



Toxicological profile for Aluminum hydroxide

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

Aluminium; trihydroxide (PubChem)

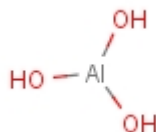
1.2. Synonyms

Aluminium hydroxide; Aluminium trihydroxide; Aluminiumtrihydroxid; GIBBSITE; Trihydroxyaluminum; Trihydroxyde d'aluminium; ALternaGEL; Amphojel; Alu-Cap; Aluminium hydroxide, dried; Aluminium tri-hydroxide; aluminium(3+) ion trihydroxide; aluminium(3+) ion trioxidanide; aluminiumhydroxide; aluminum and trihydroxide (ChemSpider).

1.3. Molecular formula

Al-(OH)₃

1.4. Structural Formula



1.5. Molecular weight (g/mol)

78.004 (ChemSpider)

1.6. CAS registration number

21645-51-2

1.7. Properties

1.7.1. Melting point

300°C (ChemSpider);

1.7.2. Boiling point

Not applicable; estimated to decompose before boiling (US EPA, 2014a); 300°C (ChemSpider)

1.7.3. Solubility

Insoluble in water; soluble in alkaline solutions, acid solutions (HSDB, 2013); Practically insoluble in water; soluble in alkaline aqueous solution, HCl, H₂SO₄ solution (ChemSpider); 1.673E+05 mg/L at 25°C (estimated) (EPISuite, 2017*); ≤ 0.09 mg/L at pH 6-7, 0.0117-0.0947 mg/L at pH 7.5-8.1 and 21-24°C, 1.5 mg/L at 20°C and pH 7, 1.5x10⁻² at 20°C and pH 8-9 (US EPA, 2014a)

1.7.4. pKa

2.42 g/cu cm at 20°C; not applicable (determination of dissociation constant is not possible due to the insolubility of the test substance) (US EPA, 2014a)

1.7.5. Flashpoint

No data available to us at this time.

1.7.6. Flammability limits (vol/vol%)

Not flammable (US EPA, 2014a)

1.7.7. (Auto)ignition temperature

No data available to us at this time.

1.7.8. Decomposition temperature

Begins to decompose at 230°C with the release of 35.4% of its original mass as /non-combustible/ water vapor (HSDB, 2013); estimated to decompose before boiling, 150-300°C (US EPA, 2014a);

1.7.9. Stability

1.7.9. Stability

Forms gels on prolonged contact with water; absorbs acids, carbon dioxide (HSDB, 2013); Stable, incompatible with strong bases (ChemSpider)

1.7.10. Vapor pressure

1.7.10. Vapor pressure

Not applicable; 9.71E-20 mmHg at 25°C (estimated) (EPISuite, 2017*); <10⁻⁸ mm Hg (estimated) (US EPA, 2014a)

1.7.11. log Kow

-0.12 (estimated) (EPISuite, 2017*)

* WARNING: Inorganic Compound (Outside Estimation Domain); Estimations NOT VALID

2. General information

2.1. Exposure

“.....Other than Al-containing antacids and buffered aspirin, food is the primary source of Al exposure for most healthy people.....” As taken from Willhite CC et al. 2012. Crit. Rev. Toxicol. 42(5), 358-442. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22512666>

“....Wide variations in diet can result in Al intakes that are often higher than the World Health Organization provisional tolerable weekly intake (PTWI), which is based on studies with Al citrate. Comparing daily dietary Al exposures on the basis of "total Al" assumes that gastrointestinal bioavailability for all dietary Al forms is equivalent to that for Al citrate, an approach that requires validation. Current occupational exposure limits (OELs) for identical Al substances vary as much as 15-fold....” As taken from Willhite CC et al. 2014. Crit. Rev. Toxicol. 44(Suppl. 4), 1-80. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25233067>

Aluminium hydroxide is used in stomach antacids as a desiccant powder, in antiperspirants and dentifrices, in packaging materials, as a chemical intermediate, as a filler in plastics, rubber, cosmetics and paper, as a soft abrasive for brass and plastics, as a glass additive to increase mechanical strength and resistance to thermal shock, weathering and chemicals, and in ceramics. Aluminium hydroxide is also used pharmaceutically to lower the plasma phosphorus levels of

patients with renal failure. Aluminium salts have become the standard adjuvant in vaccines such as those against diphtheria, tetanus and pertussis (DTP), Haemophilus influenzae type b, pneumococcus conjugates, and hepatitis A and B. Aluminium salts are added to vaccines in the form of aluminium potassium sulphate, aluminium sulphate or aluminium hydroxide (NEG DECOS, 2011).

Aluminum hydroxide (CAS RN 21645-51-2) is listed as an ingredient (at given concentrations, where specified) in auto (1–5%), home maintenance (0.1–30%, includes “old” products), inside the home (0.1-20%) and personal care products by the CPID.

“Aluminum hydroxide, also known as alumina trihydrate, is the largest volume flame retardant in use today.”

As taken from US EPA, 2014a.

Aluminium hydroxide (CAS RN 21645-51-2) is used as a skin conditioning - emollient, humectant, opacifying, skin protecting, and viscosity controlling ingredient in cosmetics in the EU. As taken from CosIng (Cosmetic substances and ingredients database). Aluminum hydroxide (CAS RN 21645-51-2) is listed as #15 in the top 20 chemicals used in children's products (top use: plastic and rubber products, foam seating and bedding products, and floor coverings).

As taken from US EPA, 2014b.

Threshold Limit Values:

8 hr Time Weighted Avg (TWA): 1 mg/cu m, respirable fraction. /Aluminum metal and insoluble compounds/ [American Conference of Governmental Industrial Hygienists. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH 2012, p. 11] **PEER REVIEWED**

Excursion Limit Recommendation: Excursions in worker exposure levels may exceed 3 times the TLV-TWA for no more than a total of 30 minutes during a work day, and under no circumstances should they exceed 5 times the TLV-TWA, provided that the TLV-TWA is not exceeded. /Aluminum metal and insoluble compounds/ [American Conference of Governmental Industrial Hygienists. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH 2012, p. 5] **PEER REVIEWED**

NIOSH Recommendations:

Recommended Exposure Limit: 10-hour Time-Weighted Average: 10 mg/cu m (total). /Aluminum/ [NIOSH. NIOSH Pocket Guide to Chemical Hazards. Department of Health & Human Services, Centers for Disease Control & Prevention. National Institute for Occupational Safety & Health. DHHS (NIOSH) Publication No. 2010-168 (2010). Available from: <http://www.cdc.gov/niosh/npg> **PEER REVIEWED**

Recommended Exposure Limit: 10-hour Time-Weighted Average: 5 mg/cu m (resp). /Aluminum/ [NIOSH. NIOSH Pocket Guide to Chemical Hazards. Department of Health & Human Services, Centers for Disease Control & Prevention. National Institute for Occupational Safety & Health. DHHS (NIOSH) Publication No. 2010-168 (2010). Available from: <http://www.cdc.gov/niosh/npg> **PEER REVIEWED**

Recommended Exposure Limit: 10-hour Time-Weighted Average: 2 mg/cu m. /Aluminum (soluble salts and alkyls, as Al)/ [NIOSH. NIOSH Pocket Guide to Chemical Hazards. Department of Health & Human Services, Centers for Disease Control & Prevention. National Institute for Occupational Safety & Health. DHHS (NIOSH) Publication No. 2010-168 (2010). Available from: <http://www.cdc.gov/niosh/npg> **PEER REVIEWED**

Recommended Exposure Limit: 10-hour Time-Weighted Average: 5 mg/cu m. /Aluminum (pyro powders and welding fumes, as Al)/ [NIOSH. NIOSH Pocket Guide to Chemical Hazards. Department of Health & Human Services, Centers for Disease Control & Prevention. National

Institute for Occupational Safety & Health. DHHS (NIOSH) Publication No. 2010-168 (2010). Available from: <http://www.cdc.gov/niosh/npg> **PEER REVIEWED**

According to the 2006 TSCA Inventory Update Reporting data, the number of persons reasonably likely to be exposed in the industrial manufacturing, processing, and use of aluminum hydroxide is 1000 or greater; the data may be greatly underestimated(1). [(1) US EPA; Inventory Update Reporting (IUR). Non-confidential 2006 IUR Records by Chemical, including Manufacturing, Processing and Use Information. Washington, DC: U.S. Environmental Protection Agency. Available from, as of Sept 20, 2012: <http://cfpub.epa.gov/iursearch/index.cfm> . As taken from HSDB, 2013.

“One sub-scenario has been identified for which a risk characterisation has been performed. The data used for the risk characterisation for consumers, including reasonable worst case exposure concentrations, derived no effect levels (DNELs) and the risk characterisation ratio (RCR) are compiled in the table below.”

Exposure scenario	Route of exposure	Exposure estimate	DNEL	RCR*
Airborne particles	Inhalation	0.052 mg/m ³	0.14 mg/m ³	0.37

*The risk characterisation ratio (RCR) is the quotient of the exposure estimate and the respective DNEL (derived no-effect level). If the RCR is < 1 the use can be regarded as safe.

As taken from European Commission, 2011.

Exposure Assessment:

TLV (ACGIH) 1 mg/m³

PEL (OSHA) 15 mg/m³

MAK = 4 mg/m³ (inhalable fraction), 1.5 mg/m³ (respirable fraction)
(Haz-Map, 2020)

OEL-AUSTRALIA: TWA 2 mg(Al)/m³, JUL2008

OEL-BELGIUM: TWA 2 mg(Al)/m³, MAR2002

OEL-FINLAND: TWA 2 mg(Al)/m³, NOV2011

OEL-FRANCE: VME 2 mg(Al)/m³, FEB2006

OEL-KOREA: TWA 2 mg(Al)/m³, 2006

OEL-NEW ZEALAND: TWA 2 mg(Al)/m³, JAN2002

OEL-RUSSIA: TWA 6 mg/m³, JUN2003

OEL-SWEDEN: TWA 1 mg(Al)/m³, JUN2005

OEL-SWITZERLAND: MAK-W 3 mg/m³, resp, JAN2011

OEL-UNITED KINGDOM: TWA 2 mg(Al)/m³, OCT2007

OEL IN ARGENTINA, BULGARIA, COLOMBIA, JORDAN check ACGIH TLV;

OEL IN SINGAPORE, VIETNAM check ACGIH TLV

As taken from RTECS, 2018.

The occupational exposure limit (as 8-hour TWA) for metal hydroxides in Germany is 4 mg/m³ in the inhalable fraction and 1.5 mg/m³ in the respirable fraction (NEG DECOS, 2011).

US Army Military exposure guidelines (MEGs) for Short-Term exposures to chemicals in ambient air:

1 hour Critical Air MEG 1.3E+02 mg/m³

1 hour Marginal Air MEG 1.3E+02 mg/m³

1 hr Negligible air MEG 1.2E+01 mg/m³

As taken from US EPA ACToR Database (US EPA, 2015).

Found in toothpaste products as an abrasive (SCCS, 2022).

“Used in various immunologic preparations to improve immunogenicity, aluminum hydroxide adjuvant consists of aluminum hydroxide gel in a saline solution. In vaccines, this agent binds to the protein conjugate, resulting in improved antigen processing by the immune system.”

As taken from PubChem

Aluminum hydroxide (CAS RN 21645-51-2) is used as an abrasive, absorbent, base, binder, bulking agent, colour additive, emollient, opacifying agent, skin protectant and thickening agent in non-medicinal natural health products (Health Canada, 2021).

“Exposure of adults to aluminium in antacids (in mg/kg bw/week)

Product	Active ingredients	Aluminium content	Prescribed dose ¹	Exposure
Regla pH chewable tablets	aluminium hydroxide; magnesium carbonate	450 mg Al(OH) ₃ ·MgCO ₃ coprecipitate per tablet ²	1–2 tablets after every meal and before sleeping (If necessary 1–2 tablets every 2 hours in between)	48–95

¹ According to the Summary of Product Characteristics (Antagel, 2016; Gastilox Forte/Gastilox, 2019; Gastilox Plus Dimeticon, 2019; Maalox, 2018; Maalox Plus Dimeticon, 2020; Regla pH, 2015), specifying no contra-indication for use during pregnancy; www.cbg-meb.nl

² Ratio between 2 active ingredients not specified in SPC. Ratio 3:1 is assumed, given that on SPC it is mentioned that ‘in proper ratio of the combination aluminium and magnesium (3: 1) no problems such as constipation and laxation are to be expected’.”

As taken from RIVM, 2020

2.2. Combustion products

No data available to us at this time.

2.3. Ingredient(s) from which it originates

No data available to us at this time.

