It has not been possible to get detailed application data compared to DEHP, DBP and BBP for DINA from producers. Among the adipates, DEHA (or DOA) is the most used. It was however not included for further investigation in this study because it was reported by SCENIHR (2008) to have reproductive toxicity. Instead DINA was chosen for further study. In PVC DINA has similar hardness and volatility as DEHP, but higher extractability in water and kerosene. DINA has mostly been used for low temperature PVC applications and in PVC film/wrapping. According to the producers, PVC plasticized with DINA has far less volatility than, for example, PVC plasticized with DEHA. DINA seems therefore potentially more suitable than DEHA, from a technical point of view, as an alternative to DEHP than DEHA. DINA seems currently only to have a small European market and data for DINA are scarcer than for DEHA. In fact two producers have ceased marketing of DINA on the European market. However, DINA was found in 6% and 4%, respectively, of products analysed in two European studies of large samples of toys and childcare articles. It was also reported as used for toys by Danish toy manufactur-

ers (with contract production in China). The data available for this study does not allow clear-cut conclusions as regards DINA's suitability as alternative to DEHP, but DINA could perhaps be worth investigating in future technical explorations for alternatives.

The price for DINA is currently somewhat higher than for DEHP, but as mentioned the market is small and DINA is used as a specialty plasticiser.

5.8 DINCH (di-isononyl-cyclohexane-1,2dicarboxylate)

DINCH is the hydrogenated parallel to DINP, with the difference that the ring structure is cyclohexane (a cyclic alkyl hydrocarbon) instead of a benzene ring (an aromate). Its CAS no. is 166412-78-8. It is marketed by BASF as Hexamoll DINCH. There may be other producers outside the EU.

Producer's description (extracts)

BASF describes DINCH as follows (BASF, 2009): The combination of an good toxicological profile and a very low migration rate makes DINCH the plasticizer of choice for medical devices made with soft PVC products such as tubes for internal feeding and haemodialysis bags, respiratory tubes, catheters, gloves and breathing masks.

DINCH is the ideal additive for toys. Thanks to its low migration rate, lack of odour and technical suitability, DINCH is the plasticizer of choice for toys and children’s articles such as dolls, inflatables and balls, figurines, modelling clay, swimming aids, baby and childcare articles, wire and cable for toys.

Thanks to its toxicological profile, its low migration rate, and especially the low solubility in water and ethanol, this additive is developed for food contact applications such as cling film, hoses, sealants and cap closures, crown corks, artificial wine corks, gaskets and gloves.

DINCH is also suitable for other applications where safety is needed, also outside PVC: Thermoplastics and polar rubbers, coatings and printing inks, dispersions, adhesives, cosmetics (e.g. nail polish), masterbatches, artificial leather, textile coatings (e.g. rain coats), erasers, film and sheets (e.g. lifestyle bags).

Application and market experience

BASF has not wished to provide detailed feedback for this project on DINCH's suitability for substituting for DEHP, DBP and BBP.

In 2007, BASF raised its DINCH production capacity from 25,000 to 100,000 tonnes/yr (MPW, 2008), indicating an increasing demand.

Key characteristics

Table 5.23 below describes some key characteristics of DINCH as alternative to DEHP, DBP and BBP.

Table 5.23
key characteristics of DINCH as alternative to DEHP, DBP and BBP

Parameter	Value	Remarks
Efficiency (as plasticiser in PVC compared to DEHP)*1	NA	
Price	$0.91 /lb	TURI (2006)
Price relative to DEHP (2006: 0.70 USD/Lb)	130%	TURI (2006)
Effective price relative to DEHP	NA	
Compatibility/solubility in PVC		Compatible
Permanency (migration, evaporation, extraction)		Migration levels eight times lower than that of DEHP (MPW, 2008).
Processability (fusing speed and temperature, viscosity, etc.)		NA
Limitations in use, if any, noted by supplier in data for this study		NA

Notes: *1: Efficiency indicator, also called substitution factor, indicating the concentration of plasticiser in PVC needed, compared to DEHP, to achieve a specified flexibility according to a well defined method. DEHP has substitution factor 1 per definition, while plasticisers needing lower concentration (more effective) have lower values, and plasticisers needing higher concentrations have higher effectiveness value. NA = not available

Conclusions

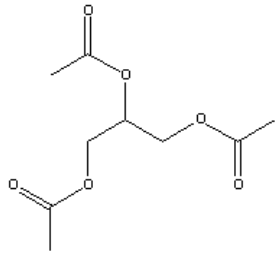
The producer's sales appraisal indicates a relatively wide usage of DINCH for general plasticiser purposes, where safety is prioritised. The production capacity has been raised substantially, indicating a growing demand and market experience. More detailed information of applications substituting for DEHP; DBP and BBP has not been available from the producer. DINCH was the most frequently found plasticiser in two European studies of large samples of toys and childcare articles. It was found in 25% and 48%, respectively, of the analysed products. It was also reported as used for toys by Danish toy manufacturers (with contract production in China). The data available does not allow a closer assessment of DINCH's technical suitability as alternative to DEHP, DBP and BBP.

Sales prices in 2006 were somewhat higher than DEHP. As with many other substitution processes, a price decrease may occur if the market increases in open competition between producers.

5.9 GTA (glycerol triacetate)

GTA is an ester of glycerol and three acetate groups, see diagram below. Its CAS no. is 102-76-1. It is marketed by Lanxess and Eastman under the name Triacetin.

Glyceryl triacetate (GTA, Triacetin)



Producer's description (extracts)

Lanxess (2009) presents GTA as follows: Triacetin is used for the solidification of acetyl cellulose fibres in the manufacture of cigarette filters. The water content must be kept constant to achieve constant solidification. Triacetin is also used as a support for flavourings and essences in the food industry and as a plasticiser for chewing gum. In technical applications, Triacetin is used for example as a core sand binder in the metal foundry sector. Another application is inks and printing inks. Triacetin is used as a highly effective plasticiser for cellulose-based plastics.

The major features of Triacetin are:

- good suitability for the solidification of acetyl cellulose fibres for the manufacture of cigarette filters
- very good dissolving power for a number of organic substances
- good plasticising effect for various plastics such as cellulose acetates or celluloseacetobutyrates
- good plasticising effect for cellulose-based paints
- good compatibility with natural and synthetic rubber
- good light resistance

Eastman presents GTA as follows (Eastman, 2009d): GTA is used as a plasticizer for cellulosic resins and is compatible in all proportions with cellulose acetate, nitrocellulose, and ethyl cellulose. GTA is useful for imparting plasticity and flow to laminating resins, particularly at low temperatures, and is also used as a plasticizer for vinylidene polymers and copolymers. It serves as an ingredient in inks for printing on plastics, and as a plasticizer in nail polish. GTA is approved by the FDA for food packaging and many other food-contact applications.

Application and market experience

Lanxess has provided information on application areas for GTA among the traditional DEHP, DBP and BBP applications shown in Table 5.24. The table also indicates the level of market experience in each application area according to Lanxess (2009; interpreted from qualitative text by the report authors). Note that Lanxess has indicated significant market experience for adhesives, coatings and inks and examples of full scale experience in a number of other non-polymer traditional DBP and BBP uses. Lanxess has not indicated use of GTA in any traditional DEHP uses.

Table 5.24
Applications of GTA and level of market experience in each application, data from Lanxess provided for this study

Application	Market experience *1
Substituting for DEHP	
Plasticiser in PVC	
Plasticiser in other polymers	
Adhesives	2
Printing inks	3
Miscellaneous:	
Sealants	
PU foam sealants	
Nitrocellulose paints	3
Film coatings	
Glass fibre production	
Cosmetics	
Substituting for BBP	
Polymer applications:	
General PVC (e.g. for moulded plastic parts)	
Plastisol coating, for flooring	
Extrusion or spreadcoating: Leather and cloth coating (e.g. for furniture, shoes, bags, suitcases)	
Films, calendering (e.g. for packaging, calendered flooring, wall covering, etc.)	
Non polymer applications:	
Sealants (polysulfide based, polyurethane foam sealants, acrylic based; e.g. for windows, construction etc.)	
Coatings and inks (e.g. for car care products, construction, paper, board)	2
Adhesives (polymer based, e.g. for construction, paper)	

*1: Market experience categories interpretation: 1) Main alternative on market. 2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience.

Key characteristics

Table 5.25 describes some key characteristics of GTA as alternative to DEHP, DBP and BBP.

Table 5.25
key characteristics of GTA as alternative to DEHP, DBP and BBP

Parameter	Value	Remarks
Efficiency (as plasticiser in PVC compared to DEHP)*1	NA	
Price (primo 2009)	€1,50/KG	Lanxess (2009)
Price relative to DEHP (≈0.8-1€/kg in 2008/2009; 1€ used for calculations)	150%	
Effective price relative to DEHP	NA	
Limitations in use, if any, noted by supplier in data for this study		NA

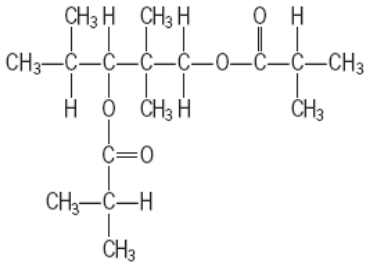
Notes: *1: Efficiency indicator, also called substitution factor, indicating the concentration of plasticiser in PVC needed, compared to DEHP, to achieve a specified flexibility according to a well defined method. DEHP has substitution factor 1 per definition, while plasticisers needing lower concentration (more effective) have lower values, and plasticisers needing higher concentrations have higher effectiveness value. NA = not available

Conclusions
According to a producer, GTA can substitute for DBP and BBP in adhesives, inks and coatings. The price of GTA is somewhat higher that DEHP (and DBP and BBP). The data available does not allow a closer assessment of GTA's technical suitability as alternative to DEHP, DBP and BBP.

5.10 TXIB (trimethyl pentanyl diisobutyrate)

TXIB is an ester of the branched alkane trimethyl pentanyl with two butyrate groups. Its CAS no. is 6846-50-0. Until 2006, it was marketed by Eastman as TXIB plasticiser, but since then it has been renamed TXIB formulation additive.

TXIB



(Eastman, 2009e)

Producer's description (extracts)
Eastman has given the following presentations of TXIB (Eastmann, 2006, 2009f): TXIB formulation additive is a superior primary plasticiser for PVC plastisols. It has good compatibility with PVC, and it is compatible with all common primary and secondary plasticisers. TXIB provides low viscosity characteristics in plastisols with good viscosity stability over time. TXIB is the lowest viscosity (9 cps) additive available to the flexible PVC industry. TXIB is completely compatible with PVC in all proportions and is usually blended with general-purpose plasticizers such as DOP or DOTP. The unique low viscosity makes this material particularly suitable for PVC plastisols and often allows adding additional fillers to the plastisol, resulting in a cost savings. TXIB has efficiency generally equal to DOP, which makes substitution in a vinyl formulation very easy. It imparts a dry surface to the vinyl, excellent resistance to staining, and physical properties equivalent to DOP. TXIB is also used in inks, coatings, urethane elastomers, and nail polish lacquers.

Application/Uses:

- Automotive OEM
- Coatings for automotive plastics
- Lithographic and letterpress oil-based inks
- Nail care
- Phthalate-free diluent for MEKP formulations
- Plastisols
- Sheet vinyl flooring
- Toys/Sporting goods
- Traffic cones
- Vinyl compounding
- Vinyl gloves
- Wall coverings

Application and market experience

Eastman has not wished to provide detailed feedback for this project on TXIB's suitability for substituting for DEHP, DBP and BBP. Eastman has informed that TXIB cannot be used as a direct replacement for DEHP, DBP or BBP. TXIB is used to lower the viscosity of plastisols; one function DBP has been used for. TXIB does however not increase gellation speed for faster production, as DBP and BBP is used for. TXIB cannot work as a primary plasticiser (Eastman, 2009).

In a study of plasticiser alternatives for non-PVC applications (COWI, 2000), TXIB was proposed by market actors as a substitute for phthalates in adhesives and sealants.

Key characteristics

Table 5.26 below shows selected comparisons from Eastman (2009c) between TXIB, DEHP ("DOP"), DEHT ("168") and other plasticisers of interest for selected parameters (more parameters are shown in reference). Note that TXIB in PVC has lower extractability in oil and hexane than DEHP, but higher in soapy water. The modulus (resistance to elongation) and low temperature flexibility is similar to DEHP, while the volatility of TXIB is a factor three higher than DEHP. Plastisol viscosities are lower than for DEHP.

Table 5.26
Comparison between DEHT ("168"), DEHP ("DOP"), TXIB and other plasticisers (from Eastman, 2009c)

Soapy Water Extraction (% wt loss)			Oil Extraction (% wt loss)			Hexane Extraction (% wt loss)		
Eastman Plasticizer	Plastisols	Milled	*Eastman* Plasticizer	Plastisols	Milled	*Eastman* Plasticizer	Plastisols	Milled
TOTM	0.2	0.1	*TXIB*[f]	14	6.3	*TXIB*[f]	31	24
168	0.5	0.4	DOP	15	8.3	168	31	26
DOP	1.1	0.3	168	16	10	DOP	34	26
TXIB[f]	1.7	1.2	TOTM	24	10	TOTM	35	26
DOA	1.9	0.9	DOA	31	18	DOA	35	29

100% Modulus psi (MPa)[a]			Low-Temperature Flexibility Temperature Where T = 35,000 psi (241 MPa),[b] °C			Activated Carbon Extraction (% wt loss)[c]		
Eastman Plasticizer	Plastisols	Milled	*Eastman* Plasticizer	Plastisols	Milled	*Eastman* Plasticizer	Plastisols	Milled
DOA	800 (5.5)	1,050 (7.2)	DOA	–57	–54	TOTM	0.8	0.5
TXIB[f]	1,000 (6.9)	1,600 (11.0)	168	–38	–26	168	1.2	1.0
DOP	1,050 (7.2)	1,550 (10.7)	DOP	–38	–26	DOP	2.5	1.5
168	1,250 (8.6)	1,600 (11.0)	*TXIB*[f]	–38	–24	DOA	3.7	2.8
TOTM	1,250 (8.6)	1,850 (12.8)	TOTM	–36	–20	*TXIB*[f]	7.0	6.0

Plastisol Viscosity P (Pa·s)[d]		
Eastman Plasticizer	1 Day	21 Days
DOA	45 (4.5)	90 (9.0)
168	75 (7.5)	110 (11.0)
TXIB[f]	95 (9.5)	180 (18.0)
DOP	120 (12.0)	220 (22.0)
TOTM	190 (19.0)	265 (26.5)

Notes: Plastisols contain 60 phr plasticiser; milled and calendered PVC contains 50 phr plasticiser; phr meaning parts per 100 parts hard PVC by weight.
a) Stress at which PVC is elongated 100%. Lower value indicates higher efficiency of plasticiser (ASTM D638). b) Temperature at which the shown stiffness (torsion) is reached (ASTM D1043). c) Indication of volatility at elevated temperatures (ASTM D1203). d) Brookfield viscosity, determined with a number 4 spindle at 6rpm and 23 C.

Table 5.27 below shows some other performance dataset for TXIB compared to DEHP, DBP and BBP. As shown, here TXIB has higher hardness (lower efficiency) than the phthalates, high volatility (yet lower than DBP) and much higher extractability in water. Extractability in kerosene is higher than BBP, but lower than DEHP and DBP.

Table 5.27
Technical key parameters of TXIB compared to DEHP, DBP and BBP (from Sears and Darby, 1982)

Plasticiser in PVC, conc. 40% =67 phr in same PVC resin	Shore A hardness	Volatility,% lost, 1 day at 87 °C over activated carbon	Extracted in water,%	Extracted in kerosene (jet fuel, etc.),%
DEHP	69	4.5	0.01	44
DBP	62	45.4	0.25	9.1
BBP	68	7.7	0.07	3.4
TXIB	76	23.7	2.83	5.2

Table 5.28 below describes some key characteristics of TXIB as alternative to DEHP, DBP and BBP.

Table 5.28
key characteristics of TXIB as alternative to DEHP, DBP and BBP

Parameter	Value	Remarks
Efficiency (as plasticiser in PVC compared to DEHP)*1		Close to 1 (Eastman, 2009f)
Price (primo 2009)	NA	
Price relative to DEHP	NA	
Effective price relative to DEHP	NA	
Compatibility/solubility in PVC		Compatible
Permanency (migration, evaporation, extraction)		High volatility, see below (Wilson, 1995)
Processability (fusing speed and temperature, etc.)		Gives low viscosity to plastisols (Eastman, 2009f)
Limitations in use, if any, noted by supplier in data for this study		NA

Notes: *1: Efficiency indicator, also called substitution factor, indicating the concentration of plasticiser in PVC needed, compared to DEHP, to achieve a specified flexibility according to a well defined method. DEHP has substitution factor 1 per definition, lower = more effective, higher = less effective. NA = not available

According to Wilson (1995), TXIB shows unique performance parameters in PVC plastisols. It is a useful component of plastisols formulated to give hard end products since it confers little viscosity at low levels of addition. It has been widely used in cushion vinyl flooring for this purpose, usually in conjunction with BBP; this use has however declined greatly in the 1990s as its high volatility causes unacceptable emissions from end products.

Conclusions

TXIB seems to have some technically relevant characteristics as plasticiser. TXIB was found in many products analysed, 25% and 11% respectively, in two European studies of large samples of toys and childcare articles (its presence need not have been as a primary plasticiser). Given the fact that the producer does not consider TXIB an alternative to DEHP, DBP or BBP, and the information that the usage of TXIB in vinyl flooring has declined in the 1990s due to high emissions from end products, it seems that TXIB should maybe not be seen as a suitable alternative to any of these substances.

5.11 Summary and discussion of technical and economical assessment of alternative plasticisers

The technical description in this report of ten selected alternatives to DEHP, DBP and BBP is based on the producers' assessments of relevant application fields and experience on the market, as well as the evidence of already established practises, especially in the toys, foodstuffs and medical product fields, but also for other end-uses. Based on the available information, a number of suitable alternative plasticisers have been identified for most applications. Some of the alternative plasticisers have a broad application scope, others are more specialised. A summary of the assessed alternatives is given in Table 5.29. A summary of some technical performance parameters for the assessed alternatives compared to DEHP, DBP, BBP and other selected phthalates is given below in annex 3. For some of the substances the manufacturers have provided information on market experience. The data are summarised in Table 5.30. Some of the substances, for which specific information on market experience has not been supplied (e.g. DINCH), certainly have some experience as indicated by the production volumes of the substances.

Industry may have, or may get in the future, more knowledge on the possibilities and limitations of the described plasticisers, which can feed into the decision-making process as regards regulation of DEHP, DBP and BBP. So far, the dominance for many years of DEHP and other ortho-phthalate plasticisers may have naturally limited the motivation to get more full scale experience with other plasticiser types. Under other circumstances, driven by other priorities, the experience with so far less favoured plasticisers would inevitably increase. The expenses associated with such additional research and implementation has not been assessed in this study. The research would however not have to start from scratch, as many relevant substances have been investigated for plasticiser characteristics in early research.

DINP and DIDP have become dominating alternatives to DEHP due to their closeness in performance to DEHP, their availability and their only moderately higher costs. As mentioned, these ortho-phthalates were not included for deeper assessment in this study, because they are already well described, technically and environmentally.

In some cases, blends of different alternative plasticisers may be needed to attain the desired technical characteristics. This is also a well known practice with many DEHP uses. More blending may be needed with some of the non-phthalate alternatives to achieve general plasticiser characteristics. By way of example, a Danish toy producing company attempted a switch to ATBC as primary plasticiser in all PVC toys etc. for small children. However in the existing production setup, it suffered from a variety of technical drawbacks when compared with DINP: ATBC would not take decoration, it had high migration into adjacent materials leading to swelling and splitting, and there was a consequent need for tooling changes. Development led to the use of a mixture of ATBC, DINCH and DEHT, which could be blended in a variety of combinations to achieve softened PVC that performed to the required standards with the existing production setup, and could be used as a one-to-one alternative to DINP. Also, some of the marketed plasticiser products consist of several substances, pre-mixed to provide desired performance characteristics. The products Soft-n-safe and Benzoflex 2088 described in this report are examples of such mixed plasticiser products.

Table 5.29
summary of the technical assessment of alternative plasticisers

Substance	Overall technical assessment
ASE	ASE is a general plasticiser alternative to DEHP. The producer has indicated significant market experience for most traditional DEHP, DBP and BBP uses.
ATBC	The performance of ATBC on some parameters seems similar to DEHP, indicating technical suitability for substitution of DEHP for some applications. The higher extractability in aqueous solutions and the higher volatility may reduce the performance of ATBC as a plasticiser in PVC. The data available does not allow a closer assessment of ATBC's technical suitability as alternative to DEHP, DBP and BBP
COMGHA	The producer has indicated significant market experience in several of the traditional DBP and BBP specialty plasticiser applications and certain DEHP applications, notably in the non-polymer (adhesives, sealants, etc.) and PVC spread coating (plastisol) application fields. According to the producer, Benzoflex 2088 (with DEGD) has become the main non-phthalate alternative to DBP or BBP in vinyl flooring production in Europe. The higher extractability in water may limit its use for some applications.
DEGD	According to the producer, COMGHA still has relative moderate market experience, albeit with many examples of full scale usage and pilot/lab scale tests, and significant market experience in some plastisol application and cosmetics. The producer found good performance on key technical parameters indicating a potential for substituting for DEHP and perhaps for DBP and BBP in some traditional uses og these substances.
DGD	DEHT is a general plasticiser alternative to DEHP. Today, terephthalates like DEHT are more commonly used in the USA than elsewhere.
DEHT	DINA has mostly been used for low temperature PVC applications and in PVC film/wrapping . The data available for this study does not allow clear-cut conclusions as regards DINA's suitability as alternative to DEHP
DINA	The producer's sales appraisal indicates a relatively wide usage of DINCH for general plasticiser purposes. DINCH was the most frequently found plasticiser in two European surveys of plasticisers in toys and childcare articles. The data available does not allow a closer assessment of DINCH's technical suitability as alternative to DEHP, DBP and BBP.
DINCH	The fact that DGD for many years has been a well known and much used competitor to BBP, especially in PVC flooring and in PVA adhesives, indicates a clear potential for substituting DGD for BBP, from a technical point of view. DGD may probably also substitute for some traditional uses of DEHP and DBP.
GTA	According to a producer, GTA can substitute for DBP and BBP in adhesives, inks and coatings. The data available does not allow a closer assessment of GTA's technical suitability as alternative to DEHP, DBP and BBP.
TXIB	TXIB was found in more than 10% of the samples in surveys of plasticisers in toys and childcare articles. However, the producer does not consider TXIB an alternative to DEHP, DBP or BBP, and the usage of TXIB in vinyl flooring has declined in the 1990's due to high emissions from end products. Consequently, TXIB seems not to be a suitable alternative to DEHP, DBP or BBP.

Table 5.30
Alternatives to DEHP, BBP and DBP proposed by contacted manufactures, by application and with indication of market experience

Application	ASE	GTA	DGD	Mix of DGD, DEGD, TGD	ATBC	COMGHA
Substitute for DEHP						
Polymer applications:						
Calendering of film, sheet and coated products	2	2	4	4	3	3
Calendering of flooring, roofing, wall covering	4	2	3	3		3
Extrusion of hose and profile	2	2	3	3	3	3
Extrusion of wire and cable	2	2	3	3		3
Extrusion of miscellaneous products	2	2	2	2	2	3
Injection moulding of footwear and miscellaneous	?	2	2	2		3
Spread coating of flooring	2	2	2	2		2
Spread coating	2	2	2	2		3
Car undercoating	2		3	3		
PVC medical articles		2			2	
Toy and childcare articles		2			1	
Non polymer applications:	0					
Adhesives/sealant, rubber	2	2	1	1	2	4
Lacquers and paint	2	2	2	2		4
Printing ink	2	2	2	2	2	3
Production of ceramics						
Substitute for DBP						
Plasticiser in PVC	2		1	1	2	2
Plasticiser in other polymers	2					2
Adhesives	2	2		1	3	4
Printing inks	2	3			2	3
Miscellaneous:						
Sealants	2				3	4
PU foam sealants	2				4	
Nitrocellulose paints	2	3	2	2	2	
Film coatings	3				3	
Glass fibre production						4
Cosmetics						2
Substitute for BBP						
Polymer applications:						
General PVC (e.g. for moulded plastic parts)	2					4
Plastisol coating, for flooring	2		1	1		3
Extrusion or spread coating	2			2		2
Films, calendering	2		4	4		3
Non polymer applications:						
Sealants	2		1	1		
Coatings and inks)		2	1		3	
Adhesives	2			1		
Nail polish					1	

*1: Market experience categories interpretation: 1) Main alternative on market. 2) Significant market experience. 3) Examples of full scale experience. 4) Pilot/lab scale experience

Prices of alternative plasticisers

Some of the alternative plasticisers investigated have similar or only slightly higher prices than the relevant competing substances among DEHP, DBP and BBP; see Table 5.31 below. Others have higher or substantially higher prices. As shown in the table, the non-phthalate alternatives DGD, DEGD and DEHT were in the same price range as the DEHP, DBP and BBP, (as well as the ortho-phthalate alternatives DINP and DIDP), whereas ASE, DINA , DINCH and GTA were somewhat more expensive and ATBC and COMGHA were considerably more expensive (counted as direct relative price). We have not been able to find a price for TXIB for this study. Note that here BBP and DEHP had the same price per weight unit in this case. In older literature, BBP is reported to be a specialty plasticiser with higher price than DEHP.

Prices of chemicals (and other industrial products) tend to decrease as production capacity and competition is increased. Different chemicals are however based on different raw materials and more or less complex and resource demanding chemical synthesis technologies. This of course sets limits to the minimum prices attainable even in a mature market, and some of the alternative plasticisers described may likely remain at higher price levels. It should be noted that the prices of DEHP have dropped significantly over the last decade or more.

According to a Danish manufacturer, when the Danish ban of DEHP and 5 other phthalates in toys etc. came into force, the price of products for one Danish toy company rose by approximately 50% because the international manufacturers had to produce special deliverances to the Danish marked without phthalates. Later, when the ban comprised the entire EU the prices dropped again. The company estimates that the ban has resulted in a remaining increase in prises of approximately 10-20% because the alternative substances generally are more expensive even after the preliminary reduced costs related to changing production methods.

Table 5.31
Prices and relative prices to DEHP of the assessed alternatives and some other reference plasticisers

Substance	Price	Relative price to DEHP,%	Substitution factor	Effective relative price,%	Remarks
Phthalates and other reference plasticisers:					
DEHP (2006)	0.70 USD/Lb	-	-	-	TURI (2006)
DEHP (2006-2009)	≈0.8-1 €/kg	-	-	-	ExxonMobil (2009), Arbeitsgemeinschaft PVC (2006)
BBP (2006)	0.70 USD/Lb	100%	0.94	94%	TURI (2006)
DINP (2006)	0.73 USD/Lb	104%	1.06	111%	TURI (2006)
DIDP (2006)	0.77 USD/Lb	110%	1.10	121%	TURI (2006)
Assessed alternatives:					
ASE (2009)	1,75 €/kg	175% *1	NA	NA	Lanxess (2009)
ATBC	NA	300%	NA	NA	ExxonMobil (2009); Karbæk (2003)
COMGHA	3.5€/kg	≈350% *1	≈1	≈350%	Danisco (2009)
Benzoflex 2088 (with DEGD)		"Slightly higher"			Genovique (2009)
DGD (2006)	0.73 USD/Lb	104%	0.98	102%	TURI (2006)
DEHT (2006)	0.74 USD/Lb	106%	1.03	109%	TURI (2006)
DINA		150-200%			ExxonMobil (2009)
DINCH (2006)	0.91 USD/Lb	130%	NA	NA	TURI (2006)
GTA	€1,50/KG	150% *1	NA	NA	Lanxess (2009)
TXIB	NA	NA	NA	NA	

Notes: *1: DEHP price in 2006-2009 ≈0.8-1 €/kg; 1 € is used for calculations. NA = Not available for this study.

6 Assessment of alternative flexible polymers

A number of studies have been undertaken on replacing PVC with other materials for different applications. The conclusion of many studies has been that it - on the basis of the available data - was not possible to make a full assessment of the materials.

To focus the efforts in this study, it was decided to include an assessment of polyolefin (polyethylene/polypropylene) elastomers as alternatives to flexible PVC - on an overall screening level - of its lifecycle impacts, supplemented by brief description of other flexible polymers based on avail-able aggregated reviews.

6.1 Assessment of polyolefin elastomers

A detailed life cycle assessment (LCA) was performed by Stripple ***et al.*** (2007) assessing the life cycle impacts of three flexible polymers in their use as urinary catheters, a disposable medical care product consisting of a thin flexible tube and a cone-shaped flexible connector in one end. The materials assessed were (Stripple ***et al.,*** 2007, Melitek, 2006, 2009):

- DEHP-plasticised PVC;
- Thermoplastic polyurethane (TPU[1]);
- An elastomer, marketed by Melitek (Denmark) under the product name Meliflex (here designated PO), based on polypropylene, styrene block copolymer polyethylene and (non-phthalate) additives in ppt concentrations.

The functional unit was one year's supply of catheters for one person. The LCA seems comprehensive and was performed by the independent institute IVL in Sweden. It was conducted using 4 different LCA methods, the Eco-indicator 99 system, the CML 2 system, and the EPS 2000 system, as well as a classification and characterisation in line with the EPD system (environmental product declaration system).

The result varied somewhat depending on the assessment methodology used, but in broad lines the TPU elastomer was assessed as having higher environmental impact than the PO elastomer and plasticised PVC, whereas the last two were assessed as having quite equal overall impacts. It should be noted that while some human toxicity aspects were included, the health effects of DEHP could not be included in the assessment, as no conclusive toxicity data suited for the methodology had been identified. The major assessed effects appeared quite influenced by energy resource depletion and energy related emissions.

[1] The assumed TPU composition studied was based on hydrogenated methylene diisocyanate (HMDI), polytetramethylene ether glycol (PTMEG) and 1,4-butadiol.

The overall conclusion can be drawn that a DEHP-free medical grade flexible polymer is available. It is primarily based on low toxic olefins and has similar or lower life cycle impacts than plasticised PVC. The material, Meliflex, is more expensive per weight, but as less material is needed per unit of the medical functions investigated, this partly outbalances the price difference (Melitek, 2009). Meliflex is designed and produced specifically for pharmaceutical packaging and medical devices applications. Grades are available for tubing extrusion, films blown by cast extrusion, for injection moulding and for blow moulding.

Previously an environmental and health assessment of two alternative materials has been conducted by Stuer Lauridsen et al., 2001: PU (polyurethane) and LDPE (low density polyethylene). On the basis of the available data it was not possible to make a full assessment of the materials. It is however in the report recognised that LDPE has a low toxicity and that LDPE does not release large quantities of monomers or oligomers.

A study on alternatives to soft PVC in building materials among others concludes that polyethylene and other polyolefins have better environmental characteristics than PVC for many applications in the building industry (Andersson, 2002).

6.2 Summary on other flexible polymers

As described above, another DEHP-free flexible medical grade material, TPU, is available. The LCA performed by Stripple ***et al.*** (2007) indicated, that its life cycle is more energy-intensive and have higher emissions of prioritised pollutants. According to Stripple ***et al.*** (2007), while plasticised PVC is the traditional flexible material of choice in the medical market, TPU also has a significant part of the market. No price data have been collected for TPU for this study.

Alternative materials for toys

Postle et al. (2000) note that a number of companies have undertaken substitution to entirely different plastic products rather than simply different plasticisers. For those products which are specifically intended to be placed in the mouth, the substitute plastics which appeared to be most widely used were polyethylene (PE) and ethylene vinyl acetate (EVA). These materials can reportedly be used adequately in the products in question. However, the technical performance of the final product has been indicated to be often slightly inferior to that obtained with PVC. For example, products produced from these materials may sometimes have lower resistance to biting and tearing than plasticised PVC. The products may also have reduced longevity. In terms of the wider range of toys and childcare articles, plastics which are reported to be used as substitutes for plasticised PVC include various forms of polyethylene (LDPE, and LLDPE) styrenic block copolymers and again EVA, as shown in Table 6.1.

Table 6.1
Summary of technical suitability and use of alternative flexible materials for use in toys (Postle, et al, 2000)

Table 2: Technical Suitability of Substitute Plastics		
Plastic Type	**Technical Suitability**	**Actual Use as Substitute**
Polyethylene (various forms)	I, II (some)	I, II (some)
Ethylene Vinyl Acetate (EVA)	I, II (some)	I, II (some)
SBS Block Copolymers	I (possibly), II (some)	I (unknown), II (some)
Polyester Elastomers	II (some)	Unknown
Key: I - products intended to be placed in the mouth II - other toys and childcare articles		

Alternative materials for medical devises

The Toxics Use Reduction Institute (TURI, 2006) investigated a number of alternatives materials for three application areas: Resilient flooring, wall coverings and medical devices for neonatal care. For medical application several alternative materials were assessed for both sheet (EVA, polyolefins and glass) and tubing (polyolefins, silicone and TPU) applications. Many manufacturers were offering non-DEHP and/or non-PVC alternatives for both sheet and tubing uses. The study does not provide a clear conclusion for medical applications. For the detailed assessment summary reference is made to the study report. Products utilising the alternative materials, either singly or in multilayer laminates, were commercially available for sheet and tubing device applications with the notable exception of red blood cell storage.

Review of life cycle assessments (LCA) of PVC and alternative materials

In a study for the European Commission, Baitz ***et al.*** (2004 compiled an overview of the publicly available information on LCA on PVC and competing materials, for a variety of applications. Approximately 100 LCAs related to PVC were identified, of these 30 included comparisons at the application level. For roofing applications the study concludes that higher quality of the systems (thermal conductivity per thickness of roofing sheet layers) as well as the accuracy of the laying and maintenance processes have a large influence over the reduction of environmental impacts. Additionally, the study concludes that 'green roofing' (e.g. planting on the roof) further decreases environmental impacts because of the subsequent longer lifetime of the roofing systems. Three polymer solutions (one PVC system and two competing systems) have the potential to perform better, with similar environmental impacts on global warming, acidification and ozone formation over the life cycle. The study reports that some polymer solutions tend to have lower environmental impacts than competitive systems. Few comparative LCA studies pertaining to consumer goods are available. No useful general conclusions on material comparisons could be drawn.

In a review of various studies on alternative materials to plasticised PVC it is concluded that the available reviewed studies demonstrate that for many applications of DEHP/PVC alternative materials exist at similar prices (COWI, 2009a). Many of the materials seems to have equal or better environmental, health and safety, performance and cost profiles, but clear conclusion are complicated by the fact that not all aspects of the materials' lifecycles have been included in the assessments.

Pedersen (1999) produced a simplified matrix indicating a gross differentiation of polymer materials in some overall categories of health and environment impacts. It is presented in Table 6.2 based on its presentation in the

publication Nordic Ecolabelling (2007). Being simplified, and being based on late 1990 knowledge, the table should likely be interpreted with some caution. Note that the low impact classes 1 and 2 include the substances polyethylene (PE), poly(isobutylene) (PIB), ethylene vinyl acetate (EVA), styrene ethylene butylene styrene co-block polymer (SEBS), styrene isoprene block polymer and silicone.

Conclusions

A number of flexible polymers are available which can substitute for many traditional uses of flexible PVC. Polyethylene (PE), polyolefin elastomers, different polyurethane (PU) qualities, ethylene vinyl acetate (EVA) and different rubber types are examples of among others. For many flexible PVC uses, also other substitute materials than flexible polymers exist. The LCA-based, application-focused assessments are few, and often clear-cut conclusions could not be made. But many materials exist with seemingly equal or better environmental, health and safety, performance and cost profiles. The assessment made here does not allow for a more detailed analysis of possibilities and limitations in the coverage of alternative flexible polymers.

Table 6.2
Simplified categorisation of polymers according to overall health and environment pressure (From Pedersen, 1999, as cited by Nordic Ecolabelling, 2007; extracts on flexible polymers)

Category	Description	Material
1	The polymer materials in this category contain particularly health or environmentally hazardous substances, which are crucial for the manufacturing or for the properties in use of the polymer. The substances added or generated in the production, use or disposal phase may require special end-of-pipe precautions or protective equipment and may result in significant health or environmental impacts. It should be noted that where the necessary end-of-pipe precautions and protective equipment are adequately installed during manufacturing, the impacts on health and environment can be made negligible.	Polyethylene – PE Poly (isobutylene) – PIB Ethylene vinyl acetate – EVA
2	The polymer materials in this category contain health or environmental hazardous substances, which are crucial for the manufacturing or for the properties in use of the polymer. The substances added or generated in the production, use or disposal phases may not according to law, require any special end-of pipe treatment or special for protective equipment but might have health or environmental impacts. The polymer materials, which fulfil the first criteria in Category 1 but require large energy consumption to manufacture or which generate relatively low levels of energy upon incineration, are also listed in Category 2.	Styrene ethylene butylene styrene co-block polymer – SEBS Styren isoprene block polymer Silicone
3	The polymer materials in this category contain particularly health or environmentally hazardous substances, which are crucial for the manufacturing or for the properties in use of the polymer. The substances added or generated in the production, use or disposal phase may require special end-of-pipe precautions or protective equipment and may result in significant health or environmental impacts. It should be noted that where the necessary end-of-pipe precautions and protective equipment are adequately installed during manufacturing, the impacts on health and environment can be made negligible.	Latex/Natural rubber (cispolyisoprene) – NR Polyvinyl chloride not plasticized with DEHP – PVC (soft) Thermoplastic Polyurethane – TPU Polyurethane foam – PUR foam
4	The polymer materials in this category are regarded as particularly hazardous to health and environment. This category includes polymer materials that otherwise would be in category 1-3 but which contain additives considered as hazardous to health and environment.	Polyvinyl chloride plasticized with DEHP – PVC(soft) Halogenated additives Additives with heavy metals Fire-retardant based on bisphenols or diphenyl Plasticizers based on DEHP Other additives with the ability to act as endocrine disrupters

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[Data sources for the environmental and health assessment are included in Annex 3]

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Annex 1
Companies and organisations contacted

Organisations

Plastindustrien i Danmark, Copenhagen

Foreningen af Legetøjsfabrikanter i Danmark

Nordic Association of Toy Manufacturers

Companies

Baby Sam A/S

BASF

BRIO AB

Danisco

Dantoy A/S

Dracco, Allerød

Eastman Chemicals

Genovique

Hama

Hasbro

Indo-Nippon ChemicalsExxon Mobil

K.E. Mathiasen A/S

Lanxess (formerly Bayer)

Lego

Poul Willumsen A/S

Ripladan

TOP-TOY A/S

Vertellus (formerly Morflex)

Annex 2
Introduction to plasticiser families

This Annex provides some basic information on the different plasticiser substances families summarised in section 3.2.

Terephthalates

Terephthalic acid is identical to phthalic acid, except for the physical placement of one part of the molecule. It may be reacted with an appropriate alcohol to produce terephthalate esters which are used as plasticisers. In practice, terephthalates are more commonly used in the USA than elsewhere. An example of a commonly used terephthalate is DEHT, which in spite of its close chemical similarity with DEHP has distinctly different health and environment characteristics (TURA, 2006). According to Krauskopf and Godwin (2005), DEHT is commercially available at similar price as DEHP.

Benzoates

Benzoates are the esterification products of benzoic acid and selected glycols, usually diols. Preferred glycols are dipropylene glycol and butane diols. One commonly used benzoate is dipropylene glycol dibenzoate, DGD (commercially Benzoflex® 9-88). Its preferred use is in PVC flooring products, owing to its strong solvating strength, and it reportedly controls plasticiser bleeding into asphalt adhesives. In vinyl sheet flooring, the benzoate enhances processing, while the low molecular weight contributes a hardened, stain resistant surface, due to volatilization, similar to the effect of BBP in flooring. Benzoates are generally strong solvaters due to the high aromaticity, as are lower molecular weight phthalates such as dihexyl (DHP) and butyl, octyl (BOP), as well as butylbenzyl (BBP). Commercial practice includes the use of up to 10–20% of the plasticiser system as “strong solvating” type plasticisers, such as arylalkyl phthalates (e.g. BBP), benzoates, sulfonates, and so forth (Krauskopf and Godwin, 2005).

Citrates

Citrate plasticisers are tetraesters (Krauskopf and Godwin, 2005). Examples of citrate plasticiser esters include triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate and tri-(2-ethylhexyl)-citrate. They are produced from citric acid and are traditionally used to plasticise vinyl resins used in applications including medical equipment and packaging films. Of the approximately 230,000 tons of citric acid used annually in Western Europe, 9% are applied for industrial uses such as for plasticisers. Tributyl citrate is used in PVC, polyvinyl chloride/vinylidene chloride copolymers or polyvinyl chloride/vinyl acetate resins that are subsequently used for such items as food-wrapping film. Among the advantages of tributyl citrate is that it is heat-stable and does not discolour when processed in compounded resins. Acetyl tributyl citrate is used in electrical coatings and casings because of its solvating characteristics. It is also used in inks. Acetyl tributyl citrate and acetyl triethyl citrate are also used in hair sprays and aerosol bandages. Triethyl citrate has applications in the food industry as flavour and flavour emulsion (ECPI 2009).

Trimellitates

These materials are produced by the esterification of a range of alcohols with trimellitic anhydride (TMA), which is similar in structure to phthalic anhydride with the exception of a third carbonyl group on the aromatic ring. Consequently, esters are produced in the ratio of three moles of alcohol to one mole of anhydride. Common esters in this family are Tris-2-ethyhexyl trimellitate (Tri-octyl trimellitate - TOTM), L79TM (an ester of mixed semi-linear C7 and C9 alcohols, and L810TM, an ester of mixed C8 and C10 linear alcohols. The principle features of these esters, when processed with PVC, is their low volatility, and consequently large volumes of trimellitate esters are used in high specification electrical cable insulation and sheathing. The extraction and migration resistance of these materials are also significantly improved relative to the phthalates. The low volatile loss also results in usage in automotive interior applications where the issue of windscreen fogging is important. In this respect they often compete with the linear high molecular weight phthalates such as 911P (ECPI 2009).

Adipates

Alcohols of similar chain length to those used in phthalate manufacture can be esterified with adipic acid, rather than phthalic anhydride, to produce the family of adipate plasticisers which are a part of the "aliphatic dibasic esters" in the table above. For example, esterification of 2-ethylhexanol with adipic acid yields di-2-ethylhexyl adipate (DEHA), also known as di-octyl adipate (DOA), which is reported to be the most used adipate plasticiser (ECPI 2009; Krauskopf and Godwin 2005). The family of adipic acid esters used in PVC applications improves low temperature performance relative to phthalates and give significantly lower plastisol viscosities in plastisol applications, due to the lower inherent viscosities of the plasticisers themselves. Adipates used are typically based on alcohols in the C8 to C10 range (ECPI 2009). Typically, lower molecular weight alcohols are used with higher molecular weight acids, and vice versa, such that the total carbon content per molecule ranges between C_{18} and C_{26}. This maintains the apolar/polar ratio required to provide PVC compatibility along with low temperature properties (Krauskopf and Godwin, 2005).

Relative to phthalates, adipates have higher volatilities and higher migration rates, and are generally higher priced. As a result, it is not uncommon for adipates to be used in blends with phthalates to produce a compromise of properties (ECPI, 2009). Diisononyl adipate (DINA) is used for low temperature applications requiring lower plasticiser volatility (Krauskopf and Godwin, 2005).

Sebacatesa and azelates

Esters produced from 2-ethylhexanol and higher alcohols with linear aliphatic acids are used in some demanding flexible PVC applications where superior low temperature performance is required. Di-2-ethylhexyl sebacate (DOS) and di-2-ethylhexyl azelate (DOZ) are the most common members of this group, but di-isodecyl Sebacate (DIDS) is also used. They give good low temperature performance in combination with adipates. Their usage has generally been limited to extremely demanding low temperature flexibility specifications (e.g. underground cable sheathing in arctic environments) (ECPI 2009).

Phosphates

Phosphate plasticisers may be considered as “inorganic esters”, where the phosphate plays the role otherwise played by carboxylic acids, and bonds with

alcohols or phenols to form the desired plasticisers. An important feature of phosphate plasticisers is that they, in addition to plasticising the PVC, act as a flame retardant. While hard PVC is quite resistant to fire, the addition of plasticisers generally decreases the fire resistance, and additional fire resistance can be provided by adding a fire retarding plasticiser. Commercial phosphate plasticisers use combinations of aryl (aromatic) and C8 and C10 alkyl (carbon chain) groups to offer a balance of fire reduction, volatility, and efficiency. 2-ethyhexyl diphenyl phosphate has widespread use in flexible PVC applications due to its combination of properties of plasticising efficiency, low temperature performance, migration resistance and fire retardancy. Tris(2-ethylhexyl) phosphate, tricresyl phosphate (TCP) are other examples of phosphate plasticisers. Phosphate plasticisers may be combined with other plasticisers to reduce formulating costs (ECPI 2009; Krauskopf and Godwin 2005).

Sulfonates

Sulfonates exhibit strong solvency for PVC. One example is the phenyl cresyl esters of pentadecyl sulfonic acid. It is reportedly resistant to hydrolyses and diffusion controlled plasticiser losses (Krauskopf and Godwin, 2005). ASE (alkylsulfonic phenylester) is also an example of a sulfonate plasticiser.

Epoxides

Epoxy plasticisers enhance thermal and UV stability of PVC. They are the only class of plasticisers that undergo a chemical grafting (side-chain bonding) onto the PVC polymer. They are thus internal plasticiser, contrary to phthalates. This chemical family is composed of essentially two types of epoxidized natural products. Epoxidized oils are prepared from soybean oil (ESBO or ESO) and linseed oil (ELSO). These oils have molecular weights of approx. 1,000, causing them to perform as low volatility plasticisers. The primary performance attributes of epoxy plasticisers are their role in PVC stabilization, which is accomplished at low concentrations in the PVC.

Polymeric plasticisers

Polymeric plasticisers are typically polyesters, with a molecular weight range from 1,000 to 8,000. Polyester plasticisers often have the structure of combined (bonded) propylene glycol or butylene glycol with aliphatic dibasic acids such as adipates. The greater the plasticiser viscosity, or molecular weight, the greater its permanence (e.i. resistance to loss by diffusion and evaporation). Polymeric plasticisers composed of branched structures are more resistant to diffusivity losses than those based on linear isomeric structures; on the other hand they are more susceptible to oxidative attack (degradation). The polarity, or the oxygen-to-carbon ratio, also impacts extraction resistance of the polymerics. Lower polarity materials exhibit better extraction resistance towards polar extraction fluids such as soapy water (Krauskopf and Godwin, 2005).

Other plasticiser types

Other plasticisers exist, many of which are also (like phthalates, etc.) esters of alcohols and carboxylic acids.

Pentaerythritol esters are a type of “miscellaneous” plasticisers that impart both low volatility and diffusivity. Pentaerythritol is a tetra alcohol esterified with straight chain fatty acids to make plasticisers (Krauskopf and Godwin, 2005). Trimethyl pentanyl diisobutyrate (TXIB) is another example (Eastman, 2009).

Annex 3
Summary of technical performance parameters

A summary of some technical performance parameters for the assessed alternatives compared to DEHP, DBP, BBP and other selected phthalates is given below..

Technical key parameters of some plasticisers' performance in PVC (from Sears and Darby, 1982; Monsanto research work; unless noted)

Plasticiser in PVC, conc. 40% =67 phr in same PVC resin*1	Shore A hardness*2	Volatility,% lost, 1 day at 87 °C over activated carbon	Extracted in water,%	Extracted in kerosene (jet fuel, etc.),%
Phthalates:				
DEHP	69	4.5	0.01	44
DEHP (PVC2)*3	73	3.6	0.02	54.7
DBP	62	45.4	0.25	9.1
BBP	68	7.7	0.07	3.4
DIDP	71	1.8	0.03	74
DINP	73	2.1	0.07	76.7
Non-phthalates:				
ASE	72	5.3	0.03	4.8
ATBC	73	17.8	0.09	
DEGD (as single substance)	69	5.5	0.75	3.4
DGD	71	7.9	0.45	2.9
DEHT (PVC2)*3	76	1.9	0.09	70.8
DINA	72	4.1	0.14	80.4
TXIB	76	23.7	2.83	5.2
COMGHA*4	88.0	NA	NA	NA
DEHP *4	90.0	NA	NA	NA

Notes: *1: phr = parts per hard resin, meaning parts per weight of hard PVC. *2: A measure for the plasticiser's efficiency in making PVC flexible; the lower the number, the softer the PVC and the more efficient plasticiser. *3 Measured performance in another PVC resin (the same for DEHP and EHT). *4 Data from Danisco; at concentration 40 phr; PVC resin type not specified.

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Background data for the environmental and health assessment

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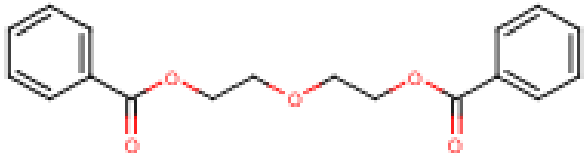
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Diethylene glycol dibenzoate, DEGD

Identification of the substance

CAS No.	120-55-8	
EINECS No.	204-407-6	[1]
EINECS Name	Oxydiethylene dibenzoate	[1]
Synonyms	Diethylene glycol dibenzoate	
	DEGD	
Molecular Formula	$C_{18}H_{18}O_5$	[1]
Structural Formula		
Major Uses	Plasticizer	[3]
IUCLID	Is listed as a LPV chemical	[1]
EU classification	This substance is not classified in the Annex I of Directive 67/548/EEC as such, but it may be included in one of the group entries.	[1]

Physico-chemical Characteristics

Physical Form	Colourless liquid with mild ester odour	[3], [4]
Molecular Weight (g/mole)	314.4	[2]
Melting Point/range (°C)	28 ºC	[2]
	24 ºC	[4]
	33.5ºC	[6]
Boiling Point/range (°C)	236 ºC (at 0.7 kPa)	[2]
	225-227 ºC (at 3 mm Hg)	[3]
Decomposition Temperature (°C)	> 230 ºC	[4]

Diethylene glycol dibenzoate, DEGD

Vapour Pressure (mm Hg at °C)	1.3×10^{-7} mm Hg (at 25 ºC) [1.73×10^{-5}Pa]	[4]
	3.2×10^{-6} mm Hg (at 50 ºC) [4.26×10^{-4}Pa]	
	5.1×10^{-4} mm Hg (at 100 ºC) [6.79×10^{-2}Pa]	
Density (g/cm^3 at °C)	1.2 (at 20 ºC)	[2], [3]
Vapour Density (air=1)	9.4	[2]
Henry's Law constant ($atm/m^3/mol$ at °C)	7.0×10^{-10}	[4]
	3.0×10^{-12} at 25ºC	[3], [6]
Solubility (mg/l water at °C)	Soluble in water	[3]
	38.3 mg/l (at 30 ºC and pH 7)	[4]
Partition Coefficient (log P_{ow})	3.2	[4]
	3.04	[7]
pK_a	-	
Flammability	-	
Explosivity	-	
Oxidising Properties	-	
Migration potential in polymer	-	
Flash point (ºC)	232 ºC	[2]
Viscosity (mPas)	110 (at 20 ºC)	[3]
Atmospheric OH rate constant $cm^3/(molecule\ sec)$	1.9 x 10-11 at 25ºC	[6]

Emission Data

During production

Diethylene glycol dibenzoate, DEGD

Exposure Data

Aquatic environment, incl. sediment	Diethylene glycol dibenzoate's production and use as a plasticizer may result in its release to the environment through various waste streams.	[3]
Terrestrial environment	Diethylene glycol dibenzoate's production and use as a plasticizer may result in its release to the environment through various waste streams.	[3]
Sewage treatment plant	-	
Working environment	NIOSH (NOES Survey 1981-1983) has statistically estimated that 25,414 workers (10,937 of these are female) are potentially exposed to diethylene glycol dibenzoate in the USA. Occupational exposure may be through inhalation and dermal contact with this compound.	[3]
Consumer goods	-	
Man exposed from environment	-	
”Secondary poisoning”	-	
Atmosphere	-	
Dermal	-	

Toxicological data

Observations in humans	Observed symptoms: Nausea, vomiting and headaches; with continued use obdominal pain, polyuria followed by oliguria, anuria and renal failure. Also drowsiness, coma, respiratory arrest and pulmonary edema. Range of toxicity: A) The average fatal dose is difficult to estimate. Much of the data is from historical sources or from epidemics that have occurred in patients in third world countries with limited access to medical care. Extrapolation from these sources must therefore be interpreted with caution. B) The average fatal dose in people who drank a sulfanilamide elixir with diethylene glycol as the vehicle was approximately 1 ml (72% concentration of DEG) per kilogram body weight. However, the actual reported fatal doses were highly variable. C) Adult 1) Three men died after consuming approximately 2 to 3 cups (473 – 709 ml) each of 100% diethylene glycol, as an ethanol substitute. 2) A 56-year-old man died after ingesting 8 ounces (236 ml) of 100% diethylene glycol in a suicide attempt. 3) Adults who ingested sulfanilamide contaminated with diethylene glycol survived doses of 1 to 240 milliliters (of a 72% solution). D) Pediatric 1) Median diethylene glycol dose that was fatal in 85 (98%) of 87 children was estimated to be 1.34 ml/kg (range 0.22 to 4.42 ml/kg). Twelve children ingested less than 1.0 ml/kg. 2) Forty-nine children survived ingestion of a median dose of 0.67 ml/kg (range of 0.05 - 2.48 ml/kg) diethylene glycol present in contaminated acetaminophen syrup.	[3]

Diethylene glycol dibenzoate, DEGD

Acute toxicity

Oral	LD_{50} = 4190 mg/kg body weight (rat, combined)	[4], [5]
	LD_{50} = 2830 mg/kg body weight (rat)	[6]
Dermal	LD_{50} > 2000 mg/kg body weight (rat, combined)	[4], [5]
	LD_{50} = 20 ml/kg body weight (rabbit)	[6]
Inhalation	LC_{50} (4 h, mist) > 200 mg/l (rat)	[5]
Other routes	-	
Skin irritation	No dermal reaction was reported following a single semi-occlusive application of diethylene glycol dibenzoate to intact rabbit skin for 4 hours.	[5]
Eye irritation	A single instillation of diethylene glycol dibenzoate into the eye of the rabbit elicited transient very slight conjunctival irritation only. No allergic skin reaction was reported in guinea pigs after repeated skin contact (intradermal and topical) using the Magnusson and Kligman method.	[5]
Irritation of respiratory tract	-	
Skin sensitisation	Not sensitising to Guinea pig	[4]

Subchronic and Chronic Toxicity

Oral	NOAEL = 1000 mg/kg/day (rat, 13 weeks) Diethylene glycol dibenzoate was administered to rats by dietary admixture to achieve dosages of 0, 250, 1000, 1750 or 2500 mg/kg/day over 13 weeks. Selected Control and Group 5 animals were subsequently maintained off dose for 4 weeks to assess reversibility of any treatment related changes. There were no findings of toxicological importance at a dosage of 1000 mg/kg/day or below. In animals receiving 1750 or 2500 mg/kg/day, there was an adverse effect on bodyweight gain, changes in clinical pathology parameters and an increased incidence/degree of haemosiderosis in the spleen. In addition, at 2500 mg/kg/day, a few treatment-related clinical signs were evident, minimal periportal hepatocyte hypertrophy was noted in both sexes. Plasma enzyme activities (transaminases and/or AP or OCT) were elevated at Week 13 in rats receiving 1750 or 2500 mg/kg/day with an associated minimal increase in liver weight, At necropsy, minimal periportal hepatocyte hypertrophy was detected only at 2500 mg/kg/day. The slight effects in the liver may be a physiological adaptation to treatment at the highest doses. Following 4-weeks recovery, most enzyme activities were normal, liver weights were unremarkable and there was no residual hepatic pathology. Epithelial hyperplasia was detected in the colon of males and the caecum of both sexes. In general, however, dosages of up to 2500 mg/kg/day of diethylene glycol dibenzoate were tolerated. When selected animals previously receiving 2500 mg/kg/day were maintained off-dose for 4-weeks, all treatment related changes showed evidence of, or complete, recovery. No effects were reported in dogs administered up to 300 mg/kg/day of diethylene glycol dibenzoate in their diet for 90 days.	[4], [5] [5]
Inhalation	-	
Dermal	-	

Diethylene glycol dibenzoate, DEGD

Metabolism	Metabolism in the Rat. The metabolism of diethylene glycol dibenzoate was studied after both single oral low level (50 mg/kg) and high level (750 mg/kg) doses to groups of 4 male and 4 female rats. The tissue distribution of radioactivity was studied after low-level doses. The proportions and nature of metabolites were also investigated. Virtually all of single oral doses of 50 and 750 mg/kg of diethylene glycol dibenzoate administered to Sprague-Dawley CD rats were adsorbed, metabolized and excreted in the urine within 24 hours of administration. Diethylene glycol dibenzoate was metabolized via hydrolysis of the ester bonds to benzoic acid; this free acid was then conjugated with either glycine (major pathway) or glucuronic acid (minor pathway) prior to excretion.	[4]

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	S.typhimurium and E.coli (metabolic activator Sprague-Dawley rat liver (S9)) Cytotoxic conc: No toxicity with or without metabolic activation Genotoxic conc: No genotoxic effects observed with or without metabolic activation No evidence of mutagenic activity in this bacterial system.	[4]
	Mouse lymphoma (metabolic activator Sprague-Dawley rat liver (S9)) Genotoxic Effects: In the absence of S9-increases in mutant frequency were observed 350 µg/ml on Test 1 and 200 and 325 µg/ml in Test 2. The increases were not 100 above the control level and were within the historical control range. It was concluded that diethylene glycol dibenzoate did not demonstrate mutagenic potential in the absence of S9 mix. There was no substantive increases in mutant frequency observed in the presence of S9 mix. It is concluded that diethylene glycol dibenzoate did not demonstrate mutagenic potential in this in vitro gene mutation assay	[4]

Chromosome Abnormalities	Chinese Hamster Lung (metabolic activator Sprague-Dawley rat liver (S9)) Genotoxic Effects: No statistically significant increases in the proportion of aberrant cells, when compared to the solvent control, were seen in either the presence or the absence of S9 mix. A small response seen in the first test, with S9 mix, was not reproduced in the repeat test or at the later harvest. This response was not considered to be indicative of clastogenic activity.	[4]
Other Genotoxic Effects	-	
Estrogenic activity	Rat Diethylene glycol dibenzoate for Estrogenic Activity Using Vaginal Cornification and the Uterotrophic Response in the Ovariectomized Adult Rat as the Endpoints. Diethylene glycol dibenzoate did not induce vaginal cornification at doses of 500, 1000, 1500 or 2000 mg/kg/day for 7 days by oral gavage in ovariectomized adult Spraque-Dawley (CD) rats. Diethylene glycol dibenzoate did not stimulate a uterine weight increase or an increase in the uterine weight to final body weight ratio at doses of 500, 1000, 1500 or 2000 mg/kg/day for 7 days. When compared with the vehicle control (corn oil) and positive control (diethylstilbestrol), these data demonstrate that Diethylene glycol dibenzoate did not exhibit estrogenic activity up to and including the maximally tolerated dose.	[4]
Carcinogenicity	-	

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	Rat (38 weeks duration) The evidence from this study suggested that a dietary concentration of 10,000 ppm should be considered as the No-Observed-Adverse-Effect-Level (NOAEL) for the FO and Fl parent animals. The No-observed-Adverse-Effect-Level (NOAEL) for the developing offspring is considered to be 3300 ppm. The No-Observed-Effect-Level (NOEL) for reproductive parameters is considered to be 10000 ppm.	[4]

Teratogenicity	-	
Developmental toxicity	Rat (20 days duration from gestation) Maternal Toxicity NOEL : 1000 mg/kg/day Clinical Signs: The general condition of females at all dosages remained satisfactory throughout the study and there were no deaths. Salivation after dosing was observed at all dosages. The incidence was dosage related but this finding was not considered to be of toxicological importance. At 1000 mg/kg/day, there were no detectable signs of maternal toxicity; there were no maternal deaths and all females had a live litter at sacrifice. Litter Responses and Fetal Changes Prenatal development NOAEL: 500 mg/kg/day. Although a small number of fetuses with cervical ribs at 1000 mg/kg/day precludes defining this dosage as a NOEL for developmental anomalies, there were no findings at this dosage that were considered indicative of any substantial disturbance of morphological development. Fetal Growth and Development NOEL: 250 mg/kg/day Post-implantation loss was higher in all treated groups compared to the concurrent Control, differences attaining significance at 500 and 1000 mg/kg/day. However values were comparable with recent background control data and it is considered that the test groups were disadvantaged by a particularly high survival rate in the Control. It was concluded that in utero survival had not been adversely affected by treatment since live litter size was unaffected and was similar in all groups.	[4]

Toxicokinetics

Diethylene glycol dibenzoate, DEGD

Toxicokinetics

Ecotoxicity Data

Algae	EL_{50} (area under the curve 72h) = 5.2 mg/l	[4]
	EL_{50} (growth rate 0-72h) = 11 mg/l	
	EL_{50} (area under the curve 96h) = 5.9 mg/l	
	EL_{50} (growth rate 0-96h) = 15 mg/l	
Daphnia magna	EL_{50} (48h) = 6.7 (Daphnia magna)	[4]
	No-observed effect loading rate = 1.0 mg/l (Daphnia magna)	
Other aquatic organisms	-	
Fish	LL_{50} (96h) = 3.9 mg/l (fathead minnow)	[4]
	No-observed effect = 1.5 mg/l (fathead minnow)	
Bacteria	EC_{50}: >10 mg/l, Bacteria (Pseudomonas putida) 10 mg/l was the highest attainable concentration that could be prepared due to the limited solubility to the test material in water and auxiliary solvent and the limitations imposed by the addition of nutrient solutions and bacterial suspension to the test material stock solution.	[5]
Terrestrial organisms	Acute toxicity LC_{50} > 1000ppm (earthworm, eisenia foetida)	[4]
	NOEL = 1000 ppm	
Sludge	Diethylene glycol dibenzoate had no inhibitory effect on the respiration rate of activated sludge at concentrations up to 100 mg/l.	[5]

Environmental Fate

BCF	An estimated BCF value of 120 was calculated for diethylene glycol dibenzoate, using an estimated log Kow of 3.04 and a recommended regression-derived equation. According to a classification scheme, this BCF value suggests that bioconcentration in aquatic organisms is high.	[3]
Aerobic biodegradation	17% of TCO_2 at 2 days	[4]
	71% of TCO_2 at 10 days	
	93% of TCO_2 at 28 days	
	Readily biodegradable	
	Diethylene glycol dibenzoate is considered readily biodegradable in the CO_2 evolution test (modified Sturm test). The mean CO_2 production by mixtures of diethylene glycol dibenzoate was equivalent to 16% of the theoretical value (TCO_2, 106.4 mg CO_2) after 2 days of incubation and 63% after 10 days; a mean level of 83% degradation was achieved by the end of the test on Day 29.	[5]
	The mean BOD5 = 0.77 gO_2/g Diethylene glycol dibenzoate (34% of it's ThOD = 2.05 gO_2/g)	
	The mean COD = 2.22 gO_2/g Diethylene glycol dibenzoate (109% of the ThOD)	
	The BOD5 of Diethylene glycol dibenzoate was 32% of it's COD. Substances are generally considered readily biodegradable in the Closed Bottle test if the ratio of BOD5:COD or ThOD is >50. Component 1 therefore cannot be considered readily biodegradable in this screening test.	
Anaerobic biodegradation	Diethylene glycol dibenzoate is considered ultimately biodegradable under anaerobic conditions in the biogas production test. The level of anaerobic biodegradation, based on biogas measurements alone, was equivalent to 65% by Day 60 and the total level of biodegradation (dissolved inorganic carbon plus biogas) was calculated to be 70% of the theoretical level.	[5]
Abiotic degradation	The rate constant for the vapour-phase reaction of diethylene glycol dibenzoate with photochemically produced hydroxyl radicals has been estimated as 1.8×10^{-11} cm^3/(molecule sec) at 25 ºC using a structure estimation method. This corresponds to an atmospheric half-life of about 20 hours at an atmospheric concentration of $5 \times 10^{+5}$ hydroxyl radicals	[3]

	per cm^3. Diethylene glycol dibenzoate has an estimated base-catalyzed hydrolysis rate of 0.16 l/mol-sec at a pH of 8, which corresponds to a half-life of 49 days at a pH of 8 and 1.3 years at a pH of 7	
Metabolic pathway	-	
Mobility	Using a structure estimation method based on molecular connectivity indices, the Koc for diethylene glycol dibenzoate can be estimated to be about 540. According to a recommended classification scheme, this estimated Koc value suggests that diethylene glycol dibenzoate has low mobility in soil.	[3]
Volatilization from water/soil	The Henry's Law constant for diethylene glycol dibenzoate is estimated as 3 x 10^{-12} atm/m^3/mol using a fragment constant estimation method. This value indicates that diethylene glycol dibenzoate will be essentially nonvolatile from water surfaces. Diethylene glycol dibenzoate's estimated values for vapour pressure, 0.09 mm Hg and Henry's Law constant indicate that volatilization from dry and moist soil surfaces should not occur.	[3]
Terrestial fate	Based on a recommended classification scheme, an estimated Koc value of 540, determined from a structure estimation method, indicates that diethylene glycol dibenzoate will have low mobility in soil. Volatilization of diethylene glycol dibenzoate should not be important from moist soil surfaces given an estimated Henry's Law constant of 3 x 10^{-12} atm/m^3/mol, using a recommended regression equation. Volatilization from dry soil surfaces is not expected based on an estimated vapour pressure of 0.09 mm Hg, determined from a fragment constant method. No data are available to determine the rate or importance of biodegradation of diethylene glycol dibenzoate in soil.	[3]
Aquatic fate	Based on a recommended classification scheme, an estimated Koc value of 540, determined from a structure estimation method, indicates that diethylene glycol dibenzoate should adsorb to suspended solids and sediment in the water. Diethylene glycol dibenzoate will be essentially non-volatile from water surfaces based on an estimated Henry's Law constant of 3 x 10^{-12} atm/m^3/mole, developed using a fragment constant estimation method. According to a classification scheme, an estimated BCF value of 120, from an estimated log Kow, suggests that bioconcentration in aquatic organisms is high. Diethylene glycol dibenzoate has an estimated base-	[3]

	catalyzed hydrolysis rate of 0.16 l/mol-sec at a pH of 8, which corresponds to a half-life of 49 days at a pH of 8 and 1.3 years at a pH of 7. Insufficient data are available to determine the rate or importance of biodegradation of diethylene glycol dibenzoate in water.	
Atmospheric fate	According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere, diethylene glycol dibenzoate, which has an estimated vapor pressure of 0.09 mm Hg at 25 °C, will exist solely as a vapour in the ambient atmosphere. Vapour-phase diethylene glycol dibenzoate is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals; the half-life for this reaction in air is estimated to be about 20 hours. Particulate-phase diethylene glycol dibenzoate may be physically removed from the air by wet and dry deposition.	[3]