3. Status in legislation and other official guidance

“A4: Not classifiable as a human carcinogen. Aluminum metal and insoluble compound”/ [American Conference of Governmental Industrial Hygienists TLVs and BEIs. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH, 2008, p. 11]**QC REVIEWED**

FIFRA Requirements:

"Inert ingredients used pre- and post-harvest; exemptions from the requirement of a tolerance. Residues of the following materials 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 growing crops or to raw agricultural commodities after harvest. Aluminum hydroxide as a diluent, carrier is included on this list". [40 CFR 180.910; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 1, 2004: <http://www.gpoaccess.gov/ecfr>]**PEER REVIEWED**

Federal Drinking Water Guidelines:

EPA 50-200 ug/l /Aluminum/ [USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93), p.]**QC REVIEWED**

State Drinking Water Standards:

(CA) CALIFORNIA 1000 ug/l /Aluminum/ [USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93), p.]**QC REVIEWED**

State Drinking Water Guidelines:

(AZ) ARIZONA 73 ug/l /Aluminum/ [USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93), p.]**QC REVIEWED**

(CA) CALIFORNIA 200 ug/l /Aluminum/ [USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93), p.]**QC REVIEWED**

(ME) MAINE 1430 ug/l /Aluminum/ [USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93), p.]**QC REVIEWED**

FDA Requirements:

"The Approved Drug Products with Therapeutic Equivalence Evaluations List identifies currently marketed over-the-counter drug products, incl aluminum hydroxide, approved on the basis of safety and effectiveness by FDA under sections 505 of the Federal Food, Drug, and Cosmetic Act". [DHHS/FDA; Electronic Orange Book-Approved Drug Products with Therapeutic Equivalence Evaluations. Available from, as of July 1, 2004: <http://www.fda.gov/cder/ob/>]**PEER REVIEWED**

"Substances migrating to food from paper and paperboard products used in food packaging that are generally recognized as safe for their intended use, within section 409 of the Act. Aluminum hydroxide is included on this list". [21 CFR 182.90; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 1, 2004: <http://www.gpoaccess.gov/ecfr>]**PEER REVIEWED**

"Antacid products for over-the-counter human use. Listing of specific active ingredients: aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated) ". [21 CFR 331.11; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 1, 2004: <http://www.gpoaccess.gov/ecfr>]**PEER REVIEWED**

Anorectal drug products for over-the-counter human use. Protectant active ingredients. The following active ingredient may be used as the sole protectant active ingredient in a product if the ingredient as identified constitutes 50 percent or more by weight of the final product. In addition, the following active ingredients may be used in concentrations of less than 50 percent by weight only when used in combinations in accordance with part 346.22 (a), (b), or (n). Aluminum hydroxide gel

is included on this list.
[21 CFR 346.14 (USFDA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 30, 2012: <http://www.gpoaccess.gov/ecfr> .

Skin protectant drug products for over-the-counter human use. Skin protectant active ingredient:
Aluminum hydroxide gel, 0.15 to 5 percent

[21 CFR 347.10 (USFDA); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 30, 2012: <http://www.gpoaccess.gov/ecfr>.

"Certification of this color additive when used to color drugs generally is not necessary for the protection of the public health, and therefore batches thereof are exempt from the certification pursuant to section 721(c) of the act". [21 CFR 73.1010; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 1, 2004: <http://www.gpoaccess.gov/ecfr> **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: aluminum hydroxide is included in topical acne drug products". [21CFR 310.545; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 1, 2004: <http://www.gpoaccess.gov/ecfr> **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: aluminum hydroxide is included in antidiarrheal drug products". [21CFR 310.545; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 1, 2004: <http://www.gpoaccess.gov/ecfr> **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: aluminum hydroxide is included in digestive aid drug products". [21CFR 310.545; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of July 1, 2004: <http://www.gpoaccess.gov/ecfr> **PEER REVIEWED**

As taken from HSDB, 2013.

Aluminum hydroxide is listed in the US EPA InertFinder Database (2022) as approved for food and non-food use pesticide products. For food use, it is regulated under 40 CFR Part 180.910 (Inert ingredients used pre- and post-harvest exemptions from the requirement of a tolerance; Uses: diluent, carrier) (US EPA, 2022).

"Maximum contaminant levels are used to control potential health hazards posed by chemicals in drinking water, but no primary national or international limits for aluminum (Al) have been adopted. Given the differences in toxicological profiles, the present evaluation derives total allowable concentrations for certain water-soluble inorganic Al compounds (including chloride, hydroxide, oxide, phosphate and sulfate) and for the hydrated Al silicates (including attapulgite, bentonite/montmorillonite, illite, kaolinite) in drinking water.....Application of 3x interspecies uncertainty factor and a 3x factor to account for study duration results in a chronic oral RfD of 6 mg

Al/kg-day.....The drinking water concentrations derived here are greater than the U.S. EPA secondary maximum contaminant level (MCL) for total Al of 0.05-0.2 mg/L [40 CFR 143.3]. As such, domestic use of water with these concentrations is likely self-limiting given that its cloudy appearance will be greater than the maximum permitted (0.5-5.0 nephelometric turbidity units; 40 CFR Parts 141 and 142). Therefore, the organoleptic properties of Al materials in water determine public acceptance of potable water as contrast to any potential health hazard at the concentrations ordinarily present in municipal drinking water.” As taken from Willhite CC et al. 2012. Crit. Rev. Toxicol. 42(5), 358-442. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22512666>

Aluminum hydroxide is included on the US FDA’s list of Substances Added to Food (formerly EAFUS) as a color or coloring adjunct and a processing aid, is generally recognised as safe under 21 CFR section 182.90 (Substances migrating to food from paper and paperboard products) and is also listed under 21 CFR sections 175.300 (Resinous and polymeric coatings), 176.170 (Components of paper and paperboard in contact with aqueous and fatty foods), 176.210 (Defoaming agents used in the manufacture of paper and paperboard), 177.1200 (Cellophane), 177.2600 (Rubber articles intended for repeated use), 178.3297 (Colorants for polymers) and 73.1010 (Alumina; dried aluminum hydroxide) (FDA, 2021a, 2022a).

There is a REACH dossier on aluminium hydroxide (CAS RN 21645-51-2) (ECHA).

“....The scientific literature on the adverse health effects of Al is extensive. Health risk assessments for Al must take into account individual co-factors (e.g., age, renal function, diet, gastric pH). Conclusions from the current review point to the need for refinement of the PTWI, reduction of Al contamination in PN [parenteral] solutions, justification for routine addition of Al to vaccines, and harmonization of OELs for Al substances.” As taken from Willhite CC et al. 2014. Crit. Rev. Toxicol. 44(Suppl. 4), 1-80. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25233067>

Aluminium hydroxide is listed in the US EPA Toxic Substances Control Act (TSCA) inventory and also in the US EPA 2020 CDR list (Chemical Data Reporting Rule). The Chemical Data Reporting (CDR) Rule requires companies that manufacture (including import) certain chemicals at certain volumes in the U.S. to report to EPA every four years through its CDR.

The TSCA inventory and 2020 CDR TSCA Inv Active list are available at https://sor.epa.gov/sor_internet/registry/substreg/searchandretrieve/searchbylist/search.do

Aluminium hydroxide (CAS RN 21645-51-2) is not classified for packaging and labelling under Regulation (EC) No. 1272/2008 (ECHA, 2023).

Aluminium hydroxide (Al(OH)₃) (CAS RN 21645-51-2) “poses no unreasonable risk to human health based on Tier I assessment under the NICNAS IMAP assessment framework” (AICIS, 2014).

Aluminum hydroxide 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:

Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency per unit dose
ALUMINUM HYDROXIDE	ORAL	CAPSULE	21645512	5QB0T2IUN0	NA
ALUMINUM HYDROXIDE	ORAL	TABLET	21645512	5QB0T2IUN0	50mg
ALUMINUM HYDROXIDE	TOPICAL	CREAM	21645512	5QB0T2IUN0	5%w/w

ALUMINUM HYDROXIDE	TOPICAL	OINTMENT	21645512	5QB0T2IUN0	NA

As taken from FDA, 2023.

In Canada, aluminum hydroxide (CAS RN 21645-51-2) is classified as a medicinal natural health product under Schedule 1, item 7 (a mineral) of the Natural Health Products Regulations (Health Canada, 2021).

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

“In another study on the effect of aluminium hydroxide on the mineral metabolism of rats, weanling male SD rats fed semi- synthetic diets containing 0, 257 or 1075 µg aluminium/g diet had no effect on growth and feed efficiency of the test animal. However, animals in the high dose group had significantly lower body weights than controls. Animals fed test diets accumulated significantly more aluminium in tibias, kidneys and liver than controls, but there was no significant difference between the levels of aluminium in these tissues in animals fed diet containing either 257 or 1075 µg aluminium/diet. The reported levels of aluminium in the tibias were 11.3, 10.40 for the 257, 1075 µg/g aluminium diet groups and 4.04 and 3.13 µg aluminium/g for the two control groups. The breaking strength of bones from animals fed the 1075 µg aluminium/g diet was less than that of animals in the other test groups. The concentration of phosphorous, calcium, magnesium, zinc, iron and copper in tissues was not affected in the low aluminium dose group, but some changes were observed at the high aluminium dose level (Greger et al., 1985)”. As taken from INCHEM at <http://www.inchem.org/documents/jecfa/jecmono/v024je07.htm>

“Not metabolized.”

As taken from PubChem.

4.2. Absorption, distribution and excretion

When aluminum hydroxide is injected ip in rats, highest aluminum concentration... in liver. Muscle, brain, bone, and heart also have high aluminum levels. [Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978., p. 107]

In a... study in which adequate amounts of Zn, Cu and Fe were present the animals were fed various types and levels of aluminium hydroxide namely aluminium hydroxide reagent grade (268 ug/g/diet) and aluminium hydroxide dried gel (at 261 or 205 mg aluminium/g diet). The form of aluminium hydroxide did not effect accumulation of aluminium in the tissues. Rats fed 206 ug aluminium/g diet accumulated less aluminium in their tibias and more aluminium in the kidneys than rats fed 261 or 268 ug aluminium/g diet. The presence of aluminium in the diet had no effect on tissue levels of calcium, magnesium and iron, and only minor effects on tissue levels of phosphorous, zinc and copper. [Joint FAO/WHO Expert Committee on Food Additives; WHO Food Additives Ser 24: Aluminum (1989). Available from, as of June 4, 2004: <http://www.inchem.org/documents/jecfa/jecmono/v024je07.htm>

Aluminum absorption in rabbits treated with the water insoluble compounds aluminum hydroxide (780 mg Al/kg) ... was 0.45%

[DHHS/ATSDR; Toxicological Profile for Aluminum (July 1999). Available from, as of May 21, 2004: <http://www.atsdr.cdc.gov/toxprofiles/tp22.html>

To evaluate the retention of aluminum in tissues following oral exposure, rats were fed a diet supplemented with aluminum hydroxide for an intermediate-duration exposure period. Relative to controls, treated rats had increased aluminum concentrations in bone, muscle, and kidneys. Aluminum concentrations in these tissues decreased significantly 3 days after withdrawal of aluminum hydroxide from the diet. Tissue concentrations of aluminum were similar for treated and control rats 7 days after withdrawal. [DHHS/ATSDR; Toxicological Profile for Aluminum (July 1999). Available from, as of May 21, 2004: <http://www.atsdr.cdc.gov/toxprofiles/tp22.html>

Two studies have reported on aluminium accumulation following administration in drinking-water. ...0, 0.1, 2.0 or 100 mg/litre /aluminum hydroxide/ or /aluminum chloride/ (equivalent to 0, 0.01, 0.2 or 5.5 mg Al/kg bw/day) /was administered/ in drinking-water containing acetate or citrate at various pH levels to Sprague-Dawley rats (6 rats per group) for 10 weeks. In the highest-dose group, aluminium accumulated in intestinal cells but not in other tissues investigated. The effect was more pronounced when citrate was added and when water with an acidic pH was used. [WHO; Environ Health Criteria 194: Aluminum (1997). Available from, as of June 2, 2004: <http://www.inchem.org/documents/ehc/ehc/ehc194.htm#SectionNumber:1.1>

As taken from HSDB, 2013.

A suspension of aluminium hydroxide containing 17 mg of ²⁷Al and 12.1 mg of ²⁶Al was administered to rats. The fraction of the dose that was absorbed was 0.025 + 0.041% (EFSA, 2011).