Conclusion

Physical-chemical	-
Emission	-
Exposure	-
Health	-
Environment	-

References

1 ESIS

2 InChem, WHO IPCS

3 HSDB, Toxnet

4 EPA HPV

5 MSDS, Genovique

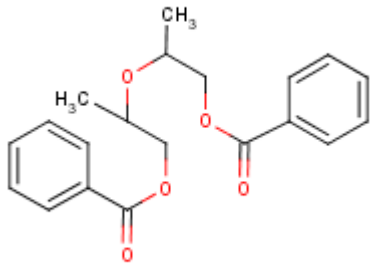
6 ChemId

Diethylene glycol dibenzoate, DEGD

7	SRC physprop database

Dipropylene glycol dibenzoate, DGD

Identification of the substance

CAS No.	27138-31-4	
EINECS No.	248-258-5	[1]
EINECS Name	oxydipropyl dibenzoate	[1]
Synonyms	Dipropylene glycol dibenzoate	
	DGD	
Molecular Formula	$C_{20}H_{22}O_5$	[1]
Structural Formula		
Major Uses	-	
IUCLID	Is listed as a LPV chemical	[1]
	OECD. Listed as a High Production Volume Chemical.	[4]
EU classification	This substance is not classified in the Annex I of Directive 67/548/EEC as such, but it may be included in one of the group entries.	[1]
	N, R51/53 (self classification)	[4]

Physico-chemical Characteristics

Physical Form	Clear colourless liquid with a mild esterlike odour	[2]
Molecular Weight (g/mole)	342.4	[3]
Melting Point/range (°C)	-30°C	[7]

Dipropylene glycol dibenzoate, DGD

Boiling Point/range (°C)	Decomposes above 270ºC without boiling at 762 mm Hg	[2]
	232ºC at 5 mm Hg	[3]
	197 ºC at 1 mm Hg	[7]
Decomposition Temperature (°C)	Decomposes above 270ºC without boiling at 762 mm Hg	[2]
Vapour Pressure (mm Hg at °C)	1.2×10^{-6} mm Hg at 25ºC [1.59×10^{-4} Pa]	[2]
	1.1×10^{-5} mm Hg at 50ºC [1.46×10^{-3} Pa]	
	3.8×10^{-4} mm Hg at 100ºC [0.0506 Pa]	
Density (g/cm^3 at °C)	1.12	[3]
	1.129 at 25ºC	[7]
Vapour Density (air=1)	11.8	[4]
Henry's Law constant (atm/m^3/mol at °C)	3.8×10^{-8}	[2]
	1.38×10^{-8} at 25ºC	[5], [6], [7]
Solubility (mg/l water at °C)	8.69 mg/l at 30ºC, pH = 7.0	[2]
	15 mg/l at 25ºC	[5], [6]
Partition Coefficient (log P_{ow})	3.9	[2]
	3.88	[5], [6]
pK_a	-	
Flammability	Combustible. Very slightly to slightly flammable in presence of open flames and sparks.	[4]
Explosivity	Not considered to present risk of explosion	[4]
Oxidising Properties	-	
Migration potential in polymer	-	
Flash point (ºC)	192	[2]
Viscosity	110 cP at 25ºC	[4]
Atmospheric OH rate constant cm^3/(molecule sec)	3.44×10^{-11}	[5], [6]

Dipropylene glycol dibenzoate, DGD

Emission Data

During production	-

Exposure Data

Aquatic environment, incl. sediment	-	
Terrestrial environment	-	
Sewage treatment plant	-	
Working environment	Inhalation and skin contact are expected to be the primary routes of occupational exposure to dipropylene glycol dibenzoate. This material is not expected to cause significant adverse human health effects when used in accordance with good industrial hygiene and safety practices are followed.	[4]
Consumer goods	-	
Man exposed from environment	-	
”Secondary poisoning”	-	
Atmosphere	-	
Dermal	-	

Toxicological data

Observations in humans	-

Acute toxicity

Oral	LD_{50} = 3914 mg/kg (rat, combined)	[2]
	LD_{50} = 5313 mg/kg (rat)	[4]
Dermal	LD_{50} > 2000 mg/kg (rat)	[2]
	LD_{50} > 2000 mg/kg (rat)	[4]

Inhalation	LC_{50} (mist) > 200 mg/l	[4]
Other routes		
Skin irritation	A single semi-occlusive application of dipropylene glycol dibenzoate to intact rabbit skin for four hours elicited no dermal irritation.	[2]
Eye irritation	None of the treated animals showed a positive response. No corneal damage or iridial inflammation was observed. Transient hyperemia of blood vessels only was observed in all animals. These reactions had resolved in all instances by one or two days after instillation.	[2]
Irritation of respiratory tract	-	
Skin sensitisation	Dipropylene glycol dibenzoate did not produce evidence of skin sensitization (delayed contact hypersensitivity) in any of twenty test animals. Evidence of skin sensitization was produced by hexyl cinnamic aldehyde (HCA) in all ten positive controls thus confirming the sensitivity of the method.	[2]

Subchronic and Chronic Toxicity

Oral	NOAEL = 1000 mg/kg/day (rat, 13 weeks) Dipropylene glycol dibenzoate was administered to rats by dietary admixture to achieve dosages of 0, 250, 1000, 1750 or 2500 mg/kg/day over 13 weeks. Selected Control and Group 5 animals were subsequently maintained off dose for 4 weeks to assess reversibility of any treatment related changes. Dosages of 1000 mg/kg/day or below are considered to represent a No Observable Adverse Effect Level (NOAEL) of Dipropylene glycol dibenzoate in rats by oral administration over 13 weeks. A few minor intergroup differences were noted at 1000 mg/kg/day but were insufficient to be of toxicological importance. Higher dosages of 1750 or 2500 mg/kg/day were tolerated but the adverse effect on bodyweight was more pronounced, there were increases in circulating enzyme activities, low grade hepatocyte hypertrophy and an increased incidence and degree of hemosiderosis in the spleen in one or both sexes. At 2500 mg/kg/day, an increased incidence of minimal epithelial hyperplasia was noted in the caecum. When selected animals previously receiving 2500 mg/kg/day were maintained off dose for 4 weeks, all treatment related effects showed evidence of, or complete, recovery.	[2]
Inhalation	-	
Dermal	-	
Metabolism	Studies conducted show dipropylene glycol dibenzoate is rapidly metabolized and excreted from the body. It does not accumulate in rats and this behavior is expected in other mammalian systems as well. This conclusion is supported through the test where oral doses of 14C-labeled Dipropylene glycol dibenzoate were rapidly absorbed through the gut in rats. Seventy percent of the administered dose was excreted through the urine within 48 hours as hippuric acid, and about 10% was observed in the feces. The half-life of radiocarbon in the blood was 3 hours and for other organs 2-15 hours.	[2]

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	S.typhimurium and E.coli (metabolic activator Sprague-Dawley rat liver (S9)) Genotoxic conc: No genotoxic effects observed with or without metabolic activation No evidence of mutagenic activity in this bacterial system.	[2]
	Mouse lymphoma (metabolic activator Sprague-Dawley rat liver (S9)) Genotoxic effects: No effects observed with or without metabolic activation. No evidence of mutagenicity in this in vitro gene mutation assay.	[2]
Chromosome Abnormalities	Chinese hamster lung (metabolic activator Sprague-Dawley rat liver (S9)) Genotoxic effects: No statistically significant increases in the proportion of aberrant cells, when compared to the solvent control, were seen in either the presence or the absence of S9 mix. A small response seen in the first test, with S9 mix, was not reproduced in the repeat test or at the later harvest. This response was not considered to be indicative of clastogenic activity.	[2]
Other Genotoxic Effects	-	
Estrogenic activity	Dipropylene glycol dibenzoate did not induce vaginal cornification at doses of 500, 1000, 1500 or 2000 mg/kg/day for 7 days by oral gavage in ovariectomized adult Spraque-Dawley (CD) rats. Dipropylene glycol dibenzoate did not stimulate a uterine weight increase or an increase in the uterine weight to final body weight ratio at doses of 500, 1000, 1500 or 2000 mg/kg/day for 7 days. When compared with the vehicle control (corn oil) and positive control (diethylstilbestrol), these data demonstrate that dipropylene glycol dibenzoate did not exhibit estrogenic activity up to and including the maximally tolerated dose.	[2]
Carcinogenicity	-	

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	Rat (38 weeks duration) The NOEL is 10,000 ppm for F0 and F1 parent animals and the NOAEL for survival and growth of offspring is considered to be 10,000 ppm.	[2]
Teratogenicity	-	
Developmental toxicity	Rat (20 days duration from gestation) Maternal Toxicity NOEL : 1000 mg/kg/day Clinical Signs: The general condition of females at all dosages remained satisfactory throughout the study and there were no deaths. Salivation after dosing was observed at all dosages. The incidence was dosage related but this finding was not considered to be of toxicological importance. At 1000 mg/kg/day, there were no detectable signs of maternal toxicity; there were no maternal deaths and all females had a live litter at sacrifice. Litter Responses and Fetal Changes Prenatal development NOAEL: 500 mg/kg/day. A small number of fetuses with cervical ribs at 1000 mg/kg/day precludes defining this dosage as a NOEL for developmental anomalies, in all other respects the NOAEL for pre-natal development is concluded to be 1000 mg/kg/day. Fetal Growth and Development NOEL: 250 mg/kg/day There were no effects of treatment on pre-natal survival or growth. At 1000 mg/kg/day, treatment was associated with a small but definite increase in the number of fetuses with cervical ribs. At 1000 and 500 mg/kg/day, there were a greater number of fetuses with incomplete ossification of the 5th and 6th sternebrae compared with Controls, but this finding was not considered to be of any long term toxicological significance.	[2]

Toxicokinetics

Dipropylene glycol dibenzoate, DGD

Toxicokinetics

Ecotoxicity Data

Algae	EL_{50} (area under the curve 72h) = 1.1 mg/l	[2]
	EL_{50} (growth rate 0-72h) = 4.9 mg/l	
	EL_{50} (area under the curve 96h) = 0.96 mg/l	
	EL_{50} (growth rate 0-96h) = 3.6 mg/l	
	NOEL (area under the curve 72h) = 0.22 mg/l	
	NOEL (growth rate 0-72h) = 1.0 mg/l	
	NOEL (area under the curve 96h) = not observed	
	NOEL (growth rate 0-96h) = 0.46 mg/l	
Daphnia magna	EL_{50} (24h) = 43.2 mg/l (Daphnia magna)	[2]
	EL_{50} (48h) = 19.31 mg/l (Daphnia magna)	
	No-observed effect loading rate = 2.2 mg/l (Daphnia magna)	
Other aquatic organisms	-	
Fish	LC_{50} (0.25-48h) > 4.9 mg/l (fathead minnow)	[2]
	LC_{50} (72h) = 4.7 mg/l (fathead minnow)	
	LC_{50} (96h) = 3.7 mg/l (fathead minnow)	
	No-observed effect concentration = 1.2 mg/l (fathead minnow)	
Bacteria	EC_{50} > 10 mg/l (pseudomonas putida)	[4]

Dipropylene glycol dibenzoate, DGD

Terrestrial organisms	Under the conditions of this study, the LC_{50} of dipropylene glycol dibenzoate to the earthworm was found to be in excess of 1000 ppm. The NOEL was considered to be 1000 ppm.	[2]
Sludge	No inhibitory effect on the respiration rate of activated sludge at concentrations up to 100 mg/l.	[4]

Environmental Fate

BCF	-	
Aerobic biodegradation	6% of TCO_2 at 2 days	[2]
	62% of TCO_2 at 12 days	
	85% of TCO_2 at 28 days	
	Readily biodegradable	
	The BOD_5 of dipropylene glycol dibenzoate was 0.65 gO2/g (30% of its ThOD; 2.15 gO_2/g) based on results obtained at a nominal concentration of 2 mg/l. The mean COD of dipropylene glycol dibenzoate (2.33 gO_2/g) was 104% of its ThOD which confirmed that the material was completely oxidized in the COD test. The mean BOD_5 of dipropylene glycol dibenzoate was 29% of its COD. For screening purposes, substances are generally considered readily biodegradable in this test if the ratio of BOD_5:COD or ThOD 50%. Dipropylene glycol dibenzoate cannot therefore be considered to be readily biodegradable under the conditions of this test. Because this type of BOD test employs both a weak microbial inoculum and a relatively short incubation time, it can be considered to be a particularly stringent test of biodegradability.	[2]

Anaerobic biodegradation	Dipropylene glycol dibenzoate was degraded to 46% after 60 days of incubation and 75% after 120 days of incubation, based on a nominal level of carbon in the culture at the start of the test (12 mgC). At Day 120 of the test, dipropylene glycol dibenzoate was degraded to 90% based on the theoretical carbon level (10 mgC) remaining in cultures following removal of samples for DIC analysis. The precise distribution of dipropylene glycol dibenzoate in test mixtures was not determined in this test so the level of carbon remaining in test mixtures after samples were removed for DIC analysis cannot be accurately determined. However, since the octanol:water partition coefficient for dipropylene glycol dibenzoate is relatively high (log Pow 3.9), it is likely that the material will adsorb onto sewage solids. Although the level of biodegradation calculated using the nominal level of carbon at the start of the test (12 mgC) gives the worst case estimate, it is likely to be the most accurate. Substances are considered to be ultimately degraded under anaerobic conditions in this test if the level of degradation is equal to or greater than 60%. Dipropylene glycol dibenzoate can therefore be considered ultimately biodegradable under anaerobic conditions.	[2]
Abiotic biodegradation	-	
Metabolic pathway	-	
Mobility	-	
Photodegradation		[2]
Stability in water	-	
Transport (fugacity)	-	

Conclusion

Physical-chemical	-
Emission	-
Exposure	-
Health	-
Environment	-

Dipropylene glycol dibenzoate, DGD

References

1 ESIS

2 EPA HPV challenge programme

3 Sigma Aldrich MSDS

4 Genovique MSDS for Benzoflex 9-88

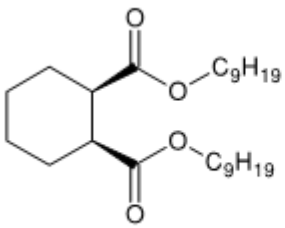
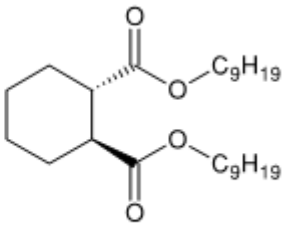
5 ChemID

6 SRC PhysProp database

7 MITI

Di-isononyl-cyclohexane-1,2dicarboxylate, DINCH

Identification of the substance

CAS No.	166412-78-8 (EU)	[4]
	474919-59-0 (USA and Canada)	
EINECS No.	431-890-2	[1]
EINECS Name	1,2-Cyclohexanedicarboxylic acid, 1,2-diisononyl ester	[2]
Synonyms	Di-isononyl-cyclohexane-1,2-dicarboxylate	
	DINCH	
	Hexamoll DINCH	
	1,2-Cyclohexanedicarboxylic acid, diisononyl ester (9CI)	
	1,2-Cyclohexanedicarboxylic acid, diisononyl ester, branched and linear	
Molecular Formula	$C_{26}H_{48}O_4$	
Structural Formula	 90±10% *cis*- isomer  10±10% *trans*- isomer	
Major Uses	The major applications for the notified chemical will use it as a plasticiser and impact modifier in food packaging, but also in general applications such as wire and cable, automotive, plastisols and other similar applications.	[2]
IUCLID	-	
EU classification	-	

Physico-chemical Characteristics

Di-isononyl-cyclohexane-1,2dicarboxylate, DINCH

Physical Form	Clear colourless liquid at 20ºC and 101.3 kPa	[2], [3]
	Almost odourless	
Molecular Weight (g/mole)	424.6	[2]
Melting Point/range (°C)	No freezing point	[2]
	Glass point < -90ºC	
	Pour point = -54ºC	
Boiling Point/range (°C)	> 351ºC at 101.3 kPa	[2]
	240 – 250ºC at 7 mbar	[3]
Decomposition Temperature (°C)	> 351ºC at 101.3 kPa, decomposes before boiling	[2]
Vapour Pressure (mm Hg at °C)	2.2×10^{-8} kPa at 25ºC [2.2×10^{-5} Pa, 1.65×10^{-7} mmgHg]	[2]
	8.9×10^{-7} kPa at 50ºC [8.9×10^{-4} Pa, 6.67×10^{-6} mmgHg]	
Density (g/cm^3 at °C)	0.947 at 20ºC	[2]
Vapour Density (air=1)	-	
Henry's Law constant ($atm/m^3/mol$ at °C)	-	
Solubility (mg/l water at °C)	< 0.00002 g/l at 25ºC [< 0.02 mg/l]	[2]
Partition Coefficient (log P_{ow})	> 6.2 at 25ºC	[2]
pK_a	-	
Flammability	Not highly flammable	[2]
Explosivity	Not explosive	[2]
Oxidising Properties	-	
Migration potential in polymer	-	
Viscosity	44-60 mPa.s at 20ºC	[2]
Absorption/Desorption (log Koc)	> 5.6 at 23ºC	[2]
log Kow	10	[4]

Autoignition temperature	330ºC	[2], [3]
Flash point	224ºC	[2], [3]

Emission Data

During production	-

Exposure Data

Aquatic environment, incl. sediment	-
Terrestrial environment	-
Sewage treatment plant	-

Working environment

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage			
Polymer stage	15	2	50
Product stage	15	1-2	40-50
Compounding and Manufacturing			
Reactor operation	50	12	20
Maintenance	20	1-2	240
QC testing	10	2	240
Transport & storage	10	2/4	240
End use	1000s	1-12	240

Transport and storage [2]

The notified chemical will be transported by road to a warehouse and then to the compounding facility. Exposure of receivers and transport personnel should only occur in the event of an accidental spillage.

Compounding	[2]

Incidental skin contact with the notified chemical may occur when the storemen insert the drum lance into the 200 L drum, or during connection of an IBC or isotank to the weighing vessel. Inhalation exposure to vapours may also occur during the transfer process. After mixing, intermittent skin contact may occur during the packaging process, from powdered blend or liquid plastisol. Quality control samples may also be taken at this stage, as technical personnel will make up small-scale compounds by hand in the laboratory.

During the subsequent compounding of dry blend into pellets, closed systems are used, and any exposure will be incidental. However, manual operations during this process may include opening of packages, connection/insertion of lines/hoses, pumping liquid products, and eventual removal of connections and closing the containers. In addition, maintenance workers may experience skin contact with the notified chemical.

For the specific formulation sites in Australia, approximately one third of the production time for the operators will be dedicated to running compound. During production runs (which can be up to 5 days long), the operators will work two 12-hour shifts, 5 days per week, and 48 weeks per year. Workers will prepare approximately 8 batches per day. Given the time that it takes to connect up and transfer product, the estimated period of direct contact with the notified chemical is less than 30 minutes per day for one person per shift.

Local exhaust ventilation will be employed at all workplace areas where natural ventilation is considered inadequate. Workers, particularly for those operators involved in any open transfer operations, wear personal protective equipment (PPE) including overalls, safety glasses/goggles and face splash shields, protective gloves, and are assumed to operate using appropriateindustrial hygiene practices.

Product manufacture [2]

Exposure to the notified chemical may occur during the processing of PVC compound or plastisol to manufacture the end-use product. Once compounded with PVC, the notified chemical is bound within the PVC matrix and exposure is unlikely. However, during product manufacture by processes such as extrusion, calendering and injection moulding, the elevated temperatures required may result in inhalation exposure to the notified chemical, whether from vapours or aerosols.

The methods for product manufacture from plastisols include spread coating, under-body coating, sealing, rotational coating, dipping and slush moulding. Although the processes are largely automated and enclosed, incidental skin contact with the notified chemical may occur during transfer of plastisol from drums to the moulding equipment. Workers are expected to wear PPE including overalls, gloves and eye protection.

End-use of products [2]

Under normal circumstances, dermal exposure to the notified chemical is not expected during handling of PVC products, as it is expected to be physically bound within the PVC matrix. Exudation may occur during any heating of plastics, leading to possible skin and inhalation exposure to low levels of the notified chemical.

Occupational exposure estimation [2]

For dermal exposure of workers involved in handling of the notified chemical during compounding and/or product manufacture, assuming non-dispersive use with some intermittent direct contact, EASE exposure modelling estimates the dermal exposure to the notified chemical to be 0-0.1 mg/cm^2/day (EC, 2003). However, the use of EASE for accurately predicting dermal exposures is thought to be limited in accuracy (EC, 2003). The RISKOFDERM project, based on measurements of industrial exposures, describes exposure levels to the hands fo r the addition of liquids into "large containers (or mixers) with large amounts (many litres) of liquids" (Marquart et al, 2006). In this study, a typical case exposure was described as 0.5 mg/cm^2/scenario, though a reasonable worst-case exposure was described as 14 mg/cm^2/scenario. Therefore, based on a reasonable exposure frequency of once daily and a whole-hand exposure (420 cm^2) to a 60 kg adult, a typical dermal exposure of 3.5 mg/kg bw/day is assumed. Worst-case, infrequent (whole-hand) exposures may be as high as 98 mg/kg bw/scenario.

Assuming a closed system with LEV, a highest-probable process temperature of 220ºC (and excluding the possibility of aerosol formation), EASE estimates that the gas/vapour exposure to the notified chemical is likely to be 0-1.8 mg/m^3 (0-0.1 ppm) (EC, 2003). The same value is estimated for an identical system at 25ºC. Therefore as a worst-case estimate, a 60 kg adult male worker exposed to vapours with an inhalation rate of 25.5 m^3/12-hour shift during medium activity (EC, 2003), might experience inhalation exposure to the no tified chemical of 0-0.77 mg/kg bw/day.

Therefore, excluding oral exposure and assuming 10% dermal and 100% inhalation absorption (EC, 2003), the typical exposure during handling of the notified chemical is estimated to be 0.35-1.12 mg/kg bw/day. [2]

Di-isononyl-cyclohexane-1,2dicarboxylate, DINCH

Consumer goods	The notified chemical has undergone assessment by the European Food Safety Authority in September 2006 (EFSA, 2006). For this assessment, the specific migration of the notified chemical was measured using various food simulants and representative foodstuffs, under different storage conditions. The specific migration of 10-17.8% notified chemical in plasticised PVC cling film into food simulants and foodstuffs was determined using a validated Gas Chromatography/Mass Spectrometry (GC/MS) method (Otter, 2007):	[2]

Test Sample	*Food*	*Extractable fat in food (%)*	*Migration conditions*	*Specific migration (mg/dm²)*
Cling film *(thickness 14 µm, 17.8% notified chemical)*	Sunflower oil	100	6-144 hours/ 10°C & 20°C	29 ± 2
	10% ethanol	0	24 hours/40°C	0.016 ± 0.002
	Turkey (escalope/Schnitzel)	1.0 ± 0.5	5 days/5°C	0.3 ± 0.1
	Pork (neck)	11.3 ± 2.5	5 days/5°C	1.2 ± 0.2
	Pork (escalope/Schnitzel)	0.7 ± 0.3	5 days/5°C	0.14 ± 0.01
		1.8 ± 0.3	5 days/5°C	0.30 ± 0.01
	Pork (liver)	5.0 ± 0.1	5 days/5°C	0.11 ± 0.02
	High fat cheese (nom. 60% fat)	44.3 ± 2.6	10 days/5°C	27.5 ± 2.2
	Low fat cheese (nom. 20% fat)	2.9 ± 1.0	10 days/5°C	2.4 ± 0.7
Cling Film *(thickness 14 µm, 12.2% not. chem.)*	Pork (neck)	14.7 ± 2.9	5 days/5°C	1.0 ± 0.3
	Pork (bacon)	22.1 ± 2.7	5 days/5°C	1.4 ± 0.1
Cling Film *(thickness 14 µm, 10% not. chem.)*	Pork (neck)	17.9 ± 0.5	5 days/5°C	0.5 ± 0.1
	Pork (bacon)	25.81 ± 2.4	5 days/5°C	0.8 ± 0.3

The notified chemical was found to migrate into foods with high fat content (e.g. .29 mg/dm^2 into sunflower oil, and .27.5 mg/dm^2 into high fat cheese). The migration of the notified chemical into food like fresh meat and low fat cheese was lower than that of foods containing higher fat levels (<2.4 mg/dm^2). The level of notified chemical in fresh meat at equilibrium was found to be proportional to the starting concentration in the cling film and relative to the fat content of the foods. In fatty foods, migration to equilibrium was achieved after 6 hours of contact. Likewise, extraction studies from bottle closures using isooctane (in which the notified chemical is very soluble) show that it is able to extract an equilibrium concentration of the notified chemical after 5.3 hours. [2]

For the use of the notified chemical in bottle sealing gaskets, artificial wine corks and beverage tubes, migration of the notified chemical into mineral water, grapefruit juice, soft drink or 15% ethanol was found to be very low (generally less than 0.11 mg/L, its solubility in 15% ethanol). This level of migration of the notified chemical is expected to apply for all aqueous foods (except alcoholic drinks with high ethanol content) as the low aqueous solubility of the notified chemical would limit its migration. Migration of the notified chemical from polystyrene (at the proposed use concentration) is expected to be lower than that from PVC. A test study using notified chemical-containing polystyrene sticks showed no migration of the notified chemical into olive oil or aqueous 10% ethanol (after 10 days at 40ºC) above the detection limit of the analytical method (unpublished study provided by the notifier). Very low levels of migration of the notified chemical from polystyrene into aqueous 50% ethanol were observed.

For conveyor belts, migration into solid or semi-solid foods is expected to be limited by contact area and short contact times. Computer modelling of fatty food with .30 minutes contact time on a conveyor belt containing 12% notified chemical estimates specific migration rates of 12.4 mg/dm^2 at 20ºC and 6.6 mg/dm^2 at 10ºC (Otter, 2007). Therefore, assuming that migration into most foods will be considerably less than migration into oil, and that only the bottom of food is in contact with the conveyor belt (1 dm^2/kg), the migration of the notified chemical is expected to be <5 mg/kg food for 0.30 minutes contact time.

Man exposed from environment	-
”Secondary poisoning”	-
Atmosphere	-
Dermal	Members of the public are likely to make limited dermal contact with food packaging, wires, cables and/or automotive parts containing the notified chemical. Significant exposure to the notified chemical in plastic products as a result of casual contact during handling is not expected, as it is expected to be sufficiently bound within the plastic matrix. However, as the notified chemical will not be chemically bound, it may be released from products in low levels over time (e.g. volatilisation from car upholstery). The expected dermal exposure from prolonged contact with plastics containing the notified chemical cannot be accurately estimated, but may be significant as the notified chemical may partition from the plastic into the skin over time.

Toxicological data

Observations in humans	-

Acute toxicity

Oral	LD_{50} > 5000 mg/kg (rat)	[2]
Dermal	LD_{50} > 2000 mg/kg (rat)	[2]
Inhalation	-	
Other routes	-	
Skin irritation	Slightly irritating (rabbit)	[2]
Eye irritation	Not irritating (rabbit)	[2]
Irritation of respiratory tract	-	

Di-isononyl-cyclohexane-1,2dicarboxylate, DINCH

Skin sensitisation	No evidence of skin sensitisation	[2]

Subchronic and Chronic Toxicity

Oral	Rat, 28-day oral repeat dose	[2]
	NOAEL = 318 mg/kg (male)	
	NOAEL = 342 mg/kg (female)	
	Rat, 90-day oral repeat dose	[2]
	NOAEL = 107.1 mg/kg (male)	
	NOAEL = 389.4 mg/kg (female)	
	Rat, 2-year chronic toxicity/carcinogenicity	[2]
	NOAEL = 40 mg/kg (male)	
	NOAEL = 200 mg/kg (female)	
Inhalation	-	
Dermal	-	

Metabolism	After oral administration DINCH showed rapid but saturable absorption and extensive elimination 24 hours after dosing approximately 80% of the radio-activity is excreted, after 48 hours more than 90 % is excreted via urine and mainly via feces.Based on the amounts of radioactivity excreted in the bile and urine, the bioavailability of 14C-1,2-yclohexanedicarboxylic acid di(isononyl)ester is es-timated to be 5-6% at the high dose and 40-49 % at the low dose. There is no indication of bioaccumulation. The characterisation of metabolites after oral and intra-venous administration of DINCH indicates two main pathways: the partial hydrolysis of DINCH to the mono-isonyl ester followed by conjugation to glucuronic acid, which is the most ab Undant me-tabolite in bile, or the hydrolysis of the remaining ester bond to yield free cyclohexane dicarboxylic acid, the predominant urinary metabolite.	[4]

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	S.typhimurium and E.coli (metabolic activator Aro-clor 1254-induced rat liver (S9)) Not mutagenic to bacteria under the conditions of the test.	[2]
	Chinese hamster (CHO cells) (metabolic activator Aroclor 1254-induced rat liver (S9)) Not observed to induce mutations in CHO cells treated ***in vitro*** under the conditions of the test.	[2]
Chromosome Abnormalities	Chinese hamster (V79 cells) (Phenobabital/3-naphthoflavone-induced rat liver S9 mix) Not clastogenic to V79 cells treated ***in vitro*** under the conditions of the test.	[2]

	Mouse Not found to be clastogenic or aneuploidogenic under the conditions of this ***in vivo*** mouse micronucleus test.	
Other Genotoxic Effects	-	
Carcinogenicity	Rat, 2-year chronic toxicity/carcinogenicity NOAEL = 40 mg/kg (male) NOAEL = 200 mg/kg (female)	[2]

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	Rat, two-generation study (37 weeks) Under the conditions of this two-generation reproduction study, the NOAEL for fertility and reproductive performance is 1000 mg/kg bw/day for F0 and F1 generation rats of both genders. The NOAEL for general toxicity is 1000 mg/kg bw/day (F0 rats of both genders) and 100 mg/kg bw/day for the F1 male and female rats (based on tubular vacuolisation and flaky thyroid follicular colloid). The NOAEL for developmental toxicity (growth and development of offspring) was 1000 mg/kg bw/day for the F1 and F2 pups.	[2]
Teratogenicity	-	
Developmental toxicity	Rabbit (exposure day 6 to day 29 post insemination) NOAEL = 1000 mg/kg, based on maternal and prenatal developmental toxicity. Rat (exposure day 6 to day 19 post coitum) NOAEL = 1200 mg/kg, based on maternal and prenatal developmental toxicity.	[2] [2]

Pre-/Postnatal developmental toxicity	Rat (exposure day 6 to day 20 post partum) Based on the conditions of this study, the No Observed Adverse Effect Level (NOAEL) for reproductive performance and systemic toxicity of the parental female rats is 1000 mg/kg bw/day. The NOAEL for developmental toxicity (based on the growth and development of the offspring, including sexual organ morphology and sexual maturation) is also 1000 mg/kg bw/day for F1 progeny.	[2]

Toxicokinetics

Toxicokinetics	Rat, toxicokinetics and metabolism Distribution to all organs and tissues was observed after rapid absorption. The oral bioavailability was calculated to be ~5-6% of a high dose and ~40-49% of a low dose, indicating saturation of gastrointestinal absorption. Accumulation was not observed in rats, and excretion was rapid, mainly via the faeces. Metabolism to several major metabolites: cyclohexanedicarboxylic acid (urine), monoisononyl cyclohexanedicarboxylate (faeces) & the glucuronide of monoisononyl cyclohexanedicarboxylate (bile)	[2]

Ecotoxicity Data

Algae	Scenedesmus subspicatus Biomass EC_{50} > 100 mg/l WAF (72h) NOEC 100 mg/l WAF Growth EC_{50} > 100 mg/l WAF (72h) NOEC 100 mg/l WAF	[2]

Di-isononyl-cyclohexane-1,2dicarboxylate, DINCH

Daphnia magna (acute)	LC_{50} > 100 mg/l WAF (48h, daphnia magna) ("Water Accommodated Fraction" (WAF)	[2]
	NOEC = 100 mg/l WAF (48h)	
Daphnia magna (chronic)	Daphnia magna (21 days)	[2]
	NOEC 0.021 mg/l	
	LOEC 0.021 mg/l	
	LCD 0.021 mg/l	
Other aquatic organisms	-	
Fish	LC_{50} > 100 mg/l (96h, zebra fish)	[2]
	NOEC = 100 mg/l (96h)	
Bacteria	-	
Terrestrial organisms	LC_{0} > 1000 mg/kg (earth worm, 14 day)	
	LC_{50} > 1000 mg/kg (earth worm, 14 day)	
	LC_{100} > 1000 mg/kg (earth worm, 14 day)	
Sludge	EC_{50} >1000 mg/L (nominal)	[2]
	The oxygen concentration decreased more significantly for the test substance than for the blank controls.	
	The oxygen consumption rate did not differ between the test substance and the controls.	
	The oxygen consumption rate of the reference substance is significantly lower than both the rate of the test substance and the blank samples and the reference met the validity criteria (EC_{50} = 6.5 mg/L).	

Higher plants	The EC50 test results, relating to dry mass of the soil, for all three species (Avena sativa, Brassica napus and Vicia sativa) are as follows: EC_{50} (emergence rate) >1000 mg/kg (nominal) EC_{50} (dry matter) >1000 mg/kg (nominal) EC_{50} (fresh matter) >1000 mg/kg (nominal) EC_{50} (shoot length) >1000 mg/kg (nominal) The NOEC/LOEC tests results relating to the dry mass of the soil for all the three species (Avena sativa, Brassica napus and Vicia sativa) are as follows: NOEC/LOEC (emergence rate) .1000 mg/kg (nominal) NOEC/LOEC (dry matter) .1000 mg/kg (nominal) NOEC/LOEC (fresh matter) .1000 mg/kg (nominal) NOEC/LOEC (shoot length) .1000 mg/kg (nominal)	[2]

Environmental Fate

BCF	BCF = 189.3 DT_{50} = 0.5 (low conc) DT_{50} = 0.6 (high conc) Not likely to bioaccumulate	[2]
Aerobic biodegradation	*Test substance* *Day* / *% Degradation* 7 / 4 14 / 10 21 / 27 28 / 41 38 / 64 49 / 76 60 / 93 The substance is not readily biodegradable.	[2]

Di-isononyl-cyclohexane-1,2dicarboxylate, DINCH

Anaerobic biodegradation	-
Metabolic pathway	-
Mobility	-

Conclusion

Physical-chemical	-
Emission	-
Exposure	-
Health	-
Environment	-

References

1 ESIS

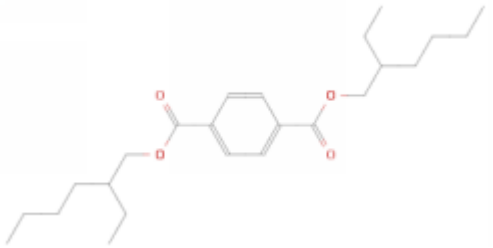
2 NICNAS

3 BASF MSDS

4 SCENIHR

Di (2-ethyl-hexyl) terephthalate, DEHT, DOTP

Identification of the substance

CAS No.	6422-86-2	
EINECS No.	229-176-9	[1]
EINECS Name	bis(2-ethylhexyl) terephthalate	[1]
Synonyms	Di-(2-ethyl-hexyl)-terephthalate	
	DEHT	
	DOTP	
Molecular Formula	$C_{24}H_{38}O_4$	[1]
Structural Formula		
Major Uses	Softeners	[2]
IUCLID	Not listed	[1]
EU classification	This substance is not classified in the Annex I of Directive 67/548/EEC as such, but it may be included in one of the group entries.	[1]

Physico-chemical Characteristics

Physical Form	Liquid	[2]
	Colourless, mobile and highly volatile liquid with a pleasant odour.	[3]
Molecular Weight (g/mole)	390.557	[3]
Melting Point/range (°C)	-48ºC	[2], [3]
Boiling Point/range (°C)	383ºC at 1015 hPa	[2], [3]
	400ºC	[7]

Decomposition Temperature (°C)	-	
Vapour Pressure (mm Hg at °C)	0.0000285 hPa at 25ºC [2.85 x 10^{-3} Pa, 2.13 x 10^{-5} mmgHg]	[2]
	1013 hPa at 398ºC [1.013 x 10^{5} Pa, 757.8 mmgHg]	
	2.14 x 10^{-5} mm Hg at 25ºC [2.85 x 10^{-3} Pa]	
	1.33 mbar at 217ºC [133 Pa , 0.99 mmHg]	[7]
	5.56 x 10^{-10} mbar at 25ºC [5.56 x 10^{-8} Pa , 4.17 x 10^{-10} mmHg]	
Density (g/cm^3 at °C)	0.984 at 20ºC	[2]
	0.9825 at 20ºC	[3]
Vapour Density (air=1)	13.5	[3]
Henry's Law constant (atm/m^3/mol at °C)	1.18 x 10^{-5}	[2]
	1.02 x 10^{-5} 25ºC	[3]
Solubility (mg/l water at °C)	0.4µg/l at 22.5ºC [GLP study from 2002]	[2]
	The aqueous solubility of DOTP has been recently determined to be 0.0004 mg/L (0.4 ppb) at 22.5 C using the slow-stir method. Results of earlier solubility studies have been reported that are significantly higher: values of 0.35 mg/L in well water, 0.61 mg/L in sea-water, and 1.5 mg/L in de-ionized water, all at 25 C. However, these earlier studies were performed using the shake-flask technique, which is no longer considered appropriate for oily hydrophobic substances such as DOTP.	
Partition Coefficient (log P_{ow})	8.39	[2]
pK_a	-	
Flammability	-	
Explosivity	-	
Oxidising Properties	-	
Migration potential in polymer	-	
Flash point	238ºC open cup	[2]
Auto flammability	399ºC	[2]

Di (2-ethyl-hexyl) terephthalate, DEHT, DOTP

Atmospheric OH rate constant $cm^3/(molecule\ sec)$	21.9554×10^{-12}	[2]
	2.2×10^{-11} at 25ºC	[4]
Log Kow	8.39	[3]

Emission Data

During production	Minimal potential for air pollution. Material has a very low volatility.	[2]

Exposure Data

Aquatic environment, incl. sediment	Bis(2-ethylhexyl) terephthalate's production and subsequent use as a plasticizer may result in its release to the environment through various waste streams	[3]
Terrestrial environment	-	
Sewage treatment plant	-	
Working environment	Production uses a closed system. Exposure could occur when chemical is put into drums or during quality control.	[2]
	Occupational exposure to bis(2-ethylhexyl) terephthalate may occur through inhalation of aerosols and dermal contact with this compound at workplaces where bis(2-ethylhexyl) terephthalate is produced or used. Use data indicate that the general population may be exposed to bis(2-ethylhexyl) terephthalate via dermal contact from products containing this compound.	[3]
Consumer goods	Minimal consumer exposure expected based on limited use in consumer products and low migration of the substance out of the polymer matrix in it's major use as a plasticizer.	[2]
Man exposed from environment	-	
”Secondary poisoning”	-	
Atmosphere	-	

Dermal	-	

Toxicological data

Observations in humans	Primary dermal irritation	[2]
	There was one adverse event reported during the course of the study that was not related to test-substance exposure. Overall irritation scores ranged from 0.00 to 0.11. Since the irritation did not occur in a concentration-dependent manner, it was not considered to be related to test substance exposure.	
	Skin sensitization	[2]
	Under the conditions of this study, DOTP was found to be non-irritating and did not elicit evidence of sensitization.	
	There were nine adverse events which occurred during the study, one of them severe. One of the events (soreness at the test site location) was clearly related to test substance exposure. However, this reaction was to another material being tested, not DOTP. Another event, (papular rash) was possibly related to test substance exposure. The rest of the events were unrelated to test substance exposure.	
	Slight erythema was observed for one to seven subjects at any given time during the induction phase of the study, and for only one subject during the challenge phase of the study.	

Acute toxicity

Oral	LC_{50} > 5000 mg/kg (rat, combined)	[2]
	LC_{50} > 3200 mg/kg (rat, male)	[2]
	LC_{50} > 3200 mg/kg (mouse, male)	[2]
	LDL_{0} = 20,000 mg/kg (mouse)	[5]
Dermal	LC_{50} > 19670 mg/kg (guinea pig, male)	[2]

Inhalation	Acute Exposure/ No deaths occured following inhalation exposure of mice for 4 hr to "saturated" vapors; however, mucosal irritation, loss of coordination and decreased mobility were noted. Recovery occured in 24 hours.	[3]
Other routes	-	
Skin irritation	Slightly irritating (guinea pig, 24h)	[2]
	Not irritating (human)	[7]
Eye irritation	Slightly irritating (rabbit)	[2]
Irritation of respiratory tract	-	
Skin sensitisation	Not sensitizing (guinea pig)	[2]

Subchronic and Chronic Toxicity

Oral	Rat, 90-day repeat dose	[2], [3]
	NOEL = 277 mg/kg (male)	
	NOEL = 309 mg/kg (female)	
	Di(2-ethylhexyl) terphthalate was evaluated for subchronic toxicity in Charles River rats (17-20/sex/group) fed diets containing concentrations of 0, 0.1, 0.5, or 1.0% for 90 days. There were statistically significant differences between treated and control animals in the following: decreased mean corpuscular hemoglobin (1% animals, 0.5% females), mean corpuscular volume (0.5% and 1% animals), hemoglobin (1% and 0.1% males), hematocrit (1% males), and serum glucose (0.1% females), and increased relative liver weight (1% animals). Variations in red blood cell morphology were observed in all groups (and therefore not considered to be treatment-related) including microcytosis, anisocytosis, poikilocytosis, and spherocytosis. No treatment-related gross or microscopic abnormalities were observed. There were no consistent, significant, exposure-related differences between treated and control animals in the following: mortality, body weight gain, food consumption, clinical signs of toxicity, clinical chemistry (except serum glucose), and absolute and relative organs weights (except relative liver weight)	[3]

	Rat, 21-day repeat dose	[2]
	NOEL = 505 mg/kg (male)	
	NOEL = 487 mg/kg (female)	
	Rat, 14-day repeat dose	[2]
	NOEL = 885 mg/kg	
Inhalation	Rat, 10-day exposure 6h per day	[2]
	NOEL = 46.3 mg/m^3	
Dermal	-	
Metabolism	Rat	[2]
	Approximately 25% of DEHT was hydrolyzed to 2EH- after about 10 minutes. The rest of the compound remained unchanged, and there was no evidence to suggest that 2EH was metabolized further. After 30 minutes, the stoichiometry indicated 2 moles of 2EH had been formed per mole of DEHT, indicating complete hydrolysis. The half-life of DEHT was calculated to be 53.3 minutes.	

	Rat	[2], [3]

The results obtained with DEHT are in contrast to DEHP, which is hydrolyzed to 2-ethylhexanol and the monoester MEHP.

The mean total recovery of 14C was 93.0 +/- 2.2%. Most of the radioactivity was eliminated in the feces (56.5 +/- 12.1%) and urine (31.9 +/- 10.9%), with smaller amounts in expired air (3.6 +/- 0.9%). Approximately 1.4 +/- 0.6% of the dose remained in the carcass. Of the approximately one half of the material that was absorbed, 73% was excreted in the urine and 8.3% was completely metabolized to 14CO2.

About half (50.5%)of the total dose (77% of the absorbed dose) was detected as unlabelled terephthalic acid (TPA) in the urine, indicating that complete hydrolysis of the diester had taken place. Almost one-third of the radioactivity in the urine (10 % of the dose) was present as glucuronide and sulphate conjugates. Several oxidation products of mono(2-ethylhexyl) phthalate (MEHT) and 2-ethylhexanol (2-EH)were identified as minor components.

Between 90-95 % of the total activity in the feces was unchanged [14C]DEHT (36.6% of the total dose). MEHT (2.5% of total dose) and the glucuronide conjugate of 2-ethyl5-hydroxyhexanoic acid were also identified. Several other minor uncharacterized radiolabelled metabolites were detected that were more polar than DEHT. The mean total amount of material recovered in the urine (as unlabeled TPA) and fecal fractions (as unmetabolized DEHT) was 87.1%, indicating that a major portion of the dose passed directly through the GI tract without hydrolysis or was completely hydrolyzed to TPA and 2-EH before or after absorption.

The rates of excretion of radioactivity in urine and feces revealed that more than 95 and 99% of the total radioactivity was excreted by 24 and 48 hours, respectively. The time course for expired 14CO2 was complex, with peaks at 1.3, 2.8, and 5.0 hours after dosing. Approximately 68% of the total radioactivity in expired air was eliminated after 4 hours and the remaining 32% was eliminated after 40 hours.

The excretion of radioactivity in the feces, urine and expired air from animals given food 4 hours after dosing was comparable to the levels seen for animals given food immediately after dosing.

Absorption	Rats readily excreted (14)C EHT given in a single dose at 100 mg/kg. 57.9%, 28.6%, and 3.6% of the (14)C was recovered in the feces, urine an expired air, respectively, within 144 hr after admin. Only 2.1% remained in the carcass	[3]
Absorption, distribution and excretion	The hydrolysis of di(2-ethylhexyl) terephthalate and di(2-ethylhexyl) phthalate were studied using rat gut homogenate fractions in vitro. Both isomers were hydrolysed by the intestinal fraction; however di(2-ethylhexyl) phthalate was hydrolysed to 2-ethylhexanol and mono(2-ethylhexyl) phthalate in about equal proportions whereas di(2-ethylhexyl) terephthalate was hydrolysed to 2-ethylhexanol and terephthalic acid. The half-lives for disappearance of the diesters were determined to be 12.6 min for di-(2-ethylhexyl) phthalate and 53.3 min for di(2-ethylhexyl) terephthalate. 2. The absorption and metabolism of di(2-ethylhexyl) terephthalate were studied by administering (hexyl-(14)C)di(2-ethylhexyl) terephthalate (in corn oil) by oral gavage at a dose level of 100 mg/kg to 10 adult male Sprague Dawley rats. Urine feces and expired air were collected for 144 hr and analysed for thepresence of radioactivity and feces and urine were analysed for unlabelled metabolites. 3. Radioactivity was eliminated in feces (56.5 +/- 12.1% of dose) primarily as unchanged di(2-ethylhexyl) terephthalate, small amounts of mono(2-ethylhexyl) phthalate and polar metabolites; excreted in urine (31.9 +/- 10.9% of dose) principally as mono(2-ethylhexyl) phthalate and metabolic products of 2-ethylhexanol; and expired as (14)C02 (3.6 +/-0.9% of dose). Less than 2% of the administered radioactivity was found in the carcass. Small amounts of (14)C were found in the tissues with the highest amounts found in liver and fat. 4. Metabolites identified in urine included terephthalic acid (equivalent to 51% of dose), oxidized metabolites of 2-ethylhexanol and mono(2-ethylhexyl) phthalate, and glucuronic and sulfuric acid conjugates (equivalent to about 10% of dose). 5. These findings indicate that di(2-ethylhexyl) terephthalate was hydrolysed more extensively than di(2-ethylhexyl) phthalate and consequently the urinary metabolite profiles for these two isomeric plasticizers were very different. The hydrolysis and metabolism of di(2-ethylhexyl) terephthalate were found to be similar to those of di(2-ethylhexyl) adipate in that hydrolysis of both ester bonds occurs.	[3]

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	Salmonella typhimurium (metabolic activator induced rat liver (S9))	[2], [3], [6]
	There was no increase in the number of revertants for any of the five strains either in the presence or absence of metabolic activation up to dose levels of 10,000 µg/plate.	
	Chinese hamster (CHO cells) (metabolic activator induced rat liver (S9))	[2]
	In the cultures treated with DOTP, no statistically significant increases in aberrations were observed at any dose level.	
	Chinese hamster (CHO cells) (metabolic activator induced rat liver (S9))	[2]
	DOTP is negative in the CHO/HGPRT mammalian cell mutation assay at dose levels up to 20 nl/ml (the limit of the test).	
	Salmonella typhimurium (metabolic activator induced rat liver (S9)	[2], [3]
	No mutagenic activity was detected with unmetabolized DEHT, and there was no evidence that mutagenic substances were excreted in the urine from rats dosed with DEHT.	
Chromosome Abnormalities	-	
Other Genotoxic Effects	-	
Estrogenic activity	NOAEL = 2000 mg/kg (rat, female)	[2]

Carcinogenicity	Bis(2-ethylhexyl) terephthalate was evaluated for combined chronic toxicity and carcinogenicity. The test substance was administered in the diets of male and female Fischer-344 inbred rats at concentrations of 20, 142, and 1000 mg/kg/day. Clinical evaluations revealed no treatment-related signs, however, eye opacities (cataracts) occurred frequently in all groups. At 1000 mg/kg/day, body weights and female liver weights were reduced. There were no consistent reductions in food consumption. There were no treatment-related effects evident from the gross and histopathologic examinations conducted at 6 and 12 months. At 18 months, two basic lesions of the females in the 1000 mg/kg/day level appear to be associated with treatment. These were hyperplasia and/or transitional cell adenomas of the urinary bladder and adenomas or adenocarcinomas of the uterus.	[3]

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	Rat, two-generation study	[2]
	NOAEL = 3000 ppm (Parental)	
	NOAEL = 3000 ppm (F1 offspring)	
	NOAEL = 3000 ppm (F2 offspring)	
Teratogenicity	Rat (exposure day 0 to 20 gestation)	[2]
	NOEL = 6000 ppm (maternal)	
	NOEL = 10000 ppm (teratogenicity)	
	Rat (exposure day 14 to postnatal day 3)	[2]
	NOEL = 750 mg/kg (maternal)	
	NOEL = 750 mg/kg (teratogenicity)	

Other Toxicity Studies	Skin absorption (in vitro) Dematomed human cadaver skin specimen The absorption rate of DEHT through dermatomed human skin was found to be 0.103 +/- 0.052 µg/cm^2/hr. According to the criteria set forth by Marzulli (1969), DEHT would be considered an "extremely slow" penetrant relative to other chemical species. The mean damage ratio for skin treated with DEHT was determined to be 1.14 +/- 0.23. This value is within the range of damage ratios for skin exposed to physiological saline (Dugard et al 1884). Therefore, under the conditions of this study, DEHT did not cause significant damage to the skin.	[2]
	Male development NOEL > 750 mg/kg No effect on male organ development	[7]
	Uterotrophic assay NOEL > 2,000 mg/kg No estrogenic activity Results of several robust studies following established guidelines to assess both reproductive and developmental toxicity potential have been conducted on Eastman 168 Plasticizer. The results of these studies indicate there is no evidence of such toxicities when tested in the diet at very high levels 1.0% (rats) and 0.7% (mice). Experimental studies have been conducted to evaluate the potential of DEHT to alter normal postnatal development in males and act as an estrogen agonist in females (uterotrophic assay). DEHT had no “endocrine”-like effects in either study.	[7]

Toxicokinetics

Toxicokinetics	-

Ecotoxicity Data

Di (2-ethyl-hexyl) terephthalate, DEHT, DOTP

Algae	EC50 > 0.86 mg/l (selenastrum capricornutum, 3h)	[2]
	NOEC 0.86 mg/l (selenastrum capricornutum, 3h)	
Daphnia magna (acute)	EC_{50} > 1.4 µg/l (daphnia magna, 48h)	[2]
	NOEC 1.4 µg/l (daphnia magna, 48h)	
	EC_{50} > 984 mg/l (planorid snail, 96h)	[2]
	NOEC 984 mg/l (planorid snail, 96h)	
	EC_{50} > 624 µg/l (eastern oyster, 96h)	[2]
	NOEC 624 µg/l (eastern oyster, 96h)	
Daphnia magna(chronic)	EC_{50} > 0.76 µg/l (daphnia magna, 21 day)	[2]
	NOEC 0.76 µg/l (daphnia magna, 21 day)	
	LOEC > 0.76 µg/l (daphnia magna, 21 day)	
	MATC > 0.76 µg/l (daphnia magna, 21 day)	
Other aquatic organisms	-	
Fish (acute)	LC_{50} > 984 mg/l (fresh water fish, 96h)	[2]
	NOEC 984 mg/l (fresh water fish, 96h)	
	EC_{50} > 1000µg/l (Fathead minnow, 96h)	[2]
	NOEC 1000µg/l (Fathead minnow, 96h)	
	LC_{50} > 0.25 mg/l (Salmo gairdneri, 7 day)	[2]
	NOEC 0.25 mg/l (Salmo gairdneri, 7 day)	
Fish (chronic)	LLC 0.28 mg/l (salmo gairdneri, 71 days)	[2]
	NOEC 0.28 mg/l (salmo gairdneri, 71 days)	
Bacteria	-	
Terrestrial organisms	-	
Sludge	EC_{50} > 10 mg/l (3h)	[2]
	NOEC 10 mg/l (3h)	
Terrestrial plants	EC_{50} > 1400 µg/l (lolium perenne, 14 days)	[2]
	NOEC 1400 µg/l (lolium perenne, 14 days)	

	EC_{50} > 1500 µg/l (Williams 82 soybean, 14 days)	[2]
	NOEC 1500 µg/l (Williams 82 soybean, 14 days)	
	EC_{50} > 1400 µg/l (Raphanus sativus, 14 days)	[2]
	NOEC 1400 µg/l (Raphanus sativus, 14 days)	

Environmental Fate

BCF	BCF = 393	[2]
	An estimated BCF of 25 was calculated in fish for bis(2-ethylhexyl) terephthalate, using an estimated log Kow of 8.39 and a regression-derived equation. According to a classification scheme, this BCF suggests the potential for bioconcentration in aquatic organisms is low	[3]
Aerobic biodegradation	40.2 % (28 days)	[2]
	Biodegradable	
	BOD20 = 0.15 g/g	[2]
	COD = 2.7 g/g	
	ThOD = 2.58 g/g	
	56% in 28 days	[7]
Anaerobic biodegradation	-	
Metabolic pathway	-	
Mobility	The Koc of bis(2-ethylhexyl) terephthalate is estimated as 2,000, using a water solubility of 4 mg/l and a regression-derived equation. According to a classification scheme, this estimated Koc value suggests that bis(2-ethylhexyl)terephthalate is expected to have slight mobility in soil.	[3]
Abiotic degradation	The rate constant for the vapor-phase reaction of bis(2-ethylhexyl) terephthalate with photochemically-produced hydroxyl radicals has been estimated as 2.2 $x10^{-11}$ cm^3/molecule-sec at 25ºC using a structure estimation method. This corresponds to an atmospheric half-life of about 18 hours at an atmospheric concentration of 5 x 10^{+5} hydroxyl radicals per cm^3. A base-catalyzed second-order hydrolysis rate constant of 0.16 L/mole-sec was estimated using	[3]

	a structure estimation method; this corresponds to half-lives of 1.4 years and 51 days at pH values of 7 and 8, respectively. Bis(2-ethylhexyl) terephthalate does contain chromophores that absorb at wave-lengths > 290 nm and therefore may be susceptible to direct photolysis by sunlight.
Volatilization	The Henry's Law constant for bis(2-ethylhexyl) terephthalate is estimated as 1.0 $x10^{-5}$ atm m^3/mole using a fragment constant estimation method. This Henry's Law constant indicates that bis(2-ethylhexyl) terephthalate is expected to volatilize from water surfaces. Based on this Henry's Law constant, the volatilization half-life from a model river (1 m deep, flowing 1 m/sec, wind velocity of 3 m/sec) is estimated as 7.3 days. The volatilization half-life from a model lake (1 m deep, flowing 0.05 m/sec, wind velocity of 0.5 m/sec) is estimated as 59 days. Bis(2-ethylhexyl) terephthalate's Henry's Law constant indicates that volatilization from moist soil surfaces may occur. Bis(2-ethylhexyl) terephthalate is not expected to volatilize from dry soil surfaces based upon an estimated vapor pressure of 2.1 $x10^{-5}$ mm Hg, determined from a fragment constant method.

Conclusion

Physical-chemical	-
Emission	-
Exposure	-
Health	-
Environment	-

References

1 ESIS

2 SIDS Dossier. OECD HPV Chemical programme

3 HSDB

4 SRC physprod database

Di (2-ethyl-hexyl) terephthalate, DEHT, DOTP

5 ChemID

6 CCRIS

7 EASTMANN

Sulfonic acids, C10 – C18-alkane, phenylesters, ASE

Identification of the substance

CAS No.	91082-17-6	
EINECS No.	293-728-5	[1]
EINECS Name	Sulfonic acids, C10-21-alkane, Ph esters	[1]
Synonyms	Sulfonic acids, C10-C18-alkane, phenylesters	
	ASE	
Molecular Formula	-	
Structural Formula	-	
Major Uses	-	
IUCLID	HPV	[1]
EU classification	This substance is not classified in the Annex I of Directive 67/548/EEC as such, but it may be included in one of the group entries.	[1]

Physico-chemical Characteristics

Physical Form	Liquid	[2]
	Light yellow clear liquid	[3]
Molecular Weight (g/mole)	-	
Melting Point/range (°C)	< -15ºC	[2]
Boiling Point/range (°C)	200ºC at 13hPa	[2]
Decomposition Temperature (°C)	Decomposes on heating > 200ºC	[3]
Vapour Pressure (mm Hg at °C)	< 0.0001 hPa at 20ºC [0.01 Pa, 7.5 x 10^{-5} mmHg]	[2]
Density (g/cm^3 at °C)	1.055 g/cm^3 at 20ºC	[2]
Vapour Density (air=1)	-	
Henry's Law constant	-	

Sulfonic acids, C10 – C18-alkane, phenylesters, ASE

(atm/m^3/mol at °C)		
Solubility (mg/l water at °C)	0.002 g/l at 22ºC [2 mg/l]	[2]
Partition Coefficient (log P_{ow})	> 6	[3]
pK_a	-	
Flammability	-	
Explosivity	-	
Oxidising Properties	-	
Migration potential in polymer	-	
Flash point	210-240ºC	[2]
Auto flammability	-	
Atmospheric OH rate constant cm^3/(molecule sec)	-	
Log Kow	-	

Emission Data

During production	-

Exposure Data

Aquatic environment, incl. sediment	-
Terrestrial environment	-
Sewage treatment plant	-
Working environment	-
Consumer goods	-
Man exposed from environment	-
”Secondary poisoning”	-

Atmosphere	-
Dermal	-

Toxicological data

Observations in humans	-

Acute toxicity

Oral	LD_{50} = 26,380-31,650 mg/kg (rat)	[2]
	LD_{50} > 15,825 mg/kg (rat)	[2]
Dermal	LD_{50} > 1055 mg/kg (rat)	[2]
Inhalation	-	
Other routes	-	
Skin irritation	Not irritating (rabbit, 24h exposure)	[2]
	Not irritating (human, 8h exposure)	[2]
Eye irritation	Not irritating (rabbit)	[2]
Irritation of respiratory tract	-	
Skin sensitisation	-	

Subchronic and Chronic Toxicity

Oral	Rat, 90-day repeat dose (male and female) NOAEL = 3000 ppm No death, no effect on behaviour, reduced body weight gain, increased feed (female) and water consumption (males) at the high dose level, absolute and relative liver weight is significantly deose-related at alle dose levels, kidney weight only increased at the high dose level, no substance-related histopathological effects (47 organs and tissue), opthalomological, hematological and clinical-chemical parameters within the normal range, slightly increased tromboplastin/time at the high dose.	[2]
	Rat, 25 day repeat dose (female) Test substance intake 360 and 1230 mg/kg bw per day No death, no effect on behaviour, no substance related histopathological effects (30 organs), haematological and clinical-chemical parameters within normal range. Absolute and relative liver weight significantly increased at 1230 mg/kg bw.	[2]
	Rat, 43 day repeat dose Dose = 100 ppm (ca. 7.5 mg/kg bw per day) Treatment time related increasing amounts of test substance in the fat tissue (up to 25µg sulfonic acid C10-21-alkane) No accumulation was observed in the liver.	[2]
	Rat, 28 day repeat dose Dose = 1000 ppm (ca. 75 mg/kg bw per day) Day 21: 235µg sulfonic acid C10-21-alkane per g fat tissue Day 43: 100µg sulfonic acid C10-21-alkane per g fat tissue An elimination half life of 15 days was calculated for the fat tissue. No accumulation was observed in the liver.	[2]

	Rat, 49 day repeat dose Dose = 1000 ppm (ca. 75 mg/kg bw per day) Day 49: 290µg sulfonic acid C10-21-alkane per g fat tissue No accumulation was observed in the liver.	
	Rat, 6 weeks repeat dose Dose = 530 mg/kg bw Males: 2 days a week Females: daily No death, normal behaviour, no substance-related histopatholical effects (m/f 8/9 organs), male rats: no substance-related alteration in oxygen consumption, female rats: Allen-Doisy test negative.	[2]
	Rat, 1 year repeat dose Dose: 265 and 530 mg/kg bw (2 days a week) Normal weight gain, no substance-related histopathological effects (m/f 9/10 organs), haematological parameters within the normal range, roentgenological findings at teeth and ankle-joint within normal range.	[2]
Inhalation	-	
Dermal	-	

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	Salmonella typhimurium (metabolic activator induced rat liver (S9)) Negative	[2]

	Chinese hamster (V79 cells) (metabolic activator induced rat liver (S9))	[2]
	Negative in the CHO/HGPRT mammalian cell mutation assay at dose levels up to 75µg/ml (the limit of the test).	
Chromosome Abnormalities	Chinese hamster (V79 cells) (rat liver S9 mix)	[2]
	Not clastogenic to V79 cells treated ***in vitro*** under the conditions of the test.	
Other Genotoxic Effects	-	
Carcinogenicity	-	

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	Rat, two-generation study	[2]
	Dose: 530 mg/kg bw	
	F0-generation: no effect on fertility	
	F1-generation: normal weight gain, normal weight of endocrine organs, normal first oestrus	
	F2-generation: no effect on fertility and body weight gain	
	F3- generation: no effect on fertility and body weight gain	
Estrogenic activity	Negative Allen-Doisy test (see above)	[2]
Teratogenicity	-	

Toxicokinetics

Toxicokinetics	-

Ecotoxicity Data

Sulfonic acids, C10 – C18-alkane, phenylesters, ASE

Algae	Non-toxic in a saturated aqueous solution (test concentration at 10 g/l). Scenedesmus subspicatus, 72h)	[2]
Invertebrates (acute)	Immobilization of test organisms (daphnia magna, 48h) at 10,000 mg/l	[2]
	No immobilization of test organisms (daphnia magna, 48h) at 100 mg/l to 1000 mg/l	[2]
Other aquatic organisms	-	
Fish (acute)	NOEC 10,000 mg/l (fresh water fish, 48h)	[2]
	LC_0 100 mg/l (fresh water fish, 96h)	[2]
	LC50 > 10,000 mg/l (zebra fish, 48h)	[3]
Bacteria	< 20 % inhibition at 1.2 mg/l (photobacterium phosphoreum, 30 minutes)	[2]
	No inhibition at 500 mg/l (photobacterium phosphoreum, 30 minutes)	[2]
Terrestrial organisms	-	
Sludge	EC_{50} > 10,000 mg/l (3h)	[2]

Environmental Fate

BCF	-	
Aerobic biodegradation	31% after 28 days	[2]
Anaerobic biodegradation	-	
Metabolic pathway	-	
Mobility	-	

Conclusion

Physical-chemical	-
Emission	-
Exposure	-

Sulfonic acids, C10 – C18-alkane, phenylesters, ASE

Health	-
Environment	-

References

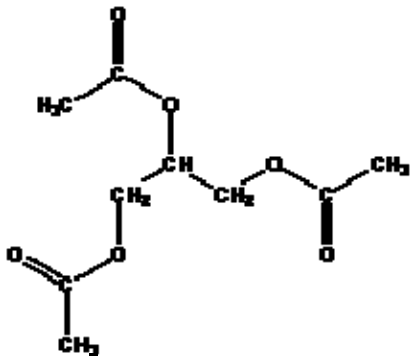
1 ESIS

2 IUCLID dataset

3 MSDS Sigma-Aldrich

Glycerol Triacetate, GTA

Identification of the substance

CAS No.	102-76-1	
EINECS No.	203-051-9	[1]
EINECS Name	triacetin	[1]
Synonyms	Glycerol triacetate	
	GTA	
Molecular Formula	$C_9H_{14}O_6$	[1]
Structural Formula		
Major Uses	Since triacetin has a variety of applications including as a plasticizer for cigarette filters and cellulose nitrate, solvent for the manufacture of celluloid, photographic films, fungicide in cosmetics, fixative in perfumery, component in binders for solid rocket fuels and a general purpose food additive, release of triacetin to the environment may occur at the production sites, specific industrial sites and consumers depending on the conditions of use in Japan	[2]
IUCLID	HPV	[1]
EU classification	This substance is not classified in the Annex I of Directive 67/548/EEC as such, but it may be included in one of the group entries.	[1]

Physico-chemical Characteristics

Physical Form	Liquid	[2]
	Colourless liquid with a fruity or fatty odour and a mild sweet tast that becomes bitter in cons. above	[3]

	0.05%	
Molecular Weight (g/mole)	218,21	[2]
pH	7	[2]
Melting Point/range (°C)	3ºC	[2]
Boiling Point/range (°C)	258ºC at 1,013 hPa	[2], [3]
Decomposition Temperature (°C)	-	
Vapour Pressure (mm Hg at °C)	0.00248 mmHg at 25ºC [0.33 Pa]	[2]
	0.003306hPa at 25ºC	
	< 0.01 hPa at 20ºC [1 Pa, 0.0075 mmHg]	[4]
Density (g/cm^3 at °C)	1.1562 at 25ºC	[2], [4]
Vapour Density (air=1)	7.52	[3]
Henry's Law constant ($atm/m^3/mol$ at °C)	1.23×10^{-8}	[2]
	1.2×10^{-8} at 25ºC	[3]
Solubility (mg/l water at °C)	70 g/l at 25ºC [70,000 mg/l]	[2], [4]
	58 g/l at 25ºC [58,000 mg/l]	[2], [4]
Partition Coefficient (log P_{ow})	0.21 at 25ºC	[2]
pK_a	None	[2]
Flammability	Not flammable	[2], [4]
Auto flammability	432ºC	[2], [4]
Explosivity	Not explosive	[2], [4]
Oxidising Properties	Stable at normal temperatures and pressures under fire exposure conditions	[2]
Migration potential in polymer	-	
Flash point	> 145ºC	[2], [4]
	138ºC	[3], [4]
Koc	10.5	[2]
logKow	0.36	[3]

Atmospheric OH rate constant $cm^3/(molecule\ sec)$	7.810×10^{-12}	[2]
	8.5×10^{-12} at 25°C	[3]
Explosion limits	Lower: 1.05%	[6]
	Upper: 7.73%	

Emission Data

During production	The production process consists of the batchwise controlled reaction of glycerol, acetic acid and acetic anhydride in a closed reaction system with adequate cooling facilities. This is followed by purification using vacuum distillation. The pungent nature of the raw materials demands a totally enclosed plant.	[4]

Exposure Data

Aquatic environment, incl. sediment	Environmental exposure: emission to aquatic compartment from waste water and evaporative emissions associated with its use in the perfume and cosmetic industries and its use as a solvent and CO_2 remover from natural gas, and disposal of consumer products containing triacetin.	[2]
	SURFACE WATER: Triacetin was detected in a sample of Tennessee River water collected in Apr 1973 (concn not reported).	[3], [4]
	RAIN/SNOW: Triacetin was found in 1 out of 10 snow samples collected early March, 1998 from Finland, Russia and Siberia. The sample that contained 0.8 µg/kg of triacetin was from Moscow State University, Russia.	[3]
Terrestrial environment	-	
Sewage treatment plant	Triacetin's production and use as a topical antifungal, fixative in perfumery, plasticizer, specialty solvent, as well as its use in the manufacture of cosmetics and removal of carbon dioxide from natural gas may result in its release to the environment through various waste streams.	[3]

	EFFLUENT CONCENTRATIONS: Triacetin was detected in secondary effluent samples from a rapid infiltration site in Fort Polk, LA sampled November 4-5, 1980 at concentrations of 0.024 and 0.51 µg/l.	[3]
Working environment	Occupational exposure: inhalation and dermal route in the industries.	[2]
	NIOSH has statistically estimated that 18,436 workers (4,103 are female) are potentially exposed to triacetin in the USA. Occupational exposure to triacetin may occur through inhalation and dermal contact with this compound at workplaces where triacetin is produced or used. The general population may be exposed to triacetin via inhalation and dermal contact from use of consumer products containing this compound.	[3]
Consumer goods	Consumer exposure: intake and dermal/inhalation route through the use as a food additive and topical antifungal and perfume fixative or cigarette filter, respectively.	[2]
	Due to its uses triacetin soon becomes diffused into small quanties and there is little possibility of large scale human contact or environmental effect after it leaves the manufacturers first line customers' premises. Its use is adhesive may give skin contact. As a carrier and solvent for food soft drinks flavouring materals ingestion will occur. Very small amounts can be found in cigarette smoke through a filter tip using triacetin as the plasticizer.	[4]
Man exposed from environment	-	
”Secondary poisoning”	-	
Atmosphere	-	
Dermal	-	

Toxicological data

Observations in humans	Very mild skin reaction	[2]
	One case report of contact eczema	
	Ingestion: 7.8 mg/day/adult	[2]

	Commercial triacetin may contain diacetin, as well as monoacetin, and when applied to human eyes causes severe burning, pain and much redness of the conjunctiva, but no injury. Diacetin causes considerably more discomfort than pure triacetin.	[2], [4]
	Glycerol triacetate appears to be innocuous when swallowed, inhaled or in contact with the skin, but may cause slight irritation to sensitive individuals.	[2], [4]
	A case of allergic contact eczema in a 29 year-old patient in a cigarette factory is reported, which was based on sensitisation towards the triacetin used for the production of cigarette filters. The allergy was demonstrated in a patch test. In addition to triacetin, the di- and mono acetate of glycerol also produced positive tests. It seems reasonable to regard the reaction as an expression of a group sensitisation towards glycerol acetate.	[2]
	A Duhring-chamber test was conducted on 20 healthy volunteers The test substance was applied as 50% dilution for 24 hours. Result: Only very mild skin reactions were observed. The substance has good skin compatibility.	[2], [4]
	No skin reactions occurred in 33 volunteers treated with 20% triacetin in petrolatum in an attempt to induce skin sensitisation using the maximization test.	[2]
	Triacetin (20 % in petrolatum) did not irritate the skin of 33 volunteers when tested in a 48-hr covered patch test.	[2]

Acute toxicity

Oral	LD_{50} > 2,000 mg/kg (rat, combined)	[2], [4]
	LD_{50} = 3,000 mg/kg (rat)	[2], [4]
	LD_{50} = 6,400-12,800 mg/kg (rat)	[2], [4]
	LD_{50} = 12,700 mg/kg (rat)	[2]
	LD_{50} = 9,300 mg/kg (mouse, male)	[2], [4]
	LD_{50} = 1,800 mg/kg (mouse, male)	[2]
	LD_{50} = 1,100 mg/kg (mouse, female)	

	LD_{50} = 3,200-6,400 mg/kg (mouse)	[2], [4]
	LD_{50} = 1,100 mg/kg (mouse)	[4]
	LD_{50} = 3,000 mg/kg (mouse)	[4]
	LD_{50} > 2,000 mg/kg (rabbit)	[4]
	LDL_{0} = 150 mg/kg (frog)	[4]
Dermal	LD_{50} > 2,000 mg/kg (rabbit)	[2], [4]
	LD_{50} > 5,000 mg/kg (rabbit)	[2], [4]
	LD_{50} > 20 ml/kg (guinea pig)	[2], [4]
Inhalation	LD_{50} > 1,721 mg/m^3 (rat, combined, 4h)	[2], [4]
	No lethal effects observed	
	NOAEL = 73,700 mg/m^3 (5 days)	[2]
Other routes	-	
Skin irritation	Not irritating (rabbit)	[2], [4]
Eye irritation	Not irritating (rabbit)	[2], [4]
Irritation of respiratory tract	-	
Skin sensitisation	Not sensitising (guinea pig)	[2]

Subchronic and Chronic Toxicity

Oral	NOAEL = 1,000 mg/kg (rat, male)	[2]
	NOAEL = 1,000 mg/kg (rat, female)	
	NOAEL = 10 g/kg per day (rat, 20% of diet)	[2]
Inhalation	NOAEL = 2,220 mg/m^3 (rat, 90 day)	[2]
	NOAEL = 250 ppm (rat, 64 day)	[4]
	NOAEL = 8271 ppm (rat, 64 day)	[4]
Dermal	-	

Metabolism	Triacetin has been administered iv to mongrel dogs. The majority of infused triacetin underwent intravascular hydrolysis, and the majority of the resulting acetate is oxidized. Triacetin was found to be hydrolyzed by human intestinal lipase.	[3]
	Triacetin is rapidly hydrolysed in vitro by all tissues of the organism including the gastrointestinal tract.	[3]

	Groups of female mongrel dogs to study the metabolic effects of isocaloric and hypercaloric infusions of 5% v/v aqueous triacetin. A primed, continuous infusion of 5 µmol/kg (0.3 µCi/kg/min) [13C]-acetoacetate and 1.0 µCi/kg (0.01 µCi/kg/min) [3H]-glucose was continued for 6 hr. Three hours after the start of the isotope infusion, dosing with triacetin was started. Six animals were infused at a rate of 47 µmol/kg/min and seven were infused at a rate of 70 µmol/kg/min triacetin for 3 hr. Blood and breath samples were taken at 15 to 30-min intervals. A group of four animals was infused with 70 µmol/kg/min glycerol and used as the control for the hypercaloric infusion. During isocaloric infusion of triacetin, plasma acetate and free fatty acid concentrations were significantly increased at 30 and 60 min, respectively, and remained elevated. During hypercaloric infusion, plasma acetate concentration increased progressively throughout the study, whereas the plasma free fatty acid concentration did not change. Plasma pyruvate and lactate concentrations were significantly decreased after 30 and 90 min, respectively, and throughout the study with both isocaloric and hypercaloric infusion. The plasma insulin concentrations were modestly increased during both infusions. Plasma glucose concentration was significantly decreased during isocaloric triacetin infusion; a slight but significant increase was observed with hypercaloric infusion. Glucose clearance decreased significantly in both groups during the last hour of triacetin infusion. Plasma ketone body concentrations increased significantly by 60 min, and they remained elevated with isocaloric infusion and increased progressively with hypercaloric infusion of triacetin; the increased concentrations were due to increased ketone body production. During the last hour of infusion, resting energy expenditure was significantly increased with isocaloric triacetin.	[3]
Absorption	Triacetin is more rapidly absorbed from the gastrointestinal tract in 3 hours than the other fats tested. Triacetin has been shown to be a source of liver glycogen and when fed in amounts equal in caloric value to 15% glucose it was utilized as efficiently as was glucose.	[3]

	Mongrel dogs were used to determine the systemic, hindlimb, gut, hepatic, and renal uptake of acetate during infusion of a 5% v/v aqueous solution of triacetin. A primed, continuous infusion of [1-14C]-acetate was continued for 7 hr with 10 animals. Three hours after the start of the tracer infusion, the animals were infused with triacetin at a rate of 47 µmol/kg/min for 4 hr. Blood and breath samples were taken at 15-min intervals for the last 30 min. Steady-state conditions were achieved in plasma acetate concentrations and specific activity and in expired [14-C02]. Plasma acetate concentrations were 1180, 935, 817, 752, and 473 µmol/L (all values approximate) in the aorta, renal vein, portal vein, femoral vein, and hepatic vein, respectively. The acetate turnover rate during triacetin infusion was 2214 µmol/min; systemic acetate turnover accounted for 68% of triacetin-derived acetate.	[3]

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	S.typhimurium and E.coli (metabolic activator Sprague-Dawley rat liver (S9)) Cytotoxic conc: No toxicity with or without metabolic activation up to 5,000µg/plate (five strains) Genotoxic conc: No genotoxic effects observed with or without metabolic activation	[2]
	S.typhimurium and E.coli (metabolic activator Sprague-Dawley rat liver (S9)) Cytotoxic conc: No toxicity with or without metabolic activation up to 5,000µg/plate (four strains) Genotoxic conc: No genotoxic effects observed with or without metabolic activation	[2], [4]

Chromosome Abnormalities	Chinese Hamster Lung (metabolic activator Sprague-Dawley rat liver (S9)) Triacetin induced structural chromosome aberrations on shortterm treatment with an exogenous metabolic activation system at the maximum concentration of 2.2 mg/ml (10 mM). However, triacetin decreased pH of the medium at 2.2 mg/ml on short-term treatment with an exogenous metabolic activation system. Therefore, chromosome aberrations induced with triacetin were likely to be caused by lowering pH of the medium rather than by damaging DNA per se. It is, however, recognized that changes in pH of the medium caused by triacetin can induce such artifacts in this assay. Polyploidy was not induced under any of the conditions on continuous and short-term treatment with and without an exogenous metabolic activation system. With metabolic activation: Not observed up to 1.2 mg/ml for 6h exposure. The 50 % inhibition of cell proliferation was calculated to be 1.8 mg/ml. Without metabolic activation: Not observed up to 2.2 mg/ml for 24- and 48-h exposure. Genotoxic effects: Equivocal.	[2]
Other Genotoxic Effects	-	
Carcinogenicity	-	

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	NOAEL = 1,000 mg/kg per day (rat m/f, reproduction) F1 NOAEL = 1,000 mg/kg per day (rat, offspring) Triacetin did not exert any toxic effects on reproductive parameters including the mating index, fertility index, gestation length, number of corpora lutea or implantations, implantation index, gestation index, delivery index and parturition or maternal behaviour at delivery and lactation. General parental toxicity: Triacetin had no effects on clinical signs, body weight, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in either sex. There were no haematological or blood chemical parameters in males. The NOAEL for reproductive toxicity is thus considered to be 1,000 mg/kg bw/day for both sexes.	[2]
Teratogenicity	NOAEL = 1,000 mg/kg per day (maternal toxicity) NOAEL = 1,000 mg/kg per day (teratogenicity) No teratological or other developmental effects were observed at any dose. General parental toxicity: Triacetin had no effects on clinical signs, body weight, food consumption, and organ weight or necropsy findings. No histopathological changes ascribable to the compound were observed in either sex. There were no haematological or blood chemical parameters in males. Pregnancy/litter data: Triacetin did not exert any toxic effects on reproductive parameters including the mating index, fertility index, gestation length, number of corpora lutea or implantations, implantation index, gestation index, delivery index and parturition or maternal behaviour at delivery and lactation Toxicity to offspring: On examination of neonates, there were no significant differences in numbers of offspring or live offspring, the sex ratio, the live birth index, the viability index or body weight. No abnormal findings ascribable to the compound were found for external features, clinical signs or necropsy of the offspring. The NOAEL for reproductive and developmental toxicity is considered to be 1,000 mg/kg bw/day for parental animals and offspring.	[2]

Other Toxicity Studies	Sheep, 175 days (male and female) Each of two basal diets (pelleted, ground hay (H), and a pelleted mixture of the same hay and corn meal (HC) was supplemented singly with triacetin (Ac^3) and glycerol (G). A given animal was fed continuously one of the four diets at one of two levels of intake (approximately, 1 or 2.2 times the maintenance level) during the 175-day feeding period. The mean rates with which the metabolizable energy (ME) ingested above the maintenance level of intake was utilized for body-energy gain, were: (in %) H + Ac^3, 59.9; HC + G, 59.5; HC + Ac^3, 63.7; and HC + G, 61.8($p > 0.3$). Ignoring the kind of basal diet, utilization rates were 62.0 and 61.2 % for the ME provided by the diets containing triacetin and glycerol, respectively. The mean pooled net utilization of ME for body-energy gain by females (65.5%) was markedly greater ($P<0.01$) than that by males (57.6 %). In a series of respiration-calorimetric experiments, the net utilization of ME provided by the acetic acid moiety of triacetin was 76.4%, between days 50 and 70 of continuous feeding. Conclusion: In a 175 day feeding study with sheep, 62 % of metabolic energy was utilized. Concentration of triacetin in food was 10 %. No data on toxicity are reported.	[2], [4]

Toxicokinetics

Toxicokinetics	Dog Significant acetate uptake was demonstrated in all tissues (liver, 559 ± 68; intestine, 342 ± 23; hindlimb, 89 ± 7; and kidney, 330 ± 37 µmol/min). Conclusion: During intravenous administration in dogs, the majority of infused triacetin undergoes intravascular hydrolysis, and the majority of the resulting acetate is oxidized. Thus, energy in the form of short-chain fatty acids can be delivered to a resting gut via intravenous infusion of a short-chain triglyceride.	[2]

	Dog	[2]
	There were no changes in serum P or Ca. The serum Mg concentration decreased from 0.7 ± 0.03 to 0.57 ± 0.03 mmol/L ($p < 0.001$) by 90 min and remained at this level for the remainder of the study. The triacetin infusion did not influence fractional urinary Mg excretion; thus, the decrease in serum Mg was likely because of an increase in cellular transport of this cation. Conclusion: An isocaloric infusion of the short-chain triglyceride triacetin in dogs resulted in modest increases in plasma acetate but did not significantly affect serum Ca or P concentrations. Serum Mg decreased by approximately 20 %, probably because of cellular uptake rather than accelerated excretion. Triacetin administered to dogs at a rate approximating resting energy expenditure has no demonstrable adverse effects on mineral metabolism.	
	Rat	[2]
	Triacetin caused no overt toxic effects at any point during the study. As the proportion of triacetin in the diet increased from 0 to 50 or 90 % of the lipid energy, cumulative nitrogen balance increased 50 or 120 %, respectively ($p < 0.05$). Whole-body and tissue leucine kinetics (determined during the last 2.5 hr of the 7-day study) were unaffected by the lipid composition of the diet. Plasma acetate concentration was not significantly different among groups. Conclusion: These results indicate that incorporation of triacetin in nutritionally balanced total parenteral nutrition formulas improves nitrogen balance with no overt toxic effects.	

Ecotoxicity Data

Algae	EC_{50} > 1,000 mg/l (Selenastrum capricornutum, 72h) NOEC = 556 mg/l (Selenastrum capricornutum, 72h) Growth inhibition: growth rate and biomass	[2]

	Growth rate	[5]
	EC_{50} > 940 mg/l (Selenastrum capricornutum, 72h)	
	NOEC = 460 mg/l (Selenastrum capricornutum, 72h)	
	Biomass (AUG)	
	EC_{50} > 1000 mg/l (Selenastrum capricornutum, 72h)	
	NOEC = 560 mg/l (Selenastrum capricornutum, 72h)	
Daphnia magna (acute)	EC_{50} = 888 mg/l (daphnia magna, 24h)	[2]
	EC_{50} = 768 mg/l (daphnia magna, 48h)	
	EC_{0} = 309 mg/l (daphnia magna, 48h)	
	EC_{50} > 974.4 mg/l (daphnia magna, 24h)	[2]
	EC_{50} = 810.9 mg/l (daphnia magna, 48h)	
	EC_{0} = 541.1 mg/l (daphnia magna, 48h)	
	EC_{50} = 380 mg/l (daphnia magna, 48h)	[2]
	EC_{0} = 65 mg/l (daphnia magna, 48h)	
	EC_{0} = 65 mg/l (daphnia magna, 24h)	[4]
	EC_{50} = 380 mg/l (daphnia magna, 48h)	
	EC_{100} = 1000 mg/l (daphnia magna, 48h)	
	EC_{50} = 770 mg/l (daphnia magna, 48h)	[5]
	Acute immobilization	
Daphnia magna (chronic)	EC_{50} > 100 mg/l (daphnia magna, 21d, reproduction)	[2]
	NOEC = 100 mg/l (daphnia magna, 21d, reproduction)	
	LC_{50} > 100 mg/l (daphnia magna, 14d, parental)	
	LC_{50} > 100 mg/l (daphnia magna, 21d, parental)	

	EC_{50} > 94 mg/l (daphnia magna, 21d)	[5]
	NOEC > 94 mg/l (daphnia magna, 21d)	
Other aquatic organisms	-	
Fish (acute)	LC_{50} > 100 mg/l (Oryzia latipes, 96h)	[2], [5]
	LC_{50} = 165.3 mg/l (Pimephales promelas, 96h)	[2]
	LC_{50} = 174 mg/l (Cyprinus carpio, 48h)	[2]
	LC_{50} = 170 mg/l (Leuciscus idus, 48h)	[2]
	LC_{50} = 300 mg/l (Branchydanio rerio, 96h)	[2]
	LC_{0} = 100 mg/l (Cyprinus carpio, 48h)	[4]
	LC_{50} = 174 mg/l (Cyprinus carpio, 48h)	
	LC_{100} = 320 mg/l (Cyprinus carpio, 48h)	
	LC_{0} = 100 mg/l (Leuciscus idus, 48h)	[4]
	LC_{50} = 170 mg/l (Leuciscus idus, 48h)	
	LC_{100} = 300 mg/l (Leuciscus idus, 48h)	
Fish (chronic)	LC_{50} > 100 mg/l (Oryzia latipes, 14d)	[2], [5]
	LC_{0} = 100 mg/l (Oryzia latipes, 14d)	
Bacteria	EC_{0} > 541.6 mg/l (Pseudomonas putida, 18h)	[2], [4]
	EC_{0} = 10,000 mg/l (Pseudomonas putida, 30 minutes)	[2], [4]
	NOEC = 3,000 mg/l (Pseudomonas putida, 16h)	[2], [4]
	FOEC = 10,000 mg/l (Pseudomonas putida, 16h)	
Terrestrial organisms	-	

Environmental Fate

BCF	1.3	[2], [4]

	An estimated BCF of 1 was calculated for triacetin, using a log Kow of 0.25 and a regression-derived equation. According to a classification scheme, this BCF suggests the potential for bioconcentration in aquatic organisms is low.	[3]
Aerobic biodegradation	77% after 14 days based on BOD	[2]
	94% after 14 days based on TOC	
	Readily biodegradable	
	64% after 28 days based on $ThCO_2$ (10 mg/l)	[2], [4]
	93% after 28 days based on $ThCO_2$ (20 mg/l)	
	Readily biodegradable	
	Triacetin, present at 100 mg/l, reached 91-94% of its theoretical BOD in 4 weeks using an activated sludge inoculum at 30 mg/l and the Japanese MITI test. Using a rapid infiltration system for treating primary and secondary effluents, triacetin, present in a feed solution at a concentration of 0.094 µg/l, was not detected in the column effluent. The specific loss process was not identified.	[3]
	79% after 30 days (5 mg/l)	[4]
	Readily biodegradable	
	93% after 4 weeks based on BOD	[5]
	97% after 4 weeks based on TOC	
	Readily biodegradable	
Anaerobic biodegradation	-	

Abiotic degradation	The rate constant for the vapour-phase reaction of triacetin with photochemically-produced hydroxyl radicals has been estimated as 8.5 $x10^{-12}$ cm^3/(molecule-sec) at 25º C using a structure estimation method. This corresponds to an atmospheric half-life of about 1.9 days at an atmospheric concentration of 5 x 10^{+5} hydroxyl radicals per cm^3. A base-catalyzed second-order hydrolysis rate constant of 6.2 x 10^{-1} l/(mole-sec) was estimated using a structure estimation method; this corresponds to half-lives of 130 and 12 days at pH values of 7 and 8, respectively. Triacetin does not contain chromophores that absorb at wavelengths → 290 nm and therefore is not expected to be susceptible to direct photolysis by sunlight.	[3]
Photodegradation	$T_{½}$ = 48h (indirect photolysis)	[2], [4]
Metabolic pathway	-	
Mobility	-	
Stability in water (abiotic)	Stable at pH 4 at 50ºC	[2]
	$T_{½}$ = 60.4 days at pH 7 at 25ºC	
	$T_{½}$ = 16.5 h at pH 9 at 25ºC	
	$T_{½}$ = 130 days at pH 7	[4]
	$T_{½}$ = 1.3 h at pH 9	
	$T_{½}$ = 13 days at pH 8	
Soil adsorption/mobility	The Koc of triacetin is estimated as 33, using a log Kow of 0.25 and a regression-derived equation. According to a classification scheme, this estimated Koc value suggests that triacetin is expected to have very high mobility in soil.	[3]
	Based upon a measured water solubility of 58 g/l at 25ºC, the Koc-value can be estimated to be 10.5 from a regression derived equation. This Koc-value indicates very high soil mobility.	[4]
Volatilization from water/soil	The Henry's Law constant for triacetin is estimated as 1.2 $x10^{-8}$ atm/m^3/mol derived from its vapour pressure, 0.00248 mm Hg, and water solubility, 58,000 mg/l. This Henry's Law constant indicates that triacetin is expected to be essentially non-volatile from water surfaces. Triacetin's estimated Henry's Law constant indicates that volatilization from moist soil surfaces is not expected to occur.	[3]

	Triacetin is not expected to volatilize from dry soil surfaces based upon a vapour pressure of 0.00248 mm Hg	
	Based on a water solubility of 58 g/l and a vapour pressure of 0.00248 mmgHg at 25ºC, a Henry's law constant of 1.23 x 10^{-8} atm/m^3/mol is estimated. This value indicates that the compound is essentially non-volatile from water.	[4]
Terrestrial fate	Based on a classification scheme, an estimated Koc value of 33, determined from a log Kow of 0.25 and a regression-derived equation, indicates that triacetin is expected to have very high mobility in soil. Volatilization of triacetin from moist soil surfaces is not expected to be an important fate process given an estimated Henry's Law constant of 1.2 x10^{-8} atm/m^3/mol derived from its vapour pressure, 0.00248 mm Hg, and water solubility, 58,000 mg/l. Triacetin is not expected to volatilize from dry soil surfaces based upon a vapour pressure of 0.00248 mm Hg. A theoretical BOD of 91-94% in 4 weeks using an activated sludge inoculum and the Japanese MITI test suggests that biodegradation may be an important environmental fate process in soil	[3]
Aquatic fate	Based on a classification scheme, an estimated Koc value of 33, determined from a log Kow of 0.25 and a regression-derived equation, indicates that triacetin is not expected to adsorb to suspended solids and sediment. Volatilization from water surfaces is not expected based upon an estimated Henry's Law constant of 1.2 x 10^{-8} atm/m^3/mol, derived from its vapour pressure, 0.00248 mm Hg, and water solubility, 58,000 mg/l. A base-catalyzed second-order hydrolysis rate constant of 6.2 x 10^{-1} l/mol/sec was estimated using a structure estimation method; this corresponds to half-lives of 130 and 12 days at pH values of 7 and 8, respectively. According to a classification scheme, an estimated BCF of 1, from its log Kow and a regression-derived equation, suggests the potential for bioconcentration in aquatic organisms is low. A theoretical BOD of 91-94% in 4 weeks using an activated sludge inoculum and the Japanese MITI test suggests that biodegradation may be an important environmental fate process in water.	[3]
Atmospheric fate	According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere, triacetin, which has a vapour pressure of 0.00248 mm Hg at 25ºC, is expected to exist solely as a vapour in the ambient atmosphere. Vapour-phase tri-	[3]

	acetin is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals, the half-life for this reaction in air is estimated to be 1.9, calculated from its rate constant of 8.5 x 10^{-12} cm^3/(molecule-sec) at 25º C that was derived using a structure estimation method. Triacetin does not contain chromophores that absorb at wavelengths → 290 nm and therefore is not expected to be susceptible to direct photolysis by sunlight.

Conclusion

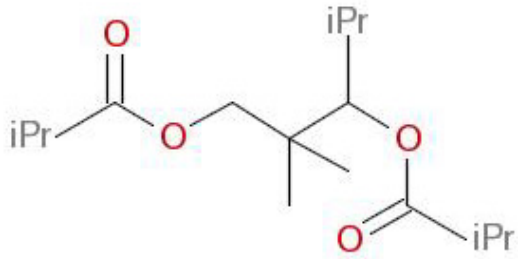
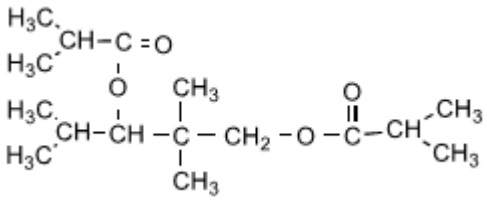
Physical-chemical	-
Emission	-
Exposure	-
Health	-
Environment	-

References

1	ESIS
2	OECD SIDS final
3	HSDB
4	IUCLID dataset
5	MITI
6	MSDS Sigma Aldrich

Trimethyl pentanyl diisobutyrate, TXIB

Identification of the substance

CAS No.	6846-50-0	
EINECS No.	229-934-9	[1]
EINECS Name	1-isopropyl-2,2-dimethyltrimethylene diisobutyrate	[1]
Synonyms	Trimethyl pentanyl diisobutyrate	
	TXIB	
Molecular Formula	$C_{16}H_{30}O_4$	[1]
Structural Formula		
		
Major Uses	Plasticizer	
IUCLID	HPV	[1]
EU classification	This substance is not classified in the Annex I of Directive 67/548/EEC as such, but it may be included in one of the group entries.	[1]

Physico-chemical Characteristics

Physical Form	Liquid	[2]
	Colourless liquid with a slight odour	[4]
Molecular Weight (g/mole)	286.41	[2]

Trimethyl pentanyl diisobutyrate, TXIB

Melting Point/range (°C)	< - 10ºC	[2]
	-70ºC	[3], [4], [5]
Boiling Point/range (°C)	280ºC at 1,013 hPa	[2], [3], [4], [5]
Decomposition Temperature (°C)	-	
Vapour Pressure (mm Hg at °C)	8.8 x 10^{-2} Pa at 25ºC [6.6 x 10^{-4} mgHg]	[2]
Density (g/cm^3 at °C)	0.941	[3], [5]
	0.945 at 20ºC	[4]
Vapour Density (air=1)	9.9	[4]
Henry's Law constant (atm/m^3/mol at °C)	-	
Solubility (mg/l water at °C)	15 mg/l at 25ºC	[2]
	1-2 mg/l at 20.5ºC	[4]
Partition Coefficient (log P_{ow})	> 4.11 at 25ºC	[2]
	4.1	[4]
pK_a	-	
Flammability	-	
Explosivity	-	
Oxidising Properties	-	
Migration potential in polymer	-	
Flash point	140ºC (open cup)	[2], [5]
	113ºC (closed cup)	[3]
	128ºC (closed cup)	[4]
Explosion limits	Lower: 0.48%	[3], [4], [5]
	Upper: 3.1%	
Auto ignition point	424ºC	[5]

Trimethyl pentanyl diisobutyrate, TXIB

Emission Data

During production	-

Exposure Data

Aquatic environment, incl. sediment	-
Terrestrial environment	-
Sewage treatment plant	-
Working environment	-
Consumer goods	-
Man exposed from environment	-
”Secondary poisoning”	-
Atmosphere	-
Dermal	-

Toxicological data

Observations in humans	-

Acute toxicity

Oral	LD_{50} > 3,200 mg/kg (rat)	[2], [4]
	LD_{50} > 6,400 mg/kg (mouse)	[2], [4]
	LD_{50} > 2,000 mg/kg (rat, higest dose)	[6]
Dermal	LD_{50} > 20 ml/kg (guinea pig)	[2], [4]
	LD_{50} > 2,000 mg/kg (rabbit, higest dose)	[6]
Inhalation	453 ppm/6h (rat)	[2]

Trimethyl pentanyl diisobutyrate, TXIB

	LC_{50} > 5.3 mg/l (rat, 6h)	[4]
Other routes	-	
Skin irritation	Moderate irritating (Guinea pig)	[2]
	Slightly irritating (Guinea pig)	[4]
	Not irritating (human)	[6]
Eye irritation	Not irritating (rabbit)	[4]
Irritation of respiratory tract	-	
Skin sensitisation	Not sensitizing (Guinea pig)	[4]
	Not sensitizing (Human)	[6]

Subchronic and Chronic Toxicity

Oral	NOAEL = 30 mg/kg per day (rat) LOEL = 150 mg/kg per day (rat) The results in clinical observations did not reveal any effects attributable to the administration of test substance, and there were no mortality in all groups. Depressions of body weight gain were observed in male rats receiving 750 mg/kg/day, and food consumption of female rats receiving 750 mg/kg/day was greater than those of control. As the results of hematology, there were no essential effects of test substance. In blood clinical examination, increases in creatinine and total bilirubin were observed in rats receiving 150 and 750 mg/kg/day, and increases in total protein were observed in male rats receiving 750 mg/kg/day, suggesting that those changes were due to the effect on kidneys and liver. In organ weight analysis, increases in liver weight were observed in male rats receiving 150 and 750 mg/kg/day, moreover increases in kidneys weights were observed in male rats receiving 750 mg/kg/day. As the results of gross findings, increases in incidence of brown colored livers were observed in male rats receiving 750 mg/kg/day. As the results of histopathological findings, increases in grade of basophilic change of the renal tubular epithelium and degeneration of hyaline droplet were observed in male rats receiving 150 mg/kg/day or more. Moreover, necrosis and fibrosis of the proximal tubule, dilatation of the distal tubule, decreased fatty change and swelling of the liver cells were observed in male rats receiving 750 mg/kg/day.	[2], [5]
	Rat, 103-day repeat dose NOAEL = 0.1% LOAEL = 1%	[4]
	Rat, 52 or 99-day repeat dose NOAEL = 0.1% LOAEL = 1%	[4]
	Dog, 13 weeks repeat dose (6 days a week) NOAEL = 1%	[4]
Inhalation	-	

Dermal	-	
Adsorption, distribution, metabolism and elimination	Rat TXIB was rapidly adsorped, metabolized and excreted. The major route of elimination was urine (47 – 72% total dose) within 5 - 10 days and the majority of this occurring in the first 72 hours. Radioactivity in feces accounted for 14 – 31% of the dose with elimination being essentially complete by 7 days with the majority isolated after 48 hours. Radiolabeled CO2 was not detected. In total, excretions accounted for 95-99% of the dose. Residual radioactivity of treated animals approached control by two weeks. Identification of metabolites showed the feces to contain both 2,2,4-trimethyl pentanediol (TMPD) and TXIB-3-14C indicating esterase cleavage of the two isobutyrates. A small potion of the absorbed material in the urine was unchanged TXIB-3-14C while the majority consisted of metabolites consistent with complete cleavage to the glycol (TMPD) parent molecule. Although much of the urinary metabolite was unidentified it does, nonetheless, represent rapidly cleared material.	[6]

Reversibility of liver effects	Weight change	[6]

There were no mortalities or statistically significant changes noted in body weights, growth rates, or in food consumption and efficiency in any of the three experiments. There were no differences in absolute organ weights in any of the animals in any of the three experiments. All organs microscopically examined in all experiments appeared normal. However, all animals (M&F) fed diets containing 1.0% TXIB for 51 days, 99 days, or the last 47 days of experiment 3 showed significant increases in relative liver weight. Other relative organ weight effects were noted in the kidneys of males and females fed 1.0% TXIB for 51 days (but not 99 days or the last 47 days in experiment 3). Females also showed increases in relative thyroid and brain weights after 99 days of exposure. There were no statistically significant effects noted in the hematology or clinical chemistry parameters analyzed (Note: The manuscript in which these data were published indicated that the SGOT values were elevated in males fed 0.1 and 1.0% TXIB for either 52 or 99 straight days and for females exposed for 99 days. Enzyme levels were still elevated at both doses in males and females in experiment 3 under both the exposure scenarios i.e., test diet for 52 days than control diet for 47 days or control for 52 days than test diet. The manuscript noted their elevation although significant was not manifested in a dose or time related manner and were within historical control values for all groups.) Dose levels of material consumed in experiment one for 51 days at 1.0% were 708 mg/kg (M) and 747 mg/kg (F); while 0.1% animals received either 70 mg/kg (M) or 68 mg/kg (F). In experiment two animals on the 1.0% diet received 824 mg/kg (M) and 853 mg/kg (F); the 0.1% test diet animals received 79 mg/kg (M) and 87 mg/kg. In experiment three animals on the 1.0% diet for the first 52 days received 959 mg/kg (M) and 947 mg/kg (F) while those on the 0.1% test diet received 94 mg/kg (M) and 79 mg/kg. Animals who received 1.0% test diets for the second half of the experiment (Days 52-99) received 558 mg/kg (M) and 614 mg/kg (F); those on the 0.1% test diet averaged 55 mg/kg (M) and 59 mg/kg.

	Liver enzyme changes Males and females fed 1.0% TXIB for either 52 or 99 days showed significant increases in p-nitroanisole demethylase. Males and females fed TXIB for 52 days also had elevated UDP-bilirubin-glucuronyl transferase and UDP-p-aminophenol glucuronyl transferase levels increased. Interestingly only the UDP-bilirubin-glucuronyl transferase level was increased after 99 days of feeding and only in females. Importantly, none of the four enzymes were elevated in experiment three in which animals were fed control diets for 47 days after being fed 1.0% TXIB for the first 52 days. Seven daily IP injections of 100 mg/kg TXIB resulted in elevated levels of UDP-p-aminophenol glucuronyl transferase only.	[6]

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	S.typhimurium and E.coli (metabolic activator Sprague-Dawley rat liver (S9)) Negative with og without metabolic activation. Cytotoxic conc: No toxicity with or without metabolic activation up to 5,000µg/plate (five strains) Genotoxic conc: No genotoxic effects observed with or without metabolic activation	[2], [5]
Chromosome Abnormalities	CHL cells Negative with og without metabolic activation. Cytotoxic conc: With = 0.018 mg/ml (continuous treatment) Without = 0.04 mg/ml (short-term treatment) With > 1.30 mg/ml (short-term treatment) Genotoxic conc: No genotoxic effects observed with or without metabolic activation	[2], [5]
Other Genotoxic Effects	-	
Carcinogenicity	-	

Trimethyl pentanyl diisobutyrate, TXIB

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	Rat	[2]
	NOAEL = 750 mg/ kg per day (parental)	
	NOAEL = 750 mg/kg per day (F1, offspring)	
	The results observed in mating, fertility and estrous cycle did not reveal any effects attributable to the administration of test substance. Observation at delivery, all gestation animals delivered of pups, normally and there were not a treatment-related effect throughout the lactation period. The external examination of pups revealed no effects attributable to the administration of test substance. The body weights of pups showed the favourably growths until day 4 of lactation. The necropsy of stillborn, dead pups until day 4 of lactation and newborns at day 4 of lactation did not reveal any effects attributable to the administration of test substance.	
	Rat	[6]
	NOAEL = 4.5 ppm (276 mg/kg in males and 359 mg/kg in females)	
	NOEL = 15.0 ppm (approx. 1,000 mg/kg) (teratogenicity)	
Teratogenicity	-	

Toxicokinetics

Toxicokinetics	-	

Ecotoxicity Data

Algae	EC_{50} = 8.0 mg/l (Selenastrum capricornutum, 72h)	[2]
	NOEC = 5.3 mg/l (Selenastrum capricornutum)	
Daphnia magna (acute)	EC_{50} = 300 mg/l (daphnia magna, 24h)	[2]

	EC_{50} > 1.46 mg/l (daphnia magna, 48h)	[4]
	NOEC = 1.46 mg/l (daphnia magna, 48h)	
	EC_{50} > 1.55 mg/l (Dugesia tigrina, 96h)	[4]
	NOEC = 1.55 mg/l (Dugesia tigrina, 96h)	
	EC_{50} > 1.55 mg/l (Lumbriculus variegatus, 96h)	[4]
	NOEC = 1.55 mg/l (Lumbriculus variegatus, 96h)	
	EC_{50} > 1.55 mg/l (Helisoma trivolvis, 96h)	[4]
	NOEC = 1.55 mg/l (Helisoma trivolvis, 96h)	
Daphnia magna (chronic)	LC_{50} > 32 mg/l (daphnia magna, 24h, mortality)	[2]
	LC_{50} = 45 mg/l (daphnia magna, 48h, mortality)	
	LC_{50} = 20 mg/l (daphnia magna, 96h, mortality)	
	LC_{50} = 13 mg/l (daphnia magna, 7 d, mortality)	
	LC_{50} = 12 mg/l (daphnia magna, 14 d, mortality)	
	LC_{50} = 12 mg/l (daphnia magna, 21 d, mortality)	
	EC_{50} = 5.6 mg/l (daphnia magna, 21 d, reproduction)	
	NOEC = 3.2 mg/l (daphnia magna, reproduction)	
	LOEC = 1.0 mg/l (daphnia magna, reproduction)	
Other aquatic organisms	EC_{50} > 1.55 mg/l (Asellus intermedium, 96h)	[4]
	NOEC = 1.55 mg/l (Asellus intermedium, 96h)	
	EC_{50} > 1.55 mg/l (Gammarus fasciatus, 96h)	[4]
	NOEC = 1.55 mg/l (Gammarus fasciatus, 96h)	
Fish (acute)	LC_{50} = 18 mg/l (Oryzias latipes, 24h)	[2]
	LC_{50} = 18 mg/l (Oryzias latipes, 48h)	
	LC_{50} = 18 mg/l (Oryzias latipes, 72h)	
	LC_{50} = 18 mg/l (Oryzias latipes, 96h)	

Trimethyl pentanyl diisobutyrate, TXIB

	LC_{50} > 1.55 mg/l (pimpephales promelas, 96h)	[4]
	NOEC = 1.55 mg/l (pimpephales promelas, 96h)	
Bacteria	-	
Terrestrial organisms	-	

Environmental Fate

BCF	5.2-31 (0.3 µg/l, 6 weeks at 25ºC)	[2]
	6.0-17 (0.03 µg/l, 6 weeks at 25ºC)	
	0.6-0.8 (1 mg/l, 6 weeks)	[5]
	< 1.0 (0.1 mg/l, 6 weeks)	
Aerobic biodegradation	4-82% in 28 days (BOD)	[2]
	2-84% in 28 days (TOC)	
	3-100% in 28 days (GC)	
	Inherently biodegradable	
	> 99.9% in 12 days	[4]
	Inherently biodegradable	
	ThOD = 2.40 g O_2 per g TXIB (calculated)	[4]
Anaerobic biodegradation	-	
Photodegradation	$T_{½}$ = 90.7 years	[2]
	Rate: 1.21 x 10^{-14} mol/l/sec	
Stability in water	Stable at pH 4 and 7	[2]
	$T_{½}$ = 179 days at pH 9	
Metabolic pathway	-	
Mobility	-	

Conclusion

Trimethyl pentanyl diisobutyrate, TXIB

Physical-chemical	-
Emission	-
Exposure	-
Health	-
Environment	-

References

1 ESIS

2 OECD SIDS final

3 MSDS Sigma Aldrich

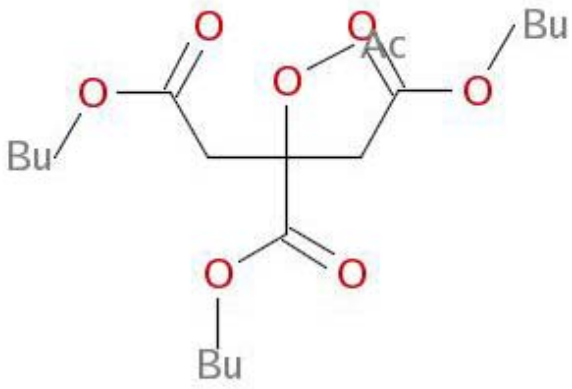
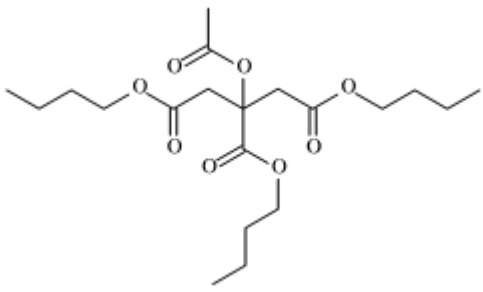
4 IUCLID dataset

5 MITI

6 EASTMAN TXIB study

Acetyl tributyl citrate, ATBC

Identification of the substance

CAS No.	77-90-7	
EINECS No.	201-067-0	[1]
EINECS Name	tributyl O-acetylcitrate	[1]
Synonyms	Acetyl tributyl citrate	
	ATBC	
	1,2,3-Propanetricarboxylic acid, 2-(acetyloxy)-, tributyl ester	
	Citric acid, tributyl ester, acetate	
	Citroflex ® A-4	
Molecular Formula	$C_{20}H_{34}O_8$	[1]
Structural Formula		
		
Major Uses	Acetyl tributyl citrate (ATBC) is used as a plasticizer with aqueous- and solvent-based polymers, including acrylic, methacrylic, ethyl cellulose, hydroxypropyl methyl cellulose, nitrocellulose, vinyl acetate, vinyl chloride, vinyl pyrrolidone, vinylidene	[2]

	chloride, and urethane polymer systems. ATBC is used in the following applications: • Medical plastics: Aqueous pharmaceutical coatings; extra-corporeal tubing. • Food contact products: Food wraps and films; beverage tubing; crown liners; food containers; tinplate lubricant; aluminum foil coatings. • Cellulosics: Nitrocellulose-based explosives/propellants. • Other industrial uses: Children's toys; animal ear tags; ink formulations; adhesives; pesticide inerts.	
IUCLID	LPV in EU	[1]
	HPV in US	[2]
EU classification	This substance is not classified in the Annex I of Directive 67/548/EEC as such, but it may be included in one of the group entries.	[1]

Physico-chemical Characteristics

Physical Form	Liquid	[3]
	Colourless liquid with a very faint sweet herbaceous odour and a mild fruity flavour.	[4]
Molecular Weight (g/mole)	402.5	[2]
Melting Point/range (°C)	- 59ºC	[2]
	- 80ºC	[4], [7]
	- 75ºC	[6]
Boiling Point/range (°C)	326ºC at 760 mmg Hg	[2]
	172-174ºC at 1 mm Hg	[4], [7]
	173ºC	[6]
Decomposition Temperature (°C)	-	
Vapour Pressure (mm Hg at °C)	5.2×10^{-2} mm Hg at 20ºC [6.93 Pa]	[2]

	4.6×10^{-6} mm Hg at 25ºC [6.13×10^{-4} Pa]	[4], [6], [7]
	1 mm Hg at 173ºC [133Pa]	
Density (g/cm^3 at °C)	1.050	[3]
	1.046 at 25ºC	[4], [6]
Vapour Density (air=1)	-	
Henry's Law constant (atm/m^3/mol at °C)	3.8×10^{-10} at 25ºC	[4], [6], [7]
Solubility (mg/l water at °C)	< 100 mg/l	[2]
	5 mg/l	[4], [7]
Partition Coefficient (log P_{ow})	4.29	[5], [7]
pK_a	-	
Flammability	-	
Explosivity	-	
Oxidising Properties	-	
Migration potential in polymer	Migration /from food packaging/ in the cheese wrapped in vinylidene chloride copolymer films (exposure 5 days, temperature 5ºC) was found at the level of 6.1 ppm or 2.0-8.0 mg/kg, and into wrapped cake, at the level of 3.2 ppm. Migration from plasticized vinylidene chloride-vinyl chloride copolymer film in fatty or aqua-type foods was determined at the levels from 0.4 mg/kg after minimal contact during microwave cooking of a soup to 79.8 mg/kg for use of the film during the microwave cooking of peanut-containing cookies. Migration /citric acid, acetyl tributyl ester/ plasticizer from plasticized polyvinylidene chloride-polyvinyl chloride films into both olive oil and distilled water during microwave heating was studied. The amount of /citric acid, acetyl tributyl ester/ migrating into olive oil after heating for 10 min was 73.9 mg/L, into distilled water it was 4.1 mg/L after heating for 8 min.	[4]
log Kow	4.92 at 22ºC	[2]
	4.3	[4]
Atmospheric OH rate constant cm^3/(molecule sec)	14.45×10^{-12}	[2]

	1.4×10^{-11} at 25ºC	[4], [7]
Flash point	113ºC (closed cup)	[3]
	204ºC	[4], [6]

Emission Data

During production	-

Exposure Data

Aquatic environment, incl. sediment	Surface water: Acetyl tributyl citrate was identified in 2 water samples taken from the River Lee, Great Britain at trace levels.	[4]
Terrestrial environment	-	
Sewage treatment plant	-	
Working environment	NIOSH has statistically estimated that 106,668 workers (98,183 of these are female) are potentially exposed to acetyl tributyl citrate in the US. Occupational exposure to acetyl tributyl citrate may occur through inhalation and dermal contact with this compound at workplaces where acetyl tributyl citrate is produced or used. The general population may be exposed to acetyl tributyl citrate via dermal contact with consumer products containing actyl tributyl citrate and by the ingestion of food containing this compound.	[4]
Consumer goods	-	
Man exposed from environment	-	
”Secondary poisoning”	Acetyl tributyl citrate's production and use as a plasticizer for vinyl, rubber and cellulosic resins and as a flavour ingredient may result in its release to the environment through various waste streams.	[4]
Atmosphere	-	
Dermal	-	

Acetyl tributyl citrate, ATBC

Toxicological data

Observations in humans	-	

Acute toxicity

Oral	LD_{50} > 30 ml/kg (rat)	[2]
	LD_{50} > 50 ml/kg (rat)	[2]
	LD_{50} = 31.4 g/kg (rat)	[4]
	LD_{50} = 4 g/kg (mouse)	[4]
	LD_{50} > 50 ml/kg (cat)	[4]
Dermal	-	
Inhalation	-	
Other routes	-	
Skin irritation	Slight irritation (Guinea pig)	[4]
Eye irritation	Slight ittitation (rabbit)	[4]
Irritation of respiratory tract	-	
Skin sensitisation	-	

Subchronic and Chronic Toxicity

Oral	Rat, 6 weeks repeat dose	[2]
	NOAEL = 5%	
	LOAEL = 10%	
	Rat, 8 weeks repeat dose	[2]
	NOEL = 10%	
	LOEL > 10%	

Cat, 2 months repeat dose [2]

NOEL < 5ml/kg

LOEL = 5 ml/kg

Rat, 90-day repeat dose [2]

NOEL = NOAEL = 300 mg/kg

LOEL = 1000 mg/kg

Rat, 2 years repeat dose [2]

NOAEL = 2000 ppm

LOAEL = 20,000 ppm

In the main study, a transient reduction in body weight gain was observed in animals in all three treated groups, 200, 2000 and 20000 ppm. This decrease in body weight gain was not seen in the additional study of animals treated for one year at dietary concentrations of 200 and 2000 ppm. Since this finding was not reproducible it is considered to be and artifact. Statistical analysis indicated that there were no significant differences between the body weights of the treated animals compared to the concurrent controls. There were no treatment-related clinical observations. Twelve of the 60 rats fed test diets and eight of the 40 control rats died prior to scheduled sacrifice. There was no significant difference in time of death or percentage mortality among the three treated groups and controls. Inflammatory disease of the lungs was the most frequent finding necropsy of these animals, it is likely that this was caused by infection rather than treatment with ATBC. Lymphoid tumors of the pleural and abdominal cavities, with some infiltration of the associated organs, were seen in both treated and control animals at comparable rates and, therefore, were not considered to be treatment-related. Careful examination of the endocrine system did not reveal evidence of abnormality in any of the animals. There were no significant differences between treated and control animals in comparisons of the pathological findings.

Rat, 13 weeks repeat dose [2]

NOAEL = 100 mg/kg per day (males)

NOAEL = 300 mg/kg per day (females)

LOEL = 300 mg/kg per day (males)

LOEL = 1000 mg/kg per day (females)

At the completion of the in utero phase, rats that had been exposed to ATBC from before conception, through gestation and continuously from the time of birth were selected (20 unrelated males and 20 unrelated females per dose group for the main study; and 10 unrelated males and 10 unrelated females for the control and high dose recovery groups) and transferred to the 13-week study. There were no significant intergroup differences in the body weights of the animals at the start of the 13-week study. In the 13-week toxicity phase of the study, administration of ATBC via the diet to Han Wistar rats at doses as high as 1000 mg/kg/day that had already received direct and indirect exposure to the test material from before conception did not produce any marked toxicity. Treatment at 1000 mg/kg/day resulted in a slight reduction in body weight gain in both sexes, which was considered to be a nonspecific indicator of toxicity. Liver weights were increased and hepatic hypertrophy occurred at 1000 mg/kg/day in both sexes. Hepatic hypertrophy resulting from an induction of metabolizing enzymes as an adaptive response to treatment is a common finding following administration of high doses of xenobiotics, and is not considered to be toxicologically significant. Weak peroxisome proliferation was measured in males at 300 mg/kg/day and both sexes at 1000 mg/kg/day. Peroxisome proliferation is universally recognized as a rodent specific effect and not relevant to hazard characterization for humans. Slight variations in urinary composition and in plasma electrolyte concentrations suggested an effect on renal function at the higher dose levels. In view of the slight nature of these changes, which were all shown to be reversible and within normal historical control ranges, and the lack of histopathological changes in the kidneys, the possible effect on renal function is considered to be due to adaptation to the excretion of high levels of the test material and/or metabolites and is not considered to be of any toxicological significance.

Inhalation	-
Dermal	-

Absorption, metabolism and excretion	Orally administered ATBC is extensively absorbed and rapidly metabolized and excreted by the rat. Measured levels of ATBC and radioactivity in the dosing solutions ranged from 90 to 115% of the target concentrations. No signs of toxicity were observed following dosing. One rat in the Rate of Absorption Study died following blood collection. The probable cause of death was complication from the blood collection procedure. Absorption and Elimination Study: Between 99 and 102% of the administered radioactivity was recovered in the urine, feces, cage wash, expired CO_2, tissues, and carcass by study end (48 hours). The following table provides the results of the recovered radiolabeled material.	[2], [4]

Route od excretion	% of recovered ^{14}C
Urine and cage rinse	59 to 70%
Feces	25 to 36%
Expiration of $^{14}CO_2$	2%
Tissues and carcass	0.36 to 1.26%

Rate of Absorption Study: Absorption of the radioactive dose was rapid (absorption $T_{½}$ = 1.0 hour) and extensive (at least 67% of ^{14}C dose absorbed). Peak concentrations of radioactivity in blood were observed 2 to 4 hours post-dosing. Most of the absorbed radiolabel was rapidly eliminated with a halflife of 3.4 hours for blood. Metabolism of absorbed ^{14}C-ATBC was rapid and essentially complete. At least 9 radiolabeled metabolites were found in urine and at least 3 in feces. The labeled metabolites in urine were more polar than ATBC and less polar than citric acid. Urinary metabolites of ATBC which were positively identified were acetyl citrate, monobutyl citrate, acetyl monobutyl citrate, dibutyl citrate, and acetyl dibutyl citrate (two isomers). The major labeled urinary metabolite was tentatively identified as monobutyl citrate. Unchanged ATBC representing about 7% of the dose was found in feces.

Metabolism	Both ATBC and the intermediate metabolite TBC undergo rapid metabolism in both human serum and rat liver homogenates, which would be expected to yield the principal metabolites acetic acid, citric acid and butanol. The butanol would then be expected to further oxidize to butanoic acid and assimilated by ß-oxidation. Although a direct stoichiometry of butanol formed from ATBC and TBC was not observed, these results are partially explained based on the fact that butanol also is metabolized in the rat liver homogenate at a rate of 37 nmoles/ml/hr. It also may be suggested that an initial single or double debutylation may yield products which are less readily hydrolyzed in the system; products which would be, as fully ionizable carboxylic acids, readily excreted in vivo. Human serum results with ATBC and TBC: The metabolism of ATBC in human serum was a linear decline in the concentration of ATBC of the 48 hour period, after which only 25% of the starting material remained. An estimated half-life of 32 hours was obtained. In addition, only traces of TBC were detected from the deacetylation of ATBC to TBC. The metabolism of TBC in human serum showed an exponential decline in the levels of TBC with complete conversion observed in the 24 hour sample. An estimated half-life of 4 hours was obtained. Rat liver homogenate results with ATBC and TBC: The metabolism of ATBC in liver homogenate was linear and rapid decline in the concentration of ATBC the first hour of the 9 hour period examined. From the slope of the linear decline, an estimated half-life of only 10 minutes can be obtained. Not even traces of TBC were detected from the deacetylation of ATBC to TBC was seen. The metabolism of TBC in rat liver homogenate showed a nearly instantaneous and complete metabolism of TBC in 15 minutes. The metabolism was so rapid that the T0 data indicated only 35 µg/ml even though 100 µg/ml was added. A repeat incubation was conducted to try to capture an earlier time point in the conversion, but a comparable value (42 µg/ml) was again obtained. Thus, a half-life of seconds could only be estimated.	[2]

	Results with butanol capillary GC analysis in human serum and rat liver homogenate: Butanol levels generated from ATBC were maximal at 1 to 2 hours, representing a level of 279 nmoles/ml at 2 hours. This represents a 37% (279 nmoles/750 nmoles) of the theoretical amount produced. Butanol levels generated from TBC, also maximal at 1 to 2 hours yielded 436 nmoles/ml, or 58% (436 nmoles/750 nmoles) of the theoretical amount. Therefore, with 3 moles of butanol theoretically produced from one mole of ATBC or TBC, the amounts observed were 1.11 mole equivalents from ATBC and 1.74 mole equivalents from TBC.	
Metabolism	The results of this study confirm that the end products of ATBC hydrolysis in hu mans are unquestionably citric, acetic and butyric acid. In human serum, ATBC was hydrolyzed relatively slowly (half-life approximately 7 hours) into the equivalent of 2 moles of n-butanol. One butyl ester group of ATBC did not appear to undergo hydrolysis, most probably due to the lower affinity for the butyl group at the 2 position. Hydrolysis in rat liver ho mogenate took place much faster (half-life < 30 minutes). Approximately 2.3 moles of n-butanol were recovered. As shown by a separate experiment, this amount is an underestimation of the true recovery value, the loss of the analyte being due to its consumption by liver enzymes, such as alcohol dehydrogenase.	[2]
	The metabolism of acetyl tributyl citrate was evaluated using groups of male rats (number of animals, weights, and strain not stated). Both the absorption and metabolism of ^{14}C-Acetyl tributyl Citrate proceeded rapidly, and the following metabolites were identified: acetyl citrate, monobutyl citrate, acetyl monobutyl citrate, dibutyl citrate, and acetyl dibutyl citrate.	[4]

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	S.typhimurium (metabolic activator Sprague-Dawley rat liver (S9)) The test substance showed no evidence of mutagenic activity when tested in this bacterial system with and without activation. Cytotoxic conc.: Not cytotoxic up to 5000 µg/plate Genotoxic effects: Negative with and without S-9 activation	[2]
	S.typhimurium (metabolic activator Sprague-Dawley rat liver (S9) and Syrian Golden Hamster) The test substance showed no evidence of mutagenic activity when tested in this bacterial system in the presence of both rat and hamster liver S-9 and in the absence of microsomal activation. Cytotoxic conc.: Not cytotoxic up to 10,000 µg/plate Genotoxic effects: Negative with and without S-9 activation	[2]
	S.typhimurium The test substance showed no evidence of mutagenic activity when tested in this bacterial system in the absence of microsomal activation Cytotoxic conc.: Not cytotoxic up to 495 µg/plate Genotoxic effects: Negative without metabolic activation	[2]
	Rat lymphocytes (metabolic activator Sprague-Dawley rat liver (S9)) The test substance showed no evidence of mutagenic activity in the presence and absence of an S-9 metabolic activation system. Cytotoxic conc.: None Genotoxic effects: Negative with and without metabolic activation	[2]

	Mouse lymphoma cells (metabolic activator S rat liver (S9)) The test substance showed no evidence of mutagenic activity when tested in this mammalian cell gene mutation assay both with and without metabolic activation. Cytotoxic conc.: Complete toxicity was observed during the initial toxicity test at concentrations of 514 µg/ml and above for nonactivated cultures and from 1028 µg/ml and above for the S-9 activated cultures. A dose-dependent increase in toxicity was observed in the mutagenicity assay, with an average Total Growth of 16%, 6% and 3% in the nonactivated cultures at concentrations of 70, 150, and 230 µg/ml, respectively with complete toxicity at 310 µg/ml and above. For the S-9 activated cultures, the average Total Growth was 16% and 8% at 410 and 480 µg/ml, respectively, with complete toxicity at 550 µg/ml. Genotoxic effects: Negative with and without metabolic activation.	[2]
	Chinese hamster ovary cells (metabolic activator Sprague-Dawley rat liver (S9)) The test substance showed no evidence of mutagenic activity when tested in this mammalian cell gene mutation assay. Genotoxic effects: Negative with and without metabolic activation.	[2]
Chromosome Abnormalities	-	

Genotoxicity	An acute dose-range finding toxicity study with 3 male Han Wistar rats indicated that a maximum of 2000 mg/kg could be used for the unscheduled DNA synthesis (UDS) assay. A lower dose of 800 mg/kg was also selected. Groups of 5 male rats were treated once with the solvent corn oil, the test substance (at 800 or 2000 mg/kg) or the required positive control, by oral gavage at a dose volume of 10 mL/kg. The positive controls used were 75 mg/kg 2-acetamindofluorene (2-AAF) suspended in corn oil (12-14 hr experiment) and 10 mg/kg dimethylnitrosamine (DMN) dissolved in purified water (2-4 hr experiment). This test substance did not induce unscheduled DNA synthesis in freshly prepared primary cultures of hepatocytes from rats dosed at up to 2000 mg/kg under the conditions employed in this assay.	[4]
	The mutagenicity of acetyl tributyl citrate was evaluated using the Ames test and the following Salmonella typhimurium strains: TA98, TA100, TA1535, TA1537, and TA1538. Acetyl tributyl citrate (29.71 mg/mL DMSO) solutions containing 9, 50, 99, and 495 µm were tested on all strains without metabolic activation. Nitrofluorene served as the positive control.Acetyl tributyl citrate was not mutagenic in any of the strains tested with or without metabolic activation.	[4]
	The mutagenicity of acetyl tributyl citrate was evaluated using the L5178Y (TK+/TK-) mouse lymphoma suspension/plate assay. Acetyl tributyl citrate, in DMSO, was tested at concentrations of 10 to 230 µg/mL (without metabolic activation) and 200 to 480 µg/mL (with metabolic activation). The test substance was not mutagenic with or without activation.	[4]
Other Genotoxic Effects	-	

Carcinogenicity	Three groups of 1-month-old rats (Sherman strain /20 rats per group) were fed diets containing 200, 2,000 and 20,000 ppm acetyl tributyl citrate, respectively for 2 years. Compared to the control group, transient reduction of the growth rate was noted in all three test groups during week 5 to 15 of the study; however, the difference was not statistically significant. The difference in mortality between the test and control groups was also not statistically significant. Twelve test animals and 8 control animals died spontaneously. Differences in behaviour between test and control animals were not observed and the incidence of diarrhea in test animals was no greater than that noted for controls. At necropsy, inflammatory disease of the lungs was the most frequent finding. Pulmonary lesions ranged from bronchitis to severe suppurative and infectious necrotizing pneumonitis. Practically all rats (test and controls) had appreciable amount of passive congestion of the viscera; however, it was assumed that these were agonal. The pathological findings between test and control groups were not statistically significant; the endocrine organs were free of abnormalities.	[4]
Cytotoxicity	The in vitro cytotoxicity of acetyl tributyl citrate in HeLa cell cultures (human cell line) was evaluated using the metabolic inhibition test, supplemented by microscopy of cells after 24 hours of incubation (the MIT-24 test system). After 24 hours, cell viability was determined by microscopy. Two endpoints of cytoinhibition (total and partial inhibition) were estimated after 24 hours, based on the absence or scarcity of spindle-shaped cells, and, after 7 days The following values for minimal inhibitory concentration were reported for acetyl tributyl citrate: 13 mg/mL (for total inhibition at 24 hours), 3.8 mg/mL (for partial inhibition at 24 hours), and 5.7 mg/mL (for total and partial inhibition at 7 days). Acetyl tributyl citrate caused little toxicity in HeLa cell cultures.	[4]

	The cytotoxicity of acetyl-tributyl-citrate and dibutyl-sebacate was studied in cultured mammalian cells. The impetus for the study was a report that acetyl-tributyl-citrate and dibutyl-sebacate, which were plasticizers found in polyvinylidene-chloride film used for packaging food, could leach out and diffuse into the foods. Human KB cells, monkey Vero cells, and canine MDCK cells were incubated with acetyl-tributyl-citrate or dibutyl sebacate over a range of concentrations for 72 hours. Cytotoxicity was evaluated by determining the extent of growth inhibition. Doses of acetyl-tributyl-citrate and dibutyl-sebacate that inhibited growth by 50% were calculated from the data. Both compounds inhibited the growth of all cells in a dose dependent manner. The inhibited growth by 50% of acetyl-tributyl-citrate in the various types were: 44.7 µg/mL in KB cells; 39.9 ug/m: in Vero cells; and 42.1 µg/mL in MDCK cells. The inhibited growth by 50% of dibutyl-sebacate in these cells were: KB cells, 1,549 µg/ml; Vero cells, 1,510 ug/ml; and MDCK cells, 1,549 µg/mL. /It was/ concluded that when comparing the results of this study with those obtained previously using tricresyl-phosphate,triphenyl-phosphate (TPP), butylated-hydroxyanisole, and butylated-hydroxytoluene in human KB cells, acetyl-tributyl-citrate is more toxic than TCP and more toxic than TPP. Acetyl-tributyl-citrate is less toxic than BHA, but shows toxicity similar to that of BHT. DBS is much less toxic than either BHT or BHA. KB, Vero, and MDCK cells show similar sensitivity to acetyl-tributyl-citrate and DBS.	[4]
Neurotoxicity	Blood pressure expt in rabbits revealed that tributyl citrates produced complete loss of blood pressure when admin in toxic doses. Tributyl citrates also found to have local anesthetic action in rabbit experiments & to block neural transmission in rats when placed in contact with a nerve trunk.	[4]
	Acetyl tributyl citrate (in 3% acacia, applied to sciatic nerve) induced complete, reversible nerve block during electrical stimulation of the sciatic nerve-anterior tibialis muscle in white rats. Complete blockage of contralateral reflex was also demonstrated	[4]

	Three drops of a 5% suspension of acetyl tributyl citrate in a 3% gum acacia medium was instilled into the conjunctival sac of the eye of a rabbit. Corneal reflex action was temporarily abolished (local anesthetic effect).	[4]

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	Ray, 2-generation reproduction, oral, repeated dose NOAEL = 100 mg/kg per day (parental) NOAEL = 100 mg/kg per day (offspring) F_0 and F_1 adult data: No treatment-related clinical observations were noted throughout the study in either F_0 or F_1 parental animals. Body weights of F_0 parents and F_1 females were largely unaffected by treatment with ATBC; however, body weights of the F_1 parental males in the 300 and 1000 mg/kg/day groups were consistently lower that controls and appeared to be related to treatment. Body weights of the F_0 females in the 1000 mg/kg/day group at the end of pregnancy (gestation days 21 or 22) was significantly lower than control values. Water consumption of the F_0 and F_1 parental animals fed ATBC at a level of 1000 mg/kg/day were consistently lower than concurrent controls throughout the study. Mating, gestation and fertility of the F_0 and F_1 generations were unaffected by treatment. There were no abnormalities seen at necropsy that were considered to be treatmentrelated. Offspring toxicity: The body weights of the pups from the 300 and 1000 mg/kg/day dose groups were slightly lower than those of the controls, and slightly higher mortality also was observed in these groups. It was considered that these effects are a consequence of the reduced water intakes in the dams at these dose levels rather than a direct effect of ATBC. No other treatment-related effects were observed in the parameters evaluated.	[2]

Acetyl tributyl citrate, ATBC

Teratogenicity	Rat, 12 months, oral NOEL = 50 mg/kg (parental toxicity) NOEL = 250 mg/kg (developmental toxicity) ATBC is rapidly and extensively absorbed, and then rapidly metabolised and virtually completely excreted by the rat. Developmental toxicity was not observed at dose levels as high as 1000 mg/kg/day in a two-generation reproductive toxicity study nor in a 13-week toxicity study with an in utero exposure phase. The metabolites that have been positively identified in the urine of rats (acetyl citrate, monobutyl citrate, acetyl monobutyl citrate, dibutyl citrate and two isomers of acetyl dibutyl citrate) have been demonstrated to undergo rapid clearance from the body and are not suspected to be developmental toxicants. Also, other ATBC metabolites, acetic acid, citric acid, butyric acid, tributyl citrate and butanol, do not pose a concern for developmental toxicity	[2]

Toxicokinetics

Toxicokinetics	

Ecotoxicity Data

Algae	EC_{50} = 0.148 mg/l (Selenastrum capricornutum, 96h)	[2]
Daphnia magna (acute)	EC_{50} = 7.82 mg/l (Ceriodaphnia dubia, 48h) NOEC = 60.2 mg/l (Ceriodaphnia dubia, 24h) NOEC = 4.82 mg/l (Ceriodaphnia dubia, 48h) LOEC > 60.2 mg/l (Ceriodaphnia dubia, 24h) LOEC = 8.7 mg/l (Ceriodaphnia dubia, 48h)	[2], [4]
Other aquatic organisms	-	
Fish (acute)	LC_{50} = 59 mg/l (Fundalus heteroclitus, 96h) NOEC = 10 mg/l (Fundalus heteroclitus, 96h)	[2], [4]

	LC_{50} = 38-60 mg/l (Lepomis macrochirus, 96h)	[2], [4]
	NOEC = 10 mg/l (Lepomis macrochirus, 96h)	
	EC_{50} = 3.5 mg/l (Pimephales promelas, 24h)	[2], [4]
	NOEC = 2.62 mg/l (Pimephales promelas, 24h)	
	LOEC = 5.01 mg/l (Pimephales promelas, 24h)	
	EC_{50} = 2.8 mg/l (Pimephales promelas, 48h)	
	NOEC = 1.28 mg/l (Pimephales promelas, 48h)	
	LOEC = 2.62 mg/l (Pimephales promelas, 48h)	
	EC_{50} = 1.9 mg/l (Pimephales promelas, 7 days)	
	NOEC = 1.28 mg/l (Pimephales promelas, 7 days)	
	LOEC = 2.62 mg/l (Pimephales promelas, 7 days)	
Bacteria	-	
Terrestrial organisms	-	

Environmental Fate

BCF	An estimated BCF of 250 was calculated for acetyl tributyl citrate, using a water solubility of 5 mg/l and a regression-derived equation. According to a classification scheme, this BCF suggests the potential for bioconcentration in aquatic organisms is high, provided the compound is not altered physically or chemically once released into the environment.	[4]
Aerobic biodegradation	14% at day 5	[2]
	26% at day 21	
	Standard BOD test	
	> 90% in 5 h	[2]
	Sewage solumn degradation	

	Acetyl tributyl citrate, present at an initial concentration of 30 mg/l, reached 80% of the theoretical BOD in 4 weeks with an activated sludge inoculum in the modified MITI test. 82% BOD 93% TOC	[4], [6]
Anaerobic biodegradation	-	[4]
Abiotic degradation	The rate constant for the vapour-phase reaction of acetyl tributyl citrate with photochemically-produced hydroxyl radicals has been estimated as 1.4×10^{-11} cm^3/(molecule-sec) at 25ºC using a structure estimation method. This corresponds to an atmospheric half-life of about 27 hours at an atmospheric concentration of $5 \times 10^{+5}$ hydroxyl radicals per cm^3. A base-catalyzed second-order hydrolysis rate constant of 5.8×10^{-2} L/(mol-sec) was estimated using a structure estimation method; this corresponds to half-lives of 3.8 years and 140 days at pH values of 7 and 8, respectively.	
Photodegradation	$T_{½}$ = 0.740 days	[2]
Stability in water	$T_{½}$ = 139.3 days at pH 8 $T_{½}$ = 3.8 days at pH7	[2]
Metabolic pathway	-	
Mobility	-	
Volatilization from water	The Henry's Law constant for acetyl tributyl citrate is estimated as 3.8×10^{-10} atm/m^3/mol using a fragment constant estimation method. This Henry's Law constant indicates that acetyl tributyl citrate is expected to be essentially nonvolatile from water surfaces. Acetyl tributyl citrate is not expected to volatilize from dry soil surfaces based upon an estimated vapour pressure of 4.6×10^{-6} mm Hg, determined from a fragment constant method.	[4]
Soil adsorption/mobility	The Koc of acetyl tributyl citrate is estimated as 1,800, using a water solubility of 5 mg/l and a regression-derived equation. According to a classification scheme, this estimated Koc value suggests that acetyl tributyl citrate is expected to have low mobility in soil.	[4]
Terrestrial fate	Based on a classification scheme, an estimated Koc value of 1,800, determined from a water solubility of	[4]

	5 mg/l and a regression-derived equation, indicates that acetyl tributyl citrate is expected to have low mobility in soil. Volatilization of acetyl tributyl citrate from moist soil surfaces is not expected to be an important fate process given an estimated Henry's Law constant of 3.8 x 10^{-10} atm/m^3/mol, using a fragment constant estimation method. Acetyl tributyl citrate is not expected to volatilize from dry soil surfaces based upon an estimated vapour pressure of 4.6 x 10^{-6} mm Hg, determined from a fragment constant method. Based on limited data, acetyl tributyl citrate is expected to biodegrade readily in the soil environment; 80% of the theoretical BOD was reached in 4 weeks using an activated sludge inoculum and the Japanese MITI test.	
Aquatic fate	Based on a classification scheme, an estimated Koc value of 1,800, determined from a water solubility of 5 mg/l and a regression-derived equation, indicates that acetyl tributyl citrate is expected to adsorb to suspended solids and sediment. Volatilization from water surfaces is not expected based upon an estimated Henry's Law constant of 3.8 x 10^{-10} atm/m^3/mol, developed using a fragment constant estimation method. According to a classification scheme, an estimated BCF of 250, from its water solubility and a regression-derived equation, suggests the potential for bioconcentration in aquatic organisms is high. Estimated hydrolysis half-lives of 3.8 years and 140 days at pH values of 7 and 8, respectively, were deteremined using an estimated base-catalyzed second-order hydrolysis rate constant of 5.8 x 10^{-2} l/(mol-sec). Based on limited data, acetyl tributyl citrate is expected to biodegrade readily in the aquatic environment; 80% of the theoretical BOD was reached in 4 weeks using an activated sludge inoculum and the Japanese MITI test.	[4]
Atmospheric fate	According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere, acetyl tributyl citrate, which has an estimated vapour pressure of 4.6 x 10^{-6} mm Hg at 25ºC, determined from a fragment constant method, is expected to exist in both the vapour and particulate phases in the ambient atmosphere. Vapour-phase acetyl tributyl citrate is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 27 hours, calculated from its rate constant of 1.4 x 10^{-11} cm^3/(molecule-sec) at 25ºC that was derived using a structure estimation method. Particulate-phase acetyl tributyl citrate may be physically re-	[4]

moved from the air by wet and dry deposition.