“.....Systemic uptake of Al after ingestion of the monomeric salts is somewhat greater from drinking water (0.28%) than from food (0.1%). Once absorbed, Al accumulates in bone, brain, liver and kidney, with bone as the major site for Al deposition in humans.....” As taken from Willhite CC et al. 2012. Crit. Rev. Toxicol. 42(5), 358-442. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22512666>

Studies in man:

“Men were fed biscuits containing alum phosphate baking powder (ca 8%) in addition to normal dietary items, and blood and urine samples collected two, four, six and eight hours after the meal. Aluminium was frequently found in blood of control men (trace - 0.1 mg/100 ml), and ingestion of the aluminium rich diet caused occasional slight increase of levels of aluminium in the blood. Urine of man before and after ingestion of the aluminium rich diets only contain small amounts of aluminium (less than 0.5 mg excreted in 26 hours) (Underhill *et al.*, 1929).

In contrast, in a study in which patients with chronic renal disease were given a daily dose of aluminium hydroxide (equivalent to 1.5 - 3.4 g aluminium) for 20-32 days, 100-568 mg of aluminium was absorbed daily, based on fecal excretion of aluminium. No aluminium was detected in the urine at quantities greater than 1 mg/day. Plasma aluminium was only slightly increased during the test period. There was no significant change in calcium balance, and phosphorous balance became more negative. Some of the absorbed aluminium was deposited in bone (Clarkson *et al.*, 1972)”.

Increased aluminium plasma levels and excessive aluminium deposition in the brain, liver, heart and muscle have also been documented following aluminium hydroxide overload... [Krewski D et al; J Toxicol Environ Health B Crit Rev 10 (Suppl 1): 1-269 (2007)]

.. Absorption and removal of injected aluminum compounds such as aluminum hydroxide from im sites and from peritoneal cavity is slow but it is complete in a few days, provided the doses are within physiologic limits and... not mixed with any irritants such as anions of chloride and nitrate. [Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978., p. 107]

Adults (with renal failure), who ingested 1.5 to 3.0 g aluminum hydroxide per day for 20 to 32 days, absorbed between 100 and 568 mg aluminum per day (7-19% of the dose). Thus, it is quite clear that the administration of large doses of aluminum (ie in amounts considerably greater than is normally available in the diet) results in significant systemic absorption of the metal. [Clarkson EM et al; Clin Sci 43: 519 (1972)]

The fraction of aluminum absorbed from aluminum-containing antacids is small. Dietary aluminum intake is normally about 3 to 25 mg daily, of which about 15 ug or about 0.1% is absorbed. However, about 0.1 to 0.5 mg of the cation may be absorbed from a standard daily dose of an aluminum-containing antacid. In persons with normal renal function, this leads to about a doubling of the average concentration of aluminum in plasma, which is normally 5 to 20 ug/L ; however, in some persons it may be increased tenfold. Aluminum is eliminated in the urine, and the renal clearance has been estimated to be 5.6 mL in persons with normal renal function. Plasma concentrations rise in renal failure, and values in excess of 300 ug/L have been reported. The accumulation of aluminum may not be simply the result of a decreased glomerular filtration; uremic patients often have hyperparathyroidism, and parathyroid hormone has been shown to increase aluminum absorption in rats. /Aluminum-containing antacids/ [Gilman, A.G., L.S.Goodman, and A. Gilman. (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 7th ed. New York: Macmillan Publishing Co., Inc., 1985., p. 982]

In metabolic studies on six patients, 12% of an oral load of aluminum in the form of a hydroxide was retained, but absorption was not calculated. At least 50% of serum aluminum is bound to proteins, which include both albumin and transferrin. [Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988., p. 1009]

Aluminum hydroxide or oxide is slowly solubilized in the stomach and reacts with hydrochloric acid to form aluminum chloride and water. In addition to forming aluminum chloride, dihydroxyaluminum sodium carbonate and aluminum carbonate form carbon dioxide, and aluminum phosphate forms phosphoric acid. About 17-30% of the aluminum chloride formed is absorbed and is rapidly excreted by the kidneys in patients with normal renal functions. In the small intestine, aluminum chloride is rapidly converted to insoluble poorly absorbed basic aluminum salts which probably /include/ a mixture of hydrated aluminum oxide, oxyaluminum hydroxide, various basic aluminum carbonates, and aluminum soaps. Aluminum-containing antacids (except aluminum phosphate) also combine with dietary phosphate in the intestine forming insoluble, nonabsorbable aluminum phosphate which is excreted in the feces. If phosphate intake is limited in patients with normal renal function, aluminum antacids (except aluminum phosphate) decrease phosphate absorption and hypophosphatemia and hypophosphaturia occur; calcium absorption is increased. In vitro studies indicate that aluminum hydroxide binds bile salts with an affinity & capacity similar to that of cholestyramine; aluminum phosphate binds bile salts, but to a much lesser degree than does aluminum hydroxide. /Aluminum antacids/ [McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 2758]

... Human inhalation /was studied/ using (26)Al given as aluminum oxide in the gamma transitional particulate form (1.2 um Mass Median Aerodynamic Diameter (MMAD)); the subjects were studied over a period of 3 months. Because lung deposition was less than expected, direct estimates of lung deposition and transfer were unreliable. However, concurrent blood, urinary, and fecal measurements permitted estimates of lung clearance; these indicated a rapid phase of lung clearance, via the tracheobronchial tract. Deep-lung deposition approximated 60% of these 1.2 um MMAD particles, hence the pattern of early clearance phase was consistent with the predicted regional deposition of particles of this size. Following this relatively rapid phase-- due largely to mechanical clearance-- a small (4.5% of the inhaled dose) amount of aluminum remained in the lung. Over the next 3 months, serial urinary aluminum analyses suggested a considerably reduced by slow, steady clearance from the lungs, calculated at 0.015% per day of the total lung deposition,

with a 72 day lung retention half-time. By the end of this period, only about 0.2% of the initially deposited dose remained; the authors suggest that slow mechanical clearance continued as indicated by the presence of (26)Al in the feces as long as 300-500 days postinhalation. These data suggested a relative near insolubility of even this comparatively high surface area gamma form of aluminium oxide. The biological near insolubility of aluminum oxide following rapid mechanical removal phase-- was 0.025% per day of retained lung dose, equivalent to a half-life of about 5.5 years. Accordingly, the lung might provide a long-term deposition (and sequestration) site rather than a major portal of entry for aluminum oxides into the body economy. Nevertheless, the apparent bioavailability suggested by the urinary excretion of this inhaled aluminum oxide might not represent simply solubilization. Another possible mode of transport could be provided by slow, particle-by-particle phagocytic uptake via numerous alveolar macrophages (wandering "dust cells") active in the lung. The phagocyte's internal environment, characterized by highly reactive oxidation-reduction systems, can readily alter pH or form highly reactive chemical species (e.g., superoxides,) within its cellular vacuoles. Under these conditions several oxides, hydroxides, and oxyhydroxides of aluminum might conceivably become biologically available. However, it is also possible that aluminum particles ingested by macrophages may remain inert in such cells, and be translocated to regional lymph nodes or ultimately enter the systemic circulation. This immediate, rapid clearance of inhaled aluminum oxide and the subsequent slow continuous excretion (mobilization?) of aluminum oxide body burden is strikingly similar to observations among welders exposed to aluminum oxide fumes and respirable flakes. /Aluminum oxides/ [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V2 369]

The rate of excretion /of aluminum/ in the urine is assumed to be 20-50 ug/day, which equals intestinal absorption. Administration of 2.29 g aluminum hydroxide raised excretion from 16-300 ug/day. [Rom, W.N. (ed.). Environmental and Occupational Medicine. 2nd ed. Boston, MA: Little, Brown and Company, 1992., p. 466]

... Two male volunteers administered a single dose of (26)Al-labeled aluminum citrate (aqueous solution) or aluminum hydroxide (colloidal suspension in water) directly to the stomach using a pediatric feeding tube; there was a 3-week interval between dosing. These forms of aluminum were used because it was suspected that they would be either relatively bioavailable (citrate) or relatively nonbioavailable (hydroxide). Based on analyses of (26)Al in the blood (collected at 1, 4, and 24 hours after dosing) and excreta (urine and feces were collected for 6 days), the absorbed fractions were determined to be 0.5% for aluminum citrate and 0.01% for aluminum hydroxide. [DHHS/ATSDR; Toxicological Profile for Aluminum (July 1999). Available from, as of May 21, 2004: <http://www.atsdr.cdc.gov/toxprofiles/tp22.html>

The biological behavior and gastrointestinal absorption of aluminium in humans ingesting aluminium compounds has been studied by using the radioactive isotope (26)Al. Significant intersubject variability has been demonstrated. Measured fractional uptakes of ... 1.04×10^{-4} for aluminium hydroxide and 1.36×10^{-3} for the hydroxide given with citrate were reported. [WHO; Environ Health Criteria 194: Aluminum (1997). Available from, as of June 1, 2004: <http://www.inchem.org/documents/ehc/ehc/ehc194.htm#SectionNumber:1.1> **PEER REVIEWED**

As taken from HSDB, 2013.

"Aluminum is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally. Approximately 0.1–0.6 % of ingested aluminum is usually absorbed, although absorption of less bioavailable forms, such as aluminum hydroxide, can be in the order of 0.1%. The unabsorbed aluminum is excreted in the feces. The toxicokinetics of aluminum can vary, depending on the nature of these complexes. For example, aluminum bound in a low-molecular-weight complex could be filtered at the renal glomeruli and excreted, while aluminum in a high-molecular-weight complex (aluminum transferrin) would not."

As taken from European Commission, 2011.

Data	Reference	Data quality
Adult humans taking aluminum antacids had a 3-fold increase of aluminum levels in the urine; minimal aluminum was absorbed and was mostly excreted in the feces.	ATSDR, 2008	Reported in a secondary source, study details were not provided.

As taken from US EPA, 2014a.

"In rats, the absorbed fraction was measured as 0.1% for aluminium hydroxide after administration of 40-200 µg isotopically labelled (26Al) aluminium by gastric intubation (Schönholzer KW et al. 1997)."

As taken from Swedish Criteria Group for Occupational Standards, 2017.

"We reviewed the three reference toxicokinetic studies commonly used to suggest innocuity of aluminum (Al)-based adjuvants. A single experimental study was carried out using isotopic ²⁶Al (Flarend et al., 1997). This study ignored adjuvant cell capture. It was conducted over a short period of time (28 days) and used only two rabbits per adjuvant. At the endpoint, Al retention was 78% for aluminum phosphate and 94% for aluminum hydroxide, both results being incompatible with quick elimination of vaccine-derived Al in urines. Tissue distribution analysis omitted three important retention sites: the injected muscle, the draining lymph node and bone. Two theoretical studies have evaluated the potential risk of vaccine Al in infants, by reference to the oral Minimal Risk Level (MRL) extrapolated from animal studies. Keith et al., 2002 used a too high MRL (2mg/kg/d), an erroneous model of 100% immediate absorption of vaccine Al, and did not consider renal and blood-brain barrier immaturity. Mitkus et al. (2011) only considered absorbed Al, with erroneous calculations of absorption duration. They ignored particulate Al captured by immune cells, which play a role in systemic diffusion and the neuro-inflammatory potential of the adjuvant. MRL they used was both inappropriate (oral Al vs injected adjuvant) and far too high (1mg/kg/d) with regard to experimental studies of Al-induced memory and behavioral changes. Both paucity and serious weaknesses of these studies strongly suggest that novel experimental studies of Al adjuvants toxicokinetics should be performed on the long-term, including post-natal and adult exposures, to ensure innocuity and restore population confidence in Al-containing vaccines." As taken from Masson JD et al. 2017. Ann. Pharm. Fr. 75(4), 245-256. PubMed, 2018 available at: <https://www.ncbi.nlm.nih.gov/pubmed/28576261>

"Oral bioavailability in rats of aluminium from 12 radioactively labelled aluminium (26Al) compounds was investigated in a study provided by the industry and evaluated by EFSA (2011a,b). The compounds included four soluble aluminium salts: citrate, chloride, nitrate and sulphate; and eight aluminium compounds administered in suspension: hydroxide, oxide, metallic, powdered pot electrolyte, FD&C red 40 aluminium lake, SALP acidic, SALP basic, and sodium aluminium silicate. The ratio was determined between the radioactivity left in the carcass seven days after oral administration of the aluminium compounds and the radioactivity left in carcass seven days after intravenous administration of radioactively labelled citrate. The oral bioavailability varied between 0.03% (aluminium hydroxide) and 0.21% (aluminium sulphate). Three compounds had carcass levels below detection limit: aluminium metal, and the two SALPs. The Panel noted that less than 10% of the bioavailable dose remained in the carcass after 7 days."

"Blood and tissue levels of aluminium were analysed in rats (n = 5) gavaged with water (controls) or six different salts of aluminium: citrate, sulphate, nitrate, chloride and hydroxide with a daily dose of 30 mg Al/kg bw per day for 7 or 14 days (Poirier et al., 2011). There were no statistically significant differences in blood or brain concentrations between the groups, while kidney and bone levels of aluminium were statistically significantly increased in the group administered aluminium citrate compared to controls or the other aluminium salts."