Conclusion

Physical-chemical	-
Emission	-
Exposure	-
Health	-
Environment	-

References

1 ESIS

2 EPA HPV programme

3 MSDS Sigma Aldrich

4 HSDB

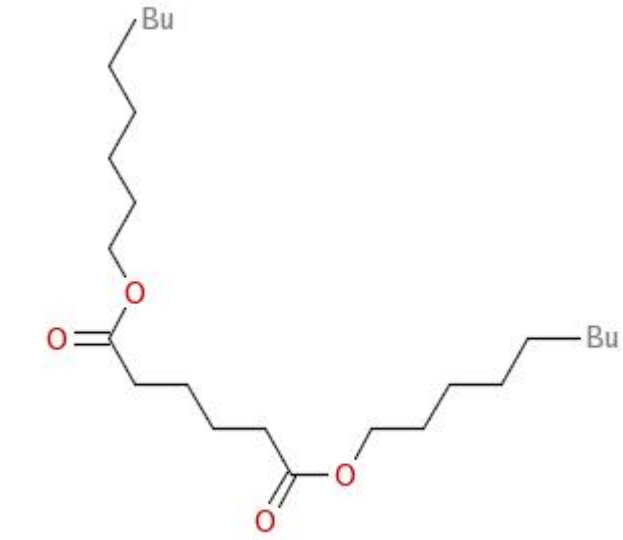
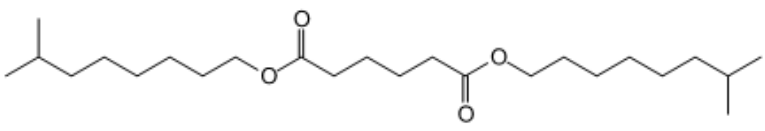
5 ChemID

6 MITI

7 SRC physprop database

Diisononyl adipate, DINA

Identification of the substance

CAS No.	33703-08-1	
EINECS No.	251-646-7	[1]
EINECS Name	diisononyl adipate	[1]
Synonyms	Diisononyl adipate	
	DINA	
Molecular Formula	$C_{24}H_{46}O_4$	[1]
Structural Formula		
		
Major Uses	Rubber and plastic products	[3]
	Electrical and electronic products	
IUCLID	HPV	[1]
EU classification	This substance is not classified in the Annex I of Directive 67/548/EEC as such, but it may be included in one of the group entries.	[1]

Diisononyl adipate, DINA

Physico-chemical Characteristics

Physical Form	Liquid	[2]
	Colourless liquid with a faint odour	[5]
Molecular Weight (g/mole)	399	[3]
Melting Point/range (°C)	- 68ºC	[2], [4], [5]
	- 60ºC	[3]
Boiling Point/range (°C)	224-228ºC at 7 hPa	[2], [4]
	> 250ºC at 1013 hPa	
	233ºC at 5 mm Hg	[3]
	239-244ºC at 7 mBar	[5]
Decomposition Temperature (°C)	-	
Vapour Pressure (mm Hg at °C)	< 0.1 hPa at 20ºC [10 Pa, 7.5 x 10^{-2} mmHg]	[2]
	1013 hPa at 430ºC (under argon) [1.013 x 10^{5} Pa, 759.8 mmHg]	
	0.9 mm Hg at 200ºC [119.9 Pa]	[3]
	< 0.075 mm Hg at 20ºC [9.99 Pa]	[4]
Density (g/cm^3 at °C)	0.923 at 20ºC	[2], [4]
	0.918-0.922 at 20ºC	[5]
Vapour Density (air=1)	-	
Henry's Law constant (atm/m^3/mol at °C)	2.9 x 10^{-5}	[3]
Solubility (mg/l water at °C)	< 1 mg/l at 20ºC	[2], [4]
	0.00022 mg/l at 20ºC	[3]
	< 0.01 g/l at 25ºC [< 10mg/l]	[5]
Partition Coefficient (log P_{ow})	9.56 – 10.4 at 25ºC	[2], [4]
	9.24	[5]

pK_a	-	
Flammability	Not flammable	[2]
Explosivity	Not explosive	[2]
Oxidising Properties	No oxidising properties	[2], [5]
Migration potential in polymer	-	
Flash point	223ºC open cup	[2]
	232ºC	[4]
	215ºC	[5]
Auto flammability	380ºC	[2]
	330ºC	[5]
LogKow	9.24	[3]
Explosion limit	Lower = 1.8% (179.5ºC and 18.8 hPa)	[5]
	Upper = 2.4% (209.7ºC and 24.6 hPa)	

Emission Data

During production	-	

Exposure Data

Aquatic environment, incl. sediment	-	
Terrestrial environment	-	
Sewage treatment plant	-	
Working environment	Maximum number of potentially exposed workers: between 100 and 999 (including those of manufacturing, industrial processing and use)	[3]
Consumer goods	-	
Man exposed from environment	-	
”Secondary poisoning”	-	

Atmosphere	-
Dermal	-

Toxicological data

Observations in humans	-

Acute toxicity

Oral	LD_{50} > 5000 mg/kg (rat)	[2]
	LD_{50} > 10,000 mg/kg (rat)	[3]
Dermal	LC_{50} > 3160 mg/kg (rabbit)	[3]
Inhalation	-	
Other routes	-	
Skin irritation	Not irritating (rabbit)	[2]
Eye irritation	Not irritating (rabbit)	[2]
Irritation of respiratory tract	-	
Skin sensitisation	Not sensitisation (human)	[5]

Subchronic and Chronic Toxicity

Oral	Rat, 13 weeks repeat dose	[2], [3]
	NOAEL = 500 mg/kg	
	NOEL = 500 mg/kg per day (male)	
	NOEL = 150 mg/kg per day (female)	
	Dog, 13 weeks repeat dose	[2]
	Hepatocytic hypertrophy and aspermatogenesis in top dose animals.	

	Dog, 13 weeks repeat dose	[3]
	LOAEL = 822 – 1644 mg/kg per day	
	NOAEL = 274 mg/kg per day	
Inhalation	-	
Dermal	-	

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	S.typhimurium (metabolic activator (S9))	[2]
	The test substance showed no evidence of mutagenic activity when tested in this bacterial system with and without activation.	
	Cytotoxic conc.: Not cytotoxic up to 5000 µg/plate	
	Genotoxic effects: Negative with and without S-9 activation	
	Mouse lymphoma (metabolic activator (S9))	[2], [3]
	Negative up to 100µl/ml	
	S.typhimurium (metabolic activator (S9))	[2]
	The test substance showed no evidence of mutagenic activity when tested in this bacterial system with and without activation.	
	Cytotoxic conc.: Not cytotoxic up to 1000 µg/plate	
	Genotoxic effects: Negative with and without S-9 activation	
	S.typhimurium (metabolic activator (S9))	[3]
	Cytotoxic conc.: Not cytotoxic up to 1000 µg/plate	
	Genotoxic effects: Negative with and without S-9 activation	
Chromosome Abnormalities	-	
Other Genotoxic Effects	-	
Carcinogenicity	-	

Diisononyl adipate, DINA

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	NOAEL = 400 mg/kg per day	[3]
	LOAEL = 800 mg/kg per day	
Teratogenicity	-	
Developmental toxicity	NOAEL = 400 mg/kg per day (maternal)	[3]
	LOAEL = 800 mg/kg per day (maternal)	
	NOAEL = 200-400 mg/kg per day (offspring)	

Toxicokinetics

Toxicokinetics	-	

Ecotoxicity Data

Algae	EC_{50} > 100 mg/l (Green algae, 72h)	[5]
Daphnia magna	NOEC > 100 mg/l (daphnia magna, 21 days)	[2]
	EC_{50} > 100 mg/l (daphnia magna, 48h)	[5]
Other aquatic organisms	-	
Fish (acute)	LC_{50} > 500 mg/l (Leuciscus idus, 96h)	[2]
	NOEC = 2.2 x 10^{-4} mg/l (Oncorhynchus mykiss, 96h)	[3]
Bacteria	EC_{10} > 10,000 (Pseudomons putida, 30 min)	[2]
	EC_{50} > 10,000 (Pseudomons putida, 30 min)	
	EC_{90} > 10,000 (Pseudomons putida, 30 min)	
	TKG > 10,000 (Pseudomons putida, 30 min)	
Terrestrial organisms	-	
Activated sludge	EC_{20} > 1000 mg/l (Sludge, 30 min)	[2]

Diisononyl adipate, DINA

Environmental Fate

BCF	1102 – 2031 (21 days)	[2]
	11,000 (35 days at 15ºC)	[2]
	3.2	[3]
Aerobic biodegradation	82% after 28 days	[2]
	Readily biodegradable	
	> 90% after 28 days	[2]
	Readily biodegradable	
	73% after 28 days	[3]
	Redily biodegradable	
Anaerobic biodegradation	-	
Photodegradation	$T_{½}$ = 0.4 days	[3]
Metabolic pathway	-	
Mobility	-	
Stability in water	4.6 years at pH 7	[3]
	169 days at pH 8	

Conclusion

Physical-chemical	-
Emission	-
Exposure	-
Health	-
Environment	-

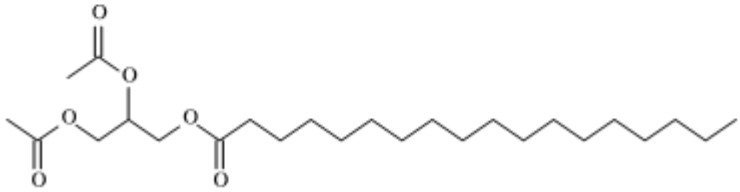
References

Diisononyl adipate, DINA

1	ESIS
2	IUCLID dataset
3	EPA HPV programme
4	MITI
5	MSDS BASF

12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester)

Identification of the substance

CAS No.	36150-63-3 (COMGHA)	[1]
	330198-91-9 (Component A, ca. 84%)	
	33599-07-4 (Component B, ca. 10%)	
EINECS No.	451-530-8	[2]
EINECS Name	-	
Synonyms	COMGHA	
	Grinsted soft'n'safe	
	Acetylated monoglycerides of fully hydrogenated castor oil.	
	Acetic acid esters of monoglycerides of fully hydrogenated castor oil.	
	12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)-propylester	
Molecular Formula	$C_{27}H_{48}O_8$ (Component A)	[1]
	$C_{25}H46O_6$ (Component B)	
Structural Formula	A  B 	
Major Uses	Plasticizer	[1]

12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester)

IUCLID	-
EU classification	

Physico-chemical Characteristics

Physical Form	Greasy substance with a slightly acid odour	[4]
Molecular Weight (g/mole)	500.7 (Component A)	[1]
	442.6 (Component B)	
Melting Point/range (°C)	- 21.5ºC	[1]
Boiling Point/range (°C)	300ºC at 1 atm (decomposition)	[1]
Decomposition Temperature (°C)	-	
Vapour Pressure (mm Hg at °C)	< 2.8 x 10^{-4} Pa at 100ºC [2.1 x 10^{-6} mmHg]	[1]
	1.1 x 10^{-7} Pa at 25ºC [8.25 x 10^{-10} mmHg]	[3]
	4.8 x 10^{-8} Pa at 20ºC [3.6 x 10^{-10} mmHg]	
Density (g/cm^3 at °C)	1.0030 at 20ºC	[3]
Vapour Density (air=1)	-	
Henry's Law constant (atm/m^3/mol at °C)	-	
Solubility (mg/l water at °C)	0.007 g/l [7 mg/l]	[1]
	< 0.33 mg/l at 20ºC pH ca. 6.8	[3]
Partition Coefficient (log P_{ow})	6.42	[4]
pK_a	-	
Flammability	-	
Explosivity	-	
Oxidising Properties	-	
Migration potential in polymer	-	
Log Kow	6.4	[1]

12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester)

Koc	Immobile and remains preferably in soil	[3]
Flash point	244ºC at 101.3 kPa	[3]
Auto ignition tempetature	ca 370ºC	[3]

Emission Data

During production	-

Exposure Data

Aquatic environment, incl. sediment	-
Terrestrial environment	-
Sewage treatment plant	-
Working environment	-
Consumer goods	-
Man exposed from environment	-
”Secondary poisoning”	-
Atmosphere	-
Dermal	-

Toxicological data

Observations in humans	-

Acute toxicity

Oral	LC_{50} > 2000 mg/kg (rat)	[3]
Dermal	-	

12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester)

Inhalation	-	
Other routes	-	
Skin irritation	Not irritating (rabbit)	[3]
Eye irritation	Not irritating (rabbit)	[3]
Irritation of respiratory tract	-	
Skin sensitisation	Not a skin sensitizer	[3]

Subchronic and Chronic Toxicity

Oral	Rat, 2-weeks	[3]
	No signs of toxicity (3%, 7.5% of the diet)	
	Rat, 90 days (extream dose)	[3]
	NOAEL < 3 ml/kg per day	
	Rat, 90 days (adequate dose)	[3]
	NOAEL = 5000 mg/kg per day	
Inhalation	-	
Dermal	-	
Metabolism	Hydrolysis of the compound is incomplete and that a proportion of the administered dose passes through the gastrointestinal tract and is excreted unchanged.	[1]
	No significant absorption across gastrointestinal epithelium	[3]

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	Not mutagenic in the Ames test	[3]
	Not clastrogenic in the in vitro mammalian cytogenetic test	[3]

12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester)

Chromosome Abnormalities	Not mutagenic in the in vitro mammalian cell gene mutation test	[3]
Other Genotoxic Effects	-	
Carcinogenicity	-	

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	-
Teratogenicity	-
Other Toxicity Studies	-

Toxicokinetics

Toxicokinetics	-

Ecotoxicity Data

Algae	EC_{50} = 106 mg/l (72h)	[3]
	70-95% loss in concentration over test period	
Invetebrates	EC_{50} = 0.92 mg/l (daphnia magna, 48h)	[3]
Other aquatic organisms	-	
Fish	LC_{100} = 0.28 mg/l (zebra fish, 96h)	[3]
Bacteria	-	
Terrestrial organisms	-	
Activated sludge	EC_{20} > 143 mg/l	[3]
	EC_{50} > 143 mg/l	
	No inhibitory effect of respiration rate	

Environmental Fate

12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester)

BCF	-	
Aerobic biodegradation	98% after 28 days	[3]
	Ready biodegradable	
Anaerobic biodegradation	-	
Metabolic pathway	-	
Mobility	-	

Conclusion

Physical-chemical	-
Emission	-
Exposure	-
Health	-
Environment	-

References

1 SCENIHR

2 ESIS

3 Danisco

4 MSDS Danisco

Final Report on the Safety Assessment of Triacetin[1]

Triacetin, also known as Glyceryl Triacetate, is reported to function as a cosmetic biocide, plasticizer, and solvent in cosmetic formulations, at concentrations ranging from 0.8% to 4.0%. It is a commonly used carrier for flavors and fragrances. Triacetin was affirmed as a generally recognized as safe (GRAS) human food ingredient by the Food and Drug Administration (FDA). Triacetin was not toxic to animals in acute oral or dermal exposures, nor was it toxic in short-term inhalation or parenteral studies, and subchronic feeding and inhalation studies. Triacetin was, at most, slightly irritating to guinea pig skin. However, in one study, it caused erythema, slight edema, alopecia, and desquamation, and did cause some irritation in rabbit eyes. Triacetin was not sensitizing in guinea pigs. Triacetin was not an irritant or a sensitizer in a clinical maximization study, and only very mild reactions were seen in a Duhring-chamber test using a 50% dilution. In humans, Triacetin reportedly has caused ocular irritation but no injury. Triacetin was not mutagenic. Although there were no available reproductive and developmental toxicity data, Triacetin was quickly metabolized to glycerol and acetic acid and these chemicals were not developmental toxins. Reports of 1,2-glyceryl diesters, which may be present in Triacetin, affecting cell growth and proliferation raised the possibility of hyperplasia and/or tumor promotion. The Cosmetic Ingredient Review (CIR) Expert Panel concluded, however, that the effects of 1,2-glyceryl diesters on cell growth and proliferation require longer ester chains on the glycerin backbone than are present when acetic acid is esterified with glycerin, as in Triacetin. On the basis of the available information, the CIR Expert Panel concluded that Triacetin is safe as used in cosmetic formulations.

INTRODUCTION

This report reviews the safety of Triacetin, an ingredient that is reported to function as a cosmetic biocide, plasticizer, and solvent in cosmetic formulations (Pepe, Wenninger, and McEwen 2002).

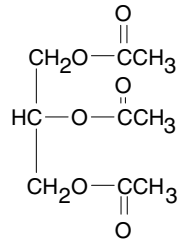
Received 4 December 2002; accepted 18 March 2003.

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. This report was prepared by Monice Zondlo Fiume, former Scientific Analyst/Report Management Coordinator, Address correspondence to F. Alan Andersen, Cosmetic Ingredient Review Director, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

CHEMISTRY

Definition and Structure

Triacetin (CAS no. 102-76-1) is the triester of glycerin and acetic acid that conforms to the formula (Pepe, Wenninger, and McEwen 2002):



Triacetin is also known as Glyceryl Triacetate (Pepe, Wenninger, and McEwen 2002; National Academy of Science [NAS] 1996; United States Pharmacopeial Convention, Inc. [USP] 1995; Unichema Chemie B.V. 1994; Lewis 1993a; Budavari 1989); Glycerol Triacetate (Unichema Chemie B.V. 1994; Lide 1993; Lewis 1993a); Glycerin Triacetate (Unichema Chemie B.V. 1994); Glycerine Triacetate (Lewis 1993a); Triacetyl Glycerine (Unichema Chemie, B.V. 1994; Budavari 1989); Acetin, Tri-; 1,2,3-Triacetoxypropane (Unichema Chemie B.V. 1994); 1,2,3-Propanetriol Triacetate (Pepe, Wenninger, and McEwen 2002; USP 1995; Unichema Chemie B.V. 1994; Lewis 1993a; Budavari 1989); 1,2,3-Propanetriyl Triacetate (ChemID 1998); and Acetic, 1,2,3-Propanetriyl Ester (Pepe, Wenninger, and McEwen 2002; Unichema Chemie B.V. 1994).

Physical and Chemical Properties

Physical and chemical properties are described in Table 1. Published data on the ultraviolet radiation absorbance of Triacetin were not found.

Manufacture and Production

Triacetin is derived by the action of acetic acid on glycerol, with vacuum distillation used as the method of purification (Lewis 1993b). It can also be prepared by esterification of glycerin with acetic anhydride (Gennaro 1990), by the acetylation of glycerol, by the reaction of oxygen with a liquid-phase mixture of allyl acetate and acetic acid using bromide as a catalyst (Budavari 1989), and from glycerin and acetic anhydride

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TABLE 1
Chemical and physical properties of Triacetin

		Reference
Physical Characterization	Colorless, oily liquid with a slight fatty odor and taste	Lewis 1993a
	Colorless, somewhat oily liquid having a slight, fatty odor and a bitter taste	NAS 1996; Budavari 1989
Empirical formula	$C_9H_{14}O_6$	Pepe, Wenninger, and McEwen 2002
Molecular weight	218.21	NAS 1996
	218.20	Budavari 1989; Grant 1972
Melting point	−78°C	Lewis 1993a; Budavari 1989
Boiling point	258°C	Lewis 1993a; Grant 1972
	258°C–260°C	Lewis 1993b
	260°C	Gennaro 1990
	258°C–260°C; 172°C (bp_{40})	Budavari 1989
Solubility	Soluble in water; miscible with alcohol, ether, and chloroform	NAS 1996; Lewis 1993a
	Soluble in acetone, ethanol, benzene, and chloroform	Unichema Chemie B.V. 1994
	Soluble in alcohol, ether, acetone, benzene, and chloroform	Lide 1993
	Slightly soluble in water; very soluble in alcohol, ether, and other organic solvents	Lewis 1993b
	Soluble in 14 parts water and in alcohol, chloroform, and ether	Gennaro 1990
	Soluble in 14 parts water; miscible with alcohol, ether, chloroform; slightly soluble in carbon disulfide	Budavari 1989
log $P_{o/w}$	0.1, 0.368	Unichema Chemie B.V. 1994
Specific gravity	1.154–1.158 (food-grade)	NAS 1996
	1.152–1.158 (USP-grade)	USP 1995
	1.1596 (20/4)	Lide 1993
	1.161	Lewis 1993a; Grant 1972
	1.160	Lewis 1993b
	1.1562 (d_4^{25}); 1.1596 (d_4^{20}); 1.163 (d_{20}^{20})	Budavari 1989
Index of refraction	1.429–1.431 (25°C) (food-grade)	NAS 1996
	1.429–1.430 (USP-grade)	USP 1995
	1.4301 (20°C)	Lide 1993
	1.4312 (20°C)	Lewis 1993b
	1.4307 (n_D^{20})	Budavari 1989
Stability	Combustible	Lewis 1993b
Reactivity	A polar substance that is easily hydrolyzed with the liberation of acetic acid	Unichema International 1996
Flash point	280°F (COC)	Lewis 1993a; Sax 1979
	300°F	Lewis 1993b
Autoignition temperature	812°F	Lewis 1993a; Sax 1979

using phosphoric acid or zinc chloride as the condensing agent (Opdyke 1978).

Triacetin occurs naturally as an oil from cod-liver oil, butter, and other fats (Grant 1972).

Analytical Methods

Triacetin has been determined using gas chromatography (Ogawa et al. 1988, 1992; Uematsu et al. 1997), thin layer chromatography, and infrared spectroscopy (Ogawa et al. 1992).

Impurities

Triacetin contains trace moisture and acetic acid (Unichema Chemie B.V. 1994). Food-grade Triacetin must be at least 98.5% $C_9H_{14}O_6$, and it must not contain >5 mg/kg heavy metals (as Pb) or >0.2% water (NAS 1996). USP-grade Triacetin must contain not less than 97.0% and not greater than 100.5% $C_9H_{14}O_6$, calculated on the anhydrous basis (USP 1994).

USE

Cosmetic

Triacetin is reported to function as a cosmetic biocide, plasticizer, and solvent in cosmetic formulations (Pepe, Wenninger, and McEwen 2002). It is a commonly used carrier for flavors and fragrances (Unichema International 1996).

As shown in Table 2, the product formulation data reported by the cosmetics industry to the Food and Drug Administration (FDA) in 1998 indicate that Triacetin was used in a total of 13 cosmetic formulations. Concentration of use data submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) indicated that Triacetin was used in a number of product types at concentrations of 0.8–4% (CTFA 1999).

According to the Ministry of Health, Labor and Welfare (MHLW) in Japan, Triacetin is not restricted in any manner in cosmetic formulations (MHLW 2001).

Triacetin does not appear in Annex II (list of substances that must not form part of the composition of cosmetic products) or Annex III (list of substances that cosmetic products must not contain except subject to the restrictions and conditions laid down) of the *Cosmetics Directive of the European Union* (European Commission 2003).

TABLE 2
Triacetin use in cosmetic formulations

Product category (total no. formulations in category) (FDA 1998)	Total no. containing ingredient (FDA 1998)	Concentration of use (%) (CTFA 1999)
Eyeliner (514)	2	1
Mascara (167)	2	2
Tonics, dressings, and other hair-grooming aids (549)	—	0.8
Makeup bases (132)	6	1
Other makeup preparations (135)	3	—
Basecoats and undercoats (manicuring preps) (48)	—	1
Nail polish and enamel (80)	—	1
Nail polish and enamel removers (34)	—	4
1998 Triacetin use	13	0.8–4

Noncosmetic

Triacetin is a generally recognized as safe (GRAS) ingredient (21 CFR 184.1901) by the FDA. It is used in foods as a flavoring agent and adjuvant, formulation aid, humectant, and solvent and vehicle; it has no limitations other than good manufacturing practice. In its determination that Triacetin was a GRAS ingredient (FDA 1983, 1989), FDA relied upon an evaluation on glycerin and glycerides prepared by the Federation of American Societies for Experimental Biology (FASEB) that included safety-test data on Triacetin. This FASEB evaluation found that Triacetin was without toxic effects in long-term feeding studies in rats that used doses that were higher than those to which consumers would be exposed (FASEB 1975). In addition, FDA contracted with a laborartory to perform a mutagenic evaluation of Triacetin, the results of which demonstrated no mutagenic activity (Litton Bionetics, Inc. 1976).

Triacetin is used in pharmaceuticals as a hydrophilic plasticizer in polymeric coatings of capsules, tablets, beads, and granules, with typical concentrations of 10% to 35% *w*/*w* (Unichema International 1996). Triacetin is used as an antifungal drug for treatment of superficial fungus infections of the skin (Gennaro 1990). However, data are inadequate to establish general recognition of the safety or effectiveness of Triacetin as an over-the-counter topical antifungal drug (21 CFR 310.545). Triacetin has been used with prostaglandin E_2 (PGE_2) to form a gel used for preinduction cervical softening (Graves et al. 1985; Noah et al. 1985). According to Yalkowsky and Roseman (1979), Triacetin stabilized PGE.

Triacetin had wide use in foundry applications as a curing agent for phenol resins used in the manufacture of sand molds (Unichema International 1996). It is used as a cellulose acetate plasticizer in the manufacture of cigarette filters, a tobacco humidifier, a plasticizer for cellulose nitrate, and a solvent for basic dyes and in the manufacture of celluloid and photographic films, as well as in the paint, lacquer, and varnish industries (Unichema Chemie B.V. 1994). Triacetin is also used in removal of carbon dioxide from natural gas (Lewis 1993b). According to Budavari (1989), technical Triacetin (a mixture of mono-, di-, and small quantities of Triacetin) is used as a solvent for basic dyes, particularly induline dyes, and tannin in dyeing.

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

In an in vitro study by Stoughton (1970), the penetration of Triacetin into the corium of human skin was determined by topical application of Triacetin to the epidermis (which was later separated from the corium), and then measuring the antimicrobial activity. Using leg skin, a plastic cylinder was attached to the epidermis, and 0.01 cc Triacetin was applied for 20 to 24 h. The skin was then washed and the epidermis removed. Six-millimeter punches of the corium were taken and implanted on the culture medium, with the epidermal side in contact with the medium. When inhibition of growth around the corium

occurred, the radius of inhibition was measured. There was no average inhibition of positive responses with Triacetin cream. The researchers speculated that an antimicrobial agent may penetrate into the corium and not diffuse into the surrounding medium when assayed, and that this might give a false-negative report of its ability to penetrate the epidermis.

von Oettingen (1960) stated that Triacetin is absorbed from the gastrointestinal tract, but no experimental details were provided.

Pharmacological Effects

In a series of studies, the use of Triacetin in total parenteral nutrition was examined.

Six female mongrel dogs were used to determine the effect of Triacetin on serum phosphorus, calcium, and magnesium metabolism (Bailey, Heath, and Miles 1989). A 5% *v*/*v* aqueous solution of Triacetin was infused intravenously at a rate of 47 μmol/kg/min for 3 h. Arterial blood was sampled at 15 to 30-min intervals, and urine was collected during infusion. No significant changes in total serum calcium or phosphorus concentrations were observed; however, serum magnesium concentrations were statistically significantly decreased 90 min after the initiation of dosing and remained decreased until the end of the study. During Triacetin infusion, the plasma acetate concentration increased from 0.13 to 1.32 mmol/L at 30 min; the concentration gradually declined to ~1 mmol/L during the last hour of the study. No change was observed in the fractional excretion of calcium, magnesium, or phosphorus. The authors speculated that the decrease in serum magnesium was probably because of cellular uptake rather than accelerated excretion. Baseline blood pH was not significantly altered.

Bailey, Haymond, and Miles (1991) also used groups of female mongrel dogs to study the metabolic effects of isocaloric and hypercaloric infusions of 5% *v*/*v* aqueous Triacetin. A primed, continuous infusion of ~5 μmol/kg (0.3 μCi/kg/min) [^{13}C]-acetoacetate and ~1.0 μCi/kg (0.01 μCi/kg/min) [^{3}H]-glucose was continued for 6 h. Three hours after the start of the isotope infusion, dosing with Triacetin was started. Six animals were infused at a rate of 47 μmol/kg/min and seven were infused at a rate of 70 μmol/kg/min Triacetin for 3 h. Blood and breath samples were taken at 15 to 30-min intervals. A group of four animals was infused with 70 μmol/kg/min glycerol and used as the control for the hypercaloric infusion.

During isocaloric infusion of Triacetin, plasma acetate and free fatty acid concentrations were significantly increased at 30 and 60 min, respectively, and remained elevated. During hypercaloric infusion, plasma acetate concentration increased progressively throughout the study, whereas the plasma free fatty acid concentration did not change. Plasma pyruvate and lactate concentrations were significantly decreased after 30 and 90 min, respectively, and throughout the study with both isocaloric and hypercaloric infusion. The plasma insulin concentrations were modestly increased during both infusions. Plasma glucose concentration was significantly decreased during isocaloric Triacetin infusion; a slight but significant increase was observed with hypercaloric infusion. Glucose clearance decreased significantly in both groups during the last hour of Triacetin infusion. Plasma ketone body concentrations increased significantly by 60 min, and they remained elevated with isocaloric infusion and increased progressively with hypercaloric infusion of Triacetin; the increased concentrations were due to increased ketone body production. During the last hour of infusion, resting energy expenditure was significantly increased with isocaloric Triacetin (Bailey, Haymond, and Miles 1991).

In a study examining the effect of Triacetin on nitrogen balance, whole-body kinetics, and muscle and liver fractional protein synthetic rates, Bailey, Barker, and Karlstad (1992) infused male Sprague-Dawley rats with isovolemic, isocaloric, and isonitrogenous parenteral diets. Thirty percent of the nonprotein energy of the diets was lipid energy, and for groups of 6, 10, and 6 animals, the lipid energy was composed of 0%, 50%, and 90% Triacetin, respectively. No difference was observed in the plasma acetate concentration of animals that received Triacetin compared to those that did not. The liver weight was significantly decreased in the animals given Triacetin. Protein concentration in the liver and rectus muscle was similar for all three groups. Cumulative nitrogen balance was positive for all animals, and no significant difference in nitrogen balance was observed on days 6 and 7. Lipid composition had very little effect on plasma leucine kinetics. Also, fractional protein synthetic rates in the rectus muscle and liver were similar for all animals.

Further work by Bailey, Miles, and Haymond (1993) reported the effect of a 5% *v*/*v* aqueous solution of Triacetin on leucine metabolism using female mongrel dogs. A primed, continuous infusion of L-[1-^{14}C]-leucine was continued for 6 h. Three hours after the start of the isotope infusion, administration of Triacetin was started. Six animals were infused at a rate of 47 μmol/kg/min and seven were infused at a rate of 70 μmol/kg/min Triacetin for 3 h. Blood and breath samples were taken at 15 to 30-min intervals. A group of four animals was infused with 70 μmol/kg/min glycerol and a group of five animals was infused with saline; both were used as control groups. During the last hour of dosing, plasma acetate concentrations increased from 0.13 to 0.99 and from 0.10 to 11.8 for the animals infused with 47 and 70 μmol/kg/min Triacetin, respectively. Plasma glucose concentration decreased slightly but significantly for the animals given 47 μmol/kg/min Triacetin. Plasma leucine concentration decreased significantly in the animals given 70 μmol/kg/min Triacetin. Plasma α-ketoisocaproate concentration and specific activity increased with both doses. $^{14}CO_2$ excretion was increased with the low dose and decreased with the high dose of Triacetin.

The conclusion of this series of studies was that due to the water solubility, minimal effect on mineral metabolism, improved nitrogen balance, lack of toxicity, and favorable effects

on protein metabolism, Triacetin warranted further study as a parenteral nutrient.

Bleiberg et al. (1993) used mongrel dogs to determine the systemic, hindlimb, gut, hepatic, and renal uptake of acetate during infusion of a 5% *v*/*v* aqueous solution of Triacetin. A primed, continuous infusion of [1-^{14}C]-acetate was continued for 7 h with 10 animals. Three hours after the start of the tracer infusion, the animals were infused with Triacetin at a rate of 47 μmol/kg/min for 4 h. Blood and breath samples were taken at 15-min intervals for the last 30 min. Steady-state conditions were achieved in plasma acetate concentrations and specific activity and in expired $^{14}CO_2$. Plasma acetate concentrations were $\approx$1180, $\approx$935, $\approx$817, $\approx$752, and $\approx$473 μmol/L in the aorta, renal vein, portal vein, femoral vein, and hepatic vein, respectively. The acetate turnover rate during Triacetin infusion was 2214 μmol/min; systemic acetate turnover accounted for 68% of Triacetin-derived acetate. The researchers concluded that the majority of triacetin undergoes intravascular hydrolysis, and the majority of the resulting acetate is oxidized.

Lynch, Miles, and Bailey (1994) determined the metabolic effect of Triacetin on intestinal mucosa cells and plasma substrates in a 30-day feeding study in which male Sprague-Dawley rats were given a diet that contained Triacetin. Groups of eight animals were fed a diet in which 30% of the energy was supplied as lipids, and Triacetin composed either 0 or 95% of the lipids (long-chain triglyceride [LCT] or Triacetin group, respectively); the remainder of the lipid was a long-chain triglyceride. (In the Triacetin-containing feed, Triacetin composed 19% of the diet by weight.) A control group of eight animals was fed chow that supplied 5% of the energy as LCTs. Body weights and feed consumption were measured throughout the study.

At study termination, animals of the LCT group weighed more than the animals of the Triacetin or control groups. Feed consumption was not statistically significantly different between the Triacetin and LCT groups; however, during week 2 for the Triacetin group and weeks 2 to 4 for the LCT group, feed consumption was significantly greater than that of controls. No significant differences in lactate, ketone body, or glucose concentration were observed among the groups. Plasma pyruvate concentration in the Triacetin group was significantly decreased compared to the LCT group, and plasma free fatty acids were significantly decreased and the plasma triglyceride concentration was significantly increased in the Triacetin group compared to animals of the control and LCT groups. Total intestinal DNA, RNA, protein, and protein: DNA ratio were measured. No significant difference in mucosal protein concentration was observed in the jejunum and colon. Jejunal and colonic DNA content was significantly increased (and therefore protein: DNA ratio decreased), whereas jejunal RNA was significantly decreased in animals fed Triacetin. No significant differences in crypt depth or mean villus height were observed (Lynch, Miles, and Bailey 1994).

Lynch and Bailey (1995) fed groups of eight male Sprague-Dawley rats the diets described in the preceding paragraph for 30 days, and the effect on total adiposity, fat distribution, and body composition was determined. At study termination, animals of the LCT group weighed more than the animals in the Triacetin or control groups. Feed consumption was not significantly different between the Triacetin and LCT groups; however, the controls ate less than animals of the test groups. Also, energy intake was not significantly different between animals of the Triacetin and LCT groups, but it was significantly less in animals of the control group during weeks 2 to 4. Animals of the Triacetin group had the least adipose tissue mass (measured in three depots) compared to the other groups; animals in the LCT group had the greatest adipose tissue mass. Triacetin decreased adipocyte size, but total fat cell number did not differ among the groups.

ANIMAL TOXICOLOGY

Table 3 summarizes the acute toxicity findings as a function of the route of administration and animals used.

Acute Oral Toxicity

Gast (1963) stated that the oral LD_{50} of Triacetin for male and female mice was 1.8 and 1.1 g/kg, respectively, although study details were not provided.

The acute oral toxicity of Triacetin was determined using a group of 10 mice (Lawrence, Malik, and Autian 1974). The animals were given a single dose and observed for 7 days. The calculated oral LD_{50} for mice was 8.0 ml/kg.

Groups of five mice and five rats were used to determine the acute oral toxicity of Triacetin (Anstadt 1976). The dose ranges tested were 1.6 to 25.6 and 0.8 to 12.8 g/kg for mice and rats, respectively. The approximate LD_{50} was 3.2 to 6.4 g/kg for mice and 6.4 to 12.8 g/kg for rats.

Additional oral LD_{50} values were 3.2 to 6.1 g/kg for mice, 3.0 and $>$2.0 g/kg for rats, and $>$2.0 g/kg for rabbits (Unichema Chemie B.V. 1994).

Groups of eight Long-Evans rats were given as a continuous nasogastric infusion 462 kJ/kg of a diet containing either 16% or 32% Triacetin (Robertson et al. 1992). No adverse effects, such as diarrhea or change in normal activity, were observed.

Acute Dermal Toxicity

The acute dermal LD_{50} of Triacetin was determined using groups of five albino rabbits (Food and Drug Research Laboratories, Inc. 1976). A dose of 5 g/kg was applied to intact and abraded skin. The animals were observed for 7 days after dosing. None of the animals died. The dermal LD_{50} of Triacetin for rabbits was $>$5 g/kg. Additional dermal LD_{50} values were $>$20 ml/kg for guinea pigs and $>$2 g/kg for rabbits (Unichema Chemie B.V. 1994).

Acute Inhalation Toxicity

Unichema Chemie B.V. (1994) stated that, using five male and five female rats and a 4-h exposure, the LC_{50} of Triacetin was $>$1.721 mg/L. The particle size was not specified.

TABLE 3
Triacetin acute toxicity studies

Route of administration	Animal	LD_{50}	Reference
Oral	Mice (male)	1.8 g/kg	Gast 1963
Oral	Mice (female)	1.1 g/kg	Gast 1963
Oral	Mice (sex not given)	8 ml/kg	Lawrence, Malik, and Autian 1974
Oral	Mice (sex not given)	3.2–6.4 g/kg	Anstadt 1976
Oral	Mice (sex not given)	3.2–6.1 g/kg	Unichema Chemie B.V. 1994
Oral	Rats (sex not given)	6.4–12.8 g/kg	Anstadt 1976
Oral	Rats (sex not given)	3.0 and >2.0 g/kg	Unichema Chemie B.V. 1994
Oral	Rabbits (sex not given)	>2.0 g/kg	Unichema Chemie B.V. 1994
Dermal	Rabbits (sex not given)	>5 g/kg	Unichema Chemie B.V. 1994
Dermal	Rabbits (sex not given)	>2 g/kg	Unichema Chemie B.V. 1994
Dermal	Guinea pigs (sex not given)	>20 ml/kg	Unichema Chemie B.V. 1994
Parenteral	Mice (sex not given)	2.3 cc/kg	Li, Sah, and Anderson 1941
Parenteral	Mice (sex not given)	1.6 g/kg	Wretlind 1957
Parenteral	Mice (male)	1.7 g/kg	Gast 1963
Parenteral	Mice (female)	1.4 g/kg	Gast 1963
Parenteral	Mice (sex not given)	1.52 ml/kg	Lawrence, Malik, and Autian 1974
Parenteral	Mice (sex not given)	~0.8–1.6 g/kg	Anstadt 1976
Parenteral	Mice (sex not given)	1.2 ml/kg	Tarr, Sambandan, and Yalkowsky 1987
Parenteral	Rats (sex not given)	2.8 cc/kg	Li, Sah, and Anderson 1941
Parenteral	Rats (sex not given)	~0.8–1.6 g/kg	Anstadt 1976
Parenteral	Rabbits (sex not given)	0.75 ml/kg	Opdyke 1978
Parenteral	Guinea pigs (sex not given)	1.5 cc/kg	Lipschitz et al. 1942
Parenteral	Dogs (sex not given)	1.5–2.0 ml/kg	Opdyke 1978
Parenteral	Dogs (sex not given)	>70 μmol/kg/min	Bailey, Haymond, and Miles 1991
Inhalation	Rats (male and female)	>1.721 mg/L (LC_{50})	Unichema Chemie B.V. 1994

Acute Parenteral Toxicity

Li, Sah, and Anderson (1941) determined the subcutaneous (SC) LD_{50} of Triacetin for inbred white mice and inbred albino rats. Groups of 10 mice were dosed with 1.0 to 3.0 cc/kg and groups of 10 rats were dosed with 2.0 to 10.0 cc/kg aqueous Triacetin. The mice and rats were observed for 5 and 15 days after dosing, respectively. Two, 2, 7, and 10 mice of the 1.0-, 2.0-, 3.0-, and 3.5-cc/kg groups and 1, 6, and 10 rats of the 2.0-, 3.0-, and 4–10-cc/kg groups died, respectively. The animals usually died within 20 min to 3 or 4 h after injection. The authors noted marked depression, weakness, prostration, and in some animals, labored respiration just before death. Hemorrhagic areas in the lungs and some swelling of the convoluted tubules of the kidney were observed, along with hydropic degeneration and necrosis of the tubules in some areas. Also, the authors stated that the liver appeared to be congested. The SC LD_{50} was calculated to be 2.3 and 2.8 cc/kg for mice and rats, respectively. Diacetin was slightly less toxic than Triacetin, and the researchers concluded that the order of toxicity of the acetins appears to increase with the degree of acetylation.

Lipschitz et al. (1942) determined the intramuscular (IM) toxicity of Triacetin using guinea pigs. The lethal dose was 1.5 cc/kg, and dyspnea followed by death was observed. The researchers stated that the behavior of the animals suggested to them that the lethal effect might be attributable to the large amount of the acids liberated by relatively rapid hydrolysis.

Wretlind (1957) determined the intravenous (IV) LD_{50} of a 25% emulsion of Triacetin. Six groups of 10 animals were dosed with 1 to ~2.5 g/kg Triacetin. The IV LD_{50} of Triacetin was 1.6 g/kg for mice. Injection with Triacetin produced almost immediate convulsions, failure of the righting reflexes, and respiratory arrest.

von Oettingen (1960) reported a study using rabbits in which a SC injection of 0.8 g/kg of Triacetin given in three fractional doses caused a temporary stimulation of respiration with no narcosis. This author also reported that a slow IV injection of 1.48 g/kg Triacetin given in three fractional doses of 2.4 g/kg given in two fractional doses, and of 1.46 g/kg given as a single dose caused deep sleep, reduction of the tendon reflexes, and reduction of sensitivity to pain in rabbits. Respiration became slow and labored, and the authors stated that animals died from respiratory arrest.

Gast (1963) reported that the intraperitoneal (IP) LD_{50} of Triacetin for male and female mice was 1.7 and 1.4 g/kg, respectively. Based on a study using a limited number of adult rats,

this author also stated that the IP LD_{50} was 2.1 g/kg, although no study details were provided.

Lawrence, Malik, and Autian (1974) determined the acute IP toxicity of Triacetin using a group of 10 mice. The animals were given a single injection and observed for 7 days. The calculated IP LD_{50} for mice was 1.52 ml/kg.

Anstadt (1976) used groups of five mice and five rats to determine the acute IP toxicity of Triacetin. The dose ranges tested were 0.4 to 6.4 and 0.8 to 6.4 for mice and rats, respectively. The approximate LD_{50} was 0.8 to 1.6 g/kg for both mice and rats.

The IV LD_{50} of Triacetin for rabbits and dogs has been reported as 0.75 and 1.5 to 2.0 ml/kg, respectively (Opdyke 1978).

Tarr, Sambandan, and Yalkowsky (1987) determined the IV LD_{50} of an emulsion consisting of 50% Triacetin, 1.5% soy lecithin, 1.5% pluronic F68, and 2.0% ethyl oleate for Swiss-Webster mice. Groups of eight animals were dosed intravenously with 0.8 to 2.0 ml/kg of the emulsion. The IV LD_{50} for mice of the Triacetin emulsion was 1.2 ml/kg.

Bailey, Barker, and Karlstad (1991), in a study described earlier, infused female mongrel dogs with 47 or 70 μmol/kg/min Triacetin for 3 h, reported no evidence of acute toxicity.

Short-Term Oral Toxicity

According to Opdyke (1978), rats fed diets containing 55% Triacetin instead of fat gained weight.

Shapira et al. (1969) stated that, in 3-month feeding studies, rats tolerated up to 20% Triacetin without weight loss as compared to control values; but that diets containing 60% Triacetin were associated with a large loss in weight and considerable mortality. The authors stated that the type and quantity of protein present influenced weight gain.

Shapira, Vann, and Furst (1975) stated that, in groups of eight male Sprague-Dawley rats that were fed diets containing 30% Triacetin (and 30% glycerin or propylene glycol) as a starch substitute for 3 to 4 or 12 to 13 weeks, growth was relatively poor. Liver enlargement was observed in all animals.

In a study by Lynch, Miles, and Bailey (1994) described previously, the metabolic effect of Triacetin on intestinal mucosal cells and plasma substrates in male Sprague-Dawley rats was assessed. Rats were fed for 30 days a diet in which 28.5% of the total calories were supplied by Triacetin. No overt signs of toxicity were observed.

Short-Term Inhalation Toxicity

Anstadt (1976) stated that no toxicity was observed when rats were exposed to 8200 ppm Triacetin (saturated vapor) for 6 h per day for 5 days.

Unichema Chemie B.V. (1994) exposed a group of three rats to 250 ppm Triacetin for 6 h per day, 5 days per week, for 64 days. The no-observed-effect level (NOEL) was 250 ppm. Three rats were also exposed to 8271 ppm Triacetin for 6 h per day for 64 days. The NOEL was 8271 ppm.

Short-Term Parenteral Toxicity

Bailey, Barker, and Karlstad (1992) infused rats intravenously with 0%, 50%, or 90% (15.2 and 27.2 g/L) Triacetin for 7 days. No overt signs of toxicity were observed.

Subchronic Oral Toxicity

Blumenthal (1964) stated that Triacetin was not toxic to groups of five male rats fed a diet containing 1%, 2%, 4%, or 8% Triacetin for 16 weeks. A control group was fed basal diet.

Subchronic Inhalation Toxicity

Unichema International (1996) exposed rats to concentrations of 250 ppm Triacetin, which was produced by using heated vapor, 5 days per week for 13 weeks. No changes in liver and kidney weight, blood counts, or urinalysis were observed.

Chronic Toxicity

Published data on the chronic toxicity of Triacetin were not found.

Dermal Irritation

Anstadt (1976) determined the dermal irritation potential of Triacetin using two guinea pigs. Doses of 5 and 10 cc/kg were applied under an occlusive patch for 24 h. Slight erythema was observed. Occlusive patches with 5 to 20 cc/kg were tested using three animals. Slight edema and "1-3 erythema" were observed. Slight skin irritation was observed in the high dose animals.

Unichema Chemie B.V. (1994) stated that groups of three, three, and two guinea pigs were used to determine the irritation potential of Triacetin, but no study details were provided. At the end of a 14-day observation period, erythema, slight edema, alopecia, and desquamation were observed. They also stated that another study found no skin irritation in guinea pigs, but no details were available.

Other reports stated that Triacetin was not a skin irritant in guinea pigs (Unichema International 1996; Opdyke 1978) or rabbits (Unichema Chemie B.V. 1994).

Dermal Sensitization

Anstadt (1976) reported that no sensitization was observed using the "drop-on method" in a test using five guinea pigs.

Unichema Chemie B.V. (1994) evaluated the sensitization potential of Triacetin in acetone, dioxane, and guinea pig fat (7:2:1) using guinea pigs. The animals were initially dosed three times over 5 days and challenged after 1, 2, or 3 weeks. A vehicle and positive control were used. Triacetin was nonsensitizing.

Other reports found that Triacetin was not a sensitizer in guinea pigs (Unichema International 1996; Unichema Chemie B.V. 1994; Opdyke 1978).

Ocular Irritation

Li, Sah, and Anderson (1941) stated that application of 50% Triacetin (and diacetin) into the conjunctival sac of the eyes of rabbits resulted in "marked congestion and moderate edema."

In the original work of Draize, Woodard, and Calvery (1944), undiluted Triacetin, 0.1 ml, instilled into the conjunctival sac of the eyes of rabbits yielded average scores of 2.1 and 1.5/110 after 1 and 24 h, respectively.

Conquet et al. (1977) determined the ocular irritation potential of Triacetin using albino rabbits. In the first study, 0.1 ml undiluted Triacetin was instilled into the conjunctival sac of the eyes of six rabbits, and the eyes were scored according to the methods of Draize; corneal thickness was also measured. In a second study using groups of four rabbits, in which ocular tissue sampling was done, 0.1 ml was instilled into both eyes. A control group of four rabbits was not treated. Animals were killed after 2 or 24 h. In the Draize test, Triacetin had a total Draize score of 1 after 2 h (0 for the cornea and 0.7 for the conjunctiva); corneal thickness did not change. After 2 h, the corneal percentage of dry weight/wet weight was significantly decreased, but not after 24 h, compared to controls. No difference was observed for conjunctival percentage of dry weight/wet weight or Evan's blue concentration/dry weight at 2 or 24 h.

Unichema Chemie B.V. (1994) reported a study in which one drop of Triacetin was placed into the eyes of two rabbits; the eye of one rabbit was washed. The eyes were evaluated after 1, 24, and 48 h. Triacetin was slightly irritating. The authors stated that Triacetin, as tested using rabbits according to Organization for Economic Cooperation and Development (OECD) guidelines, was reported to be nonirritating.

In other reports, Triacetin, 100 μl, was a low-to-moderate irritant in rabbit eyes (Unichema International 1996). No damage was observed when a rabbit eye was irrigated continuously for 6 min (Unichema International 1996; Opdyke 1978).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Published data on the reproductive and developmental toxicity of Triacetin were not found.

GENOTOXICITY

In Vitro

Several laboratories have reported results from different versions of the Ames test for bacterial genotoxicity.

Litton Bionetics, Inc. (1976) evaluated the mutagenic potential of Triacetin in a plate test using *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 with and without metabolic activation. Test concentrations were 0.0013%, 0.00065%, and 0.000325% and the solvent was dimethyl sulfoxide (DMSO). A negative control (solvent) and appropriate positive controls were used and gave expected results. Triacetin was not mutagenic with or without metabolic activation.

The mutagenic potential of Triacetin was also evaluated in a suspension test with and without metabolic activation. Test concentrations were 0.0013%, 0.00065%, and 0.000325% with *S. typhimurium* strains TA1535, TA1537, and TA1538 and 1.25%, 2.5%, and 5.0% with *Saccharomyces cerevisiae* strain D4. DMSO was used as the solvent. Appropriate negative and positive controls were used and gave expected results. Triacetin was not mutagenic in the suspension tests with or without metabolic activation (Litton Bionetics, Inc. 1976).

Unichema Chemie B.V. (1994) reported that Triacetin was not mutagenic at 50 to 5000 μg/plate in an Ames test using *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 with and without metabolic activation.

In Vivo

The mutagenic potential of Triacetin was determined using adult *Drosophila melanogaster* (Efremova 1962). A dose of 0.2 to 0.3 mg Triacetin had a spontaneous mutation rate of approximately one mutation per 750 chromosomes.

CARCINOGENICITY

Published data on the carcinogenicity of Triacetin were not found.

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

A maximization test for undiluted Triacetin was completed using 33 subjects (Epstein 1976). Triacetin was applied under an occlusive patch to the volar aspect of the forearm for 48 h on 5 alternate days. Because a pretest indicated the Triacetin was not an irritant, the test site was pretreated for 24 h with 2% sodium lauryl sulfate (SLS) under an occlusive patch prior to application of the initial test patch. After a 10 to 14-day nontreatment period, challenge patches were applied to a previously unexposed site on the right side of the back. Prior to challenge, 2% SLS was applied for 30 min under an occlusive patch to the left side of the back. Additional SLS control patches and petrolatum patches were placed on the left and right sides, respectively, and used as controls. Undiluted Triacetin did not produce an irritant or sensitization reaction.

A Duhring-chamber test was performed using 20 subjects (Unichema Chemie B.V. 1994). Triacetin was applied as a 50% dilution for 24 h. No further details were available. The authors stated that only very mild skin reactions were observed.

Ocular Irritation

According to Unichema Chemie B.V. (1994), commercial Triacetin, which can contain diacetin and monoacetin, caused severe burning, pain, and much redness of the conjunctiva, but no injury. The authors claimed that diacetin causes considerably more discomfort than pure Triacetin.

Toxicity

The safety and effectiveness of a mucosa-adhesive polymer film used to alleviate acute radiation-induced oral mucositis and prevent infections was analyzed using 25 patients (Oguchi et al. 1998). The film contained 24 mg Triacetin, 600 mg hydroxypropylcellulose, 5 mg each of tetracaine hydrochloride, ofloxacine, and miconazole nitrate, 0.6 mg guaiazulene, and 100 ml ethyl alcohol. No acute or chronic adverse effects on the oral mucosa or gastrointestinal tracts were observed, and no allergic dermal reactions were reported. No changes in liver or renal function and no hematological toxicity were noted.

Unichema Chemie B.V. (1994) stated that Triacetin "appears to be innocuous when swallowed, inhaled or in contact with the skin, but may cause slight irritation to sensitive individuals."

SUMMARY

Triacetin, also known as Glyceryl Triacetate, is reported to function as a cosmetic biocide, plasticizer, and solvent in cosmetic formulations. In 1998, it was reported to FDA that Triacetin was used in a total of 13 cosmetic formulations. Industry reported that it was used at concentrations of 0.8% to 4%. Triacetin was affirmed as a GRAS human food ingredient by FDA.

The acute dermal LD_{50} of Triacetin was >5 g/kg for rabbits and >20 ml/kg for guinea pigs. The oral LD_{50} for mice has been reported as 1.8 and 1.1 g/kg for males and females, respectively, and as 3.2 to 6.4 g/kg; it has been calculated as 8.0 ml/kg. For rats, the oral LD_{50} was 6.4 to 12.8 g/kg. The inhalation LC_{50} was >1.721 mg/L for rats. The SC LD_{50} was 2.3 cc/kg for mice and 2.8 cc/kg for rats. For mice, the IV LD_{50} values of 25% and 50% emulsions of Triacetin were 1.6 g/kg and 1.2 ml/kg, respectively. For rabbits, the IV LD_{50} of Triacetin was 0.75, and for dogs, it was 1.5 to 2.0 ml/kg. The IP LD_{50} for Triacetin in mice was determined to be 1.7 and 1.4 g/kg for males and females, respectively, and 0.8 to 1.6 g/kg; it was also calculated as 1.52 ml/kg for mice. The IP LD_{50} for rats was 2.1 g/kg; in another study, it ranged from 0.8 to 1.6 g/kg. The IM lethal dose was 1.5 cc/kg for guinea pigs.

In short-term feeding studies, Triacetin affected weight gain. Triacetin was not toxic in short-term studies when administered via inhalation or parenterally or in subchronic studies when administered via feed or inhalation.

Triacetin was, at most, slightly irritating to guinea pig skin. However, in one study, it caused erythema, slight edema, alopecia, and desquamation. Triacetin was not sensitizing in guinea pigs; however, test concentrations were not stated. Triacetin caused some irritation in rabbit eyes.

Triacetin, with and without metabolic activation, was not mutagenic in the Ames assay or a suspension test. It was also not mutagenic in an in vivo assay using *Drosophila*.

Triacetin (test concentrations not provided) was not an irritant or a sensitizer in a clinical maximization study, and only very mild reactions were seen in a Duhring-chamber test using a 50% dilution. In humans, commercial Triacetin has caused ocular irritation but no injury.

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel reviewed the safety of Triacetin for use as a cosmetic ingredient. The Expert Panel considered the FDA affirmation of glycerides, including Triacetin, as a GRAS human food ingredients to be supportive of the overall safety of this ingredient.

The Expert Panel did recognize that reproductive and developmental toxicity data on Triacetin are absent from the report. Because Triacetin is thought to be hydrolyzed to glycerol and acetic acid and these chemicals are not developmental toxins, the Expert Panel concluded that the use of Triacetin in cosmetics does not present a risk of reproductive or developmental toxicity.

The Expert Panel also noted that there are reports indicating that 1,2-glyceryl diesters (also known as 1,2-diacylglycerols) can affect cell growth and proliferation, raising the possibility of hyperplasia and/or tumor promotion. This was an issue for discussion because, although Triacetin is a glyceryl triester, it is recognized that there would be some small amounts of glyceryl diesters present, some of which could be 1,2-glyceryl diesters. The Panel concluded, however, that the effects of 1,2-glyceryl diesters on cell growth and proliferation require ester chains longer than two carbon atoms on the glycerin backbone. Thus, any glyceryl 1,2-diacetyl esters present in Triacetin would be inactive in hyperplasia and tumor promotion.

CONCLUSION

On the basis of the animal and clinical data included in this report, the CIR Expert Panel concludes that Triacetin is safe as used in cosmetic formulations.

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Draft Screening Assessment

Esters Group

Environment and Climate Change Canada
Health Canada

March 2022

Synopsis

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of 14 of 16 substances referred to collectively under the Chemicals Management Plan (CMP) as the Esters Group. These 14 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns. Two of the 16 substances were determined to be of low concern through other approaches, and the decisions for these substances are provided in a separate report.[1] Accordingly, this screening assessment addresses the 14 substances listed in the table below, which will hereinafter be referred to as the Esters Group. The Chemical Abstracts Service Registry Numbers (CAS RN[2]), their *Domestic Substances List* (DSL) names and their common names are listed in the table below.

Substances in the Esters Group

CAS RN	DSL name	Common name
79-20-9[a]	Acetic acid, methyl ester	Methyl acetate
102-76-1	1,2,3-Propanetriol, triacetate	Triacetin
106-70-7 [a]	Hexanoic acid, methyl ester	Methyl hexanoate
109-60-4	Acetic acid, propyl ester	Propyl acetate
110-19-0	Acetic acid, 2-methylpropyl ester	Isobutyl acetate
111-82-0	Dodecanoic acid, methyl ester	Methyl dodecanoate
577-11-7	Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt	Docusate sodium
623-42-7[a]	Butanoic acid, methyl ester	Methyl butanoate
1119-40-0	Pentanedioic acid, dimethyl ester	Dimethyl glutarate
3234-85-3	Tetradecanoic acid, tetradecyl ester	Tetradecyl tetradecanoate

[1] Conclusions for the substances bearing CAS RNs 111-55-7 and 122-79-2 are provided in the Substances Identified as Being of Low Concern using the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Screening Assessment.

[2] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society, and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior written permission of the American Chemical Society.

CAS RN	DSL name	Common name
6846-50-0	Propanoic acid, 2-methyl-, 2,2-dimethyl-1-(1-methylethyl)-1,3-propanediyl ester	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate
25265-77-4	Propanoic acid, 2-methyl-, monoester with 2,2,4-trimethyl-1,3-pentanediol	Texanol
68990-53-4[b]	Glycerides, C14-22 mono-	C14-22 monoglycerides
70657-70-4[a]	1-Propanol, 2-methoxy-, acetate	2-Methoxypropyl acetate

[a] This substance was not identified under subsection 73(1) of CEPA but was included in this assessment as it was considered a priority on the basis of other human health concerns.

[b] This CAS RN is a UVCB (unknown or variable composition, complex reaction products, or biological materials).

According to information submitted in response to CEPA section 71 surveys, 12 of the 14 substances were reported to be manufactured or imported in Canada in 2009 or 2011. Methyl acetate, isobutyl acetate, dimethyl glutarate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate and docusate sodium were reported to be manufactured in Canada at volumes between 100 kg and 10 000 kg, whereas triacetin was reported to be manufactured between 10 000 kg and 100 000 kg. Reported import volumes of the substances in the Esters Group ranged from approximately 5 000 kg to more than 3 000 000 kg. Methyl hexanoate and methyl butanoate were not reported to be imported or manufactured above reporting threshold values in 2011.

Seven of the 14 substances in the Esters Group (methyl acetate, triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate and methyl butanoate) are naturally occurring in various fruits or plants. Several substances in the Esters Group are primarily used as solvents, including methyl acetate, propyl acetate, isobutyl acetate, methyl dodecanoate, dimethyl glutarate, triacetin, and 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. Other primary uses include as plasticizers (triacetin, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate) or as skin conditioning agents (tetradecyl tetradecanoate). Most of the substances in the Esters Group are used in a range of industrial and commercial products and are also used in products available to consumers, including cosmetics, natural health products, prescription and/or non-prescription drugs, as well as in paints, adhesives, air fresheners, paint removers, fiberglass repair products, and concrete crack repair products. Methyl acetate, triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate and methyl butanoate may be used as food flavouring agents. Triacetin and docusate sodium are permitted food additives in Canada. C14-22 monoglycerides is included with the substances monoglycerides or mono- and di-glycerides, which are also permitted food additives in Canada.

The ecological risks of the substances in the Esters Group were characterized using the ecological risk classification of organic substances (ERC), which is a risk-based approach that employs multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are established based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Metrics considered in the exposure profiles include

potential emission rate, overall persistence and long-range transport potential. A risk matrix is used to assign a low, moderate or high level of potential concern for substances on the basis of their hazard and exposure profiles. Based on the outcome of the ERC analysis, substances in the Esters Group are considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from the substances in the Esters Group. It is proposed to conclude that methyl acetate, triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

With respect to human health, 8 of the 14 substances in the Esters Group were considered to be of low hazard potential, namely triacetin, propyl acetate, isobutyl acetate, methyl dodecanoate, dimethyl glutarate, tetradecyl tetradecanoate, texanol, and C14-22 monoglycerides. Risk to human health for these substances is therefore considered to be low.

Developmental toxicity is a potential critical effect of methyl acetate due to the rapid hydrolysis of the substance to methanol. Potential developmental effects of methanol were reviewed in the draft screening assessment for the Alcohols Group under the CMP and were taken into consideration in the characterization of risk to human health from exposure to methyl acetate. The predominant routes of exposure to methyl acetate for the general population are expected to be through natural occurrence in food and indoor air and through the use of various products containing the substance including nail products, cleaning products, automotive products (e.g., aerosol paints, tire cleaners), adhesives (e.g., construction adhesives, aerosol adhesives for fabric and tube glues), adhesive removers, lubricants, paint strippers or removers (referred to as paint removers in this document), and floor coatings. On the basis of comparisons of the levels of exposure to methyl acetate from environmental media and food as well as through the use of products available to consumers outlined above (excluding paint removers and aerosol adhesives) with established reference levels for methanol that were adjusted for exposure to methyl acetate, potential risk to human health is expected to be low. Methanol reference levels of exposure were used because methanol is a hydrolysis product of methyl acetate and because no reference levels currently exist for methyl acetate. Use of paint remover products and aerosol adhesives containing methyl acetate resulted in estimates of exposure to methyl acetate that were higher than established reference concentrations for methanol (when adjusted for exposure to methyl acetate), suggesting a potential risk to human health.

Following absorption, methyl hexanoate and methyl butanoate are expected to undergo hydrolysis to form their respective carboxylic acids (i.e., hexanoic acid and *n*-butyric acid, respectively) and methanol.

Developmental toxicity is a potential critical effect of methyl hexanoate and methyl butanoate due to the hydrolysis of these substances to form methanol.

Exposure of the general population to methyl hexanoate and methyl butanoate may occur via indoor air or use as a food flavouring agent. Methyl hexanoate is also found in nail products. On the basis of comparisons of the levels of exposure to methyl hexanoate and methyl butanoate with established reference levels for methanol (with methanol reference values adjusted for exposure to methyl hexanoate and methyl butanoate, respectively), the potential risk to human health is expected to be low. Methanol reference levels were used because methanol is a hydrolysis product of both methyl hexanoate and methyl butanoate and because no reference levels currently exist for the aforementioned substances.

The critical effect of 2-methoxypropyl acetate is considered to be developmental toxicity. Potential sources of exposure to 2-methoxypropyl acetate for the general population are expected to be air and water, and the use of products such as cosmetics, aerosol paints or putty fillers. The margins of exposure between estimated exposure to 2-methoxypropyl acetate and critical effect levels are considered adequate to address uncertainties in the health effects and exposure datasets.

The available health effects information on 2,2,4-trimethyl-1,3-pentanediol diisobutyrate indicates potential effects on the reproductive system. Sources of exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate for the general population are expected to occur predominantly via indoor air and the use of various products containing the substance, including nail products, cosmetic adhesives, natural health products, aerosol primer, pool paint, hobby paints, fiberglass repair products, and concrete crack repair products. Oral exposure of children to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate may also result from its migration from baby bottles made from materials used as substitutes for polycarbonate and plastic toys. The margins of exposure between critical effects and estimates of exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are considered adequate to account for uncertainties in the health effects and exposure datasets.

Docusate sodium was reviewed in the United States Environmental Protection Agency (US EPA) screening-level hazard characterization of the sulfosuccinates category in 2009, and that review informs the health effects characterization in this assessment. Critical effects following subchronic oral exposures to docusate sodium were site-of-contact effects on the gastrointestinal tract and decrease in body weight gain observed in rats. Repeated oral exposure to docusate sodium in rats was also associated with developmental effects, but only in the presence of maternal toxicity. Sources of exposure to docusate sodium for the general population are expected to be through its use as a permitted food additive and from the use of products containing the substance, including cosmetics, natural health products, prescription and/or non-prescription drugs,

cleaning products, wallpaper paste activator and hardener products. The margins of exposure between estimated exposure to docusate sodium and critical effects level are considered adequate to address uncertainties in the health effects and exposure datasets.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that methyl acetate meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed to conclude that methyl acetate meets one or more of the criteria set out in section 64 of CEPA.

It is also proposed to conclude that triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet any of the criteria set out in section 64 of CEPA.

It is also proposed that methyl acetate meets the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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1. Introduction

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment of 14 of 16 substances, referred to collectively under the Chemicals Management Plan (CMP) as the Esters Group, to determine whether these 14 substances present or may present a risk to the environment or to human health. These 14 substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns (ECCC, HC [modified 2017]).

The other 2 substances (CAS RN[3] 111-55-7, 1,2-ethanediol, diacetate; CAS RN 122-79-2, acetic acid, phenyl ester) were considered in the Ecological Risk Classification of Organic Substances (ERC) and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Science Approach Documents (ECCC 2016a; Health Canada 2016), and were identified as being of low concern to both human health and the environment. As such, they are not further addressed in this report. Conclusions for these 2 substances are provided in the Substances Identified as Being of Low Concern Using the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Screening Assessment (ECCC, HC 2018). The 14 substances addressed in this screening assessment will hereinafter be referred to as the Esters Group.

The ecological risks of substances in the Esters Group were characterized using the ERC approach (ECCC 2016a). The ERC describes the hazard of a substance using key metrics including mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity, and considers the possible exposure of organisms in the aquatic and terrestrial environments on the basis of factors including potential emission rates, overall persistence and long-range transport potential in air. The various lines of evidence are combined to identify substances as warranting further evaluation of their potential to cause harm to the environment or as having a low likelihood of causing harm to the environment.

Some substances in the Esters Group have been reviewed internationally by the European Union (EU), the United States Environmental Protection Agency (US EPA), and through the Organisation for Economic Co-operation and Development (OECD) Cooperative Chemicals Assessment Programme. Health Canada considers these

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assessments to be reliable, and they were used to inform the health effects characterization in this screening assessment.

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to March 2021. Empirical data from key studies as well as results from models were used to reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This draft screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The human health portion of this assessment has undergone external peer review and/or consultation. Comments on the technical portions relevant to human health were received from Dr. Warren Foster (McMaster University), Dr. David Dorman (North Carolina State University) and Dr. Calvin Willhite (Risk Sciences International). External peer review comments provided on the methanol section of the Alcohols Group draft screening assessment were also relevant to this assessment. The ecological portion of this assessment is based on the ERC document (published July 30, 2016), which was subject to an external review as well as a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution.[4] This draft screening assessment presents the critical information and considerations on which the proposed conclusions are based.

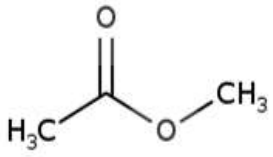
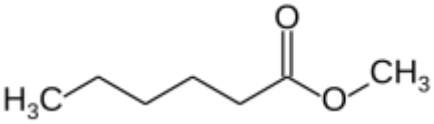
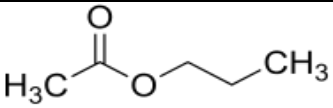
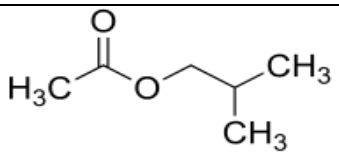
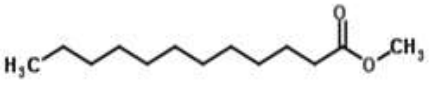
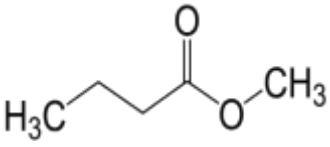
2. Identity of substances

The CAS RN, *Domestic Substances List* (DSL) names and common names for the individual substances and/or representative substances in the Esters Group are

[4]A determination of whether one or more of the criteria of section 64 of CEPA are met is based on an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other acts.

presented in Table 2-1 to Table 2-1. Although each ester is assessed individually, for presentation of the information in this screening assessment, they have been organized into four subgroups based on similarities in chemical structure. Subgroup A consists of esters of acyclic linear or branched alcohols with linear carboxylic acid(s); subgroup B contains esters of di/tri-ols; subgroup C contains esters of 2,2,4-trimethylpentane-1,3-diol with isobutyric acid; and subgroup D contains one individual substance which is a salt of a diester.

Table 2-1. Substance identities (subgroup A): Esters of acyclic linear or branched alcohols with linear carboxylic acid(s)

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
79-20-9	Acetic acid, methyl ester (methyl acetate)	 $C_3H_6O_2$	74.08
106-70-7	Hexanoic acid, methyl ester (methyl hexanoate)	 $C_7H_{14}O_2$	130.19
109-60-4	Acetic acid, propyl ester (propyl acetate)	 $C_5H_{10}O_2$	102.13
110-19-0	Acetic acid, 2-methylpropyl ester (isobutyl acetate)	 $C_6H_{12}O_2$	116.16
111-82-0	Dodecanoic acid, methyl ester (methyl dodecanoate)	 $C_{13}H_{26}O_2$	214.35
623-42-7	Butanoic acid, methyl ester (methyl butanoate)	 $C_5H_{10}O_2$	102.13

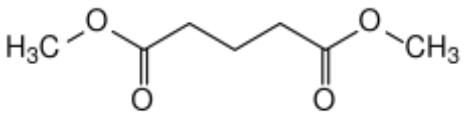
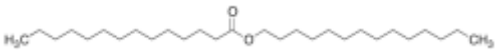
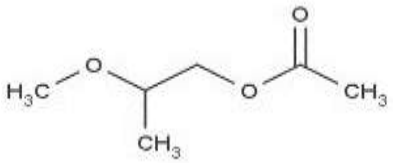
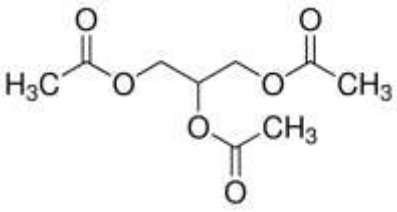
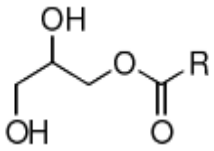
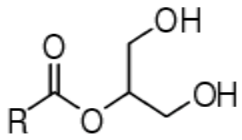
CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
1119-40-0	Pentanedioic acid, dimethyl ester (dimethyl glutarate)	 $C_7H_{12}O_4$	160.17
3234-85-3	Tetradecanoic acid, tetradecyl ester (tetradecyl tetradecanoate)	 $C_{28}H_{56}O_2$	424.75
70657-70-4	1-Propanol, 2-methoxy-, acetate (2-methoxypropyl acetate)	 $C_6H_{12}O_3$	132.16

Table 2-2. Substance identities (subgroup B): Esters of di/tri-ols

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
102-76-1	1,2,3-Propanetriol, triacetate (triacetin)	 $C_9H_{14}O_6$	218.20

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
68990-53-4 [a]	Glycerides, C14-22 mono-	Representative structures: 1-monoacylglycerol:  2-monoacylglycerol:  	N/A

Abbreviation: N/A, Not applicable

[a] This CAS RN is a UVCB (unknown or variable composition, complex reaction products, or biological materials). These materials are derived from natural sources or complex reactions and cannot practicably be synthesized by simply combining individual constituents. A UVCB is not an intentional mixture of discrete substances and is considered a single substance.

Table 2-3. Substance identities (subgroup C): Esters of 2,2,4-trimethylpentane-1,3-diol with isobutyric acid

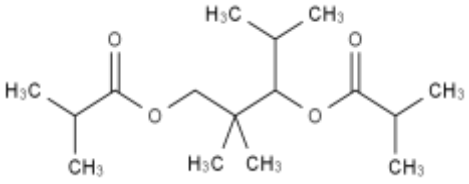
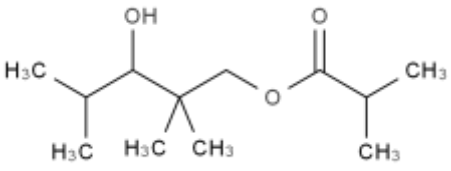
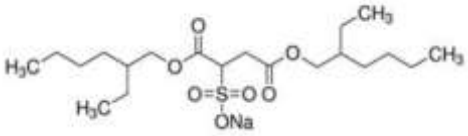
CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
6846-50-0	Propanoic acid, 2-methyl-, 2,2-dimethyl-1-(1-methylethyl)-1,3-propanediyl ester (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	 $C_{16}H_{30}O_4$	286.41
25265-77-4	Propanoic acid, 2-methyl-, monoester with 2,2,4-trimethyl-1,3-pentanediol (texanol)	 $C_{12}H_{24}O_3$	216.32

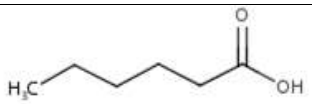
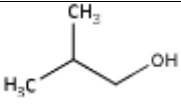
Table 2-4. Substance identities (subgroup D): Salt of a diester

CAS RN	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
577-11-7	Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt (docusate sodium)	 $C_{20}H_{37}NaO_7S$	444.57

2.1 Use of metabolite and analogue data

Data from metabolites as well as analogues have been used to inform the human health assessment of certain substances in subgroup A. After absorption, esters undergo rapid hydrolysis by non-specific esterases present in the body. Data on the expected metabolites (acid and alcohols) were used to inform the human health assessment of certain substances in subgroup A. Analogues that were structurally and/or functionally similar to substances within this group (similar physical-chemical properties, toxicokinetics) were selected and used for read-across. A list of the various metabolites and analogues used to inform the Esters Group assessment is presented in Table 2-5 and Table 2-6, respectively. For further information on the physical-chemical properties of analogues, please refer to Appendix A. Details of the selection of analogues are further discussed in the relevant sections of this report.

Table 2-5. Metabolite identities

CAS RN	Common name	Chemical structure and molecular formula	Molecular weight (g/mol)	Used to inform assessment of:
67-56-1	Methanol	 CH_3OH	32.04	Methyl acetate ; Methyl hexanoate; Methyl butanoate
142-62-1	Hexanoic acid	 $C_6H_{12}O_2$	116.16	Methyl hexanoate
71-23-8	*n*-Propyl alcohol	 C_3H_8O	60.10	Propyl acetate
78-83-1	Isobutanol	 $C_4H_{10}O$	74.12	Isobutyl acetate

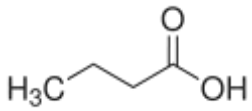
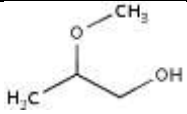
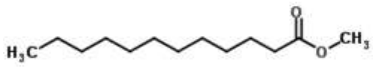
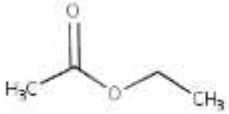
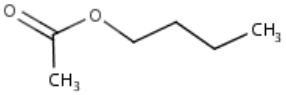
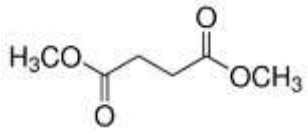
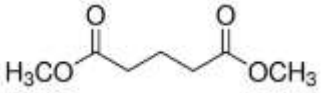
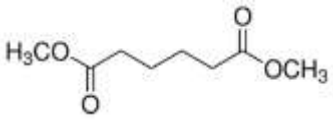
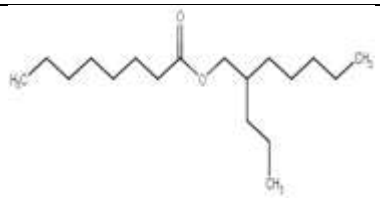
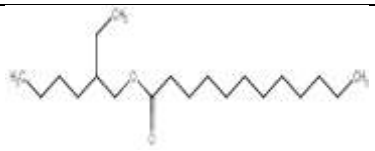
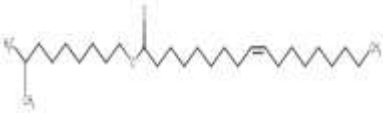
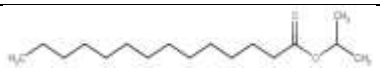
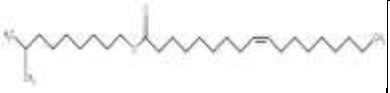
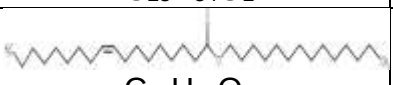
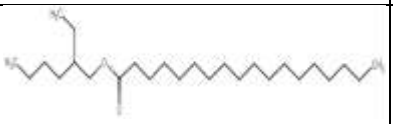
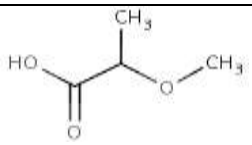
CAS RN	Common name	Chemical structure and molecular formula	Molecular weight (g/mol)	Used to inform assessment of:
107-92-6	*n*-Butyric acid	 $C_4H_8O_2$	88.11	Methyl butanoate
544-63-8	Myristic acid	 $C_{14}H_{28}O_2$	228.37	Tetradecyl tetradecanoate
75782-87-5	Alcohols, C14-15	 $C_{14}H_{30}O$	214.39	Tetradecyl tetradecanoate
112-72-1	Tetra-decanol	 $C_{14}H_{30}O$	214.39	Tetradecyl tetradecanoate
1589-47-5	2-Methoxy-propanol	 $C_4H_{10}O_2$	90.12	2-Methoxypropyl acetate

Table 2-6. Analogue identities

CAS RN	Common name (acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)	Used to inform assessment of:
111-82-0	Methyl dodecanoate	 $C_{13}H_{26}O_2$	214.35	Methyl hexanoate; Methyl butanoate
141-78-6	Ethyl acetate	 $C_4H_8O_2$	88.11	Propyl acetate
123-86-4	*n*-Butyl acetate	 $C_6H_{12}O_2$	116.16	Propyl acetate

CAS RN	Common name (acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)	Used to inform assessment of:
95481-62-2	Dibasic esters (DBE)	Mixture: Dimethyl succinate (CAS RN 106-65-0)  $C_8H_{14}O_4$ Dimethyl glutarate (CAS RN 1119-40-0  $C_7H_{12}O_4$ Dimethyl adipate (CAS RN 627-93-0)  $C_6H_{10}O_4$	N/A	Dimethyl glutarate
868839-23-0	Propylheptyl caprylate	 $C_{18}H_{36}O_2$	284.48	Tetradecyl tetradecanoate
20292-08-4	Ethylhexyl laurate	 $C_{20}H_{40}O_2$	312.53	Tetradecyl tetradecanoate
94247-10-6	Isodecyl laurate	 $C_{22}H_{44}O_2$	340.59	Tetradecyl Tetradecanoate

CAS RN	Common name (acronym)	Chemical structure and molecular formula	Molecular weight (g/mol)	Used to inform assessment of:
110-27-0	Isopropyl myristate	 $C_{17}H_{34}O_2$	270.45	Tetradecyl tetradecanoate
59231-34-4	Isodecyl oleate	 $C_{28}H_{54}O_2$	422.73	tetradecyl tetradecanoate
22393-85-7	Tetradecyl oleate	 $C_{32}H_{62}O_2$	478.84	Tetradecyl tetradecanoate
17671-27-1	Behenyl behenate	 $C_{44}H_{88}O_2$	649.18	Tetradecyl tetradecanoate
22047-49-0	2-Ethylhexyl stearate	 $C_{26}H_{52}O_2$	396.69	Tetradecyl tetradecanoate
4324-37-2	2-Methoxy-propanoic acid	 $C_4H_8O_3$	104.10	2-Methoxypropyl acetate

Abbreviation: N/A, Not applicable

3. Physical and chemical properties

A summary of physical and chemical property data for the substances in the Esters Group is presented by subgroup in Table 3-1. to Table 3-3. When experimental information was limited or not available for a given property, (quantitative) structure-activity relationship ([Q]SAR) models were used to generate predicted values for the substance. Additional physical and chemical properties are presented in ECCC (2016b).

Table 3-1. Experimental physical and chemical property values (at a standard temperature of 25°C) for substances in the Esters Group (subgroup A)

Property	Methyl acetate	Methyl hexanoate	Propyl acetate	Isobutyl acetate	Methyl dodecanoate
Physical state	liquid	liquid	liquid	liquid	liquid
Melting point (°C)	-98.0	-71	-93	-98.8	5.2
Vapour pressure (Pa)	28 800	496	4786	2373	0.55

Property	Methyl acetate	Methyl hexanoate	Propyl acetate	Isobutyl acetate	Methyl dodecanoate
Henry's law constant ($atm \cdot m^3/mol$)	1.15×10^{-4}	3.67×10^{-4}	2.18×10^{-4}	4.54×10^{-4}	2.98×10^{-3}[a]
Water solubility (mg/L)	243 000 (at 20°C)	1 330 (at 20°C)	18 900 (at 20°C)	6 300	0.9-1.4[a]
log K_{ow} (dimensionless)	0.18	2.34[a]	1.24	1.78	5.41
log K_{oc} (dimensionless)	0.49-0.96[a]	1.55-2.1[a]	1.0-1.5[a]	1.2-1.8[a]	3.1-3.9[a]
pK_a (dimensionless)	-7[b]	-7[b]	-7[b]	-7[b]	-7[b]

Abbreviations: K_{ow}, octanol–water partition coefficient; log K_{oc} soil adsorption coefficient; pK_a, negative log function of the acid dissociation constant
All references from ChemIDplus (1993-) except when noted otherwise
[a] Estimated from EPI Suite (c2000-2012)
[b] Wishart et al. (2013) (estimated values found in (Human Metabolome Database (HMDB))

Table 3-2. Experimental physical and chemical property values (at a standard temperature of 25°C) for substances in the Esters Group (subgroup A, continued)

Property	Methyl butanoate	Dimethyl glutarate	Tetradecyl tetradecanoate	2-Methyoxypropyl acetate
Physical state	liquid	liquid	solid	liquid
Melting point (°C)	-85.8	-42.5	162.8[a]	-50.3[a]
Vapour pressure (Pa)	4 306	24	2.1×10^{-6}[a]	1029[a]
Henry's law constant ($atm \cdot m^3/mol$)	2.05×10^{-4}	6.43×10^{-7}	2.1×10^{-1} -6.3×10^{-1}[a]	3.62×10^{-6} – 5.9×10^{-7}[a]
Water solubility (mg/L)	15 000	59 000	3.4×10^{-8}[a]	32 660[a]
log K_{ow} (dimensionless)	1.29	0.62	12.7[a]	0.52[a]
log K_{oc} (dimensionless)	1.0-1.6[a]	1.0-1.1[a]	7.0-7.9[a]	0.60-1.1[a]
pK_a (dimensionless)	-7[b]	N/A	N/A	N/A

Abbreviations: K_{ow}, octanol–water partition coefficient; log K_{oc} soil adsorption coefficient; pK_a, negative log function of the acid dissociation constant; N/A, not available
All references from ChemIDplus (1993-) except when noted otherwise.
[a] Modelled using EPI Suite (c2000-2012)
[b] Wishart et al. (2013) (estimated values found in HMDB database)

Table 3-3. Experimental physical and chemical property values (at a standard temperature of 25°C) for substances in the Esters Group (subgroups B, C and D)

Property	Triacetin	Glycerides, C14-22 mono-	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	Texanol	Docusate sodium
Physical state	liquid	solid[a]	liquid	liquid	solid
Melting point (°C)	-78.0	139[b]	-70[c]	-50[c] ;-70[d]	176
Vapour pressure (Pa)	0.33	6.4×10^{-7}[b]	1.13[b]	1.3[c] (at 20°C)	1.63×10^{-12}[b]
Henry's law constant ($atm \cdot m^3/mol$)	1.23×10^{-8}[b]	1.2×10^{-8} – 3.1×10^{-12}[b]	1.1×10^{-5} [b]	1.1×10^{-7} - 8.21×10^{-8}[b]	5.00×10^{-12}[b]
Water solubility (mg/L)	58 000	Insoluble in water[a]	0.94[b]- 13[d]	322[b]	71 000
log K_{ow} (dimensionless)	0.25	4.65[b]	4.91[b]	3.0[b]	2.0[g] - 3.95[b]
log K_{oc} (dimensionless)	0.9-1.6[b]	1.9-2.6[b]	2.7-3.5[b]	1.5 – 2.1[b]	2.80[b]
pK_a (dimensionless)	-6.5[e]	N/A	N/A	16.97[f]	N/A

Abbreviations: K_{ow}, octanol–water partition coefficient; log K_{oc} soil adsorption coefficient; pK_a, negative log function of the acid dissociation constant; N/A, not available
All references from ChemIDplus (1993-) except when noted otherwise.
[a] Norn (2015)
[b] Modelled using EPI Suite (c2000-2012)
[c] PubChem (NCBI 2004-)
[d] ECHA (c2007-2017a)
[e] Wishart et al. (2013) (HMDB database of estimated values)
[f] ECHA (c2007-2017b) (estimated value)
[g] ECHA (c2007-2017c)

4. Sources and uses

All of the substances in the Esters Group have been included in surveys issued pursuant to section 71 of CEPA (Canada 2009, 2012). Table 4-1 presents a summary of information reported on the total manufacture and import quantities for the Esters Group. According to information submitted in response to a CEPA section 71 survey, methyl hexanoate and methyl butanoate were not reported to be manufactured in or imported into Canada above the reporting threshold in 2011 (Environment Canada 2013). For the remaining 12 esters, manufacturing quantities ranged from 0 kg to 100 000 kg and import quantities ranged from 5 000 kg to more than 3 000 000 kg in

2011 (for 11 substances) or 2009 (for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate) (Environment Canada 2009, 2013).

Table 4-1. Summary of information on Canadian manufacturing and imports of the substances in the Esters Group submitted in response to CEPA section 71 surveys

Common name (CAS RN)	Total manufacture[a] (kg)	Total imports[a] (kg)	Reporting year
Methyl acetate (79-20-9)	9 600	323 602	2011
Methyl hexanoate (106-70-7)	NR	NR	2011
Propyl acetate (109-60-4)	NR	3 341 393	2011
Isobutyl acetate (110-19-0)	710	100 000 – 1 000 000	2011
Methyl dodecanoate (111-82-0)	NR	10 000 – 100 000	2011
Methyl butanoate (623-42-7)	NR	NR	2011
Dimethyl glutarate (1119-40-0)	1 000 – 10 000	122 144	2011
Tetradecyl tetradecanoate (3234-85-3)	NR	31 626	2011
2-Methoxypropyl acetate (70657-70-4)	NR	5 752	2011
Triacetin (102-76-1)	10 000 – 100 000	100 000 – 1 000 000	2011
Glycerides, C14-22 mono- (68990-53-4)	NR	43 000	2011
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (6846-50-0)	100 – 10 000	594 600	2009
Texanol (25265-77-4)	NR	2 541 030	2011
Docusate sodium (577-11-7)	100 – 1 000	1 081 185	2011

Abbreviation: NR, not reported above the reporting volume of 100 kg.

[a] Values reflect quantities reported in response to the surveys conducted under section 71 of CEPA (Canada 2009, 2012). See surveys for specific inclusions and exclusions (schedules 2 and 3).

Subgroup A

Methyl acetate is primarily used as a solvent in a variety of commercial products and in products available to consumers in Canada, including paints and coatings, paint strippers or removers (referred to as paint removers in this document), adhesives and sealants, cleaning products, and furnishing care products (Environment Canada 2013; SDS 2018a). Propyl acetate has reported uses as a solvent, pigment and paint additive in a range of commercial products and products available to consumers, including paints and coatings, inks, toners and colourants and personal care products (Environment Canada 2013). Isobutyl acetate is used as a solvent in paints and coatings (Environment Canada 2013). Methyl dodecanoate functions as a solvent for cleaning or degreasing (Environment Canada 2013). Functions of dimethyl glutarate include use as a processing aid, adhesive, sealant and solvent in commercial products and in products available to consumers, including paints and coatings, personal care products (cosmetics), adhesives and sealants, and building or construction materials, as well as in oil and natural gas extraction and automotive, aircraft and transportation applications (Environment Canada 2013). Tetradecyl tetradecanoate is primarily used as a skin conditioning agent in personal care products and cosmetics in Canada (Environment Canada 2013). The primary applications of 2-methoxypropyl acetate include its use in paints and coatings, as well as in plastic and rubber material, where it functions as a finishing agent (Environment Canada 2013).

Methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, and methyl butanoate have been reported to occur naturally in food and may be used internationally as food flavouring agents in a variety of foods (Burdock 2010). No definitive information is available concerning the potential uses of these substances as food flavouring agents in Canada. However, since these substances are identified as food flavouring agents internationally, it is possible that they are present as flavouring agents in foods sold in Canada (personal communication, email from Food Directorate (FD), Health Canada (HC) to Existing Substances Risk Assessment Bureau (ESRAB), HC, dated December 5, 2016, and March 15, 2021; unreferenced).

Methyl acetate, propyl acetate, isobutyl acetate and 2-methoxypropyl acetate may be used as components in the manufacture of food packaging materials with no direct food contact. Dimethyl glutarate and tetradecyl tetradecanoate have been identified as components in incidental additives[5] (e.g., hand cleaners and hand sanitizers) used in processing establishments with no direct food contact (personal communication, emails

[5] While not defined under the *Food and Drugs Act* (FDA), incidental additives may be regarded, for administrative purposes, as those substances that are used in food processing plants and that may potentially become adventitious residues in food (e.g., cleaners, sanitizers).

from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

Dimethyl glutarate is a medicinal ingredient in two registered disinfectant products; tetradecyl tetradecanoate is a non-medicinal ingredient in several over-the-counter topically applied therapeutic products, including gels, creams and lotions as well as lip moisturizers (personal communication, email from Therapeutic Products Directorate (TPD), HC, to ESRAB, HC, dated December 6, 2016; unreferenced).

Methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, and methyl butanoate are listed in the Natural Health Products Ingredients Database (NHPID) with a non-medicinal role for use as flavour enhancer. Dimethyl glutarate is listed in the NHPID with a non-medicinal role for use as solvent. Tetradecyl tetradecanoate is listed in the NHPID with a non-medicinal role for topical use only, up to 17%, when formulated to be non-irritating, as a skin-conditioning agent – emollient or skin-conditioning agent - occlusive (NHPID [modified 2021]). Tetradecyl tetradecanoate is listed in the Licensed Natural Health Products Database (LNHPD) as being present as a non-medicinal ingredient in natural health products in Canada, whereas methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, methyl butanoate and dimethyl glutarate are not listed (LNHPD [modified 2021]).

According to notifications submitted under the *Cosmetic Regulations* to Health Canada, methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, dimethyl glutarate, and tetradecyl tetradecanoate are used in certain cosmetics in Canada. Methyl acetate is used in products such as nail polishes, nail polish removers, cleansers, bath products, makeup, exfoliants and moisturizers. Methyl hexanoate was notified to be used in moisturizing products for nails. Propyl acetate was notified to be used in products such as nail polishes, makeup, and styling products. Isobutyl acetate was notified to be used in nail products and moisturizers. Methyl dodecanoate was found in face moisturizers. Dimethyl glutarate was notified to be used in products such as cleansers, adhesive removers and nail polish removers. Tetradecyl tetradecanoate was notified to be used in products such as antiperspirants, bath products, bleach, cleansers, conditioners, exfoliants, fragrance products, hair colours, makeup, massage products, moisturizers, nail polishes, shampoos, shaving products, styling products and sunless tanning products (personal communication, email from the Consumer and Hazardous Products Safety Directorate [CHPSD], HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

2-Methoxypropyl acetate is described on the List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist) as a prohibited substance. This list is an administrative tool that Health Canada uses to communicate that certain substances may contravene the general prohibition found in section 16 of the *Food and Drugs Act* (FDA), or may contravene one or more provisions of the *Cosmetic Regulations.* Section 16 of the FDA states that “No person shall sell any cosmetic that has in or on it any substance that may cause injury to the

health of the user.” In addition, the Hotlist includes certain substances that may make it unlikely for a product to be classified as a cosmetic under the FDA (Health Canada 2015).

Methyl butanoate is not reported to be used in cosmetics in Canada (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

The following substances in subgroup A have been identified as formulants in pest control products registered in Canada: methyl acetate, propyl acetate, isobutyl acetate, methyl dodecanoate, and 2-methoxypropyl acetate.

Methyl acetate and isobutyl acetate have been identified as possible ingredients in vaping products (US FDA 2019), which may represent an additional source of exposure to methyl acetate and isobutyl acetate. Vaping products (such as electronic cigarettes and vaping devices containing cannabis) are being addressed through separate legislative frameworks (HC [modified 2020]).

Table 4-2 and Table 4-3 present a summary of the major uses of the esters in subgroup A according to information submitted in response to a CEPA section 71 survey (Environment Canada 2013). Additional uses of the esters in subgroup A are also identified in Table 4-5.

Table 4-2. Summary of Canadian uses of substances in the Esters Group (subgroup A) submitted in response to a CEPA section 71 survey

Major uses[a]	Methyl acetate	Propyl acetate	Isobutyl acetate	Methyl dodecanoate	Dimethyl glutarate
Adhesive and sealants	Y	N	Y	N	Y
Automotive aircraft and transportation	N	Y	Y	N	Y
Batteries	Y	N	N	N	N
Building or construction materials	N	N	N	N	Y
Cleaning and furnishing care	Y	N	N	N	N
Fabric, textile and leather articles	Y	N	N	N	N
Ink, toner and colourants	Y	Y	N	N	Y
Natural health products	Y	N	N	N	N
Oil and natural gas extraction	N	N	N	N	Y
Paints and coatings	Y	Y	Y	N	Y
Paper products, mixtures or manufactured items	Y	N	N	N	N
Personal care and cosmetics	N	Y	N	N	Y
Plastic and rubber materials not otherwise covered	Y	Y	N	N	N
Toys, playground and sporting equipment	N	N	N	N	Y
Water treatment	N	N	N	N	N
Other[b]	Y	Y	Y	Y	Y

Abbreviations: Y, yes; N, no

[a] Non-confidential uses reported in response to a CEPA section 71 survey (Environment Canada 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

[b] Other refers to minor uses and/or uses that cannot be disclosed as a result of confidentiality claims.

Table 4-3. Summary of Canadian uses of substances in the Esters Group (subgroup A, continued) submitted in response to a CEPA section 71 survey

Major uses[a]	Tetradecyl tetradecanoate	2-Methoxypropyl acetate
Automotive aircraft and transportation	N	Y
Drugs	Y	N
Natural health products	Y	N
Personal care and cosmetics	Y	N
Plastic and rubber materials not otherwise covered	N	Y

Abbreviations: Y, yes; N, no

[a] Non-confidential uses reported in response to a CEPA section 71 survey (Environment Canada 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

Subgroup B

According to information submitted in response to a CEPA section 71 survey, reported applications of triacetin include its use in personal care and cosmetic products, inks, toners and colourants, adhesives and sealants, and in food and beverages in Canada (Environment Canada 2013).

Triacetin has been identified as a component in an incidental additive (lubricant) used in food processing establishments with no direct food contact (personal communication, email from the FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced). Glycerides, C14-22 mono- has been identified in food packaging materials as a component in polystyrene-based materials (e.g., foam cups, containers) and polypropylene-based materials (e.g., containers, pails) and has been identified in incidental additives (e.g., lubricants and release agents) (personal communication, email from the FD, HC, to ESRAB, HC, dated November 23, 2015; unreferenced).

Both triacetin and glycerides, C14-22 mono- are considered to be permitted food additives in Canada. Triacetin is permitted for use as a wetting agent in cake mixes and as a solvent in flavours as prescribed in the *List of Permitted Food Additives with Other Accepted Uses* and the *List of Permitted Carrier or Extraction Solvents,* respectively, incorporated by reference into their respective Marketing Authorization issued under the *Food and Drugs Act.* Glycerides, C14-22 mono-, would be included under the permitted food additives uses for monoglycerides and mono- and di-glycerides, which are permitted for use as an emulsifying, gelling, stabilizing or thickening agent, as an antifoaming, humectant or release agent and as a carrier or extraction solvent in a variety of foods, as prescribed in the *List of Permitted Emulsifying, Gelling, Stabilizing or Thickening Agents*, the *List of Permitted Food Additives with Other Accepted Uses* and the *List of Permitted Carrier or Extraction Solvents*, incorporated by reference into their respective Marketing Authorization issued under the *Food and Drugs Act*.

Triacetin is listed in the NHPID with a non-medicinal role for use as a cosmetic biocide, flavour enhancer, fragrance ingredient, humectant, plasticizer or solvent, as well as in

the LNHPD as being present as a non-medicinal ingredient in natural health products in Canada (NHPID [modified 2021]; LNHPD [modified 2021]). Triacetin is also used as a non-medicinal ingredient in approximately 25 prescription and/or non-prescription drugs registered in Canada. Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, triacetin is used in certain cosmetics in Canada such as adhesives, cleansers, exfoliants, makeup, makeup removers, massage products, moisturizers and nail polishes (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Triacetin is also a formulant in registered pest control products in Canada.

Subgroup C

According to information submitted in response to a CEPA section 71 survey, major uses of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in Canada include its use as a solvent in plastic and rubber materials, as well as in inks, toners and colourants, and in adhesives and sealants (Environment Canada 2009). It is also used as a curing agent and polymerization initiator, as well as in paints and coatings, floor coverings and formed automotive parts. In a separate survey, texanol was reported to be used in paints and coatings, adhesives and sealants, building or construction materials, automotive, aircraft and transportation applications, floor coverings, and fuels and related products (Environment Canada 2013).

Both 2,2,4-trimethyl-1,3-pentanediol diisobutyrate and texanol may be used as a component in the manufacture of food packaging materials with no direct food contact (personal communication, emails from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is listed in the NHPID with a non-medicinal role for topical use only, up to 9.8%, as plasticizer, as well as in the LNHPD as being present as a non-medicinal ingredient in a natural health product in Canada (NHPID [modified 2021]; LNHPD [modified 2018]).

According to notifications submitted under the *Cosmetic Regulations* to Health Canada, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate is used in certain cosmetics in Canada such as adhesives, nail moisturizers, nail polishes and nail polish removers. Texanol (identified by International Nomenclature of Cosmetic Ingredients [INCI] name of trimethyl pentanyl diisobutyrate) is used in nail polishes and make-up in Canada (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Texanol is also a formulant in registered pest control products in Canada.

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is a plasticizer and may migrate from baby bottles made from materials used as substitutes for polycarbonate. It has also been measured in plastic toys and other plastic items intended for use by children (Onghena et al. 2016; Simoneau et al. 2012; Bouma and Schakel 2002; Tonning et al. 2009; Janssen and Bremmer 2009).

Subgroup D

Major uses of docusate sodium in Canada include applications in oil and natural gas extraction, food and beverages, drugs, and paints and coatings. A primary function of docusate sodium is as a surface-active agent (Environment Canada 2013). Other applications in Canada include uses in plastic and rubber materials, as a drying agent, adhesive and sealant, in personal care products and cosmetics, fuels and related products, mixtures or manufactured items, cleaning and furnishing care, water treatment, building and construction materials, paper products, inks, toners and colourants, floor coverings, laundry and dishwashing and mining applications (Environment Canada 2013). Docusate sodium (as dioctyl sodium sulfosuccinate) is permitted for use in a limited number of foods, as prescribed in the *List of Permitted Food Additives with Other Accepted Uses*, incorporated by reference into its respective Marketing Authorization issued under the *Food and Drugs Act*. Docusate sodium may be used as a component in the manufacture of food packaging materials, with no direct food contact (personal communication, email from FD, HC, to ESRAB, HC, dated March 15, 2021; unreferenced).

Docusate sodium is also listed in the NHPID with a non-medicinal ingredient role for use as an emulsifying agent, solubilizing agent or wetting agent, as well as with a non-natural health product role because it is not a naturally occurring substance included in Schedule 1 of the *Natural Health Products Regulations*. It is listed in the LNHPD as being present as a non-medicinal ingredient in natural health products in Canada (NHPID [modified 2021]; LNHPD [modified 2021]). Docusate sodium is an active ingredient in prescription and/or non-prescription drugs (primarily laxatives) in Canada and a non-medicinal ingredient in a wide range of products including oral and topical applications and aerosol disinfectants (personal communication, email from TPD, HC, to ESRAB, HC, dated December 5, 2016, and March 18, 2021; unreferenced). Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, docusate sodium (INCI name: diethylhexyl sodium sulfosuccinate) is used in certain cosmetics in Canada such as adhesive, bath products, bleach, cleaners, exfoliant, hair colour, makeup, makeup remover, shampoo, shaving products, styling products and sunless tanning products (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Docusate sodium is a formulant in registered pest control products in Canada.

Table 4-4 summarizes the major uses of the esters in subgroups B, C and D submitted in response to CEPA section 71 surveys (Environment Canada 2009, 2013). Additional uses of the esters in subgroups B, C and D are outlined in Table 4-5.

Table 4-4. Summary of Canadian uses of substances in the Esters Group (subgroups B, C, D) submitted in response to CEPA section 71 surveys

Major uses[a]	Triacetin	Glycerides, C14-22 mono-	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	Texanol	Docusate sodium
Adhesive and sealants	Y	N	Y	Y	Y
Automotive aircraft and transportation	N	N	N	Y	Y
Building or construction materials	N	N	N	Y	Y
Cleaning and furnishing care	N	N	Y	N	Y
Drugs	N	N	N	N	Y
Fabric, textile and leather articles	N	N	Y	N	N
Floor coverings	N	N	Y	Y	Y
Food and beverages	Y	N	N	N	Y
Food packaging	N	Y	N	N	Y
Fuels and related products, mixtures or manufactured items	N	N	N	Y	Y
Ink, toner and colourants	Y	N	Y	N	Y
Laundry and dishwashing	N	N	N	N	Y
Oil and natural gas extraction	N	N	N	N	Y
Paints and coatings	N	N	Y	Y	Y
Paper products, mixtures or manufactured items	N	N	N	N	Y
Personal care and cosmetics	Y	N	N	N	Y
Plastic and rubber materials not otherwise covered	N	N	Y	N	Y
Water treatment	N	N	N	N	Y
Other[b]	Y	N	Y	N	N

Abbreviations: Y, yes; N, no

[a] Non-confidential uses reported in response to CEPA section 71 surveys (Environment Canada 2009, 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

[b] Other refers to minor uses and/or uses that cannot be disclosed as a result of confidentiality claims.

Table 4-5. Additional uses in Canada for each of the substances in the Esters Group

Use	Subgroup A	Subgroup B	Subgroup C	Subgroup D
Food additive[a]	N	Triacetin Glycerides, C14-22 mono-[b,c]	N	Docusate sodium
Food flavouring[a]	Methyl acetate Methyl hexanoate[c] Propyl acetate Isobutyl acetate[c] Methyl dodecanoate Methyl butanoate	Triacetin	N	N
Food packaging materials[a]	Methyl acetate Propyl acetate Isobutyl acetate[c] 2-Methoxypropyl acetate	Glycerides, C14-22 mono-[c]	2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol	Docusate sodium
Incidental additive[a]	Dimethyl glutarate Tetradecyl tetradecanoate	Triacetin Glycerides, C14-22 mono-[c]	N	N
Internal Drug Product Database as medicinal or non-medicinal ingredients in disinfectant, human or veterinary drug products in Canada[d]	Methyl dodecanoate Tetradecyl tetradecanoate	Triacetin	N	Docusate sodium
Natural Health Products Ingredients Database[e]	Methyl acetate Methyl hexanoate Propyl acetate Isobutyl acetate Methyl dodecanoate Methyl butanoate Dimethyl glutarate Tetradecyl tetradecanoate	Triacetin	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	Docusate sodium
Licensed Natural Health Products	Tetradecyl tetradecanoate	Triacetin	2,2,4-Trimethyl-	Docusate sodium

Use	Subgroup A	Subgroup B	Subgroup C	Subgroup D
Database as medicinal or non-medicinal ingredients in natural health products in Canada[e]			1,3-pentanediol diisobutyrate	
List of Prohibited and Restricted Cosmetic Ingredients[f]	2-Methoxypropyl acetate	N	N	N
Notified to be present in cosmetics, on the basis of notifications submitted under the *Cosmetic Regulations* to Health Canada[f]	Methyl acetate Methyl hexanoate Propyl acetate Isobutyl acetate Methyl dodecanoate Dimethyl glutarate Tetradecyl tetradecanoate	Triacetin	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate Texanol	Docusate sodium
Formulant in pest control products registered in Canada[g]	Methyl acetate Propyl acetate Isobutyl acetate Methyl dodecanoate 2-Methoxypropyl acetate	Triacetin	Texanol	Docusate sodium

Abbreviation: N, this use was not reported for this subgroup

[a] Personal communication, e-mails from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced.

[b] "Glycerides, C14-22 mono-" is included in the listings for two approved food additives in Canada. Monoglycerides or mono- and di-glycerides, as set out in Canada's List of Permitted Food Additives (see Subgroup B of section 4 for details).

[c] Personal communication, e-mail from Risk Management Bureau, HC, to ESRAB, HC, dated August 17, 2015; unreferenced.

[d] Personal communication, e-mail from TPD, HC, to ESRAB, HC, dated December 6, 2016, and March 3, 2021; unreferenced.

[e] Personal communication, e-mail from Natural and Non-prescription Health Products Directorate (NNHPD), HC, to ESRAB, HC, dated December 6, 2016, and February 11, 2021; unreferenced.

[f] Personal communication, e-mail from CHPSD, HC, to ESRAB, HC, dated December 8, 2016, and March 5, 2021; unreferenced.

[g] Personal communication, e-mail from RMB, HC, to ESRAB, HC, dated December 12, 2016; unreferenced; personal communication e-mail from Pest Management Regulatory Agency, HC, to ESRAB, HC, dated March 26, 2021; unreferenced.

5. Environmental fate and behaviour

5.1 Environmental persistence

According to models used in ERC (ECCC 2016b), methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl butanoate and dimethyl glutarate are expected to persist in air, but not in water, sediment or soil.

According to models used in ERC (ECCC 2016b), docusate sodium is expected to persist in water, sediment and soil, but not in air.

According to models used in ERC (ECCC 2016b), triacetin, methyl dodecanoate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides and 2-methoxypropyl acetate are not expected to persist in air, water, sediment or soil.

5.2 Potential for bioaccumulation

Given their low log K_{ow} and low bioconcentration factors (BCF) (ECCC 2016b), methyl acetate, triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, docusate sodium, methyl butanoate, dimethyl glutarate, texanol, and 2-methyoxypropyl acetate are not expected to significantly bioaccumulate in organisms.

Although the log K_{ow} values for methyl dodecanoate, tetradecyl tetradecanoate and C14-22 monoglycerides are moderate to high, the BCFs for these substances are low (ECCC 2016b). As a result, they are not expected to significantly bioaccumulate in organisms.

Although 2,2,4-trimethyl-1,3-pentanediol diisobutyrate has a high log K_{ow} value, given that this substance has a high empirical BCF (5340 L/kg) (ECCC 2016b), it is expected to significantly bioaccumulate in organisms.

6. Potential to cause ecological harm

6.1 Characterization of ecological risk

The ecological risks of the substances in the Esters Group were characterized using the ecological risk classification of organic substances (ERC) approach (ECCC 2016a). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. The various lines of evidence are combined to discriminate between substances of lower or higher potency and lower or higher potential for exposure in various media. This approach reduces the overall uncertainty with risk characterization compared to an approach that relies on a single metric in a single medium (e.g., median

lethal concentration) for characterization. The following summarizes the approach, which is described in detail in ECCC (2016a).

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, and fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from the scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox 2014), and from responses to surveys issued pursuant to section 71 of CEPA, or they were generated using selected (Q)SAR or mass-balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

Hazard profiles were based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Exposure profiles were also based on multiple metrics including potential emission rate, overall persistence, and long-range transport potential. Hazard and exposure profiles were compared to decision criteria in order to classify the hazard and exposure potentials for each organic substance as low, moderate, or high. Additional rules were applied (e.g., classification consistency, margin of exposure) to refine the preliminary classifications of hazard or exposure.

A risk matrix was used to assign a low, moderate or high classification of potential risk for each substance on the basis of its hazard and exposure classifications. ERC classifications of potential risk were verified using a two-step approach. The first step adjusted the risk classification outcomes from moderate or high to low for substances that had a low estimated rate of emission to water after wastewater treatment, representing a low potential for exposure. The second step reviewed low risk potential classification outcomes using relatively conservative, local-scale (i.e., in the area immediately surrounding a point source of discharge) risk scenarios, designed to be protective of the environment, to determine whether the classification of potential risk should be increased.

ERC uses a weighted approach to minimize the potential for both over- and under-classification of hazard and exposure and of subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC (2016a). The following describes two of the more substantial areas of uncertainty. Error with empirical or modelled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from (Q)SAR models (OECD QSAR Toolbox 2014). However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue value used for critical body residue analysis. Error with underestimation of acute toxicity will be mitigated through the use of other hazard metrics such as structural profiling of mode of action, reactivity and/or estrogen binding affinity. Changes or errors in chemical quantity could result in differences in classification of exposure as the exposure and risk classifications are highly sensitive to emission rate and use quantity. The ERC classifications thus

reflect exposure and risk in Canada on the basis of what is estimated to be the current use quantity and may not reflect future trends.

Critical data and considerations used to develop the substance-specific profiles for the substances in the Esters Group and the hazard, exposure and risk classification results are presented in ECCC (2016b).

The hazard and exposure classifications for the substances in the Esters Group are summarized in Table 6-1.

Table 6-1. Ecological risk classification results for the substances in the Esters Group

Substance	ERC hazard classification	ERC exposure classification	ERC risk classification
Methyl acetate	low	low	low
Triacetin	low	low	low
Methyl hexanoate	low	low	low
Propyl acetate	low	high	low
Isobutyl acetate	low	high	low
Methyl dodecanoate	low	low	low
Docusate sodium	moderate	low	low
Methyl butanoate	low	low	low
Dimethyl glutarate	low	low	low
Tetradecyl tetradecanoate	low	low	low
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	moderate	low	low
Texanol	low	low	low
C14-22 monoglycerides	low	low	low
2-Methoxypropyl acetate	low	low	low

On the basis of low hazard and low exposure classifications according to information considered under ERC, methyl acetate, triacetin, methyl hexanoate, methyl dodecanoate, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate were classified as having a low potential for ecological risk. It is therefore unlikely that these substances are resulting in concerns for the environment in Canada.

According to information considered under ERC, docusate sodium was classified as having a low exposure potential and a moderate hazard potential, the latter being based on the agreement between the reactive mode of action and elevated ecotoxicity ratio, both of which suggest that this chemical is likely of high potency. However, the potential effects and how they may manifest in the environment were not further investigated due to the low exposure potential of this substance. Considering current use patterns, it is unlikely that docusate sodium is resulting in concerns for the environment in Canada.

According to information considered under ERC, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate was classified as having a low exposure potential and a moderate hazard potential, the latter being based on a moderate potential to cause adverse effects in aquatic food webs given its moderate bioaccumulation potential. The potential effects and how they may manifest in the environment were not further investigated due to the low exposure potential of this substance. It is unlikely that 2,2,4-trimethyl-1,3-pentanediol diisobutyrate is resulting in concerns for the environment in Canada.

According to information considered under ERC, propyl acetate and isobutyl acetate were classified as having high exposure potentials on the basis of relatively large annual import quantities and long half-lives in air. Both substances were classified as having low hazard potentials and as having low potential for ecological risk. Although the current use patterns result in high exposure potentials, considering the low hazard potentials, propyl acetate and isobutyl acetate are unlikely to be resulting in concerns for the environment in Canada.

7. Potential to cause harm to human health

7.1 Subgroup A: Esters of acyclic linear/branched alcohol with linear carboxylic acid

7.1.1 Methyl acetate

Exposure assessment

Environmental media

Methyl acetate is a liquid with a very high vapour pressure. Methyl acetate has been measured in ambient air in four Canadian studies in Windsor, Regina, Halifax and Edmonton (Health Canada 2010a, 2010b, 2012, 2013a). Concentrations of methyl acetate in ambient air from these Canadian studies ranged from below the method detection limit (MDL) to 6.32 $\mu g/m^3$, with geometric mean concentrations ranging from below the MDL to 0.22 $\mu g/m^3$. The highest 95th percentile concentration of methyl acetate in ambient air, based on a large sample size (i.e., > 30), was selected as being representative of general population for ambient air exposure (0.57 $\mu g/m^3$ based on 24-hour samples from the Edmonton study) (Health Canada 2013a).

Methyl acetate was also measured in indoor air in the four Canadian studies noted above. Concentrations of methyl acetate in indoor air ranged from below the MDL to 34.32 $\mu g/m^3$, with geometric mean concentrations ranging from 0.41 $\mu g/m^3$ to 2.4 $\mu g/m^3$ across these Canadian indoor air monitoring studies. The highest 95th percentile indoor air concentration measurement from the four studies was 11.5 $\mu g/m^3$, based on data from the Windsor study collected in 2006 (Health Canada 2010a). This value was used to estimate exposure to the general population of Canada associated with indoor air.

Personal air sampling was also carried out in the Windsor exposure assessment study where adult participants carried a 1.0 L volatile organic compound (VOC) canister, deployed every 24 hours for 5 consecutive days. Concentrations of methyl acetate in personal air samples ranged from below MDL to 10.1 $\mu g/m^3$ in 2005. The geometric means of the personal sampling measurements taken in winter and summer of 2005were 0.72 $\mu g/m^3$ and 2.5 $\mu g/m^3$, respectively, whereas the 95th percentiles for winter and summer measurements were 2.4 $\mu g/m^3$ and 7.0 $\mu g/m^3$, respectively.

Methyl acetate is highly soluble in water. However, a measured Henry's law constant of 1.15×10^{-4} atm m^3/mol indicates that volatilization from water surfaces is expected (HSDB 1983-). No data measuring methyl acetate in water in Canada were identified. Concentrations in surface water were estimated with the New Substances Assessment and Control Bureau (NSACB) Environmental Assessment Unit (EAU) Drinking Water Spreadsheets using the industrial release scenario (Health Canada 2015a). This is considered a conservative estimate of potential presence in water, as much of methyl acetate is likely to volatilize.

Methyl acetate was not identified in soils or dust studies in Canada or internationally. Methyl acetate is expected to have a very high mobility in soil and is expected to volatilize from moist and dry soil surfaces.

Food

Methyl acetate may be used as a component in the manufacture of food packaging materials with no direct food contact. Therefore, dietary exposure is not expected (personal communication, emails from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

Methyl acetate has been measured in several foods primarily as a result of its natural occurrence. In addition, methyl acetate may be used as a flavouring agent in food. The Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) evaluated esters of aliphatic acyclic primary alcohols with aliphatic linear saturated carboxylic acids (including methyl acetate) using the Procedure for the Safety Evaluation of Flavouring Agents which concluded that methyl acetate presents "no safety concern" based on currently levels of intake as a food flavouring agent (WHO 1998). As part of this evaluation, JECFA estimated the per capita intake of methyl acetate in the United States to be 110 μg/person/day (1.8 μg/kg bw/day based on an average body weight of 60 kg for the general population). The intake is estimated using a maximized survey-derived daily intake (MSDI) approach, based on the reported annual production amount of methyl acetate in the United States (International Organization of the Flavour Industry 1995, as cited in WHO 1998; US National Academy of Sciences 1987, as cited in WHO 1998).

The potential dietary exposure from possible food uses of methyl acetate as a flavouring agent is expected to be small relative to intakes of this substance from its natural occurrence in food. Stofberg and Grundschober (1984) calculated consumption ratios

for various flavouring agents, comparing the average intakes of the added flavouring agent to quantities consumed as a result of their natural occurrence in foods. They indicated that this substance is primarily consumed through its natural occurrence in food rather than through its addition as a flavouring agent.

In order to characterize the potential exposure of the general population from dietary sources of methyl acetate from its natural presence in food, quantitative exposure estimates were derived (personal communication, e-mail from FD, HC, to ESRAB, HC, dated December 8, 2017). Methyl acetate is listed in the Volatile Compounds in Food (VCF) database as being present in a range of foods, including apple, banana, cherry, citrus, guava, grapes, melon, nectarines, pineapple, tomato, vinegar, beer and sherry, (Nijssen et al. 1963-2016). Quantitative exposure estimates were derived from consumption data for comparable food categories from the Canadian Community Health Survey (CCHS cycle 2.2) all-persons consumption of defined food categories (Health Canada 2015). Analytical occurrence values sourced from the VCF database and the scientific literature were applied to the consumption of each food category as appropriate. The dataset of methyl acetate occurrence was sufficiently detailed for a wide variety of foods such that all-persons consumption was considered appropriate. Estimated exposures to methyl acetate from its natural occurrence in food are shown in Table 7-1. The highest 90th percentile dietary exposure of the general population was 33.1 μg/kg bw/day based on the 1- to 2-year-old age group.

Table 7-1. Estimated exposure to methyl acetate from natural occurrence in food

	Estimated exposure (μg/kg bw/day) (based on all persons consumption)							
Age group	**0–5 months**	**6–11 months**	**1 year**	**2–3 years**	**4–8 years**	**9–13 years**	**14–18 years**	**19+ years**
Mean	0.0	8.6	14.2	13.5	10.1	6.7	5.0	8.9
90th percentile	0.0	28.1	33.1	28.3	21.9	15.0	11.2	12.1

General population exposure to methyl acetate from environmental media and food (based on 90th percentile dietary exposure) ranged from 6 μg/kg bw/day to 43 μg/kg bw/day (refer to Appendix B, Table B-1). On the basis of available information, the predominant sources of exposure to methyl acetate from environmental media and food for the general population are considered to be diet and indoor air. It is expected that most dietary exposure to methyl acetate results from its natural occurrence in foods.

Products available to consumers

Methyl acetate functions as a perfume agent and solvent in cosmetics (European Commission 2008-) and is found in cleansers, exfoliants, eye makeup, moisturizers, face masks, nail polishes and nail polish removers in Canada (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

Methyl acetate has a very high vapour pressure and is expected to have low retention time on the skin for products that are not washed off. Although dermal exposure is expected to contribute to the overall exposure during use of the product, the primary route of exposure is considered to be inhalation.

Table 7-2 summarizes the estimates of air concentrations associated with the use of cosmetics containing methyl acetate for relevant age groups. These values represent the average air concentration over a 24-hour time period, considered relevant for comparison to the reference air concentration. Air concentration values were not estimated for rinse off cosmetics due to limited inhalation exposure potential. 24-Hour average air concentrations associated with use of makeup was considered to be less than 0.03 mg/m^3.

Table 7-2. Estimated inhalation exposures to methyl acetate from the use of certain cosmetics

Product scenario	Methyl acetate conc.[a]	Mean conc. on day of exposure[b] (mg/m^3)
Nail polish (19+ years)	30%	4.3
Nail polish (2-3 years)	30%	1.4
Nail polish remover (19+ years)	100%	9
Nail polish remover (2-3 years)	100%	3.6

Abbreviation: conc., concentration

[a] Personal communication, emails from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced.

[b] Air concentration estimates were derived using Consumer Exposure Web Model (ConsExpo Web 2016); see Appendix C-3 for information regarding input parameters.

In addition to cosmetics, methyl acetate is used in a variety of other products available to consumers that may result in exposure to the general population in Canada. Many of these products are aerosols, including kitchen cleaning/polishing products (SDS 2015a), automotive products (e.g., paint [SDS 2019], tire cleaning sprays [SDS 2014a], adhesive removers [SDS 2014b]), and aerosol adhesives (SDS 2018b). Non-aerosol products include paint removers (SDS 2018a), gutter sealants (SDS 2011), construction, roof and landscaping adhesives (SDS 2018c), garage floor coating products (SDS 2015b) and general purpose adhesives (SDS 2015c). Potential air concentrations associated with the use of these products available to consumers were estimated using ConsExpo Web (ConsExpo 2016) and are summarized in Table 7-3. As with cosmetics, the 24-hour time period was considered relevant for comparison to the reference concentration.

Table 7-3. Estimated mean 24-hour air concentrations for methyl acetate from the use of products available to consumers

Product scenario	Methyl acetate conc. in product	24-Hour air conc. on day of exposure[a] (mg/m^3)
Aerosol cleaner/polish	2.5–10%	0.73
Aerosol automotive spray paint (e.g., tire rims)	5–26%	34
Aerosol spray tire cleaner (automotive)	60%	6
Trigger spray tire cleaner	60%	7.4
Aerosol adhesive remover (automotive)	80%	0.6
Aerosol adhesive (automotive/household)	40%	52
Construction adhesive; joint assembly	1–5%	10
Tube glue	50–100%	3.4 - 6.4
Aerosol lubricant	10%	0.94
Paint remover[b] - small project (lower/higher ventilation rate) - large project (lower/higher ventilation rate) - bathtub	70%	79 / 246[c] 712 / 2153[c] 1136
Garage floor coating	15% (mix/load) 10% (application)[d]	44

Abbreviation: conc., concentration

[a] Air concentration estimates were derived using Consumer Exposure Web Model (ConsExpo Web 2016); see Appendix C-3 for information regarding input parameters as well as peak and event air concentrations.

[b] Paint remover scenarios were divided into several scenarios: two sizes of projects (small and large), each under two ventilation conditions and a bathtub scenario. Details are provided in Appendix C-3.

[c] Two air concentration values represent the two ventilation scenarios.

[d] 15% represents the amount of substance in one component of a two-component product; once mixed, the applied product contains 10% of substance.

In addition to the products referred to above, methyl acetate was reported to be emitted from building materials in Canada, including caulking, hardwood flooring, medium density fiberboard and oriented strand board (Won and Lusztyk 2011). Chamber air concentrations ranged from 0.03 $\mu g/m^3$ to 98.2 $\mu g/m^3$ at 24 hours (Won and Lusztyk 2011). This source of exposure is considered to be addressed by the characterization of exposure from other scenarios in Table 7-3 (e.g., aerosol cleaner polish), which result in concentrations likely higher than those emitted from building materials.

Health effects assessment

The health effects characterization of methyl acetate in this assessment was informed by the European Union Risk Assessment Report for methyl acetate (EU RAR 2003). A

literature search was conducted from the year prior to the EU RAR (i.e., January 2002) to December 2020. No health effects studies that could impact the risk characterization conducted in the EU RAR (i.e., result in different critical endpoints or lower points of departure than those stated in EU RAR 2003) were identified for methyl acetate. The main metabolite of methyl acetate, methanol, was reviewed internationally by ECHA (2015a, 2016a) and the US EPA (2013a, 2013b); these reviews also informed the health effects assessment of methyl acetate. A literature search for methanol was conducted up to the period of April 2020 and no studies that could result in a different health effects assessment from that of these agencies was identified. Methanol was reviewed in the draft screening assessment for the Alcohols Group under the CMP (ECCC, HC 2022).

The EU RAR (2003) provided a summary of the toxicokinetics of methyl acetate. After absorption, methyl acetate undergoes rapid hydrolysis to form methanol and acetic acid by non-specific esterases present in the blood and tissues. The systemic availability of methyl acetate is low. From the available *in vitro* data, the half-life of methyl acetate in blood was estimated to be 2 to 3 hours in rats and about 2 hours in humans. Immediately after a 6-hour inhalation exposure to rats (2000 parts per million [ppm] or 6040 mg/m^3), blood concentrations were determined to be below the limit of quantification (less than 4.6 mg/L), indicating hydrolysis and high clearance of the substance (EU RAR 2003).

Repeated-dose toxicity

The EU RAR (2003) indicates that there are no repeated-dose studies available for methyl acetate following oral or dermal exposure, and no subchronic or chronic inhalation studies were identified. Data from the main metabolite of methyl acetate, methanol, have been reviewed by the EU in its assessment of methyl acetate. However, inhalation studies in which animals were exposed to methanol were deemed to be of lower quality than a short-term inhalation study for methyl acetate presented below (EU RAR 2003).

A short-term repeated-exposure study in which Sprague-Dawley rats were exposed to methyl acetate via the inhalation route was identified by the EU RAR (2003) as the basis for their selection of critical effect level for both local and systemic effects. In this study, test animals (10/sex/dose) were exposed to methyl acetate (nose-only) at concentrations of 0, 75, 350 or 2000 ppm (mean analytical concentrations 79, 335 and 2018 ppm, equivalent to 227, 1057, and 6040 mg/m^3, respectively), 6 hours daily, 5 days per week for 28 days. A no-observed-adverse-effect concentration (NOAEC) of 350 ppm (1057 mg/m^3) was identified by the EU RAR (2003) based on observed degeneration/necrosis of the rat olfactory mucosa at the next concentration of 2000 ppm (6040 mg/m^3). These were considered to be site-of-contact effects. With respect to systemic effects, the low and mid-concentrations were associated with reduced cholesterol levels and changes in adrenal and thymus weights. However, these changes were qualified as “slight” and only occurred in female animals. At the highest concentration, there were effects on both sexes, including decreased body weight and

food consumption, decreased cholesterol levels, increased alanine aminotransferase activity, increased adrenal weight, increased diuresis, decreased thymus weights, and increased levels of erythrocytes, hemoglobin, hematocrit, and calcium (HMR 1999a, as cited in EU RAR 2003). Although no morphological changes were observed, the EU RAR (2003) indicated that the aforementioned findings represented minimal adverse effects related to treatment with methyl acetate and derived a systemic NOAEC of 1057 mg/m^3 on the basis of the effects observed at the next concentration of 6040 mg/m^3.

No chronic, repeated-dose exposure studies are available for methyl acetate.

Reproductive/developmental toxicity

There are no data available on the reproductive toxicity of methyl acetate. Due to the rapid hydrolysis of the substance, the EU RAR (2003) considered it justified to base the characterization of reproductive and developmental effects of methyl acetate on its main metabolite, methanol, for which developmental effects have been demonstrated in rodents (EU RAR 2003).

The US EPA (2013a) evaluated various methanol toxicity studies comprising data from different species and endpoints and derived a reference dose (RfD) of 2 mg/kg bw/day and a reference concentration (RfC) of 20 mg/m^3 based on developmental effects. The RfD and RfC values were calculated for a population with a background blood level of methanol at or below 2.5 mg/L as a result of metabolism and consumption of foods (fruits and vegetables) with naturally occurring methanol. Developmental effects included skeletal (cervical rib or supernumerary rib) malformation, cleft palate, and exencephaly in mice pups in the absence of any maternal toxicity, reduced brain weight in adult and developing rat pups, and indications of developmental effects in monkeys following repeated-dose inhalation exposure (Kavet and Nauss 1990; Burbacher et al. 1999a, 1999b, 2004a, 2004b; Rogers et al. 1993; NEDO 1987; Fisher et al. 2000, OECD 2004). The US EPA indicated that these studies showed consistent developmental effects at similar doses in mice and rats. Notably, the biological significance of these effects is considered relevant to humans as increase in SNR and decrease in brain weight may occur in humans and are considered adverse effects (US EPA 2013a, 2013b; Chernoff 2004). Due to the developmental nature of the effects, the reference dose and reference concentration are considered relevant to both short- and long-duration exposures. The US EPA noted that although there are uncertainties regarding the relevance to humans of the effects seen in rodents, there was sufficient evidence of potential developmental effects in primates, as well as a lack of knowledge about the metabolism of methanol in human infants, to justify the use of the rodent studies to determine inhalation and oral points of departure. The RfD and RfC values for methanol (2 mg/kg bw/day and 20 mg/m^3, respectively) were adjusted to reflect exposure to methyl acetate (4.6 mg/kg bw/day and 46 mg/m^3, respectively) assuming methyl acetate is immediately degraded to methanol at a molar ratio of 1.