As taken from EFSA, 2018.

“In humans, the absorption of aluminum complexed with citrate, chloride, hydroxide or lactate has been found to range between 0.01% and 0.65%. In experimental animals, the reported values range between 0.01% and 5.1% (Environment Canada and Health Canada, 2010).”

As taken from Health Canada, 2019

Summary of oral bioavailability of aluminium from food or drinking water in humans and animals:

Species	Matrix	Dose	Fraction absorbed (%)	Reference
Human ¹	water + food	~1429 µg/kg bw	0.01-0.14 ⁴	Priest et al., 1996
Rat	food	~1079-2688 mg/kg diet	0.01-0.04 ⁴	Greger and Powers, 1992
Rabbit	water	2.7 mg/kg bw	0.45	Yokel and McNamara, 1988

¹ Based on an average body weight of 70 kg.

⁴ In the presence of citrate.

“Flarend et al. (1997) showed that in rabbits intramuscularly injected with aluminium hydroxide or aluminium phosphate adjuvant at a dose of 0.85 mg ²⁶Al/animal, dissolution begins upon administration, as ²⁶Al was already found in blood within 1 hr after injection. The blood concentration of aluminium was fairly steady from days 2 to 28, at which time the terminal phase had not been reached. It was calculated that approximately 17% and 51% of the injected aluminium hydroxide and aluminium phosphate adjuvant dose, respectively, was absorbed into the blood over 28 days (Flarend et al., 1997). It is noted that this study was later criticised by Masson et al. (2018), inter alia because of the low number of animals (2/adjuvant) and the short duration of the study (28 days), and because the aluminium hydroxide and aluminium phosphate administered (prepared by the study authors by precipitation) differed from the aluminium hydroxide and aluminium phosphate found in vaccines on the market.”

“In the rabbit study by Flarend et al. (1997), the cumulative amount of aluminium eliminated in the urine over 28 days was 6% of the aluminium hydroxide adjuvant dose and 22% of the aluminium phosphate adjuvant dose. Aluminium from both adjuvants was still being excreted at a steady rate at day 28.

While this indicates that the body is able to eliminate the aluminium absorbed from the adjuvants, elimination is slow for the aluminium phosphate adjuvant and even slower for the aluminium hydroxide adjuvant.”

“Weisser et al. (2019) observed that in rats given plain aluminium phosphate adjuvant (i.e. without antigen), approximately 67% of the aluminium dose (1.25 mg/animal) was released from injected muscle over 80 days. For plain aluminium hydroxide adjuvant this was 0%.”

“In this study [Weisser et al. (2019)], an atomic absorption spectrometry method was used to study the kinetics of aluminium-containing adjuvants following a single intramuscular injection in (adult) rats. This method measures dissolved Al³⁺ ions as well as insoluble Al species, and would thus also capture any Al particles in blood and transported via the blood to the tissues studied (bone and brain), or remaining in the injection site muscle. The study revealed systemically available Al from both aluminium phosphate and aluminium hydroxide adjuvants and adjuvanted vaccines through increased Al levels mainly in bone (but not in brain), corroborated by significant correlations with total Al release from the injection site. Different rates of absorption were noted, with markedly higher systemic availability from aluminium phosphate than from aluminium hydroxide-adjuvanted vaccines. From the very low Al levels found in brain the authors concluded that the contribution of particulate Al amounts in the brain, if there is any, is marginal. Based on dose scaling to human adults they further expected that after a single vaccination in adults, Al levels in bone, and even more so in plasma and brain,”

"[I]n view of muscle tissue being a storage depot for aluminium adjuvant following intramuscular vaccination, it is assumed that the insoluble aluminium hydroxide or aluminium phosphate particles are solubilised by citrate ions in the interstitial fluids of muscle."

"There is limited information available on the absorption of aluminium oxide and aluminium hydroxide from antacids. In the Summary of Product Characteristics (SPCs) of two antacids on the Dutch market it is stated that 'magnesium and aluminium are absorbed for about 15-30%' (Regla pH, 2015; Antagel, 2016). It is doubtful whether this is correct, as with reference to several publications ATSDR (2008) reported that when large oral loads of aluminium (1–4 g/day) in the form of (usually aluminium hydroxide) antacids are ingested, only a very small amount of this aluminium is absorbed (<1%, or even $\leq 0.01\%$, of the intake amount in healthy individuals). The ATSDR also refers to a study by Weberg and Berstad (1986) in which subjects with normal renal function were given a total of 976 mg aluminium (as aluminium hydroxide in antacid tablets). When the tablets were taken with water, the amount absorbed was calculated as 0.004%".

"Based on the available information, the ATSDR concluded that only an extremely small amount of the aluminium found in antacids will be absorbed. In their risk assessment of aluminium, Tietz et al. (2019) also presume that, with respect to antacids, the absorption rate in the gastrointestinal tract will be significantly lower with a single administration of high doses of aluminium than with a continuous intake of low doses (as with foods)."

As taken from RIVM, 2020

"The fractional uptake of ingested aluminium and aluminium compounds (aluminium citrate, aluminium nitrate, aluminium chloride, aluminium sulphate, aluminium hydroxide, aluminium oxide, aluminium metal, powdered aluminium pot electrolyte, acidic sodium aluminium phosphate (SALP), basic sodium aluminium phosphate (Kasal), sodium aluminium silicate and FD&C red 40 aluminium lake) from the gastro-intestinal tract of adult female rats was measured. This was determined by comparing retained body burden of ^{26}Al at seven days post-administration of an i.v. injection of ^{26}Al -labelled aluminium citrate with that retained following the gastric administration of ^{26}Al -labelled test compounds as either solutions or suspended solid. The calculated percentage uptake of ^{26}Al for all the aluminium solutions was similar: aluminium citrate 0.08%, aluminium chloride 0.05%, aluminium nitrate 0.05% and aluminium sulphate 0.21%. The uptake of ^{26}Al administered as insoluble particulates was lower: 0.03% for aluminium hydroxide; 0.02% for aluminium oxide; 0.04% for powdered pot electrolyte; 0.12% for sodium aluminium silicate; and 0.09% for FD&C red 40 aluminium lake. For aluminium metal, SALP and Kasal the amount of ^{26}Al present in the rats was insufficient to determine uptake and was less than 0.03%. The results produced for aluminium citrate, aluminium hydroxide and aluminium sulphate are close to those published for man." As taken from Priest ND et al. 2020. Neurotoxicology. Epub PubMed, 2021 available at <https://pubmed.ncbi.nlm.nih.gov/32605715/>

4.3. Interactions

"Concurrent use with antacids may be indicated in the treatment of duodenal ulcer to relieve pain; however, simultaneous administration is not recommended since antacids may interfere with binding of sucralfate to the mucosa; patients should be advised not to take any antacids within 1/2 hour before or after sucralfate; concurrent use with aluminum-containing antacids may cause aluminum toxicity in patients with chronic renal failure. /Aluminum-containing antacids/ [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1". Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 207]**PEER REVIEWED**

"Concurrent use /of methanamine/ with antacids that cause the urine to become alkaline may reduce the effectiveness of methanamine by inhibiting its conversion to formaldehyde; concurrent use in not recommended". /Aluminum-containing antacids/ [Thomson.Micromedex. Drug

Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 206]**PEER REVIEWED**

“Alkalinization of the urine may slow excretion and prolong the effects of mecamlamine; concurrent use /with aluminum-containing antacids/ is not recommended”. /Aluminum-containing antacids/ [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 206]**PEER REVIEWED**

“Antacids may cause increased gastrointestinal pH; concurrent administration /of ketoconazole/ with antacids may result in a marked reduction in absorption of ketoconazole; patients should be advised to take antacids at least 3 hours after ketoconazole”. /Aluminum-containing antacids/ [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 206]**PEER REVIEWED**

“Absorption /of aluminum-containing antacids/ may be decreased when oral tetracyclines are used concurrently with antacids because of possible formation of nonabsorbable complexes and/or increase in intragastric pH; patients should be advised not to take antacids within 3 to 4 hours of tetracyclines”. /Aluminum-containing antacids/ [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 207]**PEER REVIEWED**

“... In man the absorption of ... chlorpromazine and aminosalicilic acid is decreased by aluminum hydroxide-containing mixtures. Oral toxicity of atropine and homatropine in mice is reduced by aluminum antacids ... ”. [Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 962]**PEER REVIEWED**

“In rats, absorption of aspirin, pentobarbital and sulfadiazine is decreased, probably because of effects on pH partition. Absorption of penicillin and pseudoephedrine is increased. Absorption of foodstuffs and nutritional factors, such as amino acids, ascorbic acid, vitamin A and glucose is slightly ... depressed”. [Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 962]**PEER REVIEWED**

“Concurrent use /of quinine/ with aluminum-containing antacids may decrease or delay the absorption of quinine”. /Aluminum-containing antacids/ [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 206]**PEER REVIEWED**

“... Aluminum hydroxide ... can interfere with absorption ... of warfarin, digoxin ... ”. [Farm Chemicals Handbook 1980. Willoughby, Ohio: Meister, 1980., p. 953]**PEER REVIEWED**

“30 mL aluminum hydroxide given 3 times daily to volunteers. 15 mg fluoride given orally 3 times/day to controls and test group. After fluoride administration distinct rise and gradual fall in plasma fluoride noted. Administration of aluminum hydroxide decreases plasma fluoride by 41% and urinary fluoride by 51%”. [SPENCER H ET AL; TOXICOL APPL PHARMACOL 58 (1): 140 (1981)]**PEER REVIEWED**

"Antacids /including aluminum hydroxide,/ may inhibit the gastrointestinal absorption of some beta-blockers". [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 24]**PEER REVIEWED**

"Aluminum hydroxide suspension may delay procainamide absorption in dogs". [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 13]**PEER REVIEWED**

"Antacids appear to inhibit the gastrointestinal absorption of cimetidine and ranitidine. Concurrent administration of antacids may reduce the extent of cimetidine absorption, thus lowering serum cimetidine levels. However, the extent to which the therapeutic response to cimetidine would be affected has not been established. Separate doses of cimetidine and antacids. The interaction is minimal if the cimetidine is given with a meal and the antacid one hour or more after the meal". [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 384]**PEER REVIEWED**

"Alkalinization of the urine may increase renal salicylate excretion and lower serum salicylate levels; dosage adjustment of salicylates may be necessary when chronic high-dose antacid therapy is started or stopped, especially in patients receiving large doses of the salicylate, such as patients with rheumatoid arthritis or rheumatic fever". /Aluminum-containing antacids/ [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 207]**PEER REVIEWED**

"Absorption may be inhibited when these medications /phenothiazines, especially oral chlorpromazine/ are used concurrently with aluminum ... antacids; although more studies are needed to establish the significance of this interaction, simultaneous administration should be avoided". /Aluminum-containing antacids/ [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 206]**PEER REVIEWED**

"It is proposed that antacids /including aluminum hydroxide/ would increase the proportion of ionized sulfonamide, thereby decreasing its absorption. Clinical studies must be performed to assess the clinical significance of this interaction. Factors other than ionization may be involved (eg, dissolution rate). Further, a delay in absorption does not necessarily mean a decrease in absorption, and under the conditions of multiple dosing, delayed absorption may or may not have a significant clinical effect". [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 234]**PEER REVIEWED**

"Aluminum hydroxide gel (Amphojel) and, to a lesser extent, magaldrate (Riopan) appear to inhibit the gastrointestinal absorption of isoniazid. It has been proposed that this effect may be due to a delay in gastric emptying caused by the aluminum in the antacids". [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 214]**PEER REVIEWED**

"It has been suggested that some component of antacids interferes with the absorption of cimetidine. Aluminum hydroxide is a well known binding agent and has been reported to interfere with the bioavailability of several drugs, and magnesium hydroxide is also known to interfere with drug kinetics. Other studies suggest that the total neutralizing capacity of the antacid is responsible for the interaction. However, it has been shown that doubling the neutralizing capacity did not further inhibit cimetidine absorption. It is possible that magnesium and aluminum ions complex maximally to cimetidine at a neutralizing capacity between 50 and 72 mmol, have no further inhibition over 72 mmol, and may not maximally bind cimetidine below 50 mmol. The clinical significance of the reduction in cimetidine bioavailability has not been studied. If the concomitant use of antacids and cimetidine is selected, the administration of these agents should be separated by as much time as possible. It may be advisable to administer antacids one hour before or after cimetidine dosing in the fasting state. Another recommendation would be to administer cimetidine with meals, followed by the antacid 1 hour later". [Evaluations of Drug Interactions. 2nd ed. and

supplements. Washington, DC: American Pharmaceutical Assn., 1976, 1978., p. 18/1]**PEER REVIEWED**

In one study, peak plasma levels of dicumarol were earlier and higher when the dicumarol was given with magnesium hydroxide than when it was given with water. Aluminum hydroxide does not appear to affect dicumarol blood levels. Warfarin plasma levels do not appear to be affected by aluminum hydroxide, magnesium hydroxide, or a mixture of the two antacids. [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 69] .