The ECHA Committee for Risk Assessment (RAC) determined that based on available information there was insufficient evidence for classifying methanol for developmental toxicity in humans (ECHA 2015a). They concluded that the most relevant endpoint for general population exposure via the inhalation and dermal routes was transient neurological effects and supported a derived-no-effect level (DNEL) of 43.3 mg/m^3 and 6.66 mg/kg bw/day for these routes of exposure based on existing EU indicative occupational exposure limit values. ECHA subsequently proposed an oral DNEL of 88 mg/kg bw to be protective of acute methanol toxicity by ingestion. This DNEL was based on significantly reduced visual acuity at 260 mg/kg bw (ECHA 2016b).

Short-duration exposures to airborne methyl acetate in humans has been reported to result in irritation of the eyes, nose, throat, and trachea from exposure to approximately 15000 mg/m^3 (Reus 1933, as cited in EU RAR 2003). Other effects such as visual disorders, central nervous system symptoms, difficulties breathing, etc, have also been reported, although these studies did not contain sufficient exposure information and/or were related to product mixtures.

The main metabolite of methyl acetate, methanol, has been reported to cause dizziness, headache, nausea, insomnia, blurred vision and conjunctivitis (US EPA 2005). In a workplace study, exposure to mean air concentration of 1060 ppm (1400 mg/m^3) of methanol was reported to cause significantly higher frequencies of headaches, nausea, dizziness and blurred vision in school teachers (Frederick et al. 1984). In another study, workers reported eye irritation following 25-minute exposure to 1025 ppm (1300 mg/m^3) of airborne methanol (NIOSH 1981). The methanol air concentrations resulting in these effects were used to estimate air concentrations of methyl acetate (assuming methyl acetate is immediately degraded to methanol at a molar ratio of 1) resulting in estimates of 2990 mg/m^3 to 3220 mg/m^3 (based on 1300 mg/m^3 and 1400 mg/m^3 of methanol, respectively).

Genotoxicity

The EU concluded that there is no concern with respect to genotoxicity for methyl acetate (EU RAR 2003). Methyl acetate was found to be negative in bacterial mutation tests, in the absence or presence of metabolic activation (EU RAR 2003). Negative results were also reported *in vivo* in a rat bone marrow micronucleus test in which animals (5/sex/group) were exposed through inhalation at doses of 75, 350, and 2000 ppm for 6 hours, 5 days per week for 28 days (HMR 1999b, as cited in EU RAR 2003). The genotoxicity potential of methanol has been reported to be negative in the majority of *in vitro* and *in vivo* assays (IPCS 1997; NTP 2004; OECD 2004).

Carcinogenicity

The EU RAR (2003) concluded that “no available data give relevant concern for carcinogenicity following exposure to methyl acetate.” There are no data on the carcinogenic potential of the metabolite acetic acid (EU RAR 2003). Methanol has not been classified as a carcinogen by the US EPA, International Agency for Research on

Cancer (IARC) or the National Toxicology Program (NTP) (Cruzan 2009; IARC 2018). Based on this information and the absence of evidence for a mutagenic potential for methyl acetate, the EU concluded that “methyl acetate is not suspected to be carcinogenic” (EU RAR 2003).

Characterization of risk

Methyl acetate has been reviewed by the EU. The EU RAR (2003) concluded that there is no evidence that methyl acetate may be associated with carcinogenic or genotoxic effects in the available empirical data for methyl acetate and its main metabolite, methanol.

Since the only reported effects observed following inhalation exposure to methyl acetate were site-of-contact effects and minor systemic effects (likely related to a stress response) at high concentrations, a quantitative risk characterization using a methyl acetate endpoint was not considered in this assessment. No reproductive or developmental toxicity studies were identified for methyl acetate.

Although developmental studies have not been identified for methyl acetate, potential developmental effects are associated with the main metabolite, methanol, and are considered in this assessment. The RfD and RfC for oral and inhalation exposure to methanol derived by the US EPA were 2 mg/kg bw/day and 20 mg/m^3, respectively. The RfD and RfC for methanol were adjusted on the basis of differences in molecular weight (assuming that, following exposure to methyl acetate, it is immediately degraded to methanol at a molar ratio of 1). When the methanol RfD and RfC values are adjusted to reflect exposure to methyl acetate, the resulting values are 4.6 mg/kg bw/day and 46 mg/m^3, respectively. The adjusted values were compared to estimated exposures of Canadians to methyl acetate.

The predominant routes of environmental exposure to methyl acetate for the general population are through natural occurrence in food and indoor air. Inhalation exposure may also occur as a result of the use of products available to consumers.

Table 7-4 presents relevant exposure values or air concentrations for methyl acetate compared to methanol RfC and RfD (adjusted for methyl acetate). These values were used in the characterization of human health risk from exposure to methyl acetate.

Table 7-4. Comparison of exposure or estimated mean 24-hour air concentrations with RfC/RfD for methanol (adjusted for methyl acetate)

Scenario	Exposure (mg/kg bw/day) or estimated mean 24-hr air concentrations (mg/m^3)[a]	Does exposure exceed RfD or RfC for methanol (adjusted based on exposure to methyl acetate)?
Environmental media and natural occurrence in food (oral chronic; 1-year-old)	0.043 mg/kg bw/day	No
Nail polish (30%)	4.3 mg/m^3	No
Nail polish remover (100%)	9 mg/m^3	No
Aerosol stainless steel polish (10%)	0.73 mg/m^3	No
Aerosol spray paint (automotive; 26%)	34 mg/m^3	No
Aerosol spray tire cleaner (automotive; 60%)	6 mg/m^3	No
Trigger spray tire cleaner (automotive; 60%)	7.4 mg/m^3	No
Aerosol adhesive remover (automotive; 80%)	0.6 mg/m^3	No
Aerosol adhesive (automotive/household; 40%)	52 mg/m^3	Yes
Construction adhesive – joint assembly (5%)	10 mg/m^3	No
Tube glue (100%)	6.4 mg/m^3	No
Aerosol lubricant (10%)	0.94 mg/m^3	No
Paint removers (70%): - small project - large project - bathtub	 79 – 246 mg/m^3 712 – 2153 mg/m^3 1136 mg/m^3	 Yes Yes Yes
Garage floor coating; (product: 15%; during application: 10%)	44 mg/m^3	No

Abbreviations: RfD, reference dose; RfC, reference concentration; hr, hour

[a] Air concentration values for methyl acetate reflect mean 24-hour concentrations on the day of exposure; the mean 24-hour air concentration considered relevant for comparison to the reference concentration derived from methanol.

Exposure to methyl acetate from environmental media and its natural occurrence in food is less than the RfD for methanol (adjusted for methyl acetate) and therefore is not considered to be of concern for human health. The contribution of intake from the potential use of methyl acetate as a flavouring agent in foods would be minimal compared to the total exposure from environmental media and natural occurrence in food.

The general population of Canada may also be exposed to methyl acetate via the inhalation route when using various products available to consumers containing the substance, including nail products, cleaning products, automotive products (e.g., aerosol paints, aerosol adhesives), adhesives (e.g., construction adhesives, tube adhesives), lubricants, paint removers, and floor coatings. All calculated 24-hour average air concentrations associated with the use of products available to consumers, except aerosol adhesives and paint removers, are below the RfC for methanol (adjusted for exposure to methyl acetate) and therefore are not considered to be of concern. In the case of paint remover (three scenarios), the estimated 24-hour average air concentrations are estimated to be above the RfC for methanol (adjusted to methyl acetate) and, as such, are of potential concern.

It is noted that concentrations higher than 15 000 mg/m^3 for airborne exposure to methyl acetate were observed to lead to irritation. Furthermore, concentrations higher than 1025 ppm (1300 mg/m^3) for airborne exposure to methanol (equivalent to approximately 2990 mg/m^3 methyl acetate) were observed to lead to irritation and dizziness following short-duration exposures in workers (US EPA 2005; Frederick et al. 1984; NIOSH 1980). Inhalation exposures for paint or varnish remover scenarios which lead to mean event or peak concentrations of methanol higher than this value may be self-limited by the discomfort that the user may feel while exposed to the product.

7.1.2 Methyl hexanoate

Exposure assessment

Methyl hexanoate was detected in fewer than 10% of the samples in two indoor air studies conducted in Canada. In the national Canadian indoor air study conducted in 2009-2011 as part of cycle 2 of the Canadian Health Measures Survey (CHMS), methyl hexanoate was detected in only 5% of the samples (95th percentile concentration was 0.18 µg/m^3) (personal communication, e-mail from Environmental Health Science and Research Bureau (EHSRB), HC, to ESRAB, HC, dated December 2012; unreferenced). In a study of indoor air in homes in Quebec City (sampling between November 2008

and March 2010), methyl hexanoate was only detected in 8% of the samples (maximum reported concentration of 0.33 μg/m^3) (Won and Lusztyk 2011).

Measured concentrations of methyl hexanoate in ambient air, water or dust were not identified in Canada.

General population exposure to methyl hexanoate from environmental media (indoor air) ranged from 0.06 μg/kg bw/day to 0.17 μg/kg bw/day.

Methyl hexanoate has been evaluated by JECFA as a food flavouring agent which concluded that the substance posed “no safety concern” based on current levels of intake when used as a flavouring agent (WHO 2009). In the absence of data on actual use, if any, in Canada, the per capita intake estimates for the US population derived by JECFA of 41 μg/person/day (1 μg/kg bw/day based on an average body weight of 60 kg for the general population) is an acceptable estimate of possible Canadian dietary exposure to methyl hexanoate from its potential use as a food flavouring agent for the general population (1 year of age and older) (WHO 2009; personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced).

Methyl hexanoate was identified in cosmetics, specifically nail moisturizing products, at concentrations of up to 10% (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Dermal exposure to methyl hexanoate was estimated assuming an application scenario of nail polish remover. The highest estimated exposure via the dermal route was estimated to be 5.4 mg/kg bw/day for the 9- to 13-year-old age group.

This substance was not reported to be imported or manufactured in Canada, and therefore releases from industrial sources are not expected.

Health effects assessment

A literature search was conducted up to December 2020. Only limited health effects information was identified. Methyl hexanoate showed negative results in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations of 8 μg/plate to 5000 μg/plate with and without metabolic activation (Anonymous 1996, as cited in ECHA c2007-2017d).

Following absorption, it is expected that methyl hexanoate undergoes hydrolysis by non-specific esterases present in the blood and tissues to form hexanoic acid (CAS RN 142-62-1) and methanol (CAS RN 67-56-1). Information on the two metabolites was examined to inform the human health assessment of methyl hexanoate.

Methyl hexanoate is also structurally similar to another ester of its subgroup, methyl dodecanoate (CAS RN 111-82-0). As methyl dodecanoate was identified as a potential analogue for methyl hexanoate, information for methyl dodecanoate was also examined to inform the human health assessment of methyl hexanoate.

Hexanoic acid

Repeated-dose toxicity

Hexanoic acid was reviewed by the OECD as part of the Aliphatic Acids Category assessment. In the OECD report (2014), it was concluded that repeated oral exposure (via gavage or diet) to aliphatic acids (including hexanoic acid) did not result in systemic toxicity, with no-observed-adverse-effect levels (NOAELs) greater than 1000 mg/kg bw/day. The OECD identified docosanoic acid (CAS RN 112-85-6) as the closest structural analogue with data to hexanoic acid. In a combined repeated-dose and reproductive/developmental toxicity test, rats (13/sex/group) were administered docosanoic acid by oral gavage at doses of 0, 100, 300, or 1000 mg/kg/day. For males, the exposure period was 42 days; for females, the exposure period was from 14 days prior to mating to day 3 of lactation (minimum of 39 days of exposure). The NOAEL was identified to be 1000 mg/kg bw/day on the basis that no deaths or changes in general condition, no changes in body weight gain or food consumption, and no adverse histopathological, hematological or biochemical effects occurred at any of the doses tested (OECD 2014).

No inhalation or dermal studies were identified.

Reproductive/developmental toxicity

The OECD (2014) identified docosanoic acid as the closest structural analogue with data to hexanoic acid. In the combined repeated-dose and reproductive/developmental toxicity test described earlier for docosanoic acid, no reproductive effects were identified up to the highest dose tested. The NOAEL for reproductive toxicity was greater or equal to 1000 mg/kg bw/day in males and females. There were also no effects on developmental parameters. The NOAELs for maternal and developmental toxicity were greater or equal to 1000 mg/kg bw/day (OECD 2014).

In the OECD report (2014), no effects on fertility or reproductive organs, and no developmental effects were observed in studies for the aliphatic acids examined in the report. The OECD indicated that the weight of evidence supports the lack of reproductive and developmental toxicity potential of the aliphatic acids.

Genotoxicity

Negative results were reported in an Ames test for hexanoic acid using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, with and without metabolic activation (OECD 2014). According to OECD (2014), aliphatic acids are not mutagenic or clastogenic *in vitro* or *in vivo*. The OECD stated that “the weight of evidence indicates that members of the aliphatic acids category [such as hexanoic acid] are not anticipated to be genotoxic.”

Methanol

Methanol was reviewed in the draft screening assessment for the Alcohols Group under the CMP (ECCC, HC 2022), and information is also summarized in section 7.1.1 (Health Effects Assessment) of this document. Using a similar approach to that presented in section 7.1.1, the RfC and RfD values for methanol derived by the US EPA (20 mg/m^3 and 2 mg/kg bw/day, respectively) were adjusted to reflect exposure to methyl hexanoate (resulting in adjusted values of 80 mg/m^3 and 8 mg/kg bw/day, respectively), assuming methyl hexanoate is immediately degraded to methanol at a molar ratio of 1.

Methyl dodecanoate

The assessment of this substance is presented in section 7.1.5. Methyl dodecanoate was considered by the OECD (2013) to have a "low hazard profile" based on the available dataset. There were no treatment-related adverse effects observed in a combined oral repeated-dose and reproductive/developmental toxicity screening test up to and including the limit dose[6] of 1000 mg/kg bw/day. Also, methyl dodecanoate was considered non-genotoxic *in vitro*. The OECD classified this substance as low priority for further work.

Characterization of risk

Following absorption, it is expected that methyl hexanoate undergoes hydrolysis by non-specific esterases present in the body to form hexanoic acid and methanol.

Hexanoic acid has been reviewed by the OECD (2014) as part of the Aliphatic Acids Category assessment. Repeated-dose oral (gavage or diet) exposure to aliphatic acids did not result in systemic toxicity. In addition, the OECD indicated that the weight of evidence supports the lack of reproductive and developmental toxicity potential of the aliphatic acids category. In addition, according to OECD (2014), members of the aliphatic acids category are not expected to be genotoxic.

Methanol is formed through hydrolysis of methyl hexanoate. Potential developmental effects associated with methanol are considered in this assessment. The RfC and RfD derived by the US EPA for inhalation and oral exposure to methanol (20 mg/m^3 and 2 mg/kg bw/day, respectively) were adjusted to reflect exposure to methyl hexanoate and resulted in values of 80 mg/m^3 and 8 mg/kg bw/day (assuming methyl hexanoate is immediately degraded to methanol at a molar ratio of 1). The reported maximum indoor air concentration (0.33 μg/m^3) and estimated exposure of the general population via indoor air and possible use as food flavouring agent is 0.001 mg/kg bw/day. The use of methyl hexanoate in cosmetics resulted in an exposure estimate of 5.4 mg/kg bw/day

[6] Limit dose is defined as the highest dose which should be used in the absence of a maximum tolerated dose (MTD), and is typically set at 1000 mg/kg bw/day (OECD 2013).

for the 9- to 13-year-old age group assuming all substance is absorbed via the dermal route. All exposure values are below the above noted methanol reference values (adjusted for methyl hexanoate exposure).

No genotoxic or carcinogenic potential has been observed for methanol.

Methyl hexanoate is structurally similar to methyl dodecanoate, which was considered by the OECD (2013) to have a “low hazard profile.”

Considering the available information for the metabolites and the analogue methyl dodecanoate, the risk to human health from exposure to methyl hexanoate is considered low.

7.1.3 Propyl acetate

Exposure assessment

As propyl acetate is considered to be of low hazard potential (see health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to propyl acetate.

Measured concentrations of propyl acetate in ambient air, indoor air, water or dust were not identified in Canada. Given its large volume of import into Canada (> 3 341 000 kg) and its high vapour pressure and water solubility, propyl acetate may be present in air and water. Volatilization from water surfaces is expected based on the value for Henry's law constant (2.18×10^{-4} atm-m^3/mol).

Propyl acetate has been evaluated as a flavouring substance by JECFA, which concluded that the substance posed no safety concern when used as a flavouring agent (WHO 1998). In Canada, propyl acetate has been identified for use in food packaging materials as a solvent in the manufacture of polyethylene, nitrocellulose, wax, and laminate-based products and as a component in inks and pigment-based materials, all with no potential for direct food contact (personal communication, email from FD, HC, to ESRAB, HC, dated March 15, 2021; unreferenced).

Propyl acetate was reported as an ingredient in a large number of cosmetic products available to consumers in Canada, primarily nail polishes. Reported concentration ranges for nail polishes are from less than 0.1% to 30% to 100% (personal communication, emails from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

Propyl acetate was also found in a range of products available to consumers in Canada including aerosol paints, automotive paints and adhesive products (SDS 2013a, 2015d, 2017a).

Health effects assessment

Propyl acetate has been reviewed by the OECD (2008), and this review was used to inform the health effects characterization in this assessment.

A literature search was conducted from the year prior to the OECD Screening Information Dataset (SIDS) Initial Assessment Report (SIAR) (January 2007) to December 2020. An additional report of a study examining reproductive toxicity was identified.

The OECD identified ethyl acetate (CAS RN 141-78-6) and *n*-butyl acetate (CAS RN 123-86-4) as structural analogues for propyl acetate. Both ethyl acetate and *n*-butyl acetate have similar toxicity profiles. However, effect levels are lower for ethyl acetate than for *n*-butyl acetate, and according to the OECD, it is expected that propyl acetate would have effect levels between those of these two substances (OECD 2008). Following absorption, propyl acetate is also rapidly hydrolyzed to *n*-propyl alcohol (CAS RN 71-23-8). Information on this substance was also examined by the OECD.

Repeated-dose toxicity

There were no repeated-dose inhalation studies available for propyl acetate. However, inhalation studies were available for *n*-propyl alcohol and the analogue substances, ethyl acetate and *n*-butyl acetate. The reported health effects of ethyl acetate and *n*-butyl acetate were primarily site-of-contact effects, generally at high concentrations. According to the OECD, similar site-of-contact effects on the nasal epithelium are expected in response to repeated inhalation exposure to propyl acetate.

For *n*-propyl alcohol, there was no mortality, no changes in organ weights, no changes in clinical chemistry, hematology or histopathology results, and no gross or microscopic lesions observed in Sprague-Dawley rats exposed via inhalation in a short-term (9 days), repeated-dose study (OECD 2008).

In a repeated-dose study conducted in rats exposed to ethyl acetate vapour for 6 hours/day, 5 days/week, for 13 weeks, the critical effect level and corresponding hazard endpoint was a lowest-observed-adverse-effect concentration (LOAEC) of 350 ppm (1280 mg/m^3), the lowest dose tested, based on necrosis of the olfactory epithelium in some rats. At the two highest dose levels (750 ppm or 2750 mg/m^3 and 1500 ppm or 5490 mg/m^3), all rats exhibited necrosis of the olfactory epithelium, as well as decreased food consumption, decreased body weight gains and a transient decrease in alertness to an auditory stimulus (OECD 2008).

Another subchronic inhalation study was conducted in rats with *n*-butyl acetate. Animals were exposed to *n*-butyl acetate vapour at 0, 500, 1500 or 3000 ppm (0, 2350, 7050 or 14100 mg/m^3) for 6 hours/day, 5 days/week, for 13 weeks. The critical effect level was identified as a NOAEC of 500 ppm (2350 mg/m^3) on the basis of multiple effects including signs of nasal irritation and necrosis of the olfactory epithelium observed in 10/20 rats (4 males and 6 females) exposed to 1500 ppm and in all animals at the highest concentration. Signs of stomach irritation were observed in females at the

highest concentration tested. Other effects observed were nasal discharge of porphyrin and decreased food consumption at all concentrations, decreased body weight gains and increased salivation at 3000 ppm, reductions in mean body weights and minimal reductions in activity at 1500 ppm and 3000 ppm, higher testes weights at 1500 ppm and 3000 ppm, higher adrenal weights in females at 1500 ppm and both sexes at 3000 ppm, and lower spleen and higher lung weights in males at 3000 ppm (OECD 2008).

On the basis of the results of subchronic neurotoxicity studies in rats exposed to ethyl acetate and *n*-butyl acetate via inhalation, the OECD concluded that both substances show only minimal neurological effects. No neurotoxicity was observed in a subchronic study conducted using *n*-butyl acetate up to the highest tested concentration of 3000 ppm (14 100 mg/m^3). The NOAEC was thus set at 3000 ppm (14 100 mg/m^3) (OECD 2008). In the case of ethyl acetate, the NOAEC for subchronic neurotoxicity was 750 ppm (2750 mg/m^3) on the basis of the decrease in motor activity observed in exposed female rats at 1500 ppm (5490 mg/m^3) (OECD 2008).

Reproductive/developmental toxicity

No reproductive and/or developmental toxicity studies were available for propyl acetate. This substance is currently listed on ECHA's Community Rolling Action Plan (CoRAP) to be evaluated (proposed to begin in 2022) due to concerns of wide dispersive use, exposure of workers, and "reprotoxic" potential identified on the basis of available data on propyl alcohol and *n*-butyl acetate.

On the basis of the data for the metabolite propyl alcohol and the analogue *n*-butyl acetate, the OECD found that inhalation of propyl acetate has the potential to induce reproductive and developmental toxicity (reversible changes in male fertility, fetal malformations and variations), but only at very high concentrations.

In one study identified for *n*-propyl alcohol, rats (18/sex/concentration) were exposed at concentrations of 0, 3500 or 7000 ppm (0, 8610 or 17 200 mg/m^3) for 7 hours/day, 7 days/week, for 62 days, prior to being mated with unexposed rats of the opposite sex. The NOAEC for female fertility was 7000 ppm (17 200 mg/m^3), and the NOAEC for male fertility was 3500 ppm (8610 mg/m^3) on the basis of a marked reduction in fertility in males exposed at the highest concentration (reversed after a 13-week recovery period) (OECD 2008).

For *n*-butyl acetate, a report of a two-generation toxicity study in rats exposed via inhalation to 0, 750, 1500, and 2000 ppm (equivalent to approximately 0, 3563, 7126, and 9502 mg/m^3) was identified (Anonymous 2010, as cited in ECHA c2007-2020a). No treatment-related adverse effects on reproduction were observed up to the highest tested concentration of 2000 ppm (9502 mg/m^3). Furthermore, in a subchronic study described earlier (OECD 2008), no effects on male fertility (no difference in testicular spermatid head counts or epididymal spermatozoa counts relative to controls) were observed at any of the concentrations tested (up to 14 100 mg/m^3). In another study in

which female rats were exposed to *n*-butyl acetate for 7 hours/day, 5 days/week, for 3 weeks prior to mating with unexposed males, no effects on female fertility (mating and reproductive performance) were observed at any of the concentrations tested (up to 7050 mg/m^3) (OECD 2008).

One developmental toxicity study was available for *n*-propyl alcohol. In this study, pregnant female rats were exposed at concentrations of 0, 3500, 7000 or 10 000 ppm (0, 8610, 17 200 or 24 600 mg/m^3, respectively) for 7 hours/day from gestation day (GD) 1 to 19. The NOAEC for maternal and developmental toxicity was 3500 ppm (8610 mg/m^3) on the basis of reduction of food intake in dams exposed to the two highest concentrations and decrease in maternal body weight gain at 10 000 ppm and increased pre- and post-implantation losses (resulting in increased resorptions and decreased live pups per litter), decreased fetal body weights and a dose-related increase in the incidence of skeletal, visceral and external malformations in rats exposed to 10 000 ppm and 7000 ppm (24 600 mg/m^3 and 17 200 mg/m^3, respectively) *n*-propyl alcohol (OECD 2008).

For *n*-butyl acetate, inhalation developmental toxicity studies have been conducted in rats and rabbits. In both studies, animals were exposed to *n*-butyl acetate for varying intervals during pregnancy. Both studies resulted in LOAECs for developmental toxicity of 1500 ppm (7.05 mg/L or 7050 mg/m^3) on the basis of maternal toxicity (decrease in food consumption and body weight gains) and increases in skeletal variations or anomalies, but no increase in fetal malformations, at the only dose tested (OECD 2008).

Genotoxicity

On the basis of the available data for propyl acetate (negative result in a bacterial mutation assay) and its metabolite and analogues (negative result for *n*-propyl alcohol and ethyl acetate in *in vitro* SCE assays and in an *in vitro* micronucleus test and negative results for ethyl acetate and *n*-butyl acetate in *in vitro* chromosomal aberrations assays), the OECD concluded that it is unlikely that this substance induces genotoxic effects *in vivo* (OECD 2008).

Carcinogenicity

There are no carcinogenicity studies for propyl acetate. No studies were available for *n*-propyl alcohol or the structural analogues *n*-butyl acetate and ethyl acetate (OECD 2008). In its assessment of acetate esters, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) concluded that, on the basis of the limited available information, substances in this group, such as propyl acetate, are not likely to be human carcinogens (AGDH 2014).

Characterization of risk

The OECD (2008) review was used to inform the health effects characterization of propyl acetate. The OECD (2008) considered the data on ethyl acetate and *n*-butyl

acetate, two structural analogues of propyl acetate, as well as the information on *n*-propyl alcohol, formed through hydrolysis of propyl acetate once absorbed.

Inhalation is a primary route of exposure to propyl acetate for the general population in Canada as a result of intermittent use of products available to consumers (e.g., nail products, aerosol paint products, adhesives). Oral exposure to propyl acetate may occur through the diet as a result of its potential use as a food flavouring agent. However, a JECFA evaluation of this use concluded that the substance posed “no safety concern” based on current levels of intake (WHO 1998).

The main reported health effects of ethyl acetate and *n*-butyl acetate following inhalation exposure were site-of-contact effects, generally at high concentrations. According to the OECD (2008), similar site-of-contact effects on the nasal epithelium are expected in response to repeated inhalation exposure to *n*-propyl acetate. Decreases in food consumption and body weight gain were also noted in repeated-dose studies, but no adverse effect of systemic toxicity was seen. Propyl acetate is unlikely to have genotoxic or carcinogenic potential. Changes in male fertility and developmental toxicity (fetal malformations and/or variations) were observed following exposure to *n*-propyl alcohol and the analogue *n*-butyl acetate. However, the changes in male fertility were reversible, the developmental effects were noted in presence of maternal toxicity (decrease food consumption and decrease in maternal body weight gain), and these effects were observed only at very high, excessive concentrations (male fertility at 17 200 mg/m^3 for *n*-propyl alcohol and developmental toxicity at 7050 mg/m^3 (skeletal variations only) and 17 200 mg/m^3 for *n*-butyl acetate and *n*-propyl alcohol, respectively). For the purposes of this screening assessment, propyl acetate is therefore considered to be of low hazard potential.

As propyl acetate is considered to be of low hazard potential, derivation of exposure estimates was not considered to be warranted, and the risk to human health is considered to be low.

7.1.4 Isobutyl acetate

Exposure assessment

As isobutyl acetate is considered to be of low hazard potential (see health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to isobutyl acetate.

Ambient air concentrations for isobutyl acetate were measured in four Canadian studies in Windsor, Regina, Halifax and Edmonton (Health Canada 2010a, b, 2012, 2013). Geometric mean ambient air concentrations were below the MDL, with maximum values ranging from below the MDL to 4.9 µg/m^3 (Health Canada 2010a, b, 2012, 2013). The detection frequency ranged from 0% to 17%.

Indoor air concentrations for isobutyl acetate were also measured across the same four Canadian studies referred to above. Geometric mean concentrations ranged from below the MDL to 0.15 µg/m^3, with maximum values ranging from below the MDL to 58.0 µg/m^3 (Health Canada 2010a, 2010b, 2012, 2013). Summary data for isobutyl acetate measured in indoor air in homes in Quebec City using passive sampling between November 2008 and March 2010 were also available (Won and Lusztyk 2011). Isobutyl acetate was detected in 64% of the samples. The geometric mean and maximum reported concentrations of isobutyl acetate in indoor air were 0.27 µg/m^3 and 3.0 µg/m^3, respectively.

Measured concentrations of isobutyl acetate in water or dust were not identified in Canada.

Isobutyl acetate has been evaluated as a flavouring substance by JECFA, which concluded that the substance posed “no safety concern” based on current levels of intake when used as a flavouring agent (WHO 1998). There is no definitive information available concerning the potential use of isobutyl acetate as a food flavouring agent in Canada, but its use, if any, as a food flavouring agent may result in oral exposure to the general population of Canada. Isobutyl acetate may be used as a component in the manufacture of food packaging materials with no direct food contact, and therefore dietary exposure is not expected (personal communication, email from RMB, HC, to ESRAB, HC, dated August 17, 2015; unreferenced).

Isobutyl acetate was identified in cosmetic products available to consumers in Canada, primarily nail products (personal communication, emails from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Use of these products may result in inhalation exposure to the substance.

Isobutyl acetate is found in a range of products available to consumers in Canada, including primers, putties, lacquers and aerosol paints (SDS 2014d, 2018d, 2018e). Use of these products may result in inhalation and dermal exposure to the general population in Canada.

Health effects assessment

Isobutyl acetate has been reviewed by the OECD (2003a), and this review informed the health effects characterization in this assessment. A literature search was conducted from the year prior to the OECD SIAR (January 2002) to December 2020. No additional health effects studies were identified.

Isobutyl acetate was considered by the OECD to cause skin, eye and respiratory tract irritation, as well as transient effects that may become evident only at high exposure levels. The OECD classified this substance as low priority for further work (OECD 2003a).

Exposure to isobutyl acetate via dermal, inhalation, and oral administration results in the rapid appearance of isobutanol (CAS RN 78-83-1) in the systemic circulation due to complete hydrolysis of the substance by esterase enzymes present in the skin, lungs, and gastrointestinal tract. Since exposure to isobutyl acetate results in systemic exposure to isobutanol, data for this substance were taken into consideration by the OECD for the assessment of the systemic toxicity of isobutyl acetate (OECD 2003a).

Repeated-dose toxicity

No repeated-dose toxicity studies for isobutyl acetate were identified. Two isobutanol studies were considered to be key studies by the OECD. It was concluded that "repeated exposures to moderate to high concentrations of isobutanol by the inhalation and oral routes of exposure are well tolerated in rats" (OECD 2003a).

A subchronic (90-day) study was conducted on rats via inhalation at concentrations of 0, 758, 3030, and 7575 mg/m^3 (0, 250, 1000, and 2500 ppm, respectively) isobutanol. The critical effect level identified by the OECD was a NOAEC of 3030 mg/m^3 based on very slight increases (9%) in red blood cell parameters (erythrocyte count, hemoglobin, and hematocrit measures) in female rats exposed to 7575 mg/m^3. The OECD noted that these slight changes were of questionable biological significance. No evidence of neurotoxicological effects were observed at any of the concentrations tested (up to 7575 mg/m^3) (OECD 2003a).

In a subchronic (13-week), gavage study conducted on rats (30/sex/group) exposed to isobutanol at doses of 0, 100, 316, and 1000 mg/kg bw/day, the critical effect level and corresponding hazard endpoint identified by the OECD was a NOAEL of 316 mg/kg bw/day, on the basis of hypoactivity and ataxia noted at the next dose level (1000 mg/kg bw/day), effects that were resolved after four weeks of recovery (OECD 2003a).

Reproductive/developmental toxicity

No reproductive and/or developmental toxicity studies were available for isobutyl acetate.

A two-generation inhalation reproductive toxicity study conducted in rats with isobutanol identified a critical effect level (NOAEC) of 7575 mg/m^3 on the basis of no parental systemic, reproductive, or neonatal toxicity at the highest dose tested (OECD 2003a).

In two developmental toxicity studies, rats and rabbits were exposed via inhalation at concentrations of 0, 0.5, 2.5 or 10 mg/L (0, 500, 2500, and 10 000 mg/m^3) isobutanol for 6 hours/day from GD 6 to GD 15 in rats and from GD 7 to GD 19 in rabbits. No developmental effects or fetotoxicity effects were observed at any of the concentrations tested in either species in either study (OECD 2003a).

Genotoxicity

Isobutyl acetate was not mutagenic in an Ames test using *Salmonella typhimurium*, indicating that this substance is not a genotoxicant (OECD 2003a). Furthermore, isobutanol was negative in an *in vivo* mouse micronucleus study in which isobutanol was administered once orally to male and female NMRI mice at doses up to 2000 mg/kg body weight (OECD 2003a).

Carcinogenicity

There are no carcinogenicity studies for isobutyl acetate. In its assessment of acetate esters, NICNAS (2014) concluded that, on the basis of the limited available information, substances in this group (such as isobutyl acetate) are not likely to be human carcinogens (AGDH 2014).

Characterization of risk

The OECD (2003a) review informed the health effects characterization of isobutyl acetate. Exposure to isobutyl acetate via the dermal, inhalation and oral routes results in the rapid appearance of isobutanol in the systemic circulation, and available information for isobutanol was considered by the OECD in its assessment of isobutyl acetate (OECD 2003a).

Exposure of the general population in Canada to isobutyl acetate is expected to occur primarily via inhalation from its presence in products available to consumers, including nail polishes, putties, primers and aerosol paints and from its presence in indoor or ambient air. Oral exposure may occur through the diet as a result of its potential use as a food flavouring agent.

No adverse systemic effects were observed in available studies for isobutanol (at doses up to 1000 mg/kg bw/day following subchronic oral exposure and at concentrations up to 7575 mg/m^3, the highest concentration tested, following subchronic inhalation exposure). In reproductive and developmental toxicity studies conducted with isobutanol, no parental, reproductive, or neonatal adverse effects were reported in animals exposed via inhalation to concentrations up to 10 000 mg/m^3. Isobutyl acetate is unlikely to have genotoxic or carcinogenic potential.

No adverse effects on the central or peripheral nervous system were observed in rats following subchronic oral and inhalation exposure to isobutanol. Only slight and transient effects were observed in exposed animals, such as reduction in response to an external stimulus in rats exposed via inhalation and hypoactivity and ataxia in rats exposed via gavage to 1000 mg/kg bw/day isobutanol for 13 weeks.

The OECD classified this substance as low priority for further work (OECD 2003a).

Considering the available health effects information for isobutanol, isobutyl acetate is considered to be of low hazard potential.

As isobutyl acetate is considered to be of low hazard potential, characterization of exposure potential (i.e., derivation of exposure estimates) was not warranted. The risk to human health is considered to be low.

7.1.5 Methyl dodecanoate

Exposure assessment

As methyl dodecanoate is considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure of the general population were not derived. This section provides general information on exposure to methyl dodecanoate.

Methyl dodecanoate is associated with a moderate volatility and low water solubility. Exposure of the general population to methyl dodecanoate may occur via the inhalation, oral or dermal route.

Won and Lusztyk (2011) monitored indoor air concentrations of methyl dodecanoate in homes in Quebec City between November 2008 and March 2010 using passive sampling and reported its detection in 6% of the samples. The geometric mean and maximum reported concentrations of methyl dodecanoate in indoor air were 0.63 $\mu g/m^3$ and 1.01 $\mu g/m^3$, respectively. Methyl dodecanoate was also identified in household dust collected from 50 dust samples from homes in Quebec City (Won and Lusztyk 2011). The geometric mean concentration of methyl dodecanoate in dust samples was reported to be 0.87 µg/g dust (detection frequency of 10%) with a maximum value of 18.7 µg/g dust.

Methyl dodecanoate has been evaluated as a flavouring substance by JECFA, which concluded that the substance posed “no safety concern” based on current levels of intake when used as a flavouring agent (WHO 1998). There is no definitive information available concerning the potential use of methyl dodecanoate as a food flavouring agent in Canada; however, its use, if any, as a food flavouring agent may result in oral exposure to the general population of Canada.

Methyl dodecanoate is found as a non-medicinal ingredient in a dermally applied prescription and/or non-prescription drug, and use of this product may result in dermal exposure to the general population in Canada. Methyl dodecanoate is also found in face moisturizers used as cosmetics.

Health effects assessment

OECD (2013) summarized the health effects literature for methyl dodecanoate. This assessment informed the health effects characterization in this screening assessment.

A literature search was conducted from the year prior to the OECD SIAR (January 2012) to December 2020. No additional health effects studies were identified.

Methyl dodecanoate was considered by the OECD to have a “low hazard profile” based on the available dataset. There were no treatment-related adverse effects observed in rats in a combined oral repeated-dose and reproductive/developmental toxicity screening test up to and including the limit dose of 1000 mg/kg bw/day. Also, methyl dodecanoate was considered non-genotoxic *in vitro*. No data were available on the carcinogenicity of this substance.

The OECD did not identify effects of concern for human health and classified this substance as low priority for further work. Methyl dodecanoate is therefore considered to be of low hazard potential.

Characterization of risk

As methyl dodecanoate is considered to be of low hazard potential, characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted, and the risk to human health is considered to be low.

7.1.6 Methyl butanoate

Exposure assessment

Methyl butanoate was measured in only 4% of indoor air samples in homes in Quebec City between November 2008 and March 2010, with a maximum reported concentration of 0.18 μg/m^3 (Won and Lusztyk 2011).

Measured concentrations of methyl butanoate in ambient air, water soil or dust were not identified in Canada. This substance was not reported to be imported or manufactured above reporting thresholds in Canada, and therefore releases from industrial sources are not expected.

Methyl butanoate has been evaluated as a flavouring substance by JECFA, which concluded that the substance posed “no safety concern” based on current levels of intake when used as a flavouring agent (WHO 1998). In the absence of data on actual use, if any, in Canada, the per-capita intake estimate for the US population derived by JECFA of 44 μg/person/day (0.73 μg/kg bw/day based on the average body weight of 60 kg for the general population) is an acceptable estimate of possible Canadian dietary exposure to methyl butanoate from its potential use as a food flavouring agent for the general population (1 year of age and older) (WHO 1998; personal communication, email from FD, HC, to ESRAB, HC, dated March 15, 2021; unreferenced).

Health effects assessment

A literature search was conducted up to December 2020. No health effects studies were identified.

Following absorption, it is expected that methyl butanoate undergoes rapid hydrolysis by non-specific esterases present in the blood and tissues to form *n*-butyric acid (CAS RN 107-92-6) and methanol (CAS RN 67-56-1). Available information on the two metabolites was examined to inform the human health assessment of methyl butanoate. Both *n*-butyric acid and methanol were reviewed under the CMP; *n*-butyric acid was reviewed as part of the screening assessment of the Carboxylic Acids Group (ECCC, HC 2019) and methanol was reviewed as part of the draft screening assessment of the Alcohols Group (ECCC, HC 2022).

Methyl butanoate is also structurally similar to another ester in this grouping, methyl dodecanoate (CAS RN 111-82-0). Available information on this substance was also considered in this assessment.

n-Butyric acid

Repeated-dose toxicity

n-Butyric acid was reviewed by the OECD (2003), and this review was used to inform the health effects characterization of this substance in the screening assessment of the Carboxylic Acids Group (ECCC, HC 2019).

The screening assessment of the Carboxylic Acids Group concluded that, on the basis of available information on the precursors of *n*-butyric acid (*n*-butanol and *n*-butyl acetate), *n*-butyric acid was not predicted to have carcinogenic or genotoxic potential and is not expected to cause reproductive and developmental effects. Systemic effects (e.g., increased testes weights and increased adrenal weights) were observed in experimental animals following repeated inhalation exposure to *n*-butyric acid for 13 weeks, but only at high doses (e.g., as high as 7128 or 14 256 mg/m^3), doses that are considered irrelevant to potential human exposure levels. In addition, only transient effects were observed at the highest dose tested in a repeated-dose oral study. *n*-Butyric acid was therefore considered to be of low hazard potential.

Methanol

Methanol was reviewed in the draft screening assessment for the Alcohols Group under the CMP (ECCC, HC 2022), and information is summarized in section 7.1.1 (Health Effects Assessment) of this document. Using a similar approach as that used for methyl acetate and methyl hexanoate for methyl butanoate (i.e., being immediately degraded to methanol at a molar ratio of 1), the methanol reference values were adjusted to reflect exposure to methyl butanoate to derive values of 6.4 mg/kg bw/day and 64 mg/m^3.

Methyl dodecanoate

The assessment of this substance is presented in section 7.1.5. Methyl dodecanoate was considered by the OECD (2013) to have a “low hazard profile” based on the available dataset. There were no treatment-related adverse effects observed in a

combined oral repeated-dose and reproductive/developmental toxicity screening test up to and including the limit dose of 1000 mg/kg bw/day. Also, methyl dodecanoate was considered non-genotoxic *in vitro*. The OECD classified this substance as low priority for further work.

Characterization of risk

Following absorption, it is expected that methyl butanoate undergoes hydrolysis to form *n*-butyric acid and methanol.

Both *n*-butyric acid and methanol have been assessed under the CMP (ECCC, HC 2019; ECCC, HC 2022). In the CMP assessment, *n*-butyric acid was considered to be of low hazard potential, and risk to human health from exposure to this substance was also considered to be low. No genotoxic or carcinogenic potential has been observed for methanol. Potential developmental effects associated with methanol are considered in this assessment. The RfC and RfD derived by the US EPA for inhalation and oral exposure to methanol (20 mg/m^3 and 2 mg/kg bw/day, respectively) were adjusted to reflect exposure to methyl butanoate, resulting in values of 64 mg/m^3 and 6.4 mg/kg bw/day, respectively (assuming methyl butanoate is immediately degraded to methanol at a molar ratio of 1:1). The reported maximum air concentration (0.18 μg/m^3) and intake (0.73 μg/kg bw/day) for methyl butanoate are well below the adjusted methanol inhalation and oral reference values.

Methyl butanoate is also structurally similar to another ester of subgroup A, methyl dodecanoate. Methyl dodecanoate was considered by the OECD (2013) to have a “low hazard profile.”

Considering the available information for the metabolites and the analogue methyl dodecanoate, the risk to human health from exposure to methyl butanoate is considered low.

7.1.7 Dimethyl glutarate

Exposure assessment

As dimethyl glutarate is considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to dimethyl glutarate.

Dimethyl glutarate is a liquid with a moderate vapour pressure and very high water solubility. No empirical data were found for dimethyl glutarate in ambient air, water or soil in Canada. However, it was identified to be present in household dust collected from 50 dust samples from homes in Quebec City (Won and Lusztyk 2011). The geometric mean concentration of dimethyl glutarate in dust samples was reported to be 0.34 µg/g dust (detection frequency of 32%) with a maximum value of 7.8 µg/g dust.

Dimethyl glutarate may be used as a component in an incidental additive (hand sanitizer) used in food processing establishments in Canada with no potential for direct food contact. Therefore, dietary exposure is not expected (personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced).

This substance is found in adhesives, cleansers, and nail polish remover products in Canada (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Use of these products may result in dermal or inhalation exposure to the general population in Canada.

Dimethyl glutarate is used in a variety of products available to consumers that may result in dermal or inhalation exposure to the general population in Canada, including premoistened towels or hand wipes, paint/varnish removers, sealants as part of countertop refurbishing kits, graffiti removers and air freshening products (SDS [date unknown], 2013b, 2015e; Household Products Database 1993-).

In past surveys performed in Denmark, dimethyl glutarate was detected at low levels in some products (e.g., toothbrushes, wooden children's toys, and sex toys (Svendsen et al. 2004; Nilsson et al. 2006; Hansen and Pedersen 2005). These surveys did not identify dimethyl glutarate as a substance for further analysis or prioritization.

Health effects assessment

Only limited health effects information was identified for dimethyl glutarate. However, available data were identified from a mixture, dibasic esters (DBE; CAS RN 95481-62-2). DBE mainly contains dimethyl glutarate (55% to 75%) and two other structurally similar constituents, dimethyl adipate (15% to 27%; CAS RN 627-93-0) and dimethyl succinate (10% to 25%; CAS RN 106-65-0) (US EPA 2014). The data from this mixture have been considered and were used to inform this human health assessment.

Repeated-dose toxicity

In a repeated-dose oral (gavage) study, DBE did not result in systemic toxicity to rats dosed daily for 1 month up to 1000 mg/kg bw/day, the highest dose tested (HPVIS 2017).

With respect to the dermal route, no treatment-related effects were observed when rats (10/sex/dose) were exposed up to 1000 mg/kg bw/day DBE, for 6 hours/day, 7 days/week, for 2 weeks (Anonymous 2000, as cited in ECHA c2007-2017e).

A subchronic inhalation (whole-body) study was conducted with dimethyl glutarate in rats. Test animals (36/sex/dose) were exposed to 0, 10, 50 and 400 mg/m^3 for 6 hours/day, 5 days/week, for 90 days. The NOAEC was 50 mg/m^3. In groups exposed to 400 mg/m^3, decrease in body weight gain was noted in males and decreased food consumption and degeneration/atrophy of the olfactory mucosa was observed in both sexes. There were also hormonal changes (e.g., decreased serum testosterone and

serum luteinizing hormone (LH) concentrations), but these effects were considered by the authors to not be of toxicological significance as the decrease in hormone levels did not result in a reduction of epididymal sperm count (HPVIS 2017; Anonymous 2000, as cited in ECHA c2007-2017f).

Another subchronic inhalation (whole-body) study was conducted in rats (10/sex/dose) exposed for 6 hours/day, 5 days/week, for 14 weeks, to 0, 160, 400 and 1000 mg/m^3 of the mixture DBE. Dose-related degenerative effects on the olfactory epithelium were observed at all dose levels; however, pathological examination of all other tissues, excluding nasal olfactory epithelium, demonstrated no effects from DBE exposure to concentrations up to 1000 mg/m^3. Decreased relative liver weights were reported in all exposed groups. However, according to the authors of the study, the biological significance of the liver effects is not known due to the absence of a recovery period and the lack of histopathological findings in the liver (HPVIS 2017; Anonymous 1987, as cited in ECHA c2007-2017g).

In another inhalation (whole-body) study, rats were exposed for up to 13 weeks to DBE. Test animals (40/sex/dose total) were exposed 6 hours/day, 5 days/week, to 0, 20, 76 and 390 mg/m^3. After 13 weeks, degeneration of the olfactory epithelium was present at all DBE concentrations in female rats but only at the mid and high concentrations in male rats, resulting in a LOAEC for females and NOAEC for males of 20 mg/m^3. At the end of the 6-week recovery period, histological changes associated with repair of the olfactory mucosa were noted. Liver weights of females exposed to 390 mg/m^3 were decreased compared to controls, but this effect was not observed at the end of the recovery period. A slight decrease in serum sodium concentration was observed after 13 weeks in all rats exposed at the two highest doses, which mostly resolved during the recovery period (Keenan et al. 1990; Anonymous 1987, as cited in ECHA c2007-2017h).

The US EPA (2014) suggested that the degeneration of olfactory mucosa was related to the hydrolysis of dimethyl glutarate by carboxylesterases located in the nasal/olfactory epithelium due to a dicarboxylic acid metabolite. According to the US EPA, these local effects are expected to be of much lower impact in humans because of major anatomical and physiological differences between rats and humans. Rats have a larger surface of nasal epithelium, different air flow and breathing pattern (rats are obligate nose breathers), and greater carboxylesterase activity in nasal/olfactory epithelium than humans. *In vitro* studies with human nasal tissue homogenates suggest that metabolism of the mixture DBE in human nasal tissue is 100 to 1000 times less active than in rat nasal tissue. Given the absence of systemic toxicity and the expectation that humans would be much less sensitive to olfactory responses than rodents, the US EPA concluded that the local effects were not sufficiently adverse to be used as an endpoint for risk assessment (US EPA 2014).

Reproductive/developmental toxicity

In reproductive/developmental toxicity studies conducted with dimethyl glutarate and DBE, no reproductive and developmental effects were noted. The only effects observed

following inhalation exposure to those substances were site-of-contact effects (degeneration of olfactory mucosa) and decrease in food consumption and body weight gain in parental animals.

A one-generation study was conducted in rats for DBE via the inhalation route. Test animals (20/sex/dose) were exposed to 0, 160, 400 and 1000 mg/m^3 for 6 hours/day, 5 days/week, for 14 weeks prior to mating. No effect on mating performance, fertility, length of gestation, or progeny numbers, structure and viability was noted. However, a statistically significant decrease in pup weights was noted at birth and during weaning in the 1000 mg/m^3 group in presence of parental toxicity. The NOAEC for parental toxicity was 160 mg/m^3 on the basis of decreased body weight and a decrease in relative liver weight and presence of mild to moderate olfactory epithelium squamous metaplasia in both sexes at higher concentrations (Anonymous 1988 and 1998, as cited in ECHA c2007-2017i; Kelly et al. 1998).

A developmental study was conducted in rabbits with dimethyl glutarate via the inhalation route. Test animals (22 females/dose) were exposed (whole body) to 0, 30, 100, 300 and 1000 mg/m^3, 6 hours/day from GD 7 to GD 28. The NOAEC for developmental toxicity was 1000 mg/m^3, on the basis of no developmental effects observed. The NOAEC for maternal toxicity was 100 mg/m^3, on the basis of decrease in body weight gain from 300 mg/m^3. Food consumption was also significantly decreased at 1000 mg/m^3 (Anonymous 2003, as cited in ECHA c2007-2017j).

A developmental study was also conducted in rats with DBE via the inhalation (whole-body) route. Test animals (20-24 females/dose) were exposed to 0, 160, 400 and 1000 mg/m^3, 6 hours/day from GD 7 to GD 16. Dams were sacrificed on GD 21. The NOAEC for developmental toxicity was 1000 mg/m^3, on the basis of no developmental effects observed. The NOAEC for maternal toxicity was 160 mg/m^3, the lowest concentration tested, on the basis of a significant decrease in maternal body weight and food consumption at 400 mg/m^3 and an increase in perinasal staining and wet fur (significant at the highest concentration) (Alvarez et al. 1995; Anonymous 1995, as cited in ECHA c2007-2017k).

Genotoxicity

Dimethyl glutarate was negative in bacterial mutation assays using *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535, with and without metabolic activation (NTP 2016). Dimethyl glutarate did not demonstrate mutagenic potential in the *in vitro* HPRT (hypoxanthine-guanine phosphoribosyl transferase) cell mutation assay using Chinese hamster ovary cells, with and without metabolic activation (Anonymous 2002, as cited in ECHA c2007-2017l). Negative results were also reported for DBE in an *in vitro* mammalian chromosomal aberration assay conducted with human peripheral blood lymphocytes, with and without metabolic activation (HPVIS 2017).

In *in vivo* assays, dimethyl glutarate did not cause chromosomal damage or bone marrow cell toxicity in rats (5/sex/dose) exposed to up to 2000 mg/m^3 via inhalation

(whole-body) 6 hours/day for 2 days (Anonymous 2001, as cited in ECHA c2007-2017m; Huntingdon Life Sciences, Ltd 2001, as cited in HPVIS 2017).

Carcinogenicity

There are no data on the carcinogenic potential of dimethyl glutarate and the mixture DBE. However, the US EPA concluded that dimethyl glutarate did not show special alerts and was not expected to be carcinogenic in humans (US EPA 2014).

Characterization of risk

Only limited health effects information was identified for dimethyl glutarate. Available data have been identified from the mixture DBE, which is composed mainly of dimethyl glutarate and two other structurally similar components, dimethyl adipate and dimethyl succinate.

In repeated-dose oral and dermal studies (short-term to subchronic durations), no effects were observed in animals administered doses up to 1000 mg/kg bw/day. In inhalation studies, the only effects noted were reversible, such as decrease in food consumption and body weight gain, as well as site-of-contact effects (degeneration of olfactory mucosa). These site-of-contact effects could be considered transient based on evidence of repair of the mucosa 6 weeks post exposure (Keenan et al. 1990; Anonymous 1987, as cited in ECHA c2007-2017h) and may not be relevant to humans given differences in sensitivity to olfactory responses between humans and rats (US EPA 2014). While decreases in relative liver weight were noted in rats in a subchronic and a one-generation study with DBE, these decreases were not associated with histopathological findings in the liver and were transient and reversible. No reproductive or developmental effects were noted in animals exposed to concentrations up to 1000 mg/m^3. The US EPA concluded that dimethyl glutarate does not show special alerts and is not expected to be carcinogenic in humans (US EPA 2014). No evidence for genotoxicity was observed in the available empirical data for either substance.

Considering the available data for dimethyl glutarate and the mixture DBE, dimethyl glutarate is considered to be of low hazard potential, and therefore characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted. The risk to human health is considered to be low.

7.1.8 Tetradecyl tetradecanoate

Exposure assessment

As tetradecyl tetradecanoate is considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to tetradecyl tetradecanoate.

Tetradecyl tetradecanoate is a solid with negligible vapour pressure and very low water solubility. No empirical data were found for tetradecyl tetradecanoate in air (indoor or ambient), water, dust or soil in Canada.

Tetradecyl tetradecanoate may be used as a component in an incidental additive (hand cleaner) used in food processing establishments with no potential for direct food contact, and therefore dietary exposure is not expected (personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced).

In cosmetics, tetradecyl tetradecanoate is often identified as myristyl myristate. It is found in over 900 cosmetics in Canada, including antiperspirants/ deodorants, bath products, hair products, skin products, bleach, cleansers, fragrance products, massage products, nail polish, shampoo, shaving products, and sunless tanning products (email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Use of these products may result primarily in dermal exposure to the general population in Canada.

Tetradecyl tetradecanoate is found as a non-medicinal ingredient in topically applied natural health products and prescription and/or non-prescription drugs in Canada, including makeup, antiperspirants, moisturizers, sunscreens, and lip balms, with some products specifically for use on children. These products may result in dermal or oral exposure to the general population in Canada.

Health effects assessment

Limited health effects information was identified for tetradecyl tetradecanoate. After absorption, it is expected that tetradecyl tetradecanoate (also named tetradecyl myristate) undergoes rapid hydrolysis to a fatty acid (myristic acid; CAS RN 544-63-8) and long-chain alcohols (tetradecanol [CAS RN 112-72-1] and alcohols, C14-15 [CAS RN 75782-87-5]). Myristic acid has been reviewed by the OECD (2014) as part of the Aliphatic Acids Category assessment. Tetradecanol and C14-15 alcohol have also been reviewed by the OECD (2006) as part of its assessment of long-chain alcohols. These reviews were used to inform the health effects characterization of tetradecyl tetradecanoate. A literature search was conducted from the year prior to the publication of the OECD assessments up to December 2020, and no additional health effects studies which could result in points of departure lower than those identified by OECD (2006, 2014) were identified.

Hazard data from analogues were also used to inform the health effects assessment of tetradecyl tetradecanoate. Analogues were identified on the basis of structural similarity, similarity in physical-chemical properties, data availability, and the subgroupings used in Cosmetic Ingredient Review (CIR) reports (Becker et al. 2010; CIR 2013). These analogues include propylheptyl caprylate (CAS RN 868839-23-0), ethylhexyl laurate (CAS RN 20292-08-4), isodecyl laurate (CAS RN 94247-10-6), isopropyl myristate (CAS RN 110-27-0), isodecyl oleate (CAS RN 59231-34-4), tetradecyl oleate (CAS RN 22393-85-7), behenyl behenate (CAS RN 17671-27-1), and 2-ethylhexyl stearate (CAS RN 22047-49-0) (see section 2.1 and Appendix A for more information on the structures

and physical-chemical properties, respectively). Literature searches were conducted up to June 2017 for these substances.

Toxicokinetics

No toxicokinetics data have been identified for tetradecyl tetradecanoate and its analogues. Only limited data have been identified for its expected metabolites, myristic acid, tetradecanol and alcohols, C14-15. Long (>12 carbon) chain aliphatic acids, such as myristic acid, are absorbed in the intestine and distributed in the blood as chylomicrons (OECD 2014). Aliphatic alcohols are efficiently eliminated and therefore not expected to have a tissue retention or bioaccumulation potential (Bevan 2001). Aliphatic alcohols are efficiently metabolized, and the biotransformation products are very similar or indistinguishable from those derived from common dietary sources (triglycerides).

Repeated-dose toxicity

There are no data available on the repeated-dose toxicity of tetradecyl tetradecanoate. Available data were identified via the oral route for its metabolites and analogues. However, no inhalation or dermal studies were identified.

In OECD (2014), repeated-dose oral (gavage or diet) exposure to aliphatic acids, including myristic acetate, a metabolite of tetradecyl tetradecanoate, did not result in systemic toxicity, with NOAELs greater than 1000 mg/kg bw/day. The OECD identified docosanoic acid (CAS RN 112-85-6) as the closest structural analogue with data to myristic acid. In a combined repeated-dose toxicity study with reproduction/developmental toxicity screening test, rats (13/sex/group) were administered docosanoic acid by oral gavage at doses of 0, 100, 300, and 1000 mg/kg bw/day. For males, the exposure period was 42 days; for females, the exposure period was from 14 days prior to mating to day 3 of lactation (minimum of 39 days of exposure). No deaths or changes in general condition, no changes in body weight gain or food consumption, and no adverse histopathological, hematological or biochemical effects were observed at any of the doses tested (OECD 2014).

Low systemic toxicity was expected for all routes following exposure for short-term and subchronic duration to tetradecanol/C14-15 alcohol, another metabolite of tetradecyl tetradecanoate. According to the OECD (2006), repeated exposure to aliphatic alcohols is generally without significant systemic toxicological findings, and the long-chain alcohols category is regarded to be of a low order of toxicity upon repeated exposure.

Information on the results of repeated-dose studies on the analogues of tetradecyl tetradecanoate was also collected.

In a subchronic, repeated-exposure study, rats were administered propylheptyl caprylate by gavage. Test animals (10/sex/dose) were exposed 7 days/week, for 90 days to 0, 100, 300 and 1000 mg/kg bw/day propylheptyl caprylate in soybean oil. No

test article-related mortality was noted. No substance-related clinical signs of toxicity, changes in body weights, feed consumption, or estrous cycle, or effects on sperm were observed, and there were no effects on any clinical chemistry or hematology parameters. Animals exposed to the highest dose showed a statistically significant increase in the absolute and relative liver weights. No other macroscopic or microscopic changes in the organs were noted. The changes in the liver weights were considered to be a non-specific adaptive change to the high workload of the liver at the maximum dose (LPT 2006; AGDH 2008).

In a short-term oral study, rats of both sexes (number not given) were administered doses up to 4500 mg/kg bw/day of isodecyl laurate, 6 days/week, for 4 successive weeks. No treatment-related changes were observed at any dose level (AGDH 1998; CIR 2013).

A dose range-finding study was conducted with isodecyl oleate to determine the appropriate dose levels for a combined repeated-dose toxicity study and reproduction/developmental toxicity screening test. In the study, rats (5/sex/dose) were exposed by gavage to 100, 300 and 1000 mg/kg bw/day of isodecyl oleate, 7 days/week, for 14 days. There was no mortality during the study period. No treatment-related clinical signs were observed. The body weight, body weight gain and mean food consumption were comparable between the control group and treatment groups during the study period. No gross pathological changes were observed, including the appearance and size of the gonads, adrenal glands, uterus, and accessory reproductive organs (Anonymous 2012, as cited in ECHA c2007-2017n).

In the combined repeated-dose toxicity study, rats (10/sex/dose) were exposed by gavage to 100, 300 and 1000 mg/kg bw/day of isodecyl oleate, 7 days/week. In males, the daily administration of the test item was started 2 weeks before mating and lasted until test day 35, which was 1 day before sacrifice. In females, the daily administration of the test item was started 2 weeks before mating and continued up to at least day 3 of lactation (maximum 56 days of treatment). The NOAEL in females was 300 mg/kg bw/day, based on a statistically significant decrease (-9.7%) in body weight during lactation and a statistically significant reduction (-21.7%) in food consumption at the next dose of 1000 mg/kg bw/day. No effects were observed in males at any dose (Anonymous 2013, as cited in ECHA c2007-2017o).

In a dose-ranging study, rats (3/sex/dose) were exposed by gavage to 100, 300, and 1000 mg/kg bw/day of tetradecyl oleate, 7 days/week, for 2 weeks. Minor changes were observed in organ weights, including decreases in the absolute and relative thymus weight (approximately -18%) in males receiving 1000 mg/kg/day and statistically significant decreases in absolute and relative kidneys weight (-12%, for absolute weights) in females receiving 1000 mg/kg/day. The NOAEL was determined to be greater than 1000 mg/kg bw/day in both males and females (Anonymous 2013, as cited in ECHA c2007-2017p).

In a combined repeated-dose toxicity study with reproduction/developmental toxicity screening test, rats (10/sex/dose) were exposed by gavage to 100, 300 and 1000 mg/kg bw/day of tetradecyl oleate, 7 days/week. In males, the daily administration of the test item was started 2 weeks before mating and lasted until test day 28 to 29, which was 1 day before sacrifice. In females, the daily administration of the test item was started 2 weeks before mating and continued until day 3 post-partum (maximum of 54 days of treatment). Statistically significant fluctuations of some biochemical parameters (mean group values) were recorded, such as increased glucose in males dosed with 100 and 1000 mg/kg bw/day (48%), increased urea in those receiving 100 mg/kg bw/day (19%), increased aspartate aminotransferases in females dosed with 300 mg/kg bw/day (35%), and decreased bilirubin (81%) and increased potassium (10%) in those treated with the highest dose when compared to controls. Due to the lack of dose- and sex-consistency and to the absence of other relevant findings, the above alterations were considered unrelated to treatment, and the NOAEL was considered to be 1000 mg/kg bw/day (Anonymous 2014, as cited in ECHA c2007-2017q).

In a dose range-finding study, rats (3/sex/dose) were exposed by gavage to 100, 500 and 1000 mg/kg bw/day of behenyl behenate, 7 days/week, for 2 weeks. No adverse effects were reported at any dose (Anonymous 2012, as cited in ECHA c2007-2017r). In a combined repeated-dose toxicity study with reproduction/developmental toxicity screening test, rats (10/sex/dose) were administered behenyl behenate at doses of 100, 300, and 1000 mg/kg bw/day by gavage. Males were exposed 2 weeks prior to mating and at least up to and including the day before sacrifice (day 49 of treatment). Females were exposed 2 weeks prior to mating and at least up to and including the day before sacrifice (day 4 postpartum). No effects were observed at any dose in either sex (Anonymous 2014, as cited in ECHA c2007-2017s).

In a short-term study, rats (10/sex/dose) were administered 0, 100, 500 and 1000 mg/kg bw/day of isopropyl myristate by gavage, 5 days/week, for 28 days. No treatment-related changes were observed at any dose tested (Anonymous 1983, as cited in ECHA c2007-2017t).

Reproductive/developmental toxicity

There are no data available on the reproductive toxicity of tetradecyl tetradecanoate. A summary of the available data for the two expected metabolites is provided.

In a combined repeated-dose and reproductive/developmental toxicity test described earlier for docosanoic acid, no effects on reproduction or on developmental parameters were observed at any dose (up to 1000 mg/kg bw/day) (OECD 2014). Additionally, no effects on fertility or on reproductive organs and no developmental effects were observed in studies conducted with aliphatic acids. The OECD indicated that the weight of evidence supports the lack of reproductive and developmental toxicity potential of the aliphatic acids category (OECD 2014).

In the OECD report (2006), it is concluded that the long-chain alcohols category, which includes tetradecanol/alcohols, C14-15, is considered without a potential for adverse effects on fertility and reproductive toxicity. Similarly, developmental toxicity studies conducted with aliphatic alcohols have confirmed the lack of maternal toxicity and potential developmental effects of these substances.

Information on reproductive/developmental toxicity of analogues of tetradecyl tetradecanoate was also identified.

In the combined repeated-dose and reproductive/developmental toxicity test described earlier for isodecyl oleate (Anonymous 2013, as cited in ECHA c2007-2017o), the NOAEL for reproductive toxicity was determined to be 300 mg/kg bw/day on the basis of a statistically significant increase in post-implantation loss, a non-statistically significant decrease in birth index, and an increase in the number of stillbirths, leading to a statistically significant reduction in the live birth index at the highest dose tested. The NOAEL for parental toxicity was also 300 mg/kg bw/day, based on a slight reduction in body weight and food consumption in females at the highest dose. No effect in males was reported.

In the combined repeated-dose and reproductive/developmental toxicity tests described earlier for tetradecyl oleate and behenyl behenate (Anonymous 2014, as cited in ECHA c2007-2017q, Anonymous 2014, as cited in ECHA c2007-2017s), no systemic or reproductive effects were observed for either substance.

A developmental study was conducted in which female rats were administered doses of 0, 100, 300, and 1000 mg/kg bw/day of 2-ethylhexyl stearate, once daily from GD 6-15. Dams were sacrificed on GD 20. No developmental effects were observed (Anonymous 2000, as cited in ECHA c2007-2017u).

Overall, tetradecyl tetradecanoate is not considered to have potential for reproductive and developmental toxicity. No effects were expected for the two main metabolites. Furthermore, no developmental effects were noted with the analogue 2-ethylhexyl stearate. While reproductive effects were noted in a study conducted with isodecyl oleate, these effects were noted only at the limit dose (1000 mg/kg bw/day) and in presence of maternal toxicity. No equivalent reproductive or parental effects were noted in similar reproductive/developmental toxicity tests conducted with the two analogues tetradecyl oleate and behenyl behenate.

Genotoxicity

Tetradecyl tetradecanoate showed negative results in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation (Anonymous 2000, as cited in ECHA c2007-2017v).

The OECD (2014) identified docosanoic acid as the closest structural analogue with data to the metabolite myristic acid. Negative results were observed when *Salmonella*

typhimurium strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2 uvrA were exposed to docosanoic acid in the presence and absence of metabolic activation. According to OECD (2014), the weight of evidence indicates that members of the aliphatic acids category are not expected to be genotoxic.

Negative results were reported in an Ames test for alcohols, C14-15. According to the OECD (2006), the available data show a consistent lack of mutagenic activity across the whole range of linear alcohols, which include tetradecanol/alcohols, C14-15. Long-chain alcohols do not have genotoxic potential.

Information on the genotoxic potential of analogues of tetradecyl tetradecanoate was also identified.

Propylheptyl caprylate was negative in a bacterial mutation test using *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, and TA1573, with and without metabolic activation. It was not clastogenic to Chinese hamster V79 lung fibroblasts in an *in vitro* mammalian chromosomal aberration assay (AGDH 2008).

For isodecyl laurate, negative results were observed in a bacterial mutation test using *Salmonella typhimurium* strains TA98, TA100, and TA102 (AGDH 1998; CIR 2013).

For isopropyl myristate, negative results were observed in bacterial mutation tests using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation (Anonymous 1981, as cited in ECHA c2007-2017w; Anonymous 2014, as cited in ECHA c2007-2017x).

Carcinogenicity

There are no data on the carcinogenic potential of tetradecyl tetradecanoate and its analogues.

Limited data have been identified for the metabolite tetradecanol/alcohols, C14-15. According to OECD (2006), development of skin tumours was not reported for several members of the long-chain aliphatic alcohol category (such as 1-hexanol, 1-octanol, 1-decanol, 1-dodecanol, 1-tetradecanol, 1-hexadecanol, and 1-octadecanol) in mouse skin painting studies using repeated applications for periods of up to 60 to 70 weeks (Sicé 1966; Bingham 1969; Van Duuren 1976), indicating no evidence of a carcinogenic potential for this category. Long-chain aliphatic alcohols do not contain structural elements of concern for potential interaction with DNA and are non-mutagenic (OECD 2006).

Characterization of risk

After absorption, it is expected that tetradecyl tetradecanoate undergoes rapid hydrolysis to a fatty acid (myristic acid) and a long-chain alcohol (tetradecanol or alcohols, C14-15). Myristic acid has been reviewed by the OECD (2014) as part of the

Aliphatic Acids Category assessment. Repeated oral exposure to aliphatic acids in laboratory animals did not result in systemic adverse effects at doses up to 1000 mg/kg bw/day. Also, no effects on fertility or reproductive organs, and no developmental effects were observed in studies conducted on aliphatic acids. Members of the aliphatic acids category are not expected to be genotoxic.

Tetradecanol and alcohols, C14-15, have been reviewed by the OECD (2006) as part of the assessment of long-chain alcohols. According to the OECD (2006), the long-chain alcohols category is considered to be of a low order of toxicity upon repeated exposure. The substances included in this category are also considered to have a low potential for adverse effects on fertility, reproductive and developmental toxicity. Long-chain aliphatic alcohols do not contain structural elements of concern for potential interaction with DNA and are non-genotoxic.

Data from analogues (propylheptyl caprylate, ethylhexyl laurate, isodecyl laurate, isopropyl myristate, behenyl behenate, isopropyl myristate) were also considered. Short-term and subchronic repeated-dose studies as well as combined repeated-dose and reproductive/developmental toxicity tests were identified for the analogues. No systemic toxicity was seen in experimental animals after repeated-dose exposure to levels up to 1000 mg/kg bw/day for all these analogues. In addition, available information indicates that analogues are expected to lack reproductive and developmental toxicity potential. Based on the available information, the analogues are unlikely to have a genotoxic potential.

Considering the available health effects data for the metabolites and analogues, tetradecyl tetradecanoate is considered to be of low hazard potential, and therefore characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted. The risk to human health is considered to be low.

7.1.9 2-Methoxypropyl acetate

Exposure assessment

Environmental media

No empirical data were identified for 2-methoxypropyl acetate in air, water or soil in Canada or elsewhere. 2-Methoxypropyl acetate is a liquid with a high vapour pressure and very high water solubility. Considering its physical and chemical properties, 2-methoxypropyl acetate may be present in air and water.

2-Methoxypropyl acetate is a potential impurity in 1-methoxy-2-propanol acetate (also known as propylene glycol monomethyl ether acetate, PGMEA or PMA) and has been reported to be present in the range of 0.3% to 0.5% (OECD 2003b). PMA has been reported to the National Pollutant Release Inventory since 2005, with reported releases in the range of 400 tonnes annually (primarily to air) (NPRI 2017). According to the NPRI, PMA is reported to be released to air by 71 facilities in Canada (ECCC 2019).

The US EPA SCREEN3 modelling tool (SCREEN3 2011) was used to estimate ambient air concentrations of PMA in Canada based on NPRI reported releases in 2019 and facility information, assuming that 2-methoxypropyl acetate may be present in PMA as an impurity up to 0.5%. One facility released approximately 33 tonnes of PMA to air in 2019 (ECCC 2019). At a 300-m distance (representing the distance from the source facility to residential areas), the daily (24-hour) air concentration of 2-methoxypropyl acetate was 4.61×10^{-3} mg/m3. Details on the SCREEN3 model and parameters used to derive this concentration are found in Appendix E

Concentrations of 2-methoxypropyl acetate in indoor air, drinking water and soil in Canada were estimated on the basis of its presence as a potential impurity in PMA and using the level III fugacity model known as ChemCAN (ChemCAN 2003). The total volume of use of PMA in Canada was not available, and therefore an upper bounding value of 100 000 tonnes (100 000 000 kg) of PMA in Canada was assumed. This volume of PMA was considered to be upper bounding for Canada as it was the reported value to be manufactured and/or imported into the European Economic Area (ECHA 2007-2017y). Assuming 2-methoxypropyl acetate may be present in PMA at up to 0.5%, 500 000 kg was considered to be an upper bound estimate of the total volume of 2-methoxypropyl acetate in use in Canada. The modelled concentrations for 2-methoxypropyl acetate derived from this approach were used to estimate exposure of the general population of Canada (see Table B-2, Appendix B).

General population exposure to 2-methoxypropyl acetate from environmental media ranged up to 0.44 μg/kg bw/day for 1-year-olds (see Table B-2, Appendix B).

Food

2-Methoxypropyl acetate may be used as a component in the manufacture of food packaging materials with no direct food contact, and therefore dietary exposure is not expected (personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

Products available to consumers

2-Methoxypropyl acetate (identified as 2-methoxypropyl-1-acetate) is on the list of ingredients that are described as prohibited for use in cosmetics in Canada (Health Canada [modified 2015]). In cosmetics, PMA (or methoxyisopropyl acetate) is on the list of ingredients that are described as restricted for use in cosmetics in Canada, with a maximum permitted concentration of 0.5% total of 2-methoxypropanol and/or 2-methoxypropyl-1-acetate (Health Canada [modified 2015]). Worst-case inhalation exposure estimates were derived assuming nail polish products contain 2-methoxypropyl acetate concentrations at less than 0.05% (assuming nail polish contains 10% PMA). The mean event concentration (i.e., during application) is estimated to be 0.12 mg/m^3, and the 6-hour time-weighted average air concentration is estimated to be 0.012 mg/m^3.

2-Methoxypropyl acetate has been noted in one product (an automotive scratch repair pen) (SDS 2017b). Exposure associated with this product is expected to be minimal. PMA, a potential source of 2-methoxypropyl acetate, is used in household products such as cleaners, paints, lacquers, and varnishes. In Canada, PMA has been identified in a range of products available to consumers, including aerosol paints and varnishes (SDS 2018f), automotive products such as spot putties (SDS 2020), scratch repair kits (SDS 2017b), rim dust blockers (SDS 2014e), and sealing products (SDS 2017c). Typical concentrations of PMA in products available to consumers is 5% to 15%, and occasionally as high as 20% (Dow 2015).

Although specific concentrations of 2-methoxypropyl acetate were not found in these products, inhalation exposure estimates were derived for sentinel products assuming a maximum concentration of 0.1% 2-methoxypropyl acetate (i.e., 20% PMA in products and PMA containing up to 0.5% 2-methoxypropyl acetate). Table 7-5 presents inhalation exposure estimates to 2-methoxypropyl acetate in products containing PMA. Although dermal exposure is expected to contribute to the overall exposure during use of products, given the high vapour pressure of 2-methoxypropyl acetate, the primary route of exposure is considered to be inhalation.

Table 7-5. Estimated exposures to 2-methoxypropyl acetate (based on concentrations of PMA) associated with the use of certain products

Product scenario	2-Methoxy-1-propyl acetate conc.	Mean event conc. (mg/m^3)	6-hour TWA conc. (mg/m^3)
Aerosol paint	0.1%	4.6	0.25
Putty/filler	0.1%	0.7	0.48

Abbreviations: conc., concentration; TWA, time-weighted average

Health effects assessment

2-Methoxypropyl acetate is classified as a reproductive toxicant (Repr 1B) on the harmonized classification and labelling table in Annex VI to the Classification, Labelling, and Packaging (CLP) Regulation (ECHA 2008).

2-Methoxypropyl acetate is rapidly hydrolyzed to 2-methoxypropanol via esterases in the body (DECOS 1993; ECETOC 2005a). 2-Methoxypropanol is then further metabolized to 2-methoxypropanoic acid, its principal metabolite. Health effects information available for these two substances is considered relevant to inform the health effects assessment of 2-methoxypropyl acetate.

2-Methoxypropanol has been assessed by Health Canada in a screening assessment under the CMP (EC, HC 2009). In that assessment, data on 2-methoxypropyl acetate and 2-methoxypropanoic acid were taken into consideration. A literature search was conducted for 2-methoxypropyl acetate, 2-methoxypropanol, and 2-methoxypropanoic acid from June 2007 (year of latest literature search in the screening assessment) to December 2020, and no additional health effects studies were identified. Further details

of toxicity studies considered in this assessment are found in the screening assessment of 2-methoxypropanol. A summary of this information is provided below (EC, HC 2009).

Repeated-dose toxicity

Hematological effects were observed in male rats following 10 days of oral exposure (gavage) to 1800 mg 2-methoxypropanol/kg bw/day or 2600 mg 2-methoxypropyl acetate/kg bw/day (Ma-Hock et al. 2005). When rats were exposed via inhalation to 2-methoxypropyl acetate at concentrations of 0, 600, 3000, and 15 000 mg/m^3, 6 hours/day, 5 days/week for 28 days, hematological and biochemical alterations were observed at the highest dose. Thymus atrophy as well as reduced body weight gain and respiratory irritation were also observed at this concentration (Ma-Hock et al. 2005).

Reproductive/developmental toxicity

Developmental effects were observed in both pregnant rats and rabbits exposed to 2-methoxypropyl acetate by inhalation. Effects included significantly increased fetal resorption, thoracic vertebral incision and split vertebrae (in rats at 14 900 mg/m^3) and malformations of sternum, paws, major blood vessels and heart (in rabbits at 3000 mg/m^3). Maternal toxicity was also observed (significantly reduced maternal body weights, respiratory and eye irritation, and sedation in rats at 3000 mg/m^3 and 14 900 mg/m^3 and reductions in maternal body weights in rabbits at 3000 mg/m^3) (ECETOC 2005a).

Pregnant rabbits exposed via inhalation to 2-methoxypropanol for 6 hours/day from GD 6 to GD 18 demonstrated dose-related, significantly increased fetal resorption and incidence of fetal visceral and skeletal malformations/variations and significantly reduced fetal body weights starting at doses from 843 mg/m^3 in the absence of maternal toxicity. The author identified the NOAEC to be 543 mg/m^3 (equivalent to a NOAEC of 796 mg/m^3 for 2-methoxypropyl acetate on the basis of a molecular weight conversion assuming same molar amount). Pregnant rats exposed to higher concentrations of 2-methoxypropanol had fetuses with thoracic vertebral incisions and split vertebrae (BASF 1986).

No information on potential developmental toxicity via oral administration of 2-methoxypropyl acetate and 2-methoxypropanol was identified. In an oral gavage study conducted in pregnant rabbits using 2-methoxypropanoic acid from GD 7 to GD 19, significantly increased fetal resorption and incidence of fetal variations and malformations (missing ribs, delayed ossifications, retrocaval ureter and paraovarian cyst) were observed at 78 mg/kg bw/day (equivalent to 99 mg 2-methoxypropyl acetate/kg bw/day, based on molecular weight conversion assuming same molar amount), with a NOAEL of 26 mg/kg bw/day (equivalent to 33 mg 2-methoxypropyl acetate/kg bw/day) (Carney et al. 2003).

Genotoxicity

There are no genotoxicity studies available for 2-methoxypropyl acetate in the literature and only limited data are available on the genotoxicity of 2-methoxypropanol. It did not induce gene mutation in Ames tests with various *Salmonella* strains, with or without metabolic activation (BASF 1988).

Carcinogenicity

With regard to the potential carcinogenicity or chronic toxicity of 2-methoxypropyl acetate, no long-term study has been identified.

Characterization of risk

Once absorbed, 2-methoxypropyl acetate is rapidly hydrolyzed to 2-methoxypropanol via esterases in the body (DECOS 1993; ECETOC 2005a). Available information for 2-methoxypropanol, and its principal metabolite, 2-methoxypropanoic acid, was therefore considered relevant to inform the health effects characterization of 2-methoxypropyl acetate.

The critical effect for characterization of risk to human health for 2-methoxypropyl acetate is developmental toxicity. Furthermore, 2-methoxypropyl acetate has been classified as reproductive toxicant (Repr 1B, may damage the unborn child) in the harmonized classification and labelling table in Annex VI to the Classification, Labelling, and Packaging (CLP) Regulation (ECHA 2008).

A NOAEC of 543 mg/m^3 for 2-methoxypropanol was identified in a developmental study of rabbits exposed via inhalation. The equivalent NOAEC for 2-methoxypropyl acetate was determined to be 796 mg/m^3 on the basis of a molecular weight conversion assuming same molar amount. At the next dose (843 mg/m^3), the effects were a significant increase in fetal resorption and in incidence of fetal visceral and skeletal malformations/variations and a significant reduction in fetal body weights, in the absence of maternal toxicity (Hellwig et al. 1994). For the oral route, the critical effect level was identified to be a NOAEL of 26 mg 2-methoxypropanoic acid/kg bw/day (equivalent to 33 mg 2-methoxypropyl acetate/kg bw/day on the basis of a molecular weight conversion assuming same molar amount) from a developmental study in which pregnant rabbits were administered 2-methoxypropanoic acid via gavage. In this study, fetal resorption and incidence of fetal variations and malformations, such as missing ribs, delayed ossifications, retrocaval ureter, and paraovarian cyst, were observed at 78 mg 2-methoxypropanoic acid/kg bw/day (equivalent to 99 mg 2-methoxypropyl acetate/kg bw/day) (Carney et al. 2003).

The general population may be exposed to 2-methoxypropyl acetate through environmental media, mainly air and water. Concentrations of 2-methoxypropyl acetate in environmental media were estimated from modelling approaches using an estimated total volume of PMA in commerce and assuming that 2-methoxypropyl acetate is present as a potential impurity (up to 0.5%) in PMA.

It was assumed that the general population of Canada may also be exposed to 2-methoxypropyl acetate when using various products containing PMA with 2-methoxypropyl acetate as a potential impurity. Cosmetics containing up to 10% PMA and aerosol paints and putty fillers containing up to 20% PMA were identified as representative products. Table 7-6 provides relevant exposure and hazard values for 2-methoxypropyl acetate as well as resultant margins of exposure (MOEs) for the characterization of risk.

Table 7-6. Relevant oral and inhalation exposure estimates, critical effect levels and resulting margins of exposure for 2-methoxypropyl acetate

Exposure scenario	Exposure	Critical effect level	Critical health effect endpoint	MOE
Total exposure from environmental media	0.00044 mg/kg bw/day	NOAEL = 33 mg/kg bw/day	Significantly increased fetal resorption and incidence of fetal variations and malformations	75 000
Nail polish (estimated high end inhalation scenario for cosmetics (0.05%) (inhalation intermittent)	0.012 mg/m^3	NOAEC = 796 mg/m^3 [a]	Significant increase in fetal resorption and incidence of fetal visceral and skeletal malformations/variations and significant reduction in fetal body weights	66 333
Aerosol paint (inhalation intermittent)	0.25 mg/m^3	NOAEC = 796 mg/m^3 [a]	Significant increase in fetal resorption and incidence of fetal visceral and skeletal malformations/variations and significant reduction in fetal body weights	3184
Putty filler (inhalation intermittent)	0.48 mg/m^3	NOAEC = 796 mg/m^3 [a]	Significant increase in fetal resorption and incidence of fetal visceral and skeletal malformations/variations and significant reduction in fetal body weights	1658

Abbreviations: MOE, margin of exposure; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level

[a] Molecular weight conversion from NOAEC = 543 mg/m^3

On the basis of the conservative approaches used in estimating exposure to 2-methoxypropyl acetate from environmental media and modelling inhalation exposure from the use of products available to consumers, it is considered that the calculated MOEs are adequate to account for uncertainties in the health effects and exposure datasets.

While exposure of the general population to 2-methoxypropyl acetate is not of concern at current levels, this substance is considered to have a health effect of concern on the basis of its potential for developmental toxicity. Therefore, there may be a concern for human health if exposures to 2-methoxypropyl acetate were to increase.

7.2 Subgroup B: Esters of di/tri- ols

7.2.1 Triacetin

Exposure assessment

As triacetin is considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to triacetin.

Triacetin is a liquid with a moderate vapour pressure and very high water solubility. The Henry's law constant indicates that triacetin is expected to be essentially non-volatile from water surfaces, and volatilization from moist soil surfaces is not an important fate process (HSDB 1983-).

Won and Lusztyk (2011) present summary data for triacetin measured in indoor air in homes in Quebec City using passive sampling between November 2008 and March 2010. Triacetin was detected in 76% of the samples, and the geometric mean and maximum reported concentrations in indoor air were 0.52 μg/m^3 and 7.77 μg/m^3, respectively. Triacetin was also identified to be present in household dust collected from 50 dust samples from homes in Quebec City (Won and Lusztyk 2011). The geometric mean concentration of triacetin in dust samples was reported to be 0.77 μg/g dust (detection frequency of 26%) with a maximum value of 8.6 μg/g. Measured concentrations of triacetin in ambient air or water in Canada were not identified.

Triacetin is a permitted food additive for use as prescribed on the *List of Permitted Food Additives with Other Accepted Uses*, and the *List of Permitted Carrier or Extraction Solvents*, incorporated by reference into their respective Marketing Authorization issued under the *Food and Drugs Act*. It has been evaluated as a flavouring substance by JECFA, which concluded that the substance posed “no safety concern” based on current levels of intake when used as a flavouring agent (JECFA 2002). However, there is no definitive information available concerning the potential use of triacetin as a food flavouring agent in Canada. Triacetin may be used as a component in an incidental

additive (lubricant) in food processing establishments with no potential for direct food contact, and therefore dietary exposure is not expected (personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced).

This substance is found in over 100 cosmetics in Canada, including adhesives, cleansers, exfoliants, makeup, makeup removers, massage products, and nail polishes. Concentrations range from less than 0.1% to 30% (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Use of these products may result in dermal or inhalation exposure to the general population in Canada.

Triacetin is used as a non-medicinal ingredient in more than 400 natural health products in Canada. Most products are taken via the oral route, with a small number of topical, dental, and sublingual applications (personal communication, email from NNHPD, HC, to ESRAB, HC, dated December 6, 2016; unreferenced). Triacetin is also used as a non-medicinal ingredient in more than 25 prescription and/or non-prescription drugs including topical, subcutaneous, transdermal, oral, vaginal and intracervical applications (personal communication, email from TPD, HC, to ESRAB, HC, dated December 6, 2016; unreferenced), resulting in exposure to those within the general population in Canada that may use these products.

Health effects assessment and characterization of risk

OECD (2002) summarized the health effects literature for triacetin. This assessment was used to inform the health effects characterization in this screening assessment.

A literature search was conducted from the year prior to the OECD SIAR (January 2001) to December 2020. No health effects studies that could result in a different health effects characterization from that of the OECD (2002) were identified.

Triacetin was considered by the OECD to have a “low hazard potential” based on the available dataset. There were no treatment-related adverse effects observed in experimental animals in repeated-dose oral and inhalation toxicity studies, at any of the oral doses (up to 10 000 mg/kg bw/day) or concentrations (2220 mg/m^3 to 73 700 mg/m^3 [saturation]) tested. No adverse effects were observed in a combined oral repeated-dose and reproductive/developmental toxicity screening test in which doses were tested at up to and including the limit dose of 1000 mg/kg bw/day. Also, taking all data into consideration, triacetin was considered non-genotoxic *in vitro*. No data were available on the carcinogenicity of this substance.

As mentioned in OECD (2002), the JECFA considers it unnecessary to assign an acceptable daily intake (ADI) for triacetin since this substance is metabolized like other triglycerides in food. JECFA concluded that based on the available data and anticipated daily intake, triacetin did not represent a hazard to health (OECD 2002). More recently, the EU’s Scientific Committee for Food endorsed this position in their evaluation of triacetin (OECD 2002).

The OECD did not identify effects of concern for human health and classified triacetin as low priority for further work. As such, it is considered to be of low hazard potential, and therefore characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted. The risk to human health is considered to be low.

7.2.2 C14-22 monoglycerides

Exposure assessment

Given that C14-22 monoglycerides are considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to C14-22 monoglycerides.

Exposure to C14-C22 monoglycerides by the general population of Canada is expected to be mainly via the oral route through food ingestion resulting from their use as permitted food additives in Canada.

C14-22 monoglycerides are included in the listings for two approved food additives in Canada, monoglycerides and mono- and di-glycerides, as set out in the List of Permitted Food Additives, and would therefore be an acceptable food additive for these approved uses in Canada. Mono- and diglycerides have been listed by the US FDA as substances affirmed as generally recognized as safe (GRAS) as direct human food ingredients (US eCFR 2017).

C14-22 monoglycerides may be used as a component in the manufacture of food packaging materials that are in direct contact with food. However, dietary exposure is expected to be minimal compared to exposure from use as a permitted food additive. It may also be used as a component in incidental additives (e.g., lubricants and release agents) in food processing establishments. Dietary exposure, if any, is considered to be negligible (personal communication, email from the FD, HC, to ESRAB, HC, dated November 23, 2015; unreferenced).

Health effects assessment and characterization of risk

No health effects studies on C14-22 monoglycerides were identified.

In the body, monoglycerides are metabolized like other triglycerides of food fats. Monoglycerides are metabolized to free fatty acids and glycerol, both of which are then available for the resynthesis of triglycerides in the intestinal mucosa. There is no evidence that the presence of monoglycerides or diglycerides of food fats has any deleterious effect on cells or tissues. In humans, mono- and diglycerides are consumed every day in any normal mixed diet and are also formed during the digestion and absorption of meals containing fat. No harmful effects have been specifically associated with mono- and diglycerides (WHO 1974). Consequently, JECFA assigned an

acceptable daily intake (ADI) without an explicit indication of the upper limit of intake ("not limited") to mono- and diglycerides (WHO 1974).

C14-22 monoglycerides are considered to be of low hazard potential, and characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted. The risk to human health is considered to be low.

7.3 Subgroup C: Esters of 2,2,4-trimethylpentane-1,3-diol with isobutyric acid

7.3.1 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate

Exposure assessment

Environmental media

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is a liquid with a moderate vapour pressure. Summary data for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate measured in indoor air in homes in Quebec City using passive sampling between November 2008 and March 2010 were presented by Won and Lusztyk (2011). Concentrations in indoor air ranged from 0.5 to 200.5 $\mu g/m^3$, with a geometric mean concentration of 6.55 $\mu g/m^3$ (and geometric standard deviation of 2.47). Won and Lusztyk (2011) noted emissions of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from water-based paints, acrylic floor polish, acoustic ceiling tiles, and polyurethane foam underpads. 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate has also been measured in emissions from solid building materials (vinyl flooring, carpet, carpet underpads, flooring adhesive composite, and polyurethane foam) up to 10,000 $\mu g/m^2/h$, as well as from liquid building materials (paint, primer, stains, varnish, caulking) up to 77 $\mu g/m^2/h$ (Won and Yang 2012). Won and Yang (2012) also noted emissions from products for consumers, such as artistic oil paints and candles, up to rates of 0.24 $\mu g/m^2/h$.

Internationally, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate was also measured in indoor air in several studies in the United States, Germany, Iceland, Estonia and Sweden, in sites including typical homes, newly manufactured and built homes, temporary housing units, storage rooms and classrooms (Sahlberg et al. 2013; Kim et al. 2007; Wieslander et al. 1997; Hodgson et al. 2000; Maddalena 2009; Markowicz and Larsson 2015; Choi et al. 2010). Average air concentrations from these studies ranged from 1.5 $\mu g/m^3$ to 73 $\mu g/m^3$.

In Sweden, two studies have examined personal air sampling for painters during an 8-hour working day (Norbäck et al. 1995; Wieslander and Norbäck 2010), with reported geometric mean concentrations ranging from 6 $\mu g/m^3$ to 10 $\mu g/m^3$ and maximum values of 14 $\mu g/m^3$ and 40 $\mu g/m^3$, respectively.

The highest Canadian indoor air concentration value for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate based on indoor air monitoring in Quebec City (200.5 μg/m^3) was used to estimate general population exposure.

Ambient air concentrations were collected at the same time as classroom indoor air in eight schools in Sweden (Kim et al. 2007). Eight 4-hour ambient samples were collected with values ranging from 0.24 μg/m^3 to 0.75 μg/m^3 and a mean concentration of 0.41 μg/m^3. No Canadian ambient air measurements for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate were identified. As a conservative approach, the maximum Canadian indoor air concentration value (200.5 μg/m^3) was applied to ambient air to estimate daily exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in the general population in Canada from environmental sources.

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is estimated to have moderate water solubility. Based on an estimated Henry's law constant value of 1.1 × 10^{-5} atm-m^3/mol, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate is expected to volatilize from water surfaces (HSDB 1983-). No data measuring 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in water in Canada were identified.

Fifty dust samples were collected from residences in Quebec City (Won and Lusztyk 2011). 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate was detected in 62% of the samples with a reported concentration range of 1.0 μg/g to 715 μg/g and a geometric mean value of 21.2 μg/g. The maximum concentration value in dust from this Canadian study (715 μg/g) was used as an input to estimate daily intake of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate to the general population from environmental sources.

General population exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from ambient air, indoor air and dust ranged from 41 to 148 μg/kg bw/day (see Table B-3, Appendix B). The highest exposed age group was 1-year-olds, and indoor air was identified as the greatest source of environmental exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate.

Food

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate may be used as a component in the manufacture of food packaging materials, with no direct food contact, and therefore dietary exposure is not expected (personal communication, e-mail from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

Biological monitoring

Two metabolites of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (specifically 2,2,4-trimethyl-1,3-pentanediol [TMPD] and 2,2,4-trimethyl-3-hydroxyvaleric acid [HTMV]) were analyzed in the urine in participants aged 3 to 79 years in cycle 5 (2016–2017) of the Canadian Health Measures Survey (CHMS). The toxicokinetics of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in humans are not well studied. Animal studies indicate

that the metabolites are mainly excreted in urine within 72 hours; a smaller fraction is eliminated in feces over a span of approximately 1 week (CIR 2017, as cited in Health Canada 2019). Animal studies report that 2,2,4-trimethyl-1,3-pentanediol diisobutyrate is predominantly excreted as the *O*-glucuronide of TMPD in urine, and to a much lesser extent as HTMV and its glucuronides, 2-methylmalonic acid, and unchanged 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (CIR 2017, as cited in Health Canada 2019). Data from cycle 5 of the CHMS indicate a detection frequency of greater than 95% in all population groups. The geometric mean urine concentration of TMPD (primary metabolite) for ages 3 to 79 years is 17 μg/L and the 90th percentile is 69 μg/L. The highest concentrations of TMPD are found in children aged 3 to 5 years (25 μg/L geometric mean; 140 μg/L 95th percentile) followed by children aged 6 to 11 years (23 μg/L geometric mean; 74 μg/L 90th percentile).

Products available to consumers

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is found in adhesives (eye), nail moisturizers, nail polishes, and nail polish removers in Canada (personal communication, emails from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

Dermal and inhalation exposure estimates were derived for these products at the highest notified concentration levels. As inhalation exposure to cosmetics was found to contribute less than 1% of the overall exposure, only dermal exposure estimates are presented.

Table 7-7 summarizes the dermal exposure estimates for cosmetics containing 2,2,4-trimethyl-1,3-pentanediol diisobutyrate based on sentinel scenarios (i.e., those product/concentration/age group combinations with the highest exposures). Details on the method and parameters used to estimate dermal exposures to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from cosmetics are available in Appendix C-3.

Table 7-7. Estimated dermal exposures to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from the use of cosmetics

Product scenario	Substance conc.[a]	External dermal exposure[b] (mg/kg bw/day)
Adhesive (eye) (based on mascara scenario; 4-8 years)	30%	0.23
Nail polish (2-3 years)	30%	1.2
Nail polish remover (9-13 years)	1%	0.54

Abbreviation: conc., concentration

[a] Personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced.

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is also found as a non-medicinal ingredient for the purpose of being a plasticizer in one natural health product, a

topically-applied wart remover. Exposure to this product was estimated assuming an application of approximately 0.1 mL (equivalent to 2 drops/day) and a concentration of 20% of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (based on the concentration of the medicinal ingredient [27%] and considering the other non-medicinal ingredients present in the product), resulting in 0.86 mg/kg bw/day and 0.48 mg/kg bw/day for 4- to 8-year-olds and 9- to 13-year-olds, respectively.

The general population of Canada may also be exposed to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate when using various products containing the substance including aerosol primers, pool paints, liquid hardeners/fiberglass resin repair kits, concrete crack repair kits, floor polishes and hobby paints (SDS 2012, 2013, 2015f, 2015g, 2016b, 2017d, 2017e). Table 7-8 summarizes inhalation and dermal exposure estimates for products available to consumers containing 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. Details on the method and parameters used to estimate exposures to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from cosmetics are available in Appendix C-3.

Table 7-8. Estimates of exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from use of products available to consumers

Product scenario	Substance conc.	Inhalation exposure (mg/kg bw/day)	External dermal exposure (mg/kg bw/day)	Total exposure[a] (mg/kg bw/day)
Aerosol primer[b] (19+ years)	5%	0.24	1.01	1.24
Marine/pool paint (19+ years)	5%	N/A	3.6	3.6
Liquid hardener; fiberglass repair kit (m/l and apply) (19+ years)	30% (0.5% during application)	0.014	0.21	0.22
Concrete crack repair product (19+ years)	40%	0.025	0.27	0.30
Hobby paint (2-3 years)	3%	N/A	0.1	0.1

Abbreviations: conc., concentration; N/A, not applicable

[a] Total exposure estimate is the combination of inhalation and dermal routes and assumes inhalation and dermal absorption is equivalent to absorption following oral intake.

[b] Based on spray model inputs as evaporation model resulted in lower air concentration estimates. Total exposure also includes oral (non-inhaled) particles.

Exposure estimates presented in Table 7-8 were considered to address other scenarios expected to result in lower exposure potential including use of marine hardener (2,2,4-trimethyl-1,3-pentanediol diisobutyrate concentration in product up to 60%, but small use volume [less than 1 mL]) and floor polish (2,2,4-trimethyl-1,3-pentanediol diisobutyrate concentration up to 0.5%, but applied with mechanical applicator).

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is used as a plasticizer and has been found in a range of articles, including products available to children.

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate has also been shown to migrate from baby bottles made from materials used as substitutes for polycarbonate in a study of baby bottles purchased in Belgium (Onghena et al. 2016), as well as from those available in the EU market originating from several countries, including Canada (although the specific details for the Canadian samples were not provided) (Simoneau et al. 2012).

Simoneau et al. (2012) examined 277 baby bottles made of various materials including polypropylene, polyamide, polycarbonate, polyethersulfone, a new co-polyester (Triton^{TM}), and silicone purchased from 26 EU countries, Canada, Switzerland and the United States. In this study, identified as a screening study of the potential release of substances from different types of baby bottles, the bottles were sterilized prior to migration testing, and testing was performed using the protocols prescribed in the EU Regulation 10/2011 (hot fill conditions, 2 hours at 70°C) and 50% ethanol as simulant for milk. Second and third migration tests were performed. 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate migration was associated with bottles made of polypropylene, silicone and polyamide. 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate concentrations were between 1 µg/kg and 62 µg/kg, with an average of 5 µg/kg for polypropylene (72/149 detects), between 14 µg/kg and 574 µg/kg with an average of 159 µg/kg for the silicone bottles (5/5 detected), and 2 µg/kg in 3/28 polyamide bottles.

In a study by Onghena et al. (2016), 6 bottles were analyzed in a variety of tests (e.g., microwave, steam sterilization and dishwater tests). 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate was measured at 348 µg/kg in a silicone bottle using conventional EU repetitive-use migration conditions. Concentrations ranged from less than the limit of quantification (LOQ) (6.4 µg/kg) to 13 µg/kg (from a silicone bottle) in microwave heating tests and from less than the LOQ (6.4 µg/kg) to 247 µg/kg (first migration step) in the cook sterilization treatment. The highest concentration of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate for the 10th repetition of any treatment was 128 µg/kg for the cook sterilization cycle.

Oral exposure of infants aged 0 to 1 month associated with the migration of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from baby bottles was estimated to range from 57.5 µg/kg bw/day to 96.4 µg/kg bw/day (details presented in Appendix C-1).

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate was identified (but not quantified) in 15 of 47 polyvinylchloride (PVC) toys (Bouma and Schakel 2002). 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate was measured to be 21 μg/g in the outer material palm of a mitten designed for 2-year-olds in a Danish survey examining chemicals in products available to consumers (Tonning et al. 2009). Summary results of migration measurements for three non-phthalate plasticizers, including 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, from 12 different types of children's toys were also reported by Janssen and Bremmer (2009). In this report, the migration values were determined by immersing circular samples of the toys in saliva simulant rotated at 60 rpm for 60 minutes at 20°C. The mean and maximum migration for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate was reported to be 0.87 μg/min × 10 cm^2 and 2.25 μg/min × 10 cm^2, respectively. The US Consumer Product Safety Commission (CPSC) also measured migration of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from plastic child care articles. The maximum average migration was 11.3 μg/min × 10 cm^2 (US CPSC 2010).

Oral exposure to young children (aged 6 months to 1 year) from mouthing of plastic toys containing PVC was estimated to be 149 μg/kg bw/day (details presented in Appendix C-2). Dermal and hand-to-mouth exposure to children (1 year) handling toys was also estimated based on the same migration information. Total exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in children aged 1 year was estimated to be 1849 μg/kg bw/day (details presented in Appendix C-2).

In Canada, materials emissions were measured for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in various materials, including acoustic tiles, water-based paint, acrylic floor polishing, polyurethane foam underpad and vinyl sheets (Won and Lusztyk 2011). Chamber air concentrations ranged from 11.7 μg/m^3 to 418.7 μg/m^3 at 24 hours (Won and Lusztyk 2011). These exposures are considered to be captured by the other scenarios in Table 7-8, e.g., aerosol primer, which result in exposures likely higher than those from building materials.

Health effects assessment

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate has been reviewed by the OECD (1995), and this review was used to inform the health effects characterization for this substance. The OECD considered 2,2,4-trimethyl-1,3-pentanediol diisobutyrate to be of low potential risk and of low priority for further work.

A literature search was conducted for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from the year prior to the OECD review (i.e., January 1994) to December 2020. New health effects studies were identified and are considered in this assessment.

Repeated-dose toxicity

There are no repeated-dose studies available for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate following inhalation and dermal exposure. The health effects of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from oral exposure were studied in rats (n = 12

animals/group) in a combined repeated-dose and reproductive/developmental toxicity screening test conducted according to OECD guidelines. In this study, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate was administered by gavage at doses of 0, 30, 150, and 750 mg/kg bw/day, 7 days/week. In male rats, the exposure period was 44 days, including 12 days before mating (2 weeks prior to mating, 2 weeks of mating and 2 weeks after the completion of the mating period). In females, the exposure period was from 14 days before mating to day 3 of lactation. Increases in creatinine and total bilirubin were observed in rats administered 150 mg/kg bw/day and 750 mg/kg bw/day, and increases in total protein were observed in male rats at 750 mg/kg bw/day. Increases in liver weight were observed in male rats at 150 mg/kg bw/day and 750 mg/kg bw/day, and increases in incidence of brown coloured livers were noted in male rats exposed to the highest dose. However, histopathological changes were not reported in the liver. Increases in kidneys weights were observed in male rats at the highest dose. Histopathological findings observed in kidneys included increases in the grade of basophilic changes of the renal tubular epithelium and degeneration of hyaline droplet in male rats at the two highest doses. In males exposed to the highest dose, necrosis and fibrosis of the proximal tubule, dilatation of the distal tubule, and decreased fatty changes were also observed. These effects are considered to be specific to male rats and are not considered adverse. Slight swelling of the liver cells was also noted at that dose level (OECD 1995). A no-observed-effect level (NOEL) of 30 mg/kg bw/day and a lowest-observed-effect level (LOEL) of 150 mg/kg bw/day were identified by the OECD, on the basis of liver and kidney effects in parental animals.

Since the OECD review was published in 1995, a subchronic oral study has been conducted in a larger sample of rats with 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. Test animals (20/sex/dose) were fed diets containing 0, 30, 150, and 750 mg/kg bw/day of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate for 90 days. In males, cholesterol, bilirubin, and creatinine levels were statistically increased at the highest dose. A significant increase in relative kidney weight and a significant increase in incidence of hyaline droplets and in incidence (but not severity) of chronic progressive nephropathy were also observed in males at 750 mg/kg bw/day. Hyaline droplets in the kidney were also observed at lower doses. The finding was not considered adverse by the study authors as male rats are predisposed to this condition. No kidney effects were noted in females in any group. At 750 mg/kg bw/day in females, effects were limited to a statistically significant increase in cholesterol levels. The authors identified a LOEL of 750 mg/kg bw/day for males and a NOAEL of 750 mg/kg bw/day for females (Anonymous 1981, as cited in ECHA c2007-2017z). However, since the effects in males were not considered to be adverse, a NOAEL of 750 mg/kg bw/day was determined for both male and female rats from this study.

Reproductive/developmental toxicity

In the combined repeated-dose and reproductive/developmental toxicity test described earlier, no effects related to mating, fertility and estrous cycle were noted by the authors of the study at any dose tested. No other treatment-related effects were observed in

dams during the pregnancy and lactation period and in pups after their birth (OECD 1995).

Since the OECD review (1995), a reproductive/developmental toxicity screening test and a developmental toxicity study (both conducted following OECD guidelines) have been conducted in rats with 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. In the former study, test animals (12/sex/dose) were fed diets containing 0, 1.5, 4.5, and 15 mg of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate per gram of feed (dose levels in males and females calculated from dietary concentrations were 0, 91/120, 276/359 and 905/1135 mg/kg bw/day, respectively) (Study Submission 2001; Anonymous 2001, as cited in ECHA c2007-2017za). All male rats were treated from the beginning of the premating period to the final treatment of the female rats for a total of 51 days. Females were treated from the beginning of the premating period to day 4 of lactation for a total of 40 to 51 treatments.

Reproductive effects, such as a statistically significant reduction in the mean number of implantation sites and a non-statistically significant decrease in the number of corpora lutea, were observed in animals treated with 905/1135 mg/kg bw/day, the highest dose tested. At this dose level, mean litter weights were also decreased by 19% to 20% on post-natal day (PND) 0 and 4 and the number of live pups per litter was 17% lower on PND 4 (12.0 in the high-dose group vs 14.5 in the control group; $p \leq 0.05$). The mean number of pups dying between PND 0 and 4 was higher for litters from the mid-dose and high-dose groups, but the increase was not dose-related and was statistically significant at the mid-dose only (0.5 ± 0.7 at mid-dose vs. 0.0 ± 0.0 for control animals and 0.2 ± 0.4 at highest dose). These findings are of unclear relevance since no clear trend was identified. No changes were reported for any other examined parameters.

These reproductive effects were observed in presence of systemic toxicity in parental animals. Transient decreases in body weight gain and food consumption were noted in adults exposed to the highest dose on day 7 of the pre-mating phase. Mean body weight gains were significantly decreased by 27% and 48% and food consumption was reduced by 15% and 21% in male and female rats, respectively. Minimal reductions in sperm counts were seen in the testes and/or epididymides of treated male rats, but these reductions were not considered toxicologically significant by the authors (Anonymous 2001, as cited in ECHA c2007-2017za). An expert review of the study also confirmed the non-relevance of these findings (Eastman 2007).

Overall, the critical effect level identified by the authors for this reproductive toxicity study was a NOAEL of 276 mg/kg bw/day in males and 359 mg/kg bw/day in females. They were based on a statistically significant reduction in the mean number of implantation sites and a non-significant decrease in the number of corpora lutea at the highest dose tested (equivalent to 1135 mg/kg bw/day for females) (Anonymous 2001, as cited in ECHA c2007-2017za).

In a prenatal developmental toxicity study conducted according to OECD Test Guideline 414, female rats were exposed through the diet to 0, 0.15, 0.45, or 1.50% 2,2,4-

trimethyl-1,3-pentanediol diisobutyrate (0, 118, 343, or 1077 mg/kg bw/day, respectively) from GD 0 to GD 20. The NOAEL for maternal toxicity, fetal growth and developmental toxicity was determined by the authors to be 343 mg/kg bw/day. At the highest dose tested (1077 mg/kg bw/day), significantly lower mean body weight and significantly reduced mean food consumption were observed in dams for the entire exposure period. A significant and dose-dependent decrease in mean male, female and combined fetal body weight was noted in offspring of the high-dose group compared to the control group. Effects on fetal body weight at 1077 mg/kg bw/day were observed in presence of maternal toxicity. There were no test substance-related external and visceral malformations or developmental variations noted (Anonymous 2015, as cited in ECHA c2007-2017zb).

In a report of another prenatal developmental toxicity study, New Zealand White rabbits (n = 22/group) were gavaged with 0, 100, 300, or 1000 mg/kg bw/day 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from GD 1 to GD 28 (Anonymous 2018, as cited in ECHA c2007-2020b). The mean number of early resorptions and thus post-implantation losses were outside historical ranges at 1000 mg/kg bw/day. However, details on statistical significance were not provided and the effect was described as resulting in a “slightly” lower mean live litter size only. In surviving fetuses, no effects on growth or development were observed. The report authors identified a NOAEL of 300 mg/kg bw/day on the basis of reduced embryo/fetal survival at the next dose level of 1000 mg/kg bw/day.

Genotoxicity

2,2,4-Trimethyl-1,3-pentanediol diisobutyrate did not induce mutagenicity in bacteria and did not induce chromosome aberrations in mammalian cells (OECD 1995). 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate is considered as non-genotoxic (EFSA 2006).

Carcinogenicity

No carcinogenicity or chronic toxicity studies were identified in the literature for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate.

Characterization of risk

No carcinogenicity studies were identified in the literature for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. No genotoxicity was observed in the available empirical data for this substance. On the basis of the available information, critical effects associated with 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are considered to be reproductive effects.

In a reproductive/developmental toxicity screening test, a NOAEL was set at 276 mg/kg bw/day in males and 359 mg/kg bw/day in females on the basis of a statistically significant reduction in the mean number of implantation sites and non-significant decrease in the number of corpora lutea observed at the next dose (1135 mg/kg bw/day

for females) (Study Submission 2001; Anonymous 2001, as cited in ECHA c2007-2017za). However, in a combined repeated-dose and reproductive/developmental toxicity study, no adverse effects were observed in experimental animals administered doses of up to 750 mg/kg bw/day (i.e., NOAEL of 750 mg/kg bw/day) (OECD 1995). The previous study (i.e., reproductive/developmental toxicity screening test) did not include a dose level of 750 mg/kg bw/day for testing; it only examined effects at 276/359 mg/kg bw/day, and then at 905/1135 mg/kg bw/day. Since the examined parameters and exposure duration between these two studies were similar (approximately 6 to 8 weeks), the higher NOAEL of 750 mg/kg bw/day was selected for reproductive toxicity for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate on the basis of reproductive effects occurring at a maternal oral dose of 1135 mg/kg bw/day (Anonymous 2001, as cited in ECHA c2007-2017za).

The predominant route of exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from environmental media for the general population is through indoor air. The general population of Canada may also be exposed to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate when using various products containing the substance, including nail products, cosmetic adhesives, aerosol primer, pool paint, liquid hardeners/fiberglass resin repair kits, concrete repair kits, and hobby paint. Oral exposure to children may also result from 2,2,4-trimethyl-1,3-pentanediol diisobutyrate contained in plastic baby bottles and plastic toys.

Biological monitoring data from cycle 5 of the CHMS demonstrate that metabolites of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are prevalent in the urine of people aged 3 to 79 years in Canada. The pharmacokinetic data are limited and prevent the reliable use of the biological monitoring data in a quantitative risk characterization. Exposure estimates based on modelling will therefore be used to characterize the risk to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate.

Relevant exposure estimates, critical health effects levels, and resulting MOEs for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are presented for adults/teens and children in Table 7-9 and Table 7-10, respectively.

Table 7-9. Relevant exposure estimates and resultant margins of exposure for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate compared to a critical effect level of 750 mg/kg bw/day[a]

Exposure scenario	Exposure[b](mg/kg bw/day)	Margin of exposure (MOE)
Total exposure from environmental media (1 year old) (chronic)	0.148	5 067
Cosmetic eye adhesive (14–18 years) (dermal chronic)	0.09	8 333
Nail polish (9–13 years) (dermal intermittent)	0.77	974

Exposure scenario	Exposure[b](mg/kg bw/day)	Margin of exposure (MOE)
Nail polish remover (14–18 years) (intermittent)	0.36	2 083
Aerosol primer (19+ years) (intermittent)	1.24	604
Marine/pool paint (19+ years) (dermal intermittent)	3.6	208
Liquid hardener/ fiberglass repair (19+ years) (intermittent)	0.22	3 409
Concrete crack repair (19+ years) (intermittent)	0.30	2 500
Hobby paint (19+ years) (dermal intermittent)	0.05	15 000
Non-medicinal ingredient for the purpose of plasticizer in a wart remover (9–13 years) (dermal short-term)	0.48	1 562

Abbreviation: MOE, margin of exposure

[a] Critical effect level (750 mg/kg bw/day) is determined on the basis of statistically significant reduction in the mean number of implantation sites and decrease in the number of corpora lutea at the next dose of 1135 mg/kg bw/day in an oral reproductive toxicity study

[b] Dermal absorption is assumed to be equivalent to absorption following oral intake

Table 7-10. Relevant exposure estimates and resultant margins of exposure for children to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate compared to a critical effect level of 750 mg/kg bw/day[a]

Exposure scenario	Exposure (mg/kg bw/day)	Margin of exposure (MOE)
Baby bottles (0- to 1-month-old) (oral chronic)	0.058 - 0.096	12 931 – 7 812
Children mouthing plastic toys (1-year-old) (oral chronic)	0.15	5 000
Children with dermal and hand-to-mouth contact with plastic toys (1-year-old) (oral chronic)	1.85	405
Cosmetic eye adhesive (4–8 years) (dermal chronic)	0.23	3 261
Nail polish (2–3 years) (dermal intermittent)	1.2	625
Nail polish remover (9–13 years) (dermal intermittent)	0.54	1 388
Non-medicinal ingredient for the purpose of plasticizer in a wart remover (4–8 years) (dermal short-term)	0.86	872

Abbreviation: MOE, margin of exposure
[a] Critical effect level (750 mg/kg bw/day) is determined on the basis of no adverse effects in oral repeated-dose studies in which animals were exposed at up to 750 mg/kg bw/day, the highest-dose tested (OECD 1995; Anonymous 2001, as cited in ECHA c2007-2017za)

On the basis of the conservative approaches used in estimating exposure, the margins between critical effects and estimates of exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate are considered adequate to account for uncertainties in the health effects and exposure datasets.

7.3.2 Texanol

Exposure assessment

As propanoic acid, 2-methyl-, monoester with 2,2,4-trimethyl-1,3-pentanediol, or texanol, is considered to be of low hazard potential (see Health effects assessment below), quantitative estimates of exposure to the general population were not derived. This section provides general information on exposure to texanol.

Texanol is a liquid with a moderate vapour pressure. Summary data for texanol measured in indoor air in homes in Quebec City using passive sampling between November 2008 and March 2010 were presented by Won and Lusztyk (2011). Concentrations of texanol in indoor air ranged from 0.36 $\mu g/m^3$ to 633.4 $\mu g/m^3$, with a geometric mean concentration of 13.4 $\mu g/m^3$. Texanol has also been measured in emissions from solid building materials (vinyl flooring and polyurethane foam) up to 132 $\mu g/m^2/h$ and from liquid building materials (paint, primer, stains, varnish, caulking, and adhesive) up to 127 $\mu g/m^2/h$ (Won and Yang 2012). Won and Yang (2012) also noted emissions from products for consumers, such as artistic oil paints and air deodorizer, up to emission rates of 74 $\mu g/m^2/h$. Through sampling in a microscale chamber, emission rates from an acrylic latex interior paint product were measured up to 88,837 $\mu g/m^2/h$ (Won et al. 2014).

No Canadian ambient air measurements for texanol were identified. No empirical data were found for texanol in water, dust or soil in Canada.

Texanol may be used as a component in the manufacture of food packaging materials, with no direct food contact. Therefore dietary exposure is not expected (personal communication, email from FD, HC, to ESRAB, HC, dated December 5, 2016; unreferenced).

In cosmetics, texanol functions as a plasticizer (European Commission 2008-) and is found in nail polish and makeup products in Canada at concentrations up to 10% (personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced). Use of these products may result in dermal or inhalation exposure to the general population in Canada.

Texanol is used in a number of paint products (e.g., stains, sealants) and adhesive products available to consumers in Canada that may result in dermal or inhalation exposure (SDS 2015h, 2017f, 2017g).

Health effects assessment

Texanol has been reviewed by the OECD (1993), and this review was used to inform the health effects characterization for this substance. The OECD (1993) concluded that texanol has a relatively low order of toxicity and was also a low priority for further work.

A literature search was conducted for texanol from the year prior to the OECD (i.e., January 1992) to December 2020. New health effects studies were identified and are considered in this assessment.

Repeated-dose toxicity

There are no repeated-dose studies available for texanol following inhalation or dermal exposure. The OECD identified two oral studies which are described below.

Texanol was studied for oral toxicity in rats according to the OECD combined repeated-dose and reproductive/developmental toxicity test (OECD Test Guideline 422). Rats exposed by gavage at 0, 100, 300 and 1000 mg/kg bw/day for up to 51 consecutive days resulted in a NOAEL for both sexes of 1000 mg/kg bw/day with no significant treatment-related effects on mortality, clinical signs, body weight and body weight gain, feed consumption, or gross pathology in male rats. Centrilobular hepatomegaly was observed in the livers of rats at the two highest doses but this was considered an adaptive response since no degenerative changes were noted in this organ. Kidney lesions in male rats were typical of alpha 2-μ globulin nephropathy, and considered unique to rats and not likely relevant to humans (OECD 1993; Anonymous 1992, as cited in ECHA c2007-2017zc).

When rats (5/sex/dose) were administered texanol ester alcohol by gavage at 0, 100, and 1000 mg/kg bw/day, 5 days/week, for 11 days over a 15-day period, there were no significant treatment-related effects observed in either sex. A slight increase in liver weights was seen in both sexes at 1000 mg/kg bw/day. However, no treatment-related gross lesions or changes in clinical chemistry were observed in either sex and the minor hyaline droplet degeneration observed is a sex- and species-specific effect. Although a NOEL was identified to be less than 100 mg/kg bw/day for male rats and 100 mg/kg bw/day for female rats, the NOAEL was considered by the authors to be 1000 mg/kg bw/day for both sexes (OECD 1993; Anonymous 1984, as cited in ECHA c2007-2017zd).

Since the OECD (1993) review, a short-term oral study has been conducted in rats with texanol. In the study conducted according to the OECD Guideline 407, test animals (5/sex/group) were administered texanol daily by gavage at 0, 15, 150 and 1000 mg/kg bw/day for 28 days. The NOAEL for male/female systemic effects was established at

1000 mg/kg bw/day by the authors. No mortality, no treatment-related effects on body weight and food consumption, and no substance-related changes in clinical findings, clinical chemistry and hematology were observed. A statistically significant increase in liver weights was observed in female rats exposed to 1000 mg/kg bw/day, the highest dose tested. However, only minimal centrilobular hepatocyte enlargement was observed in 2 out of 5 female rats exposed to this dose level, which were considered to be adaptive and non-adverse. A dose-related increase in incidence and degree of cortical tubular eosinophilic inclusions was observed in male rats receiving 150 mg/kg bw/day (trace in 3 of 5 animals) and 1000 mg/kg bw/day (minimal in 2 of 5 animals and moderate in 3 of 5 animals) (Anonymous 1995, as cited in ECHA c2007-2017ze).

Reproductive/developmental toxicity

No reproductive/developmental toxicity studies were conducted with texanol via the inhalation or dermal route of exposure.

In the combined oral repeated-dose and reproductive/developmental toxicity test described earlier for texanol, no effect on mean number of live or dead pups/litter, total implants, prenatal loss, percent survival, total litter weight, mean pup weight, pup survival, external defects and postnatal growth was observed. The NOAEL for reproductive and developmental toxicity was the highest dose tested of 1000 mg/kg bw/day. No adverse effects were noted in parental animals. The NOAEL for systemic effects in the parental generation in this study was also 1000 mg/kg bw/day (OECD 1993; Anonymous 1992, as cited in ECHA c2007-2017zf).

Since the publication of the OECD review (1993), a developmental toxicity study was conducted in rats with texanol. In this OECD Guideline 414 study, female rats were administered 0, 100, 300 and 1000 mg/kg bw/day of texanol, by oral gavage, from GD 1-19. No effect on intrauterine growth, survival, and external, visceral, and skeletal fetal morphology was observed. The NOAEL for maternal toxicity was identified at 300 mg/kg bw/day on the basis of statistically significant reduction in mean food consumption and in mean body weight gain in dams at 1000 mg/kg bw/day. Reduction in food consumption was noted during GD 1-3 and 3-6 while the reduction in body weight gain was noted during GD 1-3 and 3-6 as well as for the entire dosing period (GD 1-19) (Anonymous 2015, as cited in ECHA c2007-2017zg).

Genotoxicity

Texanol showed negative results in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and *Escherichia coli* WP2 uvrA/PKM101, with and without metabolic activation (Anonymous 1985, as cited in ECHA c2007-2017zh; Anonymous 1995, as cited in ECHA c2007-2017zi). Negative results were also reported *in vivo* in a mouse bone marrow micronucleus test in which groups of 5 males and 5 females were administered texanol once by gavage at doses of 0, 200, 1000, and 2000 mg/kg bw (OECD 1993; Anonymous 1992, as cited in ECHA c2007-2017zj).

Carcinogenicity

No carcinogenicity or chronic toxicity studies were identified in the literature for texanol.

Characterization of risk

No effects that were considered to be adverse were seen in repeated-dose (short-term and subchronic) or reproductive and developmental toxicity studies in which experimental animals were exposed orally to texanol at levels up to the limit dose of 1000 mg/kg bw/day. No carcinogenicity studies were identified in the literature for this substance, but texanol did not show any genotoxicity potential. The OECD (1993) concluded that texanol is associated with a relatively low order of toxicity and is a low priority for further work.

Considering the available health effects information, texanol is considered to be of low hazard potential, and therefore characterization of exposure potential (i.e., derivation of exposure estimates) was not considered to be warranted. The risk to human health is considered to be low.

7.4 Subgroup D: Individual – salt of a diester

7.4.1 Docusate sodium

Exposure assessment

Environmental media

Docusate sodium is a solid with a very low vapour pressure. If released to the atmosphere, it will exist primarily in the particulate phase (HSDB 1983-). In the vapour phase, it will degrade in the atmosphere by reaction with photochemically produced hydroxyl radicals with an estimated half-life of 18 hours (HSDB 1983-). The Henry's law constant for docusate sodium was estimated to be 5×10^{-12} atm-m^3/mol (EPI Suite c2000-2012), indicating that the substance is essentially non-volatile from water (HSDB 1983-).

No empirical data were identified for docusate sodium in air or water in Canada. Docusate sodium has been measured in surface water in the Gulf of Mexico following its use as a chemical dispersant to solubilize oil and minimize formation of surface oil slicks following the Deepwater Horizon oil release in 2010 (Gray et al. 2014). A study of inland water in a local community attempted to determine whether the presence of chemicals was associated with the chemical's use in the response to the Deepwater Horizon accident (Hayworth and Clement 2012). That study determined that docusate sodium present in water samples could be attributed to point and non-point source storm water discharge from 13 locations, and not from the accident response, with a maximum concentration of 19 ppb or 19 μg/L in the water samples.

Concentrations in Canadian surface water were estimated with the NSACB EAU Drinking Water Spreadsheets using the industrial release scenario (Health Canada 2015a). Details of model parameters are found in Appendix D. Using total imports of docusate sodium into Canada (Environment Canada 2013), the model modelled a surface water concentration of 5.6×10^{-4} mg/L.

Docusate sodium was not identified in soil or dust studies in Canada. Internationally, docusate sodium has been measured in soil (sand patties) following the Deepwater Horizon spill (McDaniel et al. 2015). These values were not considered relevant for general population exposure in Canada.

Food

Docusate sodium (listed as dioctyl sodium sulfosuccinate) is a permitted food additive for uses as prescribed on the *List of Permitted Food Additives with Other Generally Accepted Uses*, incorporated by reference into its respective Marketing Authorization issued under the *Food and Drugs Act*. Exposure to docusate sodium was estimated on the basis of its permitted use in sausage casings to reduce breakage (maximum 200 ppm in the casing) and as a wetting agent in fumaric acid-acidulated dry beverage bases (maximum 10 ppm in the finished beverage), as set out in the List of Permitted Food Additives.

Exposure estimates were derived for various age groups from the mean and 95th percentile consumption scenarios based on consumption of sausages and fruits drinks reported in the CCHS cycle 2.2 (2004), assuming that casings represent 1% of the weight of sausages and that all sausages and fruit drinks consumed contain docusate sodium at the maximum permitted level. The age group with the highest 95th percentile exposure values were children aged 2 to 3 years at 337.5 µg/kg bw/day. The estimated exposure to docusate sodium from food additive uses for the various age groups is presented in Table 7-11.

Table 7-11. Estimated human exposure to docusate sodium from food additive uses

	Estimated exposure (µg/kg bw/day)[a]							
Age group	**0 – < 6 months**	**6–11 months**	**1 year**	**2–3 years**	**4–8 years**	**9–13 years**	**14–18 years**	**19+ years**
Mean	-	-	49.5	66.4	64.2	48.1	28.3	8.2
95th percentile	-	-	270.7	337.5	274.5	210.0	134.2	58.6

[a] All persons mean and 95th percentile consumption of sausages and fruits drinks reported in the CCHS cycle 2.2.

The 95th percentile exposure values from food additive uses for the various age groups were combined with estimates of exposure from drinking water to estimate total daily intake for the general population in Canada (see Table B-4 of appendix B). The

maximum total intake from all routes of exposure was 338 µg/kg bw/day for ages 2 to 3 years.

Docusate sodium may be used as a component in the manufacture of food packaging materials with no direct food contact, and therefore dietary exposure is not expected (personal communication, emails from FD, HC, to ESRAB, HC, dated December 5, 2016, and March 15, 2021; unreferenced).

General population exposure to docusate sodium from drinking water and food ranged from 0.05 µg/kg bw/day to 338 µg/kg bw/day (see Table B-4 Appendix B). The highest exposed population was the 2- to 3-year-old age group. Food appears to be a greater contributor to exposure than drinking water. However, the estimates for exposure to docusate sodium used as a food additive are considered to be conservative.

Products available to consumers

Docusate sodium functions as a cleansing agent, emulsifying agent, hydrotrope or surfactant in cosmetics (European Commission 2008-) and is found in more than 100 cosmetics in Canada, including adhesives, bath products, bleach, cleansers, exfoliants, fragrance products, hair colour, makeup (non-permanent), makeup remover, moisturizers, shampoos, shaving products, styling products and sunless tanning products (personal communication, emails from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced).

Dermal and inhalation exposure estimates were derived for these products at the highest concentration levels.

Table 7-12 summarizes the inhalation and dermal exposure estimates for cosmetics containing docusate sodium. Exposure estimates for adults and the youngest relevant age group for each product type are shown. Details on the method and parameters used to estimate inhalation and dermal exposures to docusate sodium from cosmetics are available in Appendix C-3.

Table 7-12. Estimated inhalation and dermal exposures to docusate sodium from the use of cosmetics

Product scenario	Docusate sodium conc.[a]	Dermal exposure (mg/kg bw/day)[b]	Inhalation exposure[b] (mg/kg bw/day)
Bath oil (9–13 years)	0.3%	0.001	N/A
Face cleanser (9–13 years)	30%	0.27	N/A
Hair shampoo (2–3 years)	10%	0.62	N/A
Fragrance product: massage oil (0–5 months)	0.3%	0.86	N/A

Product scenario	Docusate sodium conc.[a]	Dermal exposure (mg/kg bw/day)[b]	Inhalation exposure[b] (mg/kg bw/day)
Facial makeup (4–8 years)	10%	0.26	N/A
Makeup remover (4–8 years)	10%	1.0	N/A
Sunless tanning product (14–18 years)	1%	0.04	N/A
Hair bleach (14–18 years)	3%	1.0	N/A
Hair dye/highlight (14-18 years)	3%[d]	0.9	N/A
Hair styling product: aerosol (4–8 years)	0.1%	0.026	1.5×10^{-4} (0.00035 mg/m^3)[c]

Abbreviations: N/A, not Applicable; conc., concentration

[a] Personal communication, email from CHPSD, HC, to ESRAB, HC, dated March 5, 2021; unreferenced.

[b] Assumed absorption via dermal and inhalation route is equivalent to oral absorption.

[c] Mean concentration on day of exposure.

[d] Concentration in highlighting kit (e.g., powder); mixed with solution for application.

Docusate sodium is found as non-medicinal ingredient in six natural health products in Canada. Most of the products are for oral administration, but one is for topical application. An exposure estimate was derived for the oral natural health products using a sentinel scenario based on a tablet containing 20 mg of docusate sodium as non-medicinal ingredient for the purpose of solubilizing agent taken once daily. An exposure estimate for an adult based on 20 mg docusate sodium is 0.28 mg/kg bw/day. The potential dermal exposure associated with use of the topically applied product is considered to be addressed by the dermal cosmetic exposure estimates.

Docusate sodium is found as an active ingredient in over 70 non-prescription drugs cathartic and laxative products in Canada and as a non-medicinal ingredient in over 30 prescription and/or non-prescription drugs including oral (tablet or capsule) products and topical products. An exposure estimate for oral products was derived assuming 6 mg docusate sodium per tablet (one tablet per day) for adults, resulting in an estimate of 0.08 mg/kg bw/day. The topical products were reported or estimated to contain concentrations ranging from less than 0.05% to 0.2% docusate sodium. Exposure associated with the topically applied products was considered to be addressed by the dermal cosmetic exposure estimate. Docusate sodium is also present in products considered to be disinfectant drugs as an ingredient in aerosol and wipe disinfectant products for food premises, institutions or hospitals.

Docusate sodium is used in a variety of products available to consumers that may result in exposure in the general population in Canada, including exterior house cleaners, cleaning wipes, automotive products such as tire protectant sprays, tire cleaners (foam,

aerosol and trigger spray), liquid adhesives, and wood hardener products (SDS 2013c, 2014f, 2014g, 2015i, 2015j, 2017f; HPD 1993b). Table 7-13 summarizes inhalation and dermal exposure estimates for products available to consumers containing docusate sodium.

Table 7-13. Estimated exposures to docusate sodium from the use of products available to consumers

Product scenario	Docusate sodium conc.	Dose[a] (mg/kg bw/day)
Exterior house cleaner and mildew killer	10% (m/l) 0.5%[b] (appl.)	0.014 (m/l) 0.61 (appl.) 0.62 (m/l + appl.)
Cleaning wipes/wet tissues	5%	0.63
Aerosol spray tire cleaner (aerosol/foam)	10%	0.31
Liquid paste activator (wallpaper)	0.18%[c]	0.18
Wood hardener product	20%[d]	0.81

Abbreviations: conc., concentration, m/l, mix/load activities, appl., application activities.
[a] Assumed absorption via dermal route is equivalent to oral absorption.
Inhalation exposure estimated assuming breathing rate of 16.2 m^3/day (Health Canada 1998).
[b] Product contains docusate sodium at 10% solution; after mixing and loading the product is applied in a 1:20 dilution.
[c] 30% in product; product applied in a 0.6% (product: water) solution.
[d] 20% assumed concentration in product (concentration noted as proprietary on product).

Health effects assessment

Docusate sodium has been reviewed in the US EPA screening-level hazard characterization of the sulfosuccinates category (US EPA 2009), and this review was used to inform the health effects characterization in this assessment.

A literature search was conducted from the year prior to the US EPA assessment (January 2009) to December 2020. No additional health effects studies that could result in a different health effects characterization from US EPA (2009) were identified.

Repeated-dose toxicity

Three oral studies have been identified by the US EPA (2009). There were no repeated-dose studies available for docusate sodium following inhalation or dermal exposure.

A subchronic, repeated-exposure study was conducted in 21-day old male Osborne-Mendel rats. Test animals (5/dose) were administered docusate sodium in the diet at concentrations of 0%, 2%, 4% and 8% (corresponding to 0 and approximately 2000, 4000 and 8000 mg/kg bw/day, respectively) for 16 weeks. The critical effect level and corresponding hazard endpoint were identified as a LOAEL of 2000 mg/kg bw/day, the lowest dose tested, on the basis of a decrease in body weight gain and evidence of gastrointestinal irritation upon necropsy. Only one animal exposed to 4000 mg/kg

bw/day survived for the duration of the study. Animals exposed to the highest dose had severe gastrointestinal symptoms and died within the first week of treatment (US EPA 2009).

Another subchronic, repeated-exposure study was conducted in rats (strain not given (12/sex/dose) administered docusate sodium in the diet at concentrations of 0%, 0.5%, 1.0% and 1.5% (corresponding to 0 and approximately 250, 500 and 750 mg/kg bw/day, respectively) for 26 weeks. The critical effect level and corresponding hazard endpoint were identified as a NOAEL of 250 mg/kg bw/day on the basis of low weight gain and hemorrhagic gastroenteritis observed in rats exposed to 500 mg/kg bw/day. Two control animals and four test animals (sex not specified) exposed to the highest dose died. Two out of the four treated dead animals had hemorrhagic gastroenteritis. No other effects on body weights, food consumption, clinical chemistry or histopathology were observed (US EPA 2009).