The combined adjuvant effect of ginsenoside Rg1 and aluminum hydroxide (alum) on immune responses to ovalbumin (OVA) in mice was investigated. BALB/c mice were subcutaneously (s.c.) inoculated twice with OVA alone or in combination with Rg1, alum, or Rg1 plus alum. Samples were collected 2 weeks after the boosting for the measurement of anti-OVA immunoglobulin G (IgG) isotypes in sera and gamma interferon (IFN-gamma) and interleukin-5 (IL-5) produced in splenic splenocyte cultures. Delayed-type hypersensitivity (DTH) responses were measured in mice immunized as described above. After 10 days, the mice were injected s.c. with OVA at the footpads. Thereafter, the thickness of the footpads was measured once daily for 5 days. The results indicated that alum enhanced mainly Th2 (IgG1 and IL-5) responses ($P < 0.05$), while Rg1 enhanced both Th1 (IgG1 and IL-5) and Th2 (IgG2a, IFN-gamma, and DTH) responses ($P < 0.05$). The highest immune responses were found in the mice injected with OVA solution containing both alum and Rg1. In addition, the hemolytic activity of Rg1 was much lower than that of Quil A. ... [Sun J et al; Clin Vaccine Immunol. 15 (2): 303-7 (2008)].

"Procainamide (300 mg orally) was administered to six dogs with and without suspensions of aluminum hydroxide (1 g/10 ml) or magnesium oxide (1 g/10 l). Aluminum hydroxide lowered the maximal plasma procainamide concentration by about 20% but the reduction in the area under the procainamide plasma level time curve was not statistically significant. Antacids appear to have minimal effects on procainamide absorption in dogs, but studies in humans are lacking". [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 13]**PEER REVIEWED**

"In one study of ten patients receiving large doses of chlorpromazine, the concomitant administration of an antacid (Alurox) resulted in 10% to 45% decreases in urinary chlorpromazine excretion. Information from another study indicates that an antacid containing magnesium trisilicate and aluminum hydroxide may result in decreased blood levels of chlorpromazine given as an oral suspension. Thus, a decreased therapeutic response to chlorpromazine seems possible, and one possible case of this has been reported. In one preliminary report antacids did not affect the absorption of chlorpromazine, but until more studies are done one should assume that antacids are capable of reducing the gastrointestinal absorption of chlorpromazine (and possibly other phenothiazines)". [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 346]**PEER REVIEWED**

"Studies of digoxin absorption in normal volunteers with and without concomitant antacid administration indicate that the following antacids can reduce digoxin bioavailability: magnesium trisilicate, magnesium hydroxide, aluminum hydroxide. The magnitude of the decreases in digoxin bioavailability (based on 6-day cumulative urinary excretion) would seem large enough to reduce the therapeutic response to digoxin in some patients. However, studies in patients receiving chronic digoxin therapy are needed to confirm the clinical importance of this interaction. A study in 12 subjects indicated that a magnesium-aluminum hydroxide antacid reduced the bioavailability of digoxin tablets but not digoxin capsules". ... [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 273]**PEER REVIEWED**

"At least one study in six subjects indicates that aluminum hydroxide gel does not affect nitrofurantoin absorption as measured by cumulative urinary excretion." [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 22]**PEER REVIEWED**

"Concurrent use /of oral isoniazid/ with aluminum-containing antacids may delay and decrease absorption of oral isoniazid; concurrent use should be avoided or the patient should be advised to

take oral isoniazid at least 1 hour before the antacid. /Aluminum-containing antacids/" [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 206]**PEER REVIEWED**

"Concurrent use /of citrates/ with antacids containing aluminum ... may result in systemic alkalosis. ... Concurrent use of aluminum-containing antacids ... with citrate salts can increase aluminum absorption, possibly resulting in acute aluminum toxicity, especially in patients with renal insufficiency. /Aluminum-containing antacids/ " [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 205]**PEER REVIEWED**

"In the gut, antacids form insoluble compounds with numerous substances. Interactions are especially prominent with aluminum-containing antacids. Aluminum forms insoluble aluminum phosphate, which decreases the bioavailability of phosphate. Although aluminum fluoride is somewhat soluble, aluminum-containing antacids interfere with the absorption of fluoride, probably through the formation of more complex compounds, such as fluoroapatite. Aluminum-containing antacids adsorb bile acids, lysolecithin, and various proteins. /Aluminum-Containing antacids/" [Gilman, A.G., L.S.Goodman, and A. Gilman. (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 7th ed. New York: Macmillan Publishing Co., Inc., 1985., p. 981]**PEER REVIEWED**

"Concurrent use /of chenodiol/ with aluminum-containing antacids may result in binding of chenodiol, thus decreasing its absorption. /Aluminum-containing antacids/" [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 205]**PEER REVIEWED**

"Alkalinization of the urine may reduce the solubility of ciprofloxacin and norfloxacin in the urine, especially when the urinary pH exceeds 7.0; if antacids and one of these medications are use concurrently, patients should be observed for signs of crystalluria and nephrotoxicity. /Aluminum-containing antacids/" [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 205]**PEER REVIEWED**

"Aluminum-containing ... antacids may reduce absorption of fluoroquinolones, resulting in lower serum and urine concentrations of these medications; therefore, concurrent use is not recommended; however, if aluminum-containing ... antacids must be used concurrently with these medications, it is recommended that enoxacin be taken at least 2 hours before or 8 hours after the antacid; ciprofloxacin and lomefloxacin should be taken at least 2 hours before or 6 hours after the antacids; and norfloxacin and ofloxacin should be taken at least 2 hours before or after the antacid. /Aluminum-containing antacids/" [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 205]**PEER REVIEWED**

"Concurrent administration of antacids with enteric-coated medications may cause the enteric coating to dissolve too rapidly, resulting in gastric or duodenal irritation. /Aluminum-containing antacids/" [Thomson.Micromedex. Drug Information for the Health Care Professional. 24th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2004., p. 205]**PEER REVIEWED**

"In a case study of patients on long-term dialysis, systemic aluminum absorption with concurrent oral citrate (as an alkalinizing agent) and aluminum containing phosphate binder (eg, aluminum hydroxide or carbonate) was significantly increased. Based on the proposed mechanism and pharmacologic similarity, an interaction may be expected to occur between citric acid and other aluminum salts (eg, aluminum phosphate, aluminum glycinate, attapulgit, dihydroxyaluminum,

kaolin, magaldrate). It has been shown that following concurrent administration of citric acid (from lemon juice) and aluminum hydroxide there is an increase in serum levels of a nonionized aluminum citrate complex, which is postulated to easily pass the gastrointestinal barrier. Simultaneous administration of citric acid and aluminum hydroxide should be avoided since significant systemic absorption of aluminum may occur. This may be of additional concern in patients on long-term dialysis or with impaired renal function". [Evaluations of Drug Interactions. 2nd ed. and supplements. Washington, DC: American Pharmaceutical Assn., 1976, 1978., p. 18/0.05]**PEER REVIEWED**

As taken from HSDB, 2013.

"The objective of this work was to investigate the influence of various micronized poorly water-soluble inorganic materials on the dissolution and de-agglomeration behaviour of a micronized, poorly water-soluble model drug, indomethacin, from lactose interactive mixtures.....The addition of aluminium hydroxide and calcium phosphate to binary mixtures of indomethacin counter-intuitively improved the dissolution rate of indomethacin due to significant increases in both the estimated initial concentration and dissolution rate constant of dispersed particles of indomethacin. While some enhancement was due to pH changes in the dissolution medium, the presence of these poorly water-soluble inorganic salts caused de-agglomeration. Average particle size distributions indicated that the presence of aluminium hydroxide within the matrix of indomethacin had reduced the agglomerate concentration whilst increasing the dispersed particle concentration. These findings provide the first evidence of the ability of poorly water-soluble inorganic salts to enhance the de-agglomeration and dissolution of micronized powders, potentially translating to improved bioavailability of poorly water-soluble drugs." As taken from Tay T et al. 2011. Eur. J. Biopharm. 79(3), 674-82. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/21703348>

"The ability of different adjuvants to enhance immune responses to intradermal (ID) immunisation with a model antigen was studied in pigs. Immune responses were evaluated with respect to the intensity of systemic and mucosal antibody formation, their isotype characterisation and rate of cell-mediated immunity. These findings were compared with the intensity of adverse local reactions. Six groups of piglets were immunised with keyhole limpet haemocyanin (KLH) antigen alone or in combination with aluminium hydroxide or selected oil-based adjuvants (complete and incomplete Freund's adjuvants, Montanide ISA 206 and Emulsigen). Systemic specific antibody responses were significantly increased following ID administration of antigen together with any of the adjuvants used. IgG antibody responses were most pronounced after the first administration of antigen, being stimulated with both Freund's and Montanide ISA 206 adjuvants....." As taken from Krejci J et al. 2013. Res. Vet. Sci. 94(1), 73-6. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22929313>

"Allergen-specific immunotherapy (SIT) is a clinically effective therapy for immunoglobulin (Ig)E-mediated allergic diseases. To reduce the risk of IgE-mediated side effects, chemically modified allergoids have been introduced. Furthermore, adsorbance of allergens to aluminium hydroxide (alum) is widely used to enhance the immune response. The mechanisms behind the adjuvant effect of alum are still not completely understood. In the present study we analysed the effects of alum-adsorbed allergens and allergoids on their immunogenicity in vitro and in vivo and their ability to activate basophils of allergic donors. Human monocyte derived dendritic cells (DC) were incubated with native Phleum pratense or Betula verrucosa allergen extract or formaldehyde- or glutaraldehyde-modified allergoids, adsorbed or unadsorbed to alum. After maturation, DC were co-cultivated with autologous CD4(+) T cells. Allergenicity was tested by leukotriene and histamine release of human basophils. Finally, in-vivo immunogenicity was analysed by IgG production of immunized mice. T cell proliferation as well as interleukin (IL)-4, IL-13, IL-10 and interferon (IFN)- γ production were strongly decreased using glutaraldehyde-modified allergoids, but did not differ between alum-adsorbed allergens or allergoids and the corresponding unadsorbed preparations. Glutaraldehyde modification also led to a decreased leukotriene and histamine release compared to native allergens, being further decreased by adsorption to alum. In vivo, immunogenicity was

reduced for allergoids which could be partly restored by adsorption to alum. Our results suggest that adsorption of native allergens or modified allergoids to alum had no consistent adjuvant effect but led to a reduced allergenicity in vitro, while we observed an adjuvant effect regarding IgG production in vivo.” As taken from Heydenreich B et al. 2014. Clin. Exp. Immunol. 176(3), 310-9. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/24528247>

“INTRODUCTION: Enteral nutrition (EN) provides calories, macronutrients and micronutrients in adequate quantity and quality to meet the patient's needs. Some drugs when crushed and diluted may have their properties altered, including the reduction of bioavailability causing the reduction of the serum concentration of the drug; tube obstruction; drug-drug interaction or drug-nutrient interaction. METHODS: The study was conducted through review of submitted articles in the databases of the Virtual Health Library (VHL): MEDLINE (National Library of Medicine, USA), Lilacs (Latin American and Caribbean Literature on Health Sciences) PUBMED - NCBI (National Center for Biotechnology Information) and COCHRANE. RESULTS: For this survey, 42 articles were identified during database searching. After applying the inclusion and exclusion criteria, 08 articles were selected, obtained from the MEDLINE and Lilacs. DISCUSSION: Some interactions were found such as the aluminium hydroxide and lactulose with the enteral nutrition, which may result in a precipitation and reduction of drug bioavailability....” As taken from Ferreira Silva R & Rita Carvalho Garbi Novaes M. 2014. Nutr. Hosp. 30(3), 514-8. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25238825>

“The absorption of aluminium, administered as a single large dose of Al(OH)₃ (antacid tablets, 4 x 244 mg Al) to 10 research subjects, was increased 8- and 50-fold when the aluminium hydroxide was given with orange juice or citric acid solution, respectively, compared with when given in pure water (Weberg R and Berstad A. 1986).”

“Doravirine is a novel non-nucleoside reverse transcriptase inhibitor indicated for the treatment of human immunodeficiency virus type 1 infection. Because of potential concomitant administration with acid-reducing agents, a drug-interaction trial was conducted to evaluate the potential impact of these types of medications on doravirine pharmacokinetics. In an open-label, 3-period, fixed-sequence trial, healthy adult participants received the following: period 1, a single dose of doravirine 100 mg; period 2, coadministration of a single dose of doravirine 100 mg and an antacid (1600 mg aluminum hydroxide, 1600 mg magnesium hydroxide, and 160 mg simethicone); period 3, 40 mg pantoprazole once daily on days 1-5 coadministered with a single dose of doravirine 100 mg on day 5. There was a minimum 10-day washout between periods. Plasma samples for pharmacokinetic evaluation were collected, and safety was assessed. Fourteen participants (8 male, 6 female) were enrolled, and 13 completed the trial. Geometric mean ratios (90% confidence intervals) for doravirine AUC_{0-inf}, C_{max}, and C₂₄ for doravirine + antacid/doravirine were 1.01 (0.92-1.11), 0.86 (0.74-1.01), and 1.03 (0.94-1.12), respectively, and for doravirine + pantoprazole/doravirine were 0.83 (0.76-0.91), 0.88 (0.76-1.01), and 0.84 (0.77-0.92), respectively. Doravirine was generally well tolerated administered alone or with either of the acid-reducing agents. Coadministration of an aluminum/magnesium-containing antacid or pantoprazole did not have a clinically meaningful effect on doravirine pharmacokinetics, supporting the use of acid-reducing agents with doravirine.” As taken from Khalilieh SG et al. 2019. J. Clin. Pharmacol. 59(8), 1093-1098. PubMed, 2020 available at <https://pubmed.ncbi.nlm.nih.gov/30817001/>

“Although Al-induced maternal and/or embryonic effects were not observed when high doses of Al hydroxide were given by gavage to mice and rats (reviewed extensively in EFSA, 2008), some subtle signs of maternal and developmental toxicity were reported when Al hydroxide was given to mice concurrently with citric or lactic acids (Gomez et al., 1991).”

As taken from SCCS, 2022

5. Toxicity

5.1. Single dose toxicity

Rat Oral LD₅₀ Al(OH)₃ > 5000 mg/kg bw Source: Omya AB, Martinswerk GmbH Bergheim

As taken from IUCLID Data sheet: Aluminium hydroxide (21645-51-2).

“Oral: Because aluminium is only sparingly absorbed from the gut, the oral LD50 values for aluminium ingestion are unavailable, since death occurs from intestinal blockage due to precipitated aluminium species rather than systemic aluminium toxicity (HSDB, 1999) (cited from Stuer-Lauridsen et al. 2000). The only LD50 value (>5000 mg/kg bw) found supports this (ECB, 1996) (cited from Stuer-Lauridsen et al., 2000) (Martinswerk GmbH, 1989) (cited from ECB, 2000).”

“Dermal: No relevant experimental toxicity data via the dermal route is reported for aluminium hydroxide.”

“Inhalation: No deaths were reported following an acute 4-hour exposure to up to 1,000 mg/m³ of aluminium oxide in groups of 12–18 male Fischer 344 rats (Thomson et al., 1986) (cited from ATSDR, 2008).”

As taken from European Commission, 2011.

LD50 Rat ip 1100 mg/kg bw. [Joint FAO/WHO Expert Committee on Food Additives; WHO Food Additives Ser 24: Aluminum (1989). Available from, as of June 4, 2004: <http://www.inchem.org/documents/jecfa/jecmono/v024je07.htm>

As taken from HSDB, 2013.

Type of Test	Route of Exposure	Species Observed	Dose Data	Toxic Effects	Reference
TDLo - Lowest published toxic dose	Oral	Human - child	79 gm/kg/2Y (intermittent)	Behavioral - changes in motor activity (specific assay) Behavioral - muscle contraction or spasticity Musculoskeletal - osteomalacia	PEDIAU Pediatrics. (American Academy of Pediatrics, P.O. Box 1034, Evanston, IL 60204) V.1-1948- Volume(issue)/page/year: 71,56,1983
TDLo - Lowest published toxic dose	Oral	Human - child	122 gm/kg/4D	Gastrointestinal - other changes Nutritional and Gross Metabolic - body temperature increase	JOPDAB Journal of Pediatrics. (C.V. Mosby Co., 11830 Westline Industrial Dr., St. Louis, MO 63141) V.1-1932- Volume(issue)/page/year: 92,592,1978
TDLo - Lowest published toxic dose	Unreported	Human - infant	39 gm/kg/24D (intermittent)	Musculoskeletal - osteomalacia	NEJMAG New England Journal of Medicine. (Massachusetts Medical Soc., 10 Shattuck St., Boston, MA 02115) V.198-1928- Volume(issue)/page/year: 310,1079,1984
LDLo - Lowest published lethal dose	Intraperitoneal	Rodent - rat	150 mg/kg	Details of toxic effects not reported other than lethal dose value	LANCAO Lancet. (7 Adam St., London WC2N 6AD, UK) V.1-1823- Volume(issue)/page/year: 1,564,1972

TDLo - Lowest published toxic dose	Oral	Rodent - rat	15 mg/kg	Gastrointestinal - other changes	FTRPAE Fitoterapia. (Inverni della Beffa SpA, via Ripamonti, 99, 20141 Milan, Italy) V.18- 1947- Volume(issue)/page/year: 70,542,1999

As taken from RTECS, 2018.

“/LABORATORY ANIMALS: Acute Exposure/ Ip injection... caused heavy mortality with periorbital bleeding in both nephrectomized and control rats within 5 days /also perihepatic granuloma and fibrous peritonitis/. Sc injection... caused no mortality but... periorbital bleeding in nephrectomized rats and patchy pneumonia with desquamation of bronchial epithelium... .” [Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978., p. 109]**PEER REVIEWED**

“/LABORATORY ANIMALS: Acute Exposure/ ...Aluminum levels in plasma, urine, synovial tissue, liver and kidney were measured in saline treated rabbits and 1 to 2 days after an articular injection of 75 mg of aluminum compounds into their right knee. The methodology used was argon plasma emission spectrometry. The joint toxicity of aluminum lactate at the same dose regimen was evaluated for 2 days by a qualitative histological examination of synovial tissue and articular surfaces and a colorimetric assay (1,9-DMB) of patellar articular cartilage proteoglycan content. The single injection of 50 mg of aluminum derivatives as an inducer of inflammation was studied in the rat subcutaneous air pouch, a model for a synovial-like space. Leukocytes and eicosanoids levels were measured in pouch washout fluids from 1 to 72 hr after injection. After injection into rabbit knee, aluminum lactate largely distributed within the body while hydroxide remained locally. However, aluminum lactate resulted in perivascular edema, sparse infiltration of inflammatory cells in the synovium and a hemorrhagic effusion. Proliferation of the synovial cell layer coexisted with an apparent loss of proteoglycan in superficial zones of tibial and femoral cartilages when patellar proteoglycan content remained unchanged. Aluminum hydroxide did not affect joint structures. In the air pouch experiment, aluminum lactate increased prostaglandin E2 (PGE2) levels from 3 to 10 hr after its injection and less intensively leukotriene B4 (LTB4) levels after 6 hr, in the absence of leukocytes migration into the cavity. In contrast, aluminum hydroxide increased leukocytes count in pouch-washout fluid from 3 to 24 hr after its injection when PGE2 and LTB4 levels were little modified”. [Chary-Valckenaere I et al; J Rheumatol 21 (8): 1542-1547 (1994)]**PEER REVIEWED**

“/LABORATORY ANIMALS: Acute Exposure/ .../In a/ randomized trial, ...5 male dairy calves... were fed milk replacer at 7:30 AM and 7:30 PM. Cannulae for pH electrodes were placed in the abomasal body and pyloric antrum. Treatments consisted of oral administration of a high (50 mL) or low (25 mL) dose of the antacid agent and oral administration of milk replacer alone (control). Antacid was given at 7:30 AM, 3:30 PM, and 11:30 PM, and luminal pH was monitored continuously for 24 hours, beginning 15 minutes before administration of the first dose of antacid. Administration of the first dose of antacid at the time of the morning feeding resulted in an increase in mean abomasal body luminal pH of <1 pH unit, whereas administration of the second and third doses of the antacid caused transient (<3 hours) increases in mean luminal pH of approximately 1.5 (low dose) and 2.5 (high dose) pH units”. [Ahmed AE et al; J Am Vet Med Assoc 220 (1): 74-79 (2002)]**PEER REVIEWED**

Property / Endpoint	Data	Reference	Data quality
Acute lethality - oral	Rat oral LD50 >2,000 mg/kg bw	ECHA, 2013	Reported in a secondary source. Performed in accordance with OECD guidelines and GLP.

As taken from US EPA, 2014a.

Vaccines typically come with adjuvants that trigger the innate immune system in order to prepare best possible inflammatory conditions as to allow the adaptive immune system to become activated, generally for the induction of antibodies. The oldest approved and most abundant immunological adjuvants are salts of aluminium, which are also frequently used in animal models of immunisation and allergy desensitization. In rodents, the intraperitoneal administration of aluminium adjuvants is commonly performed and considered safe. In the current investigation, we show that intraperitoneal administration of aluminium adjuvants is associated with adose-dependent hypothermic reaction within 10 min of the injection. The body temperature of mice dropped as much as 4 °C, and the clinical symptoms included apathy, hunched posture, and piloerection. The temperature normalised and other clinical manifestations disappeared within 60–80 min of the intraperitoneal aluminium injection, which caused strong infiltration of neutrophil and eosinophil granulocytes into the peritoneal cavity, a clinical manifestations typically associated with inflammasome activation. However, the observed reactions to aluminium adjuvants were independent of NALP3, caspase-1, and interleukin-1 β , but dependent on histamine. Hence, aluminium adjuvants may have potential local and systemic side effects, which warrants further investigations into the nature of these side effects, but also into the possible implications on health in man. As taken from Freiburger et al. 2018. Eur J Pharm Sci. 2018 Mar 30;115:362-368. Available at <https://www.ncbi.nlm.nih.gov/pubmed/29410031>

5.2. Repeated dose toxicity

“There have been several repeated dose toxicity studies in which a wide range of end-points, including clinical signs, food and water consumption, growth, haematological and serum analyses, tissue and plasma concentrations of aluminium, histopathology, has been examined following oral exposure to various aluminium compounds. There were no treatment-related effects in rats fed up to 288 mg Al/kg body weight per day as sodium aluminium phosphate or 302 mg Al/kg body weight per day as aluminium hydroxide in the diet for 28 days (Hicks et al., 1987). In a subchronic study in which aluminium nitrate was administered in drinking-water to rats, the only effect observed was a significant decrease in body weight gain associated with a decrease in food consumption at 261 mg Al/kg body weight per day. (NOEL = 52 mg Al/kg body weight per day) (Domingo et al., 1987b)”.

“/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ ...Aluminum hydrate... caused rapid and massive fibrosis of lungs /intratracheal injection/; after 25 days there was dense network of coarse reticulin fibers and a few collagen fibers (grade II fibrosis); from 60th-210th day reticulin was replaced by collagen and appearances corresponded to grade III.”..[Browning, E. Toxicity of Industrial Metals. 2nd ed. New York: Appleton-Century-Crofts, 1969., p. 8]**PEER REVIEWED**

“/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Rats fed 6-10 mg aluminum (as aluminum hydroxide) daily showed significant impairment of growth at 3-4 wk. Rachitic changes occurred in bones; addition of phosphate in diet prevented these changes”. [Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978., p. 108]**PEER REVIEWED**

“/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ The effects of dietary administration of aluminum hydroxide were examined in male Sprague-Dawley rats (Charles River Breeding Laboratories, Inc, Kingston, NY). Groups of 25 rats were fed a diet containing 14,470 ppm aluminum hydroxide or a control diet for 28 days. The mean daily aluminum dose was calculated as 302 mg/kg body weight/day. Dietary administration of aluminum hydroxide did not induce any signs of toxicity. Clinical observations during the 28-day treatment period and the recovery phase were similar in control and treated rats. There were no significant changes in hematology, clinical chemistry parameters, or organ weights. Histopathological examination of tissues revealed no treatment-related changes. Ingestion of aluminum hydroxide caused no significant deposition of Al in bone samples. The levels of aluminum in femurs in rats fed the Al-containing diet (n= 5) and in

controls (n= 5) ranged from 0.2 to 0.4 ppm and from 0 to 0.3 ppm, respectively". [Hicks JS et al; Food Chem Toxicol 25 (7): 533-8 (1987)]**PEER REVIEWED**

"/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ ...Male weanling and adult Wistar rats were fed sucrose diets with the addition of aluminum hydroxide (Al(OH)₃) or aluminum potassium sulfate (AlK(SO₄)₂) for 67 days. ...No Al-induced anemia or hypophosphatemia was observed and serum Al did not exceed 20 ng/mL. Serum triglyceride (TG) was decreased by aluminum. Serum TG was significantly correlated with the serum nonesterified fatty acid (NEFA) concentration in both the Young groups (R=0.757, n=22, p< 0.01) and the Adult groups (R=0.727, n=19, p<0.01). Neither serum cholesterol nor phospholipids was affected by Al ingestion. Aluminum caused a decrease in hepatic glycogen in all groups, but the decrease was significant only in Adult groups. Glycerol tri[9,10(n)-³H]oleate was administered by gastric tube into rats fed for 81 days with experimental diets. In all the Al-treated groups serum 3H was significantly greater than in control groups at 3 hr after intubation. At 24 hr after intubation, serum 3H did not differ between Control and Al-treated groups. Total 3H at 24 hr found in serum, liver, and epididymal adipose tissue was not changed significantly by Al feeding. These effects were observed without measurable increase of Al in the serum".[Sugawara C et al; Fundam Appl Toxicol 10 (4): 616-623 (1988)]**PEER REVIEWED**

"/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Aluminium hydroxide was not carcinogenic after daily ip administration to mice for 4 months at dosages up to about 200 mg aluminium/kg/day". [Joint FAO/WHO Expert Committee on Food Additives; WHO Food Additives Ser 24: Aluminum (1989). Available from, as of June 4, 2004: <http://www.inchem.org/documents/jecfa/jecmono/v024je07.htm>]**PEER REVIEWED**

"/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Sequential effects of intoxication with aluminum hydroxide (Al) (80 mg/kg bw, ip, 3 times/wk), were studied on rats from weaning and up to 28 weeks. The study was carried out on hematological and iron metabolism-related parameters on peripheral blood, at the end of the 1st, 2nd, 3rd, 4th, 5th and 6th months of exposure. ...Renal function was measured at the same periods. The animals treated developed a microcytosis and was accompanied by a decrease in mean corpuscular hemoglobin (MCH). Significantly lower red blood cell counts (RBC million/uL) were found in rats treated during the 1st month. These values matched those obtained for control rats during the 2nd month. From the 3rd month onwards, a significant increase was observed as compared to control groups, and the following values were obtained by the 6th month: (T) 10.0 +/- 0.3 versus (C) 8.7 +/- 0.2 (million/uL). Both MCH and mean corpuscular volume (MCV) were found to be significantly lower in groups treated from the 2nd month. At the end of the 6th month the following values were found: MCH (T) 13.3 +/- 0.1 versus (C) 16.9 +/- 0.3 (pg); MCV (T) 42.1 +/- 0.7 versus (C) 51.8 +/- 0.9 (fl)". [Mahieu S et al; Toxicol Lett 111 (3): 235-242 (2000)]**PEER REVIEWED**

"/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ ...Saline (2 mL) or aluminum hydroxide [2 mL (0.15 g/mL)] was instilled intrapleurally in anesthetized male rats. The animals were studied 7 or 30 days after the instillation. Respiratory system, lung, and chest wall elastic, resistive, and viscoelastic/inhomogeneous pressures were measured by the end-inflation occlusion method. We studied the pleural remodeling process by means of semiquantitative analysis of the induced inflammation and quantitative analysis of the collagen extracellular matrix component. The effects on the underlying lung were analyzed morphometrically. Chest wall elastic and viscoelastic pressures increased after aluminum hydroxide instillation independent of time after instillation. Pleural inflammation was observed 7 days after instillation, while pleural adherence with a marked increase in the type I/type III collagen ratio was present 30 days after instillation. Histological examination demonstrated no differences in lung parenchyma among the groups". [Albuquerque DA et al; Lung 179 (5): 293-303 (2001)]**PEER REVIEWED**

"/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Young and adult rats were fed a sucrose diet with addition of aluminum hydroxide. A decrease in serum triglyceride was observed in rats fed with 2,000 ppm aluminum hydroxide in the diet for 67 days". [Sheftel, V.O.; Indirect Food

Additives and Polymers. Migration and Toxicology. Lewis Publishers, Boca Raton, FL. 2000., p. 434]**PEER REVIEWED**.

As taken from HSDB, 2013.

“Oral: No aluminium-related deaths in healthy humans have been reported after oral exposure. No mortality was observed in male Sprague-Dawley rats (7–10 per group) orally exposed to 70 mg Al/kg/day as aluminium chloride in water for 30, 60, or 90 days (Dixon et al., 1979), or up to 158 mg Al/kg/day as aluminium hydroxide in the feed for 16 days (Greger, Donnaubauer, 1986); these doses do not include aluminium in the base diet (cited from ATSDR, 2008).”

“Dermal: No relevant experimental toxicity data via the dermal route is reported for aluminium hydroxide. However, a dermal absorption rate in the range of 0.1 % can be anticipated for aluminium hydroxide, which is not considered to be “significant”.”

“Inhalation: Pigott et al. (1981) did not find evidence of lung fibrosis in rats exposed to 2.18 or 2.45 mg/m³ for 86 weeks, 5 days per week, 6 hours per day. Exposure was towards manufactured or aged Saffil alumina fibers, being a refractory material containing aluminium oxide and about 4% silica. Exposed was followed by a 42-week observation period. A NOAEL of 2.45 mg/m³ will be used for hazard assessment (ATSDR, 2008).”

“Summary of human health effect data for aluminium hydroxide brought forward to the risk characterisation:”

Route	Endpoint	Species/treatment period/Dose regimen	Point of departure	DNEL*
Inhalation Rat / 28-days inhalation/	Repeated dose toxicity – animal data	0, 2.15, 2.45 mg/m ³	NOAEC: 2.45 mg Al/m ³	0.14 mg/m ³

*DNEL: A detailed description of the DNEL (derived no effect limit) can be found in Annex 10 of the reference.

As taken from European Commission, 2011.

“.....Oral Al hydroxide is used routinely to bind phosphate salts in the gut to control hyperphosphatemia in people with compromised renal function. Signs of chronic Al toxicity in the musculoskeletal system include a vitamin D-resistant osteomalacia (deranged membranous bone formation characterized by accumulation of the osteoid matrix and reduced mineralization, reduced numbers of osteoblasts and osteoclasts, decreased lamellar and osteoid bands with elevated Al concentrations) presenting as bone pain and proximal myopathy. Aluminum-induced bone disease can progress to stress fractures of the ribs, femur, vertebrae, humerus and metatarsals. Serum Al ≥100 µg/L has a 75-88% positive predictive value for Al bone disease. Chronic Al toxicity is also manifest in the hematopoietic system as an erythropoietin-resistant microcytic hypochromic anemia. Signs of Al toxicity in the central nervous system (speech difficulty to total mutism to facial grimacing to multifacial seizures and dyspraxia) are related to Al accumulation in the brain and these symptoms can progress to frank encephalopathy. There are four groups of people at elevated risk of systemic Al intoxication after repeated ingestion of monomeric Al salts: the preterm infant, the infant with congenital uremia and children and adults with kidney disease. There is a dose-dependent increase in serum and urinary Al in people with compromised renal function, and restoration of renal function permits normal handling of systemically absorbed Al and resolution of Al bone disease. Clinical experience with 960 mg/day of Al(OH)(3) (~5 mg Al/kg-day) given by mouth over 3 months to men and women with compromised renal function found subclinical reductions in hemoglobin, hematocrit and serum ferritin. Following adult males and females with reduced kidney function found that ingestion of Al(OH)(3) at 2.85 g/day (~40 mg/kg-day Al) over 7 years increased bone Al, but failed to elicit significant bone toxicity.....A number of studies of Al exposure in relation to memory in rodents have been published, but the results are inconsistent. At

present, there is no evidence to substantiate the hypothesis that the pathogenesis of Alzheimer's Disease is caused by Al found in food and drinking water at the levels consumed by people living in North America and Western Europe.....Chronic ingestion of insoluble hydrated Al silicates (in kg) can result in disturbances in iron and potassium status, primarily as a result of clay binding to intestinal contents and enhanced fecal iron and zinc elimination. Sufficiently high doses of ingested Al silicates (≥ 50 g/day) over prolonged periods of time can elicit a deficiency anemia that can be corrected with oral Fe supplements. There is essentially no systemic Al uptake after ingestion of the hydrated Al silicates. Rats fed up to 20,000 ppm Ca montmorillonite (equivalent to 1,860 ppm total Al as the hydrated Al silicate) for 28 weeks failed to develop any adverse signs. The results of dietary Phase I and II clinical trials conducted in healthy adult volunteers over 14 days and 90 days with montmorillonite found no adverse effects after feeding up to 40 mg/kg-day as Al. Since the Al associated with ingestion of hydrated Al silicates is not absorbed into the systemic circulation, the hydrated Al silicates seldom cause medical problems unless the daily doses consumed are substantially greater than those used clinically or as dietary supplements. A no-observable-adverse-effect-level (NOAEL) of 13 mg/kg-day as total Al can be identified based on histologic osteomalacia seen in adult hemodialysis patients given Al hydroxide for up to 7 years as a phosphate binder. Following U.S. EPA methods for calculation of an oral reference dose (RfD), an intraspecies uncertainty factor of 10x was applied to that value results in a chronic oral reference dose (RfD) of 1.3 mg Al/kg-day; assuming a 70-kg adult consumes 2 L of drinking water per day and adjusting for a default 20% relative source contribution that value corresponds to a drinking water maximum concentration of 9 mg/L measured as total Al. A chronic NOAEL for montmorillonite as representative of the hydrated Al silicates was identified from the highest dietary concentration (20,000 ppm) fed in a 28-week bioassay with male and female Sprague-Dawley rats. Since young rats consume standard laboratory chow at ~ 23 g/day, this concentration corresponds to 56 mg Al/kg-day. Application of 3x interspecies uncertainty factor and a 3x factor to account for study duration results in a chronic oral RfD of 6 mg Al/kg-day. Of note, this RfD is 5-10 fold less than oral doses of Al silicates consumed by people who practice clay geophagy and it corresponds to a maximum drinking water concentration of 40 mg Al/L. To utilize the values derived here, the risk manager must recognize the particular product (e.g., alum) or source (e.g., groundwater, river water, clay or cement pipe) of the Al found in tap water, apply the appropriate analytical methods (atomic absorption, energy dispersive X-ray diffraction, infrared spectral analysis and/or scanning transmission electron microscopy) and compare the results to the most relevant standard....." As taken from Willhite CC et al. 2012. Crit. Rev. Toxicol. 42(5), 358-442. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22512666>

"Sub-cutaneous immunotherapy is an effective treatment for allergy. It works by helping to modify or re-balance an individual's immune response to allergens and its efficacy is greatly improved by the use of adjuvants, most commonly, aluminium hydroxide. Aluminium salts have been used in allergy therapy for many decades and are assumed to be safe with few established side-effects. This assumption belies their potency as adjuvants and their potential for biological reactivity both at injection sites and elsewhere in the body. There are very few data purporting to the safety of aluminium adjuvants in allergy immunotherapy and particularly so in relation to longer term health effects. There are, if only few, published reports of adverse events following allergy immunotherapy and aluminium adjuvants are the prime suspects in the majority of such incidents. Aluminium adjuvants are clearly capable of initiating unwanted side effects in recipients of immunotherapy and while there is as yet no evidence that such are commonplace it is complacent to consider aluminium salts as harmless constituents of allergy therapies. Future research should establish the safety of the use of aluminium adjuvants in sub-cutaneous allergy immunotherapy." As taken from Exley C. 2014. Allergy Asthma Clin. Immunol. 10(1), 4. PubMed, 2014 available at <http://www.ncbi.nlm.nih.gov/pubmed/24444186>

"The safety of four different adjuvants was assessed in lupus-prone New Zealand black/New Zealand white (BW)F1 mice. Four groups of mice were injected intraperitoneally with incomplete Freund's adjuvant (IFA), complete Freund's adjuvant (CFA), squalene (SQU) or aluminium

hydroxide (ALU). An additional group received plain phosphate-buffered saline (PBS) (UNT group). Mice were primed at week 9 and boosted every other week up to week 15. Proteinuria became detectable at weeks 17 (IFA group), 24 (CFA group), 28 (SQU and ALU groups) and 32 (UNT group). Different mean values were obtained among the groups from weeks 17 to 21 [week 17: one-way analysis of variance (anova) $P = 0.016$; weeks 18 and 19: $P = 0.048$; weeks 20 and 21: $P = 0.013$] being higher in the IFA group than the others [Tukey's honestly significant difference (HSD) post-test $P < 0.05$]. No differences in anti-DNA antibody levels were observed among groups. Anti-RNP/Sm antibody developed at week 19 in only one CFA-treated mouse. Mean mouse weight at week 18 was lower in the ALU group than the IFA (Tukey's HSD post-test $P = 0.04$), CFA ($P = 0.01$) and SQU ($P < 0.0001$) groups, while the mean weight in the SQU group was higher than in the IFA ($P = 0.009$), CFA ($P = 0.013$) and UNT ($P = 0.005$) groups. The ALU group weight decreased by almost half between weeks 29 and 31, indicating some toxic effect of ALU in the late post-immunization period. Thus, SQU was the least toxic adjuvant as it did not (i) accelerate proteinuria onset compared to IFA; (ii) induce toxicity compared to ALU or (iii) elicit anti-RNP/Sm autoantibody, as occurred in the CFA group." As taken from Favoino E et al. 2014. Clin. Exp. Immunol. 175(1), 32-40. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/24112107?dopt=AbstractPlus>

Type of Test	Route of Exposure	Species Observed	Dose Data	Toxic Effects	Reference
TDLo - Lowest published toxic dose	Oral	Rodent - rat	8040 mg/kg/67D (continuous)	Blood - changes in serum composition (e.g. TP, bilirubin, cholesterol) Nutritional and Gross Metabolic - changes in phosphorus	FAATDF Fundamental and Applied Toxicology. (Academic Press, Inc., 1 E. First St., Duluth, MN 55802) V.1-40, 1981-97. For publisher information, see TOSCF2 Volume(issue)/page/year: 10,616,1988
TDLo - Lowest published toxic dose	Intraperitoneal	Rodent - rat	6240 mg/kg/26W (intermittent)	Blood - pigmented or nucleated red blood cells Nutritional and Gross Metabolic - weight loss or decreased weight gain Nutritional and Gross Metabolic - changes in iron	TOLED5 Toxicology Letters. (Elsevier Science Pub. B.V., POB 211, 1000 AE Amsterdam, Netherlands) V.1- 1977- Volume(issue)/page/year: 111,235,2000
TDLo - Lowest published toxic dose	Oral	Rodent - mouse	80880 mg/kg/23W (continuous)	Liver - other changes Musculoskeletal - other changes Nutritional and Gross Metabolic - changes in metals, not otherwise specified	PHTOEH Pharmacology and Toxicology (Copenhagen). (Munksgaard International Pub., POB 2148, DK-1016 Copenhagen K, Denmark) V.60- 1987- Volume(issue)/page/year: 86,135,2000
TDLo - Lowest published toxic dose	Intraperitoneal	Rodent - rat	1920 mg/kg/8W (intermittent)	Blood - microcytosis with or without anemia	TOLED5 Toxicology Letters. (Elsevier Science Pub. B.V., POB 211, 1000 AE Amsterdam, Netherlands) V.1- 1977- Volume(issue)/page/year:

					111,235,2000
TDLo - Lowest published toxic dose	Intraperitoneal	Rodent - rat	960 mg/kg/4W (intermittent)	Blood - changes in erythrocyte (RBC) count	TOLED5 Toxicology Letters. (Elsevier Science Pub. B.V., POB 211, 1000 AE Amsterdam, Netherlands) V.1- 1977- Volume(issue)/page/year: 111,235,2000
TDLo - Lowest published toxic dose	Oral	Human - infant	68040 mg/kg/24W (intermittent)	Musculoskeletal - osteoporosis Nutritional and Gross Metabolic - weight loss or decreased weight gain Nutritional and Gross Metabolic - changes in phosphorus	APHRER Annals of Pharmacotherapy. (Harvey Whitney Books Co., POB 42696, Cincinnati, OH 45242) V. 26- 1992- Volume(issue)/page/year: 38,265,2004
TDLo - Lowest published toxic dose	Oral	Human - woman	73912.5 mg/kg/26W (intermittent)	Blood - changes in serum composition (e.g. TP, bilirubin, cholesterol) Musculoskeletal - osteoporosis Nutritional and Gross Metabolic - changes in phosphorus	APHRER Annals of Pharmacotherapy. (Harvey Whitney Books Co., POB 42696, Cincinnati, OH 45242) V. 26- 1992- Volume(issue)/page/year: 38,265,2004
TDLo - Lowest published toxic dose	Intramuscular	Rodent - mouse	600 ug/kg/12D (intermittent)	Behavioral - muscle weakness Behavioral - changes in psychophysiological tests	TXCYAC Toxicology. (Elsevier Scientific Pub. Ireland, Ltd., POB 85, Limerick, Ireland) V.1- 1973- Volume(issue)/page/year: 375,48,2016

As taken from RTECS, 2018.

Property Endpoint	Data	Reference	Data quality
Repeated Dose Effects	6-Week human, oral, LOAEL = 25 mg Al/kg-day (Reduction in primed cytotoxic T-cells, only dose tested)	ATSDR, 2008	Reported in a secondary source.

As taken from US EPA, 2014a.

5.3. Reproduction toxicity

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ The present study was conducted to assess in rats the effects of oral aluminum (Al) exposure on calcium (Ca), magnesium (Mg), manganese (Mn), copper (Cu), zinc (Zn), and iron (Fe) accumulation and urinary excretion. Three groups of plug-positive Sprague-Dawley (SD) rats were given by gavage 0, 200, and 400 mg/kg/d of Al(OH)₃ on gestational days 1-20. Three groups of nonpregnant female SD rats of the same age received Al(OH)₃ by gavage at the same doses for 20 consecutive days. At the end of

the treatment period, 24-hr urine samples were collected for analysis of Al and essential elements. Subsequently, all animals were sacrificed and samples of liver, bone, spleen, kidneys, and brain were removed for metal analyses. With some exceptions, the urinary amounts of Al, Mn, and Cu excreted by pregnant animals as well as the urinary levels of Al excreted by nonpregnant rats were higher in the Al-treated groups than in the respective control groups. Although higher Al levels were found in the liver of pregnant rats, the concentrations of Al in the brain of these animals were lower than those found in the same tissues of nonpregnant rats. With regard to the essential elements, tissue accumulation was most affected in pregnant than in nonpregnant animals. In pregnant rats, the hepatic and renal concentrations of Ca, Mg, Mn, Cu, Zn, and Fe, as well as the levels of Ca in bone, and the concentrations of Cu in brain were significantly higher in the Al-exposed groups than in the control group. According to the current results, oral Al exposure during pregnancy can produce significant changes in the tissue distribution of a number of essential elements. [Belles M et al; Biol Trace Elem Res. 79 (1): 67-81 (2001)].

“/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ ...When high doses ($\leq$ or $=$ 1094 mg/kg/day) of aluminum hydroxide were orally administered to pregnant rats and mice during embryogenesis, no maternal or developmental toxicity occurred. ...When the hydroxide (104 mg Al/kg) was given orally to pregnant rats simultaneously with ascorbate (85 mg Al/kg), no fetal developmental defects were produced. In contrast, when aluminum hydroxide and citric acid (133 mg Al/kg and 62 mg/kg, respectively) were simultaneously given orally to mice, fetal skeletal development defects resulted”. [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V2 373]**PEER REVIEWED**

“/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ The influence of lactate on the potential developmental toxicity of high doses of aluminum (57.5 mg/kg/day) was evaluated. Three groups of pregnant Swiss mice were given by gavage daily doses of Al(OH)₃ (166 mg/kg), aluminum lactate (627 mg/kg), or Al(OH)₃ (166 mg/kg) concurrent with lactic acid (570 mg/kg) on gestational days 6-15. An additional group of pregnant mice received lactic acid (570 mg/kg) during the same period. Cesarean sections were performed on gestation day 18, and live fetuses were sexed, weighed and examined for morphological defects. Maternal toxicity was observed in the groups treated with aluminum lactate, and Al(OH)₃ concurrent with lactic acid. The reproductive data did not show embryotoxic effects in any group, whereas fetal body weight was significantly reduced in the aluminum lactate group. In this group, morphological changes included cleft palate and an increased incidence of parietals with delayed ossification. Although not statistically significant, the incidence of skeletal variations was also increased in the group given Al(OH)₃ concurrent with lactic acid”. [Colomina MT et al; Res Commun Chem Pathol Pharmacol 77 (1): 95-106 (1992)]**PEER REVIEWED**

“/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ In a study designed to evaluate the influence of lactate on the developmental toxicity of aluminum mice were exposed to an estimated dose of 83 mg Al/kg/day as aluminum lactate, aluminum hydroxide, or aluminum hydroxide concurrent with lactic acid (570 mg/kg/day) by gavage and base diet on /gestation day/ (Gd) 6-15. Effects observed in the aluminum lactate-treated mice included reduced maternal food consumption and body weight gain, reduced fetal body weight, and 13-15% increased incidences of cleft palate, dorsal hyperkyphosis (i.e., excessive flexion of spine), and delayed parietal ossification. No exposure-related developmental effects occurred in the fetuses that were exposed to aluminum hydroxide alone or combined with lactic acid. Other studies by the same group of investigators also found no developmental changes in mice that were exposed to < 141 mg Al/kg/day as aluminum hydroxide, or 129 mg Al/kg/day as aluminum hydroxide alone or combined with ascorbic acid (85 mg/kg), by gavage and base diet on Gd 6-15. [DHHS/ATSDR; Toxicological

Profile for Aluminum (July 1999)". Available from, as of May 21, 2004: <http://www.atsdr.cdc.gov/toxprofiles/tp22.html> **PEER REVIEWED**

As taken from HSDB, 2013.

"Aluminium hydroxide did not produce either maternal or developmental toxicity when it was administered by gavage during embryogenesis to rats (Gómez et al., 1990) or mice (Domingo et al., 1989) (cited from WHO, 1997)."

"Chronic studies showed no histological changes in the testes or ovaries of male and female Wistar rats fed a diet containing unspecified levels of aluminium phosphide/ammonium carbamate for 24 months (Hackenberg, 1972), or in B6C3F1 mice that ingested 979 mg Al/kg/day as dietary aluminium potassium sulfate for 20 months (Oneda et al., 1994). The doses in the latter study do not include aluminum in the base diet. Neither mouse study assessed reproductive function (cited from ATSDR, 2008). Mating success (numbers of litters and offspring) was not affected in a three-generation study with Dobra Voda mice that were exposed to 49 mg Al/kg/day as aluminium chloride in drinking water and base diet over a period of 180–390 days (Ondreicka et al., 1966) (cited from ATSDR, 2008)."

"In one study, concentrations of aluminium ranging from 500 to 1,000 ug/g body weight were added to the diets of pregnant rats from day 6 to day 19 of gestation, when the fetuses were removed by Caesarean section. Aluminium in the diet did not affect embryo or foetal mortality rate, litter size, foetal body weight, or length (HSDB, 1999) (cited from Stuer-Lauridsen et al., 2000). 5-16 days' exposure of mice did not lead to material toxicity, embryo/foetal toxicity or teratogenicity (ECB, 1996) (cited from Stuer-Lauridsen et al., 2000). One teratogenicity study on mice (dosage: 0, 66.5, 133, 266 mg/kg, gavage), duration of test from gestation days 6-18 and exposure from days 6-15 showed no evidence of maternal toxicity, embryo/foetal toxicity or teratogenicity (Domingo et al., 1989) (cited from ECB, 2000; cited from ATSDR, 2008)."

As taken from European Commission, 2011.

Regarding compounds not soluble in water, no effects on prenatal development were seen following administration of aluminium hydroxide by gavage on gestational days 6-15 at the highest levels tested, i.e. ca. 100 mg Al/kg bw/day in mice and ca. 270 mg Al/kg bw/day in rats (NEG DECOS, 2011).

Type of Test	Route of Exposure	Species Observed	Dose Data	Sex/Duration	Toxic Effects	Reference
TDLo - Lowest published toxic dose	Oral	Human - woman	84 gm/kg	female 1-40 week(s) after conception	Reproductive - Effects on Newborn - physical	APAMEB Archives of Pediatrics and Adolescent Medicine. (American Medical Association, 515 N State St., Chicago, IL 60610) V.148- 1994- Volume(issue)/page/year: 152,511,1998

As taken from RTECS, 2018.

"Aluminum hydroxide is estimated to be of low hazard for reproductive effects based on professional judgment and comparison to analogous aluminum compounds."

Property Endpoint	/ Data	Reference	Data quality

Prenatal Development	Low potential for developmental neurotoxicity (Estimated)	Professional judgement	Estimated based on analogy to structurally similar compounds.
Prenatal Development	Mouse, oral, NOAEL = 268 mg/kg-day (highest dose tested)	Gomez et al., 1989	Abstract only
Prenatal