In the third study, Beagle dogs (4/sex/dose) were administered docusate sodium via oral tablets at doses of 0 or 30 mg/kg bw once a day, 7 days/week, for 1 year. No treatment-related effects on body weights, food consumption, clinical chemistry, hematology and urinalysis parameters or histopathology were observed at the only dose tested. No evidence of gastric irritation was noted (US EPA 2009).

Overall, it was concluded by the US EPA (2009) that repeated oral exposures to docusate sodium in rats showed localized effects/irritation on the gastrointestinal tract at 500 mg/kg bw/day and that the NOAEL for systemic toxicity was 250 mg/kg bw/day, on the basis of decrease in body weight gain observed in rats exposed to 500 mg/kg bw/day and higher.

Reproductive/developmental toxicity

One reproductive and two developmental toxicity studies have been identified by the US EPA (2009). There are no reproductive/developmental toxicity studies available for docusate sodium following inhalation or dermal exposure.

An oral three-generation reproductive toxicity study was identified by the US EPA (2009) for docusate sodium. In this study, male and female Crl:CD(SD)BR rats were administered the substance in the diet at concentrations of 0, 0.1, 0.5 and 1% (corresponding to approximately 0, 100, 500 and 1000 mg/kg bw/day, respectively) during premating, mating and during gestation for three generations (F0, F1, F2) until weaning of the third generation (F3). The critical effect level identified in this study was a NOAEL of 100 mg/kg bw/day for both systemic and reproductive/developmental toxicity. Decreased food consumption and body weights were noted in adult animals at 500 mg/kg bw/day and higher. Male and female pups (all three generations) born to animals treated with 500 mg/kg bw/day or 1000 mg/kg bw/day weighed less than controls on day 21. An effect on lactation was also noted in animals treated with 500 mg/kg bw/day and higher; no milk was found in the abdomens on lactation day 4 in 3 control F2 pups, 7 F2 pups in the 100 mg/kg bw/day dose group, 18 F2 pups and 1 F3

pup in the 500 mg/kg bw/day dose group, and 10 F2 pups and 17 F3 pups in the 1000 mg/kg bw/day dose group. There were no treatment-related effects on the total number of pups or litters, litter size, sex ratio, or perinatal pup survival across the three generations. There were also no treatment-related mortality or microscopic observations in any animals examined (F0, F1 and F2 adults and F3 weanlings) (US EPA 2009).

In a developmental toxicity study, groups of pregnant rats were administered docusate sodium in the diet at concentrations of 0%, 1%, and 2% (corresponding to approximately 0, 500, and 1000 mg/kg bw/day, respectively) on GD 6 to GD 15. The NOAEL for maternal and developmental toxicity identified by the US EPA was 500 mg/kg bw/day, on the basis of reduction in body weight gains in dams and a significant increase in fetal resorptions and percentage of externally malformed fetuses at 1000 mg/kg bw/day. The abnormalities consisted primarily of exencephaly of varying degrees of severity. Incomplete ossification of various cranial bones and curved or open vertebral columns were also observed (US EPA 2009). In a second study, pregnant rats were exposed to docusate sodium in the diet at concentrations of 0% and 2% (corresponding to approximately 0 mg/kg bw/day and 1000 mg/kg bw/day) on GD 6 to GD 16. The LOAEL for maternal and developmental toxicity identified by the US EPA was 1000 mg/kg bw/day, the only dose tested. This LOAEL was based on decreases in maternal body weight, food intake and body weight gain, decreases in fetal body weights and crown-rump length, and increases in skeletal anomalies (unossified sternebrae) (US EPA 2009).

Repeated oral exposure to docusate sodium in rats was associated with developmental effects, such as reduced fetal and pups body weights, resorptions, malformations and skeletal anomalies, observed at 500 mg/kg bw/day or 1000 mg/kg bw/day, but only in the presence of maternal toxicity.

Genotoxicity

Docusate sodium was not mutagenic in bacterial cells nor did it induce chromosomal aberrations in mammalian cells *in vitro* (US EPA 2009).

Carcinogenicity

Docusate sodium did not show carcinogenic potential in rats (US EPA 2009). In a chronic study, male Osborne-Mendel rats (12/dose) were administered 0.25%, 0.5% or 1.0% docusate sodium in the diet for 2 years. No effect of the test substance on food intake was observed. A significant decrease in weight gain was noted in test animals exposed to 1% docusate sodium. No other treatment-related effects were observed (US EPA 2009).

Characterization of risk

Docusate sodium has been reviewed in the US EPA screening–level hazard characterization of the sulfosuccinates category (US EPA 2009), and this review was

used to inform the health effects characterization in this assessment. No evidence for carcinogenicity or genotoxicity was identified in the available empirical data for this substance.

Following subchronic oral exposures to docusate sodium, site-of-contact effects on the gastrointestinal tract and decrease in body weight gain were observed in rats from 500 mg/kg bw/day. Repeated oral exposure to docusate sodium in rats was associated with developmental effects, such as reduced fetal and pups body weights, resorptions, malformations and skeletal anomalies, all of which were observed in presence of maternal toxicity.

The critical effect level identified was a NOAEL of 100 mg/kg bw/day based on systemic and reproductive/developmental toxicity in an oral three-generation reproductive toxicity study. Decreased food consumption and body weights were noted in adult animals at 500 mg/kg bw/day and higher. Male and female pups (all three generations) born to animals treated with 500 mg/kg bw/day or 1000 mg/kg bw/day weighed less than controls. An effect on lactation (no milk found in the abdomens) was also noted in animals treated with 500 mg/kg bw/day and higher (US EPA 2009)

The predominant route of exposure to docusate sodium from environmental media and food for the general population is through the diet, based on its use as a permitted food additive.

The general population of Canada may also be exposed to docusate sodium when using various products containing the substance including cleansers, hair conditioners, massage oil, makeup, body moisturizer, sunless tanning products, hair bleach, nail polish, hair styling product, various cleaning products (outdoor liquid house cleaner, trigger spray cleaners, automotive tire cleaners), wallpaper paste activator and hardener products. Exposure to docusate sodium from use of these products is expected to be primarily via the dermal route. Table 7-14 provides the relevant exposure estimates, critical health effects levels and resultant MOEs for characterization of the risk to human health from exposure to docusate sodium.

Table 7-14. Relevant exposure estimates, critical heath effects levels and resultant margins of exposure for docusate sodium

Exposure scenario	Total exposure[a] (mg/kg bw/day)	MOE based on an oral NOAEL of 100 mg/kg bw/day[b]
Total exposure from environmental media and use as a permitted food additive (oral chronic; 2–3 years)	0.338	296
Oral exposure associated with its use as a non-medicinal ingredient in prescription and/or non-prescription drugs, or	0.28	357

Exposure scenario	Total exposure[a] (mg/kg bw/day)	MOE based on an oral NOAEL of 100 mg/kg bw/day[b]
natural health product (19+ years)		
Bath oil (9–13 years)	0.001	100 000
Facial cleanser (9–13 years) (dermal chronic)	0.27	370
Hair shampoo (2–3 years) (dermal chronic)	0.62	161
Massage oil (0–5 months) (dermal intermittent)	0.86	116
Facial makeup (4–8 years) (dermal chronic)	0.26	384
Makeup remover (4–8 years)	1.0	100
Sunless tanning product (14-18 years) (dermal intermittent)	0.04	2500
Hair bleach (14–18 years) (dermal intermittent)	1.0	100
Hair dye (14–18 years) (dermal intermittent)	0.9	111
Hair styling product (4–8 years) (dermal chronic)	0.026	4 545
Exterior house cleaner (19+ years) (dermal intermittent)	0.62	161
Cleaning wipes (19+ years) (dermal chronic)	0.63	159
Aerosol spray tire cleaner (automotive) (19+ years) (dermal intermittent)	0.31	322
Wallpaper: Liquid paste activator (19+ years) (dermal intermittent)	0.18	555
Wood hardener product (19+ years) (dermal intermittent)	0.81	123

Abbreviations: MOE, margin of exposure; NOAEL, no-observed-adverse-effect level

[a] Based on the assumption that dermal absorption is equivalent to oral absorption.

[b] Systemic and reproductive/developmental toxicity in an oral three-generation reproductive toxicity study (US EPA 2009).

Overall, the MOEs are considered adequate to account for uncertainties in the health effects and exposure datasets.

7.5 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below:

Table 7-15. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
Exposure	
In the case of methyl acetate, exposure from natural occurrence in food is based on data found in the Volatile Compounds in Food database. It was assumed that measured amounts of substance released from food are consumed.	+
For aerosol applications, instantaneous release models were used as a conservative approach.	+
Uncertainties associated with the estimate of children's exposure to 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in plastic products include the use of migration data based on saliva simulant, relevance of migration data for baby bottles in Canada, and variability in surface areas and time in contact with object.	+/-
It was assumed that dermal penetration is equivalent to oral absorption for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate and docusate sodium.	+
Hazard	
Limited hazard datasets for methyl acetate, dimethyl glutarate, and 2-methoxypropyl acetate.	+/-
There is no or limited information on repeated-dose effects via some of the relevant routes of exposure and durations, for methyl hexanoate, propyl acetate, isobutyl acetate, methyl butanoate, tetradecyl tetradecanoate, and C14-22 monoglycerides.	+/-
Lack of chronic/carcinogenicity study for methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2-methoxypropyl acetate, triacetin, C14-22 monoglycerides, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, and docusate sodium.	+/-
There is uncertainty associated with the use of available toxicological information for metabolites and analogues to characterize risk of methyl acetate, methyl hexanoate, propyl acetate, isobutyl acetate, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, and 2-methoxypropyl acetate to human health.	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure risk; +/- = unknown potential to cause over or under estimation of risk.

8. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from the 14 substances in the Esters Group. It is proposed to conclude that methyl acetate, triacetin, methyl hexanoate, propyl

acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Considering all the information presented in this draft screening assessment, it is proposed to conclude that methyl acetate meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Considering all the information presented in this draft screening assessment, it is proposed to conclude that triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore proposed to conclude that methyl acetate meets one or more of the criteria set out in section 64 of CEPA.

It is therefore proposed to conclude that triacetin, methyl hexanoate, propyl acetate, isobutyl acetate, methyl dodecanoate, docusate sodium, methyl butanoate, dimethyl glutarate, tetradecyl tetradecanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, texanol, C14-22 monoglycerides, and 2-methoxypropyl acetate do not meet any of the criteria set out in section 64 of CEPA.

It is also proposed that methyl acetate meets the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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Appendix A. Physical-chemical property values for analogues of substances in the Esters Group

Table A-1. Physical-chemical property values for analogues

Common name (CAS RN)	MW (g/mol)	Vapour pressure (mm Hg)	Water solubility (mg/L)	log K_{ow} (dimensionless)	Used to inform the assessment of
Methyl dodecanoate (111-62-6)	214.3464	0.00411	1.13	5.41	Methyl hexanoate Methyl butanoate
Ethyl acetate (141-78-6)	116.159	11.5	8400	1.78	Propyl acetate
N-butyl acetate (123-86-4)	60.0952	21	1.00E+06	0.25	Propyl acetate
Dibasic esters (DBE/DME) Dimethyl adipate (627-93-0)	174.195	-	6000	1.03	Dimethyl glutarate
Dibasic esters (DBE/DME) Dimethyl succinate (106-65-0)	146.141	0.422	2.50E+04	0.35	Dimethyl glutarate
Propylheptyl caprylate (868839-23-0)	284.4804	-	0.004287	-	Tetradecyl tetradecanoate
Ethylhexyl laurate (20292-08-4)	312.534	3.16E-05	1.44E-03	8.03	Tetradecyl tetradecanoate
Isodecyl laurate (94247-10-6)	340.5876	-	4.21E-05	-	Tetradecyl tetradecanoate
Isopropyl myristate (110-27-0)	270.4536	3.29E-04	0.0014	7.17	Tetradecyl tetradecanoate
Isodecyl oleate (59231-34-4)	422.733	-	6.13E-08	12.759	Tetradecyl tetradecanoate
Tetradecyl oleate (22393-85-7)	478.84	3.44E-10	4.93E-10	14.4	Tetradecyl tetradecanoate
Behenyl behenate (17671-27-1)	649.177	1.21E-13	2.34E-16	21.96	Tetradecyl tetradecanoate
2-Ethylhexyl stearate (22047-49-0)	396.6948	-	4.02E-07	11.994	Tetradecyl tetradecanoate
2-Methoxypropanoic acid (4324-37-2)	104.104	1.17	4.72E+05	-0.26	2-Methoxypropyl acetate

Abbreviations: MW, molecular weight; K_{ow}, octanol–water partition coefficient

Appendix B. Estimates of daily intake from environmental media and food

Table B-1. Estimates of daily intake (µg/kg bw/day) of methyl acetate

Age categories	Ambient air[a]	Indoor air[b]	Drinking water[c]	Food and beverages[d]	Total intake
0 to 5 months[e] (breast milk-fed)[f]	0.04	5.91	N/A	0.00	5.95
0 to 5 months[e] (formula fed)[g]	0.04	5.91	10.4	0.00	16.4
6 to 11 months[h]	0.04	5.97	6.7	28.1	40.8
1 year[i]	0.05	7.32	2.6	33.1	43.1
2 to 3 years[j]	0.04	6.17	2.3	28.3	36.8
4 to 8 years[k]	0.03	4.86	1.8	21.9	28.6
9 to 13 years[l]	0.02	3.33	1.4	15.0	19.8
14 to 18 years[m]	0.02	2.58	1.4	11.2	15.2
Greater than or equal to 19 years[n]	0.01	2.05	1.7	12.1	15.85

Abbreviations: N/A, not applicable.

[a] Ambient air exposure estimates based on 95th percentile value of methyl acetate (0.57 µg/m^3) measured in Edmonton study (Health Canada 2013a). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[b] Indoor air exposure estimates based on 95th percentile of indoor air concentration data (11.5 µg/m^3) measured in Windsor air study (Health Canada 2010a). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[c] Concentrations in surface water were estimated with an in-house drinking water model (industrial release scenario) (Health Canada 2015a); an estimated value for surface water was found to be 79.7 µg/L and was used for deriving estimates of daily intake from drinking water exposure.

[d] Estimates of 90th percentile dietary exposure of the general population based on natural occurrence of methyl acetate in foods are presented. Food data based on concentrations reported in the Volatile Compounds in Food database (Njissen et al. 1963-2016). Food consumption rates are described in Health Canada (2015).

[e] Assumed to weigh 6.3 kg (Health Canada 2015), to breathe 3.7 m^3 of air per day (US EPA 2011 [modified]), and to ingest 21.6 mg of dust per day (Wilson and Meridian 2015 [modified]). It is assumed that no soil ingestion occurs due to typical caregiver practices.

[f] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018), and breast milk is assumed to be the only dietary source. No breast milk monitoring data for methyl acetate were identified.

[g] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018), where water is used to reconstitute formula. No monitoring data on methyl acetate in formula were identified. Therefore, dietary intakes are only those from water. See footnote on drinking water for details.

[h] Assumed to weigh 9.1 kg (Health Canada 2015), to breathe 5.4 m^3 of air per day (US EPA 2011 [modified]), to drink 0 L of water per day (Health Canada 2017), to ingest 7.3 mg of soil per day, and to ingest 27.0 mg of dust per day (Wilson and Meridian 2015 [modified]). For breast milk-fed infants, assumed to consume 0.632 L of breast milk per day (Health Canada 2018). For formula-fed infants, assumed to drink 0.764 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details.

[i] Assumed to weigh 11.0 kg (Health Canada 2015), to breathe 8.0 m^3 of air per day (US EPA 2011 [modified]), to drink 0.36 L of water per day (Health Canada 2017), to ingest 8.8 mg of soil per day, and to ingest 35.0 mg of dust per day (Wilson and Meridian 2015 [modified]).

[j] Assumed to weigh 15 kg (Health Canada 2015), to breathe 9.2 m^3 of air per day (US EPA 2011 [modified]), to drink 0.43 L of water per day (Health Canada 2017), to ingest 6.2 mg of soil per day, and to ingest 21.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[k] Assumed to weigh 23 kg (Health Canada 2015), to breathe 11.1 m^3 of air per day (US EPA 2011 [modified]), to drink 0.53 L of water per day (Health Canada 2017), to ingest 8.7 mg of soil per day, and to ingest 24.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[l] Assumed to weigh 42 kg (Health Canada 2015), to breathe 13.9 m^3 of air per day (US EPA 2011 [modified]), to drink 0.74 L of water per day (Health Canada 2017), to ingest 6.9 mg of soil per day, and to ingest 23.8 mg of dust per day (Wilson and Meridian 2015 [modified]).

[m] Assumed to weigh 62 kg (Health Canada 2015), to breathe 15.9 m^3 of air per day (US EPA 2011 [modified]), to drink 1.09 L of water per day (Health Canada 2017), to ingest 1.4 mg of soil per day, and to ingest 2.1 mg of dust per day (Wilson and Meridian 2015 [modified]).

[n] Assumed to weigh 74 kg (Health Canada 2015), to breathe 15.1 m^3 of air per day (US EPA 2011 [modified]), to drink 1.53 L of water per day (Health Canada 2017), to ingest 1.6 mg of soil per day, and to ingest 2.6 mg of dust per day (Wilson and Meridian 2015 [modified]).

Table B-2. Estimates of daily intake (µg/kg bw/day) of 2-methoxypropyl acetate

Age categories	Ambient air[a]	Indoor air[b]	Drinking water[c]	Soil[d]	Total intake
0 to 5 months[e](breast milk-fed)[f]	0.34	0.01	N/A	N/A	0.35
0 to 5 months[e] (formula fed)[g]	0.34	0.01	0.004	N/A	0.39
6 to 11 months[h]	0.34	0.01	0.03	1.4E-6	0.38
1 year[i]	0.42	0.01	0.01	1.4E-6	0.44
2 to 3 years[j]	0.35	0.01	9.17E-3	7.4E-7	0.37
4 to 8 years[k]	0.28	8.23E-3	7.37E-3	6.81E-7	0.29
9 to 13 years[l]	0.19	5.68E-3	5.64E-3	2.96E-7	0.20
14 to 18 years[m]	0.15	4.40E-3	5.63E-3	4.1E-8	0.16
Greater than or equal to 19 years[n]	0.12	3.50E-3	6.62E-3	3.89E-8	0.13

Abbreviations: N/A, not applicable

[a] Based on SCREEN3 results, an ambient air concentration (4.61 µg/m^3) was used as a conservative approach for deriving estimates of daily exposure from ambient air. Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[b] No Canadian indoor or ambient air monitoring data were identified. Therefore, ChemCAN results for air concentration data (1.96 ng/m^3) was used as a conservative approach for deriving estimates of daily exposure from ambient and indoor air. Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[c] No Canadian water monitoring data were identified. Therefore, ChemCAN results for water concentration (0.032 µg/L) was used to derive estimates of daily intake from drinking water.

[d] No Canadian soil monitoring data were identified. Therefore, ChemCAN results for soil concentration (0.18 ng/g) was used to derive estimates of daily intake from soil.

[e] Assumed to weigh 6.3 kg (Health Canada 2015), to breathe 3.7 m^3 of air per day (US EPA 2011 [modified]), and to ingest 21.6 mg of dust per day (Wilson and Meridian 2015 [modified]). It is assumed that no soil ingestion occurs due to typical caregiver practices.

[f] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018), and breast milk is assumed to be the only dietary source. No breast milk monitoring data for 2-methoxypropyl acetate were identified.

[g] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018), where water is used to reconstitute formula. No monitoring data on 2-methoxypropyl acetate in formula were identified; therefore, dietary intakes are only those from water. See footnote on drinking water for details.

[h] Assumed to weigh 9.1 kg (Health Canada 2015), to breathe 5.4 m^3 of air per day (US EPA 2011 [modified]), to drink 0 L of water per day (Health Canada 2017), to ingest 7.3 mg of soil per day, and to ingest 27.0 mg of dust per day (Wilson and Meridian 2015 [modified]). For breast milk-fed infants, assumed to consume 0.632 L of breast milk per day (Health Canada 2018). For formula-fed infants, assumed to drink 0.764 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details.

[i] Assumed to weigh 11.0 kg (Health Canada 2015), to breathe 8.0 m^3 of air per day (US EPA 2011 [modified]), to drink 0.36 L of water per day (Health Canada 2017), to ingest 8.8 mg of soil per day, and to ingest 35.0 mg of dust per day (Wilson and Meridian 2015 [modified]).

[j] Assumed to weigh 15 kg (Health Canada 2015), to breathe 9.2 m^3 of air per day (US EPA 2011 [modified]), to drink 0.43 L of water per day (Health Canada 2017), to ingest 6.2 mg of soil per day, and to ingest 21.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[k] Assumed to weigh 23 kg (Health Canada 2015), to breathe 11.1 m^3 of air per day (US EPA 2011 [modified]), to drink 0.53 L of water per day (Health Canada 2017), to ingest 8.7 mg of soil per day, and to ingest 24.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[l] Assumed to weigh 42 kg (Health Canada 2015), to breathe 13.9 m^3 of air per day (US EPA 2011 [modified]), to drink 0.74 L of water per day (Health Canada 2017), to ingest 6.9 mg of soil per day, and to ingest 23.8 mg of dust per day (Wilson and Meridian 2015 [modified]).

[m] Assumed to weigh 62 kg (Health Canada 2015), to breathe 15.9 m^3 of air per day (US EPA 2011 [modified]), to drink 1.09 L of water per day (Health Canada 2017), to ingest 1.4 mg of soil per day, and to ingest 2.1 mg of dust per day (Wilson and Meridian 2015 [modified]).

[n] Assumed to weigh 74 kg (Health Canada 2015), to breathe 15.1 m^3 of air per day (US EPA 2011 [modified]), to drink 1.53 L of water per day (Health Canada 2017), to ingest 1.6 mg of soil per day, and to ingest 2.6 mg of dust

per day (Wilson and Meridian 2015 [modified]).

Table B-3. Estimates of daily intake (µg/kg bw/day) of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate

Age categories	Ambient air[a]	Indoor air[b]	Dust[c]	Total intake
0 to 5 months[d] (breast milk-fed)[e]	14.7	103.0	2.45	120.2
0 to 5 months[d] (formula fed)[f]	14.7	103.0	2.45	120.2
6 to 11 months[g]	14.9	104.1	2.12	121.1
1 year[h]	18.2	127.6	2.28	148.1
2 to 3 years[i]	15.4	107.6	1.02	124.0
4 to 8 years[j]	12.1	84.7	0.76	97.5
9 to 13 years[k]	8.29	58.1	0.41	66.8
14 to 18 years[l]	6.43	45.0	0.02	51.4
Greater than or equal to 19 years[m]	5.11	35.8	0.03	40.9

[a] No Canadian indoor or ambient air monitoring data were identified; maximum ambient air concentration from Canadian indoor air (200.5 µg/m^3) (Won and Lusztyk 2011) was used to derive an estimate of daily exposure from ambient air. Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[b] Indoor air concentration based on the highest concentration in indoor air samples measured in Quebec City (200.5 µg/m^3) (Won and Lusztyk 2011). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[c] Maximum value of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in Canadian house dust (715 (µg/g) from Quebec City used to derive daily exposure from dust (Won and Lusztyk 2011).

[d]Assumed to weigh 6.3 kg (Health Canada 2015), to breathe 3.7 m^3 of air per day (US EPA 2011 [modified]), and to ingest 21.6 mg of dust per day (Wilson and Meridian 2015 [modified]). It is assumed that no soil ingestion occurs due to typical caregiver practices.

[e] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018), and breast milk is assumed to be the only dietary source.

[f] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details.

[g] Assumed to weigh 9.1 kg (Health Canada 2015), to breathe 5.4 m^3 of air per day (US EPA 2011 [modified]), to drink 0 L of water per day (Health Canada 2017), to ingest 7.3 mg of soil per day, and to ingest 27.0 mg of dust per day (Wilson and Meridian 2015 [modified]). For breast milk-fed infants, assumed to consume 0.632 L of breast milk per day (Health Canada 2018). For formula-fed infants, assumed to drink 0.764 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details.

[h] Assumed to weigh 11.0 kg (Health Canada 2015), to breathe 8.0 m^3 of air per day (US EPA 2011 [modified]), to drink 0.36 L of water per day (Health Canada 2017), to ingest 8.8 mg of soil per day, and to ingest 35.0 mg of dust per day (Wilson and Meridian 2015 [modified]).

[i] Assumed to weigh 15 kg (Health Canada 2015), to breathe 9.2 m^3 of air per day (US EPA 2011 [modified]), to drink 0.43 L of water per day (Health Canada 2017), to ingest 6.2 mg of soil per day, and to ingest 21.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[j] Assumed to weigh 23 kg (Health Canada 2015), to breathe 11.1 m^3 of air per day (US EPA 2011 [modified]), to drink 0.53 L of water per day (Health Canada 2017), to ingest 8.7 mg of soil per day, and to ingest 24.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[k] Assumed to weigh 42 kg (Health Canada 2015), to breathe 13.9 m^3 of air per day (US EPA 2011 [modified]), to drink 0.74 L of water per day (Health Canada 2017), to ingest 6.9 mg of soil per day, and to ingest 23.8 mg of dust per day (Wilson and Meridian 2015 [modified]).

[l]Assumed to weigh 62 kg (Health Canada 2015), to breathe 15.9 m^3 of air per day (US EPA 2011 [modified]), to drink 1.09 L of water per day (Health Canada 2017), to ingest 1.4 mg of soil per day, and to ingest 2.1 mg of dust per day (Wilson and Meridian 2015 [modified]).

[m] Assumed to weigh 74 kg (Health Canada 2015), to breathe 15.1 m^3 of air per day (US EPA 2011 [modified]), to drink 1.53 L of water per day (Health Canada 2017), to ingest 1.6 mg of soil per day, and to ingest 2.6 mg of dust per day (Wilson and Meridian 2015 [modified]).

Table B-4. Estimates of daily intake (µg/kg bw/day) of docusate sodium

Age categories	Drinking water[a]	Food and beverages[b]	Total intake
0 to 5 months[c] (breast milk-fed)[d]	N/A	N/A	N/A
0 to 5 months[c] (formula fed)[e]	0.07	N/A	0.07
6 to 11 months[f]	0.05	0	0.05
1 year[g]	0.02	270.7	270.7
2 to 3 years[h]	0.02	337.5	337.5
4 to 8 years[i]	0.01	274.5	274.5
9 to 13 years[j]	9.9E-3	210.0	210.0
14 to 18 years[k]	9.9E-3	134.2	134.2
Greater than or equal to 19 years[l]	0.01	58.6	58.6

Abbreviations: N/A, not applicable

[a] No Canadian water monitoring data were identified; therefore, NSACB EAU Drinking Water Spreadsheet water concentration (0.56 µg/L) was used to derive estimates of daily intake from drinking water.

[b] Food values obtained from Food Directorate and represent the 95th percentile values for each age group based on consumption of sausages and fruit drinks assuming docusate sodium found at the maximum permitted level (as a Permitted Food Additive). Food consumption rates are described in Health Canada (2015)

[c] Assumed to weigh 6.3 kg (Health Canada 2015), to breathe 3.7 m^3 of air per day (US EPA 2011 [modified]), and to ingest 21.6 mg of dust per day (Wilson and Meridian 2015 [modified]). It is assumed that no soil ingestion occurs due to typical caregiver practices.

[d] Exclusively for breast milk-fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018), and breast milk is assumed to be the only dietary source.

[e] Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018), where water is used to reconstitute formula. No monitoring data on docusate sodium in formula were identified; therefore, dietary intakes are only those from water. See footnote on drinking water for details.

[f] Assumed to weigh 9.1 kg (Health Canada 2015), to breathe 5.4 m^3 of air per day (US EPA 2011 [modified]), to drink 0 L of water per day (Health Canada 2017), to ingest 7.3 mg of soil per day, and to ingest 27.0 mg of dust per day (Wilson and Meridian 2015 [modified]). For breast milk-fed infants, assumed to consume 0.632 L of breast milk per day (Health Canada 2018). For formula-fed infants, assumed to drink 0.764 L of water per day (Health Canada 2018), where water is used to reconstitute formula. See footnote on drinking water for details

[g] Assumed to weigh 11.0 kg (Health Canada 2015), to breathe 8.0 m^3 of air per day (US EPA 2011 [modified]), to drink 0.36 L of water per day (Health Canada 2017), to ingest 8.8 mg of soil per day, and to ingest 35.0 mg of dust per day (Wilson and Meridian 2015 [modified]).

[h] Assumed to weigh 15 kg (Health Canada 2015), to breathe 9.2 m^3 of air per day (US EPA 2011 [modified]), to drink 0.43 L of water per day (Health Canada 2017), to ingest 6.2 mg of soil per day, and to ingest 21.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[i] Assumed to weigh 23 kg (Health Canada 2015), to breathe 11.1 m^3 of air per day (US EPA 2011 [modified]), to drink 0.53 L of water per day (Health Canada 2017), to ingest 8.7 mg of soil per day, and to ingest 24.4 mg of dust per day (Wilson and Meridian 2015 [modified]).

[j] Assumed to weigh 42 kg (Health Canada 2015), to breathe 13.9 m^3 of air per day (US EPA 2011 [modified]), to drink 0.74 L of water per day (Health Canada 2017), to ingest 6.9 mg of soil per day, and to ingest 23.8 mg of dust per day (Wilson and Meridian 2015 [modified]).

[k] Assumed to weigh 62 kg (Health Canada 2015), to breathe 15.9 m^3 of air per day (US EPA 2011 [modified]), to drink 1.09 L of water per day (Health Canada 2017), to ingest 1.4 mg of soil per day, and to ingest 2.1 mg of dust per day (Wilson and Meridian 2015 [modified]).

[l] Assumed to weigh 74 kg (Health Canada 2015), to breathe 15.1 m^3 of air per day (US EPA

2011 [modified]), to drink 1.53 L of water per day (Health Canada 2017), to ingest 1.6 mg of soil per day, and to ingest 2.6 mg of dust per day (Wilson and Meridian 2015 [modified]).

Appendix C. Exposure parameters

Appendix C-1. Estimates of daily intake of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate for infants from baby bottles

Concentrations of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in simulated formula were associated with the use of baby bottles (Onghena et al. 2016; Simoneau et al. 2012). While new baby bottles may be introduced at any time during infancy, a scenario was developed for early infancy (i.e., 0-1 month of age) as a conservative approach by assuming (1) that concentrations of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in formula would be observed up to the highest average reported in the literature (348 µg/kg) based on the third migration of bottles at 70°C for 2 hours (Onghena et al. 2016) and (2) that this age group would be strictly bottle-fed.

Table C-1. Intake estimates for infants associated with 2,2,4-trimethyl-1,3-pentanediol diisobutyrate migration from baby bottles

Infant age group	BW (kg)	Max. conc. (µg/kg)	Average ingestion rate (kg/day)	Max ingestion rate (kg/day)	Lower intake (max conc. + average ingestion) (µg/kg bw/day)	Upper intake (max. conc. + max. ingestion) (µg/kg bw/day)
0 to 1 month	3.9[a]	348[b]	0.644[c]	1.08[c]	57.5	96.4

Abbreviations: BW, body weight; Max., maximum; Conc., concentration
[a] Based on average female infant weight of 3.9 kg (NCHS 2000)
[b] Migration value based on conventional testing in a silicone baby bottle reported in Onghena et al. (2016). Simoneau et al. 2012 was considered a screening study and examined early migrations from baby bottles
[c] Average formula intake of 644 g/day and maximum formula intake of 1080 g/day (INSPQ 2001)

Appendix C-2. Estimates of daily intake for children aged 6 to 11 months from mouthing and dermal exposure to of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate in plastic toys for children aged 6 months to 4 years

Migration rates of 2,2,4-trimethyl-1,3-pentanediol diisobutyrate from plastic toys in simulated saliva were used to estimate exposure to children mouthing toys and dermal exposure to plastic toys (Babich 2010). Migration rate data from RIVM and ANSES were also considered. However, the maximum average value from CPSC was used in the assessment (VWA 2009, as cited by Janssen and Bremmer 2009; ANSES 2016).

The parameters and intake estimates for oral exposure from mouthing as well as total potential exposure from dermal or hand-to-mouth contact are outlined in Table C-2.

Mouthing/Oral Exposure: A child with a body weight of 9.1 kg (aged 6 to 11 months) was assumed to mouth a toy for 1 to 2 hours per day (average/worst case).

Dermal and hand-to-mouth exposure: A child with a body weight of 11 kg (aged 1 year) was assumed to have dermal contact with a surface of 100 cm^2 of a toy for 3 hours per day. As no data on dermal absorption of 2,4-trimethyl-1,3-pentanediol diisobutyrate were available, it was assumed that all substance deposited on the skin would be absorbed; this assumption would also account for potential exposure through hand-to-mouth activity.

Table C-2. Intake estimates for children associated with 2,2,4-trimethyl-1,3-pentanediol diisobutyrate migration from plastic toys

Age group	BW (kg)	Migration (µg/min × 10 cm^2)	Time spent mouthing/ contacting (min/day)	Area mouthed/ touched (cm^2)	Intake (µg/kg bw/day)
6–11 months	9.1	11.3[a]	60 - 120	10	74 - 149
1 year	11	11.3[a]	180	100	1849

Abbreviation: BW, body weight
[a] US CPSC (2010)

Appendix C-3. Parameters for estimating exposure to products available to consumers

Exposure to products was estimated using ConsExpo Web (2016).

Cosmetic exposures were estimated using ConsExpo Web (2016) combined with specific parameters obtained from published literature. Exposure estimates were calculated based on default body weights of 74 kg for adults (19 years and older), 62 kg for 14- to 18-year-olds, 42 kg for 9- to 13-year-olds,15 kg for 2- to 3-year-olds, 11 kg for 1-year-olds, 9.1 kg for 6- to 11-month-olds, and 6.3 kg for 0 to 5-month-olds (Health Canada 2015). The estimated inhalation and dermal exposure parameters for cosmetics and other products available to consumers are described in Table C-3. Unless specified otherwise, the parameter values are taken from relevant ConsExpo Fact Sheet for the scenario presented.

Table C-3. Dermal and inhalation exposure parameter assumptions for esters

Exposure scenario	Assumptions
Cosmetic scenarios	
Exfoliant (mechanical) (teen/adult)	Frequency of use: 0.29 application per day (adult/teen) (Ficheux et al. 2015) Product amount: 3.1 g/application (adult/teen) (Ficheux et al. 2016) Retention factor: 0.1
Nail polish (2-3 years/adult) (methyl acetate, 2-methoxypropyl acetate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, docusate sodium) Assumes 2 coats of nail polish applied to fingernails and toenails.	From Cosmetic Fact Sheet (RIVM 2007b), with additional information on amount applied and surface area; evaporation model since substances are volatile Exposure duration: 35 minutes Product amount: 0.27 g (2-3 years); 0.8 g (adults) Room volume: 1 m^3 Weight fraction of substance: 30% (methyl acetate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate); 0.05% (2-methoxypropyl acetate) Ventilation rate: 1 hr^{-1} Mass transfer coefficient: 10 m/h (default) Release area mode: constant Release area: 8.8 cm^2 (2-3 years), 26.2 cm^2 (adult) Emission duration: 35 minutes Molecular weight matrix: 124 g/mol Dermal:

Exposure scenario	Assumptions
	Amount on skin: 0.16 g/use (adult); 0.06 g/use (2-3 years) (modified from Ficheux et al. 2014, adjusted by a factor of 0.206 for adults and 0.205 for children to account for how much nail polish ends up on skin)
Nail polish remover (2-3 years/9-13 year old; adult) (methyl acetate, methyl hexanoate, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	From Cosmetic Fact Sheet (RIVM 2007b), with additional information on amount applied and surface area; evaporation model since substances are volatile Inhalation: Exposure duration: 8 minutes Product amount: 1.82 g (2–3 years); 5.36 g (adult) Room volume: 1 m^3 Ventilation rate:1 hr^{-1} Mass transfer coefficient: 10 m/h (default) Release area mode: constant Release area: 11.6 cm^2 (2–3 years); 34 cm^2 (adult) Emission duration: 5 minutes Molecular weight matrix: 75 g/mol Dermal: Amount on skin: 2.25 g/use (9–13 year old; adult); 0.76 g/use (4–8 and 2–3 years) (modified from Ficheux et al. 2014, adjusted by a factor of 0.42 (Bremmer et al. 2006) to account for how much nail polish remover is in contact with skin).
Eye adhesive (based on mascara) (adult/child) (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	Frequency of use: 1 per day (adult/14–18 yrs/9–13 yrs) (Ficheux et al. 2015) Product amount: 0.018 g/application (adult/14–18 yrs/9–13 yrs/4–8 yrs) (Ficheux et al. 2016) Retention factor: 1
Bath oil (adult/teen) (docusate sodium)	Product amount: 15 g/application (adult/14–18 yrs/9–13 yrs) (CTFA 1983) Retention factor: 0.001 (NICNAS 2009)
Facial cleanser (child/adult) (docusate sodium)	Frequency of use: 1.6 application per day (adult) (Loretz et al. 2008) 1.2 per day (14–18 yrs/9–13 yrs) (Ficheux et al. 2015) Product amount:

Exposure scenario	Assumptions
	3.3 g/application (adult/14–18 yrs) (Ficheux et al. 2016) 3.1 g/application (9–13 yrs) (surface area adjustment factor to Ficheux et al. 2016) Retention factor: 0.01
Hair conditioner: rinse out (2–3 years/adult) (docusate sodium)	Frequency of use: 1.1 application per day (adult) (Loretz et al. 2008); assumed to be 1 application per day for all other age groups Product amount: 13.1 g/application (adult) (Loretz et al. 2008) 10 g/application (14–18 yrs) (Ficheux et al. 2016) 7.8 g/application (9–13 yrs/4–8 yrs) (Ficheux et al. 2016) 5.2 g/application (2–3 yrs) (Garcia-Hidalgo et al. 2017) Retention factor: 0.01
Fragrance product: massage oil (infant/adult) (docusate sodium)	Product amount: 3.2 g/application (adult) (Ficheux et al. 2016) 1.8 g/application (0–5 months) (Ficheux et al. 2016)
Facial makeup powder (teen/adult) (docusate sodium)	Frequency of use: 1.0 application per day (adult/14–18 yrs) (Ficheux et al. 2015) Product amount: 0.073 g/application (adult/14–18 yrs) (Ficheux et al. 2016) 0.069 g/application (9–13 yrs) (surface area adjustment factor to Ficheux et al. 2016) 0.06 g/application (4–8 yrs) surface area adjustment factor to Ficheux et al. 2016)
Sunless tanning product (docusate sodium)	Product amount: 2.7 g/application (adult) (Ficheux et al. 2016). Retention factor: 0.1 (product is applied and rinsed in shower; used face mask/face exfoliation as example of retention factor)
Hair bleach (teen/adult) (docusate sodium)	Product amount: 200 g/application (adult/14–18 yrs) (Bremmer 2006) Retention factor: 0.01
Hair dye/highlight (14–18 years) (docusate sodium)	Product amount:

Exposure scenario	Assumptions
	106 g/application hair dye (adult/14–18 yrs) (Ficheux et al. 2015); assumed 50% of application amount (for highlight product instead of hair dye) Retention factor: 0.1
Hair styling product (aerosol) (docusate sodium)	Scenario: aerosol hair spray – exposure to spray Spray duration: 0.24 minute Exposure duration: 5 minutes Mass generation rate of: 0.4 g/s Room volume: 10 m^3 Weight fraction of substance: 0.3% Ventilation rate: 2 hr^{-1} Spray toward person Cloud volume: 0.0625 m^3 Airborne fraction: 0.2 Density non-volatile: 1.5 g/cm^3 Inhalation cut-off diameter: 15 μm Aerosol diameter distribution: lognormal Median diameter: 46.5 μm Arithmetic coefficient of variation: 2.1 Dermal: Product amount: 2.6 g/application (adult) (Loretz et al. 2006) 2.3 g/application (14–18 yrs; 9–13yrs; 4–8 yrs) (Ficheux et al. 2016) Retention factor: 0.09
Other products available to consumers	
Aerosol cleaner/polish; stainless steel kitchen cleaner; (methyl acetate)	Scenario: cleaning spray scenario from Cleaning Product Fact Sheet (RIVM 2007b), but used exposure to vapour – evaporation model since substances are volatile Exposure duration: 60 minutes Product amount: 7.32 g = mass generation rate of: 0.4 g/s (based on shoe polish spray rate); area of front of fridge: = 160 cm * 80 cm = 12800 cm^2 = 1.28 m^2; (Weerdesteijn et al. 1999) 14.3 s/m^2 * 1.28 m^2 = 18.3 s 0.4 g/s * 18.3 s = 7.32 g. Room volume: 15 m^3 (kitchen) Weight fraction of substance: 13%

Exposure scenario	Assumptions
	Ventilation rate: 2.5 hr^{-1} (kitchen) Mass transfer coefficient: 10 m/h (default) Release area mode: constant Release area: 1.28 m^2 Application duration: 10 minutes (includes spray, leaving on time, cleaning time) Molecular weight matrix: 120 g/mol (based on the compound of interest is not the main solvent)
Aerosol automotive spray paint (e.g., tire rims); (methyl acetate)	Scenario: spray can scenario from Paint Fact Sheet (RIVM 2007b), exposure to vapour – instantaneous release Exposure duration: 60 minutes Product amount: 545 g 2 cans at 354 mL can; density = 0.77 g/mL; assuming one can = **272.6 g** product Room volume: 90 m^3 (garage; changed ConsExpo default of 34 m^3 to 90 m^3 as estimate of two car garage (90 m^3 is the default garage volume used in US EPA Consumer Exposure Model v. 2.0 and consistent with values in Batterman et al. (2007); this garage size allows sufficient space to work on automobile) Weight fraction of substance: 26% Ventilation rate: 1.5 hr^{-1} (garage)
Aerosol tire cleaner (automotive); (methyl acetate)	Scenario: aerosol spray scenario from cleaning products Fact Sheet (RIVM 2007b); evaporation model for volatile substances; assumed spraying, leaving on and wiping down four tires. Exposure duration: 60 minutes Product amount: 16 g = mass generation rate of: 0.4 g/s (based on shoe polish spray); 0.6 min or 40 s of spraying (assuming 10 s per tire) = 40 s * 0.4g/s= **16 g product** Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 60% Ventilation rate:1.5 hr^{-1} (garage) Mass transfer coefficient: 10 m/h (default) Release area mode: constant Release area: 2 m^2 Emission duration: 10 minutes (from all-purpose spray cleaner)

Exposure scenario	Assumptions
	Molecular weight matrix: 200 g/mol (based on product being mainly methyl acetate)
Trigger spray tire cleaner (automotive); (methyl acetate)	Scenario: all-purpose spray scenario from cleaning products Fact Sheet (RIVM 2007b); evaporation model as substances are volatile; assumed spraying, leaving on and wiping down four tires. Exposure duration: 60 minutes Product amount: 19.7 g = mass generation rate of: 0.8 g/s (based on all purpose cleaner); 0.41 min of spraying (based on all-purpose spray) = 24.6s*0.8g/s= **19.68 g product** Room volume: 34 m^3 ((ConsExpo Web value for garage) Weight fraction of substance: 60% Ventilation rate: 1.5 hr^{-1} (garage) Mass transfer coefficient: 10 m/h Release area mode: constant Release area: 2 m^2 Emission duration: 10 minutes (from all-purpose spray cleaner) Molecular weight matrix: 200 g/mol (based on product being mainly methyl acetate)
Aerosol adhesive remover (automobile); (methyl acetate)	Scenario: spray can scenario from Paint Fact Sheet (RIVM 2007b). Exposure to vapour – evaporation model Scenario: assumed small area for adhesive remover (bumper sticker); Exposure duration: 10 minutes Product amount: 4 g = mass generation rate of: 0.4 g/s (based on shoe polish); 10 s of spraying (smaller than fridge area above) = 10 s × 0.4g/s = **4 g product** Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 80% Ventilation rate: 1.5 hr^{-1} (garage) Mass transfer coefficient: 10 m/h Release area mode: constant Release area: 25 cm ×10 cm = 250 cm^2 (estimated size of bumper sticker) Emission duration: 10 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent)

Exposure scenario	Assumptions
Aerosol adhesive; (automotive/household); (methyl acetate)	Scenario: aerosol adhesive scenario from DIY products Fact Sheet (RIVM 2007b); spray model – instantaneous release (volatile substance) Exposure duration: 60 minutes Product amount: 204 g = mass generation rate of: 1.2 g/s (based on glue from spray); 170s of spraying = 170 s × 1.2 g/s = 204 g product Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 40% Ventilation rate: 1.5 hr^{-1} (garage)
Construction adhesives (joint assembly); (methyl acetate)	Scenario: cartridge gun or caulk gun application; based on assembly sealant scenario from DIY products Fact Sheet, Assembly sealant (RIVM 2007b); evaporation model as substances are volatile Exposure duration: 240 minutes Product amount: 150 g (based on product size) Room volume: 20 m^3 Weight fraction of substance: 5% Ventilation rate: 1.5 hr^{-1} (area under construction) Mass transfer coefficient: 10 m/h Release area mode: increasing Release area: 1.5 m^2 (from Fact sheet) Emission duration: 30 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent)
Tube glue; (methyl acetate)	Scenario: tube glue (contact glue) in Do-It-Yourself Fact Sheet (tur Burg et al. 2007) Exposure duration: 30 minutes (considered appropriate for small jobs; 18 mL container) Product amount: 9 g Room volume: 20 m^3 (unspecified) Weight fraction of substance: 95%–50% Ventilation rate: 0.6 hr^{-1} Mass transfer coefficient: 10 m/h Release area mode: increasing Release area: 0.02 m^2 (from Fact sheet) Emission duration: 10 minutes Molecular weight matrix: 3000 g/mol
Aerosol lubricant (e.g., gun cleaning); (methyl acetate)	Scenario: aerosol spray scenario adapted from cleaning products Fact Sheet (RIVM 2007b) – cleaning;

Exposure scenario	Assumptions
	evaporation model; assumed spraying, leaving on and wiping down gun. Exposure duration: 60 minutes Product amount: 15 g = mass generation rate of: 1.5 g/s (based on lubricant penetrating spray); 10 s of spraying (assuming 10 s per tire) = 40 × 0.4g/s = 16 g product Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 10% Ventilation rate: 1.5 hr^{-1} (garage) Mass transfer coefficient: 10 m/h Release area mode: constant Release area: 1.5 m^2 (estimated) Emission duration: 10 minutes (based on all purpose spray cleaner) Molecular weight matrix: 300 g/mol (used similar approach as stainless steel cleaner)
Paint remover; (methyl acetate)	Scenario: paint remover, approach adapted from the Do-It-Yourself Fact Sheet (RIVM 2007a); exposure to vapour model with evaporation. Exposure period: 90 minutes (20 minute application; 20 minute wait (not in room; air concentrations during this time not included in estimate); 50 minute removal activity) Project type/Product amount/Release area/Room volume/ ventilation rate - Small project: 868 g (1 m^2), 34 m^3; 0.5–2.5 hr^{-1} - Large project: 7819 g (9 m^2), 34 m^3; 0.5–2.5 hr^{-1} - Bathtub: 2867 g (3.3 m^2); 10 m^3; 2 hr^{-1} - Product amounts based on application rate in technical data sheet for product (TDS 2019) Emission factor: 50% (represents amount of substance available for evaporation to account for potential presence of evaporation barriers (used in product for efficacy); based on literature indicating 10% to 30% chemical evaporated (adapted from Van Veen et al. 2002).

Exposure scenario	Assumptions
	Weight fraction of substance: 70% Mass transfer coefficient: 3.44 m/h Release area mode: increasing Application duration: 20 minutes Molecular weight matrix: 100 g/mol (estimated) Estimated mean 24-hour air concentrations are reported in Table 7-3. Peak and Event concentrations are found below: Peak concentrations: - Small project (lower/higher vent): 7960/5820 mg/m^3 - Large project (lower/higher vent): 68 900/50 700 mg/m^3 - Bathroom: 67 000 mg/m^3 Event concentration - Small project (lower/higher vent): 3893/1257 mg/m^3 - Large project (lower/higher vent): 34 453/11 384 mg/m^3 - Bathroom: 18 183 mg/m^3
Garage floor coating; (methyl acetate)	Scenario: general coating on a floor (in a garage) in Do-It-Yourself Fact Sheet (RIVM 2007a) Exposure duration: 90 minutes Product amount: 900 g (based on application rate of 1L product/30 m^2 as outlined in technical data sheet) Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 10% (concentration in applied product, i.e., Part A and Part B mixed) Ventilation rate: 1.5 hr^{-1} (garage); Mass transfer coefficient: 10 m/h Release area mode: increasing Release area: 25 m^2 (floor surface area matches volume and amount applied) Emission duration: 90 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent)
Aerosol paint (2-methoxypropyl acetate)	Scenario: spray can scenario from Paint Fact Sheet (RIVM 2007b). Exposure to vapour – evaporation model Exposure duration: 20 minutes Product amount: 300 g Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 0.1% Ventilation rate: 1.5 hr^{-1} (garage) Mass transfer coefficient: 10 m/h

Exposure scenario	Assumptions
	Release area mode: constant Release area: 2 m^2 Emission duration: 15 minutes Molecular weight matrix: 300 g/mol (compound of interest is not a main solvent) Dermal: Contact rate: 100 mg/min Release duration: 15 minutes
Putty filler (2-methoxypropyl acetate)	Scenario: Large hole filler scenario in DIY products Fact Sheet (RIVM 2007b); evaporation model Exposure duration: 240 minutes Product amount: 150 g (from fact sheet) Room volume: 34 m^3 (ConsExpo Web value for garage) Weight fraction of substance: 0.1% Ventilation rate: 1.5 hr^{-1} Mass transfer coefficient: 10 m/h Release area mode: constant Release area: 200 cm^2 (from Fact sheet) Emission duration: 240 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent) Dermal: Product amount: 0.5 g
Aerosol primer (2,2,4-trimethyl-1,3-pentanediol diisobutyrate) (spray model)	Scenario: spray can scenario from Paint Fact Sheet (RIVM 2007b); used exposure to spray (exposure to vapour was lower) Spray duration: 15 minutes Exposure duration: 20 minutes Weight fraction of substance: 5% Room volume: 34 m^3 (ConsExpo Web value for garage) Ventilation rate: 1.5 hr^{-1} (garage) Mass generation rate: 0.45 g/s (aerosol paint) Airborne fraction: 0.7 Density non-volatile: 1.5 g/cm^3 Inhalation cut off diameter: 15 μm Lognormal aerosol diameter distribution: median diameter of 15.1 μm; Arithmetic coefficient of variation = 1.2 Dermal: Contact rate: 100 mg/min

Exposure scenario	Assumptions
	Release duration: 15 minutes
Marine/pool paint (outdoors; only dermal) (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	Based on brush/roller paint: Dermal: Contact rate: 30 mg/min Release duration: 180 minutes
Liquid hardener; fiberglass repair kit; (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	Scenario: DIY products Fact Sheet (RIVM 2007b); evaporation model; used 2-component glue scenario Mix/load - inhalation: Exposure duration: 5 minutes Product amount: 20 g (from fact sheet) Room volume: 1 m^3 Weight fraction of substance: 30% Ventilation rate: 0.6 hr^{-1} Mass transfer coefficient: 10 m/h Release area mode: constant Release area: 0.002 m^2 (from Fact sheet) Emission duration: 5 minutes Molecular weight matrix: 3000 g/mol Mix/load - dermal: Product amount: 0.05 g Apply – inhalation: Exposure duration: 240 minutes Product amount: 20 g (from fact sheet) Room volume: 20 m^3 Weight fraction of substance: 30% Ventilation rate: 0.6 hr^{-1} Mass transfer coefficient: 10 m/h Release area mode: increasing Release area: 0.05 m^2 (from Fact sheet) Emission duration: 30 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent) Dermal: Product amount: 0.1 g (100 mg)
Concrete crack repair; (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	Scenario: DIY products Fact Sheet (RIVM 2007b); filler/putty from tube evaporation model Exposure duration: 240 minutes Product amount: 40 g (from fact sheet) Room volume: 34 m^3 (ConsExpo Web value for garage)

Exposure scenario	Assumptions
	Weight fraction of substance: 40% Ventilation rate: 0.6 hr^{-1} Mass transfer coefficient: 10 m/h Release area mode: increasing Release area: 0.02 m^2 (from Fact sheet) Emission duration: 20 minutes Molecular weight matrix: 3000 g/mol (assuming the compound of interest is a main solvent) Dermal: Product amount: 0.05 g (50 mg)
Hobby paint; (2,2,4-trimethyl-1,3-pentanediol diisobutyrate)	Scenario of paint on slightly stained hand was approximately 50 mg. Assumed 50 mg on child's hand during hobby painting
Exterior house cleaner and mildew killer; (docusate sodium)	Scenario: algae green deposit remover from Disinfectant Products Fact Sheet (RIVM 2007b) Mix/load: Exposed area: 215 cm^2 Product amount: 0.01 g Application: Contact rate: 540 mg/min Release duration: 16.7 minutes
Trigger spray cleaner; (docusate sodium)	Scenario: trigger spray; exposure to spray Spray duration: 0.23 minutes Exposure duration: 60 minutes Weight fraction: 13.5% Room volume: 15 m^3 Ventilation rate: 2.5 hr^{-1} Mass generation rate of: 1.6 g/s Airborne fraction: 0.1 Density non-volatile: 1 g/cm^3 Inhalation cut off diameter: 15 μm Lognormal aerosol diameter distribution: median diameter of 2.4 μm; Arithmetic coefficient of variation = 0.37 Dermal (spray): Contact rate: 46 mg/min Release duration: 0.23 minutes Dermal (wipe):

Exposure scenario	Assumptions
	Product amount: 0.16 g
Cleaning wipes/wet tissues; (docusate sodium)	Scenario: Wet tissue wipes (hands) (Ficheux et al. 2016) Dermal: Product amount: 0.9 g remained on hand
Aerosol spray tire cleaner: foam (docusate sodium)	Scenario: based on elements from foam carpet spray spot remover scenario from Cleaning Products Fact Sheet (RIVM 2007b); Assumed 10 s spray/tire = 40 s Mass generation rate: 0.6 g/s (furniture spray can) = 24 g 1% available for dermal exposure (consistent with foam carpet cleaner) = 0.24 g = 240 mg product dermal exposure
Liquid paste activator (wallpaper); (docusate sodium)	Dermal: Contact rate: 30 mg/minute Release duration: 240 minutes
Wood hardener product; (docusate sodium)	Liquid brush on product: based on brush on paint product exposure contact rate. Dermal: Contact rate: 30 mg/minute Release duration: 10 minutes (based on type of product)

Appendix D. Parameters to estimate drinking water exposure

Table D-1. Human exposure parameter inputs and assumptions for releases to waste water scenarios derived with the NSACB EAU Drinking Water Spreadsheets

Substance	Methyl acetate	Docusate sodium
Scenario	Industrial release	Industrial release
Quantity at site	Section 71 total import value for substance (323,602 kg)	Section 71 total import values for substance (1,081,185 kg)
Wastewater treatment system (WWTS) removal rate (%)[a]	0	27.83
Number of industrial sites	1[b]	30
Release days (per year)[b]	250	250
Daily release to wastewater (%)	1[c]	1[d]
Receiving water body[b]	Thames River, London ON	Thames River, London ON

[a] ECCC (2016a)
[b] NSACB EAU Drinking Water Spreadsheet default
[c] Generic emission factor
[d] Based on 1% releases from handling of substance in powder form and 0% as transfer line/process vessel residues for dry substance.

Appendix E. SCREEN3: Model and inputs

SCREEN3 is a screening-level Gaussian air dispersion model based on the Industrial Source Complex (ISC) model (for assessing pollutant concentrations from various sources in an industry complex) (SCREEN3 2011). The driver for air dispersion in the SCREEN3 model is wind. The maximum calculated exposure concentration is selected based on a built-in meteorological data matrix of different combinations of meteorological conditions, including wind speed, turbulence and humidity. This model directly predicts concentrations resulting from point, area and volume source releases. SCREEN3 gives the maximum concentrations of a substance at chosen receptor heights and at various distances from a release source in the direction downwind from the prevalent wind 1 hour after a given release event. During a 24-hour period, for point emission sources, the maximum 1-hour exposure (as assessed by the ISC Version 3) is multiplied by a factor of 0.4 to account for variable wind direction. This gives an estimate of the air concentration over a 24-hour exposure (US EPA 1992; SCREEN3 2011). Similarly, for exposure events happening over the span of a year, it can be expected that the direction of the prevalent winds will be more variable and uncorrelated to the wind direction for a single event; thus, the maximum amortized exposure concentration for 1 year is determined by multiplying the maximum 1-hour exposure by a factor of 0.08 (US EPA 1992; SCREEN3 2011). The parameters used to estimate ambient air concentrations from 2-methoxypropyl acetate in air using the SCREEN3 model are presented in Table E-1 below.

Table E-1. Parameters used in SCREEN3 for air releases from industrial facilities for PMA

Parameter	Input
Source type	Area
Effective emission area[a]	150 m × 100 m
Receptor height[b]	1.74 m
Source release height[a]	5 m
Adjustment factor[c]	0.4
Urban-rural option	Rural
Meterology[d]	1 (full meterology)
Minimum and maximum distance	0-3000 m
Distance from source facility to residential areas[a]	300 m

[a] Site specific; based on aerial photograph analysis and professional judgement
[b] Average adult height (Curry et al. 1993)
[c] Factor to account for variable wind direction over a 24-hour period (US EPA 1992)
[d] Default value in SCREEN3

SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 6.3
Revision Date 04.04.2022
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GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifiers

Product name	:	Triacetin Triacetin
Product Number	:	525073
Brand	:	Aldrich
REACH No.	:	01-2119484873-24-XXXX
CAS-No.	:	102-76-1

1.2 Relevant identified uses of the substance or mixture and uses advised against

Identified uses	:	Laboratory chemicals, Manufacture of substances

1.3 Details of the supplier of the safety data sheet

Company	:	Merck Life Science Sp.z.o.o. Szelągowska 30 PL-61-626 POZNAN
Telephone	:	+48 61 8290-100
Fax	:	+48 61 8290-120
E-mail address	:	TechnicalService@merckgroup.com

1.4 Emergency telephone

Emergency Phone #	:	+(48)-223988029 (CHEMTREC) 998 (Straz pozarna)

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture

Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.

2.2 Label elements

Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.

2.3 Other hazards

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

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SECTION 3: Composition/information on ingredients

3.1 Substances

Synonyms	:	Glyceryl triacetate 1,2,3-Triacetylglycerol 1,2,3-Triacetoxypropane
Formula	:	$C_9H_{14}O_6$
Molecular weight	:	218,20 g/mol
CAS-No.	:	102-76-1
EC-No.	:	203-051-9

No components need to be disclosed according to the applicable regulations.

SECTION 4: First aid measures

4.1 Description of first-aid measures

If inhaled
If breathed in, move person into fresh air. If not breathing, give artificial respiration.

In case of skin contact
Wash off with soap and plenty of water.

In case of eye contact
Flush eyes with water as a precaution.

If swallowed
Never give anything by mouth to an unconscious person. Rinse mouth with water.

4.2 Most important symptoms and effects, both acute and delayed

The most important known symptoms and effects are described in the labelling (see section 2.2) and/or in section 11

4.3 Indication of any immediate medical attention and special treatment needed

No data available

SECTION 5: Firefighting measures

5.1 Extinguishing media

Suitable extinguishing media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

5.2 Special hazards arising from the substance or mixture

Carbon oxides

5.3 Advice for firefighters

Wear self-contained breathing apparatus for firefighting if necessary.

5.4 Further information

No data available

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures

Avoid breathing vapors, mist or gas.

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For personal protection see section 8.

6.2 Environmental precautions
No special environmental precautions required.

6.3 Methods and materials for containment and cleaning up
Keep in suitable, closed containers for disposal.

6.4 Reference to other sections
For disposal see section 13.

SECTION 7: Handling and storage

7.1 Precautions for safe handling
For precautions see section 2.2.

7.2 Conditions for safe storage, including any incompatibilities

Storage conditions
Keep container tightly closed in a dry and well-ventilated place. Store in cool place.

Storage class
Storage class (TRGS 510): 10: Combustible liquids

7.3 Specific end use(s)
Apart from the uses mentioned in section 1.2 no other specific uses are stipulated

SECTION 8: Exposure controls/personal protection

8.1 Control parameters

Ingredients with workplace control parameters

8.2 Exposure controls

Personal protective equipment

Eye/face protection
Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

Skin protection
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

The selected protective gloves have to satisfy the specifications of Regulation (EU) 2016/425 and the standard EN 374 derived from it.

Full contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min
Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

Splash contact
Material: Nitrile rubber
Minimum layer thickness: 0,11 mm
Break through time: 480 min

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Material tested:Dermatril® (KCL 740 / Aldrich Z677272, Size M)

data source: KCL GmbH, D-36124 Eichenzell, phone +49 (0)6659 87300, e-mail sales@kcl.de, test method: EN374
If used in solution, or mixed with other substances, and under conditions which differ from EN 374, contact the supplier of the EC approved gloves. This recommendation is advisory only and must be evaluated by an industrial hygienist and safety officer familiar with the specific situation of anticipated use by our customers. It should not be construed as offering an approval for any specific use scenario.

Body Protection
Impervious clothing, The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Respiratory protection
Respiratory protection not required. For nuisance exposures use type OV/AG (US) or type ABEK (EU EN 14387) respirator cartridges. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Control of environmental exposure
No special environmental precautions required.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a)	Physical state	clear, liquid
b)	Color	colorless
c)	Odor	No data available
d)	Melting point/freezing point	Melting point/range: 3 °C - lit.
e)	Initial boiling point and boiling range	258 °C - lit.
f)	Flammability (solid, gas)	No data available
g)	Upper/lower flammability or explosive limits	Upper explosion limit: 7,73 %(V) Lower explosion limit: 1,05 %(V)
h)	Flash point	138 °C - closed cup
i)	Autoignition temperature	433 °C
j)	Decomposition temperature	No data available
k)	pH	No data available
l)	Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
m)	Water solubility	No data available

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n)	Partition coefficient: n-octanol/water	log Pow: 0,25
o)	Vapor pressure	0,003 hPa at 25 °C
p)	Density	1,16 g/cm3 at 25 °C - lit.
	Relative density	No data available
q)	Relative vapor density	No data available
r)	Particle characteristics	No data available
s)	Explosive properties	No data available
t)	Oxidizing properties	No data available

9.2 Other safety information

Relative vapor density	7,53 - (Air = 1.0)

SECTION 10: Stability and reactivity

10.1 Reactivity
No data available

10.2 Chemical stability
Stable under recommended storage conditions.

10.3 Possibility of hazardous reactions
No data available

10.4 Conditions to avoid
No data available

10.5 Incompatible materials
Strong oxidizing agents

10.6 Hazardous decomposition products
In the event of fire: see section 5

SECTION 11: Toxicological information

11.1 Information on toxicological effects

Acute toxicity
LD50 Oral - Rat - male and female - > 2.000 mg/kg
(OECD Test Guideline 401)
LC50 Inhalation - Rat - male and female - 4 h - > 1,721 mg/l - aerosol

(OECD Test Guideline 403)
Dermal: No data available

Skin corrosion/irritation
Skin - Rabbit
Result: No skin irritation - 4 h

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(OECD Test Guideline 404)

Serious eye damage/eye irritation
Eyes - Rabbit
Result: No eye irritation
(OECD Test Guideline 405)

Respiratory or skin sensitization
No data available

Germ cell mutagenicity
Test Type: Mutagenicity (mammal cell test): chromosome aberration.
Test system: Chinese hamster lung cells
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 473
Result: Positive results were obtained in some in vitro tests.
Test Type: Ames test
Test system: S. typhimurium
Metabolic activation: with and without metabolic activation
Method: OECD Test Guideline 471
Result: negative

Carcinogenicity
No data available

Reproductive toxicity
No data available

Specific target organ toxicity - single exposure
No data available

Specific target organ toxicity - repeated exposure
No data available

Aspiration hazard
No data available

11.2 Additional Information

Repeated dose toxicity - Rat - male and female - Oral - NOAEL (No observed adverse effect level) - 1.000 mg/kg

RTECS: AK3675000
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

Handle in accordance with good industrial hygiene and safety practice.

SECTION 12: Ecological information

12.1 Toxicity

Toxicity to fish	semi-static test LC50 - Oryzias latipes - > 100 mg/l - 96 h (OECD Test Guideline 203)
Toxicity to daphnia and other aquatic invertebrates	static test EC50 - Daphnia magna (Water flea) - 380 mg/l - 48 h (Regulation (EC) No. 440/2008, Annex, C.2) Remarks: (ECHA)

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Toxicity to algae	static test ErC50 - Pseudokirchneriella subcapitata - > 940 mg/l - 72 h (OECD Test Guideline 201)
Toxicity to bacteria	static test NOEC - Pseudomonas putida - > 1.088 mg/l - 18 h Remarks: (ECHA)

12.2 Persistence and degradability

Biodegradability	aerobic - Exposure time 29 d Result: 82 % - Readily biodegradable. (OECD Test Guideline 301B)

12.3 Bioaccumulative potential

No data available

12.4 Mobility in soil

No data available

12.5 Results of PBT and vPvB assessment

This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.

12.6 Endocrine disrupting properties

No data available

12.7 Other adverse effects

No data available

SECTION 13: Disposal considerations

13.1 Waste treatment methods

Product

Offer surplus and non-recyclable solutions to a licensed disposal company.

Contaminated packaging

Dispose of as unused product.

SECTION 14: Transport information

14.1 UN number

ADR/RID: - IMDG: - IATA: -

14.2 UN proper shipping name

ADR/RID: Not dangerous goods
IMDG: Not dangerous goods
IATA: Not dangerous goods

14.3 Transport hazard class(es)

ADR/RID: - IMDG: - IATA: -

14.4 Packaging group

ADR/RID: - IMDG: - IATA: -

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14.5 Environmental hazards

ADR/RID: no IMDG Marine pollutant: no IATA: no

14.6 Special precautions for user

Further information

Not classified as dangerous in the meaning of transport regulations.

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

This material safety data sheet complies with the requirements of Regulation (EC) No. 1907/2006.

15.2 Chemical Safety Assessment

For this product a chemical safety assessment was not carried out

SECTION 16: Other information

Further information

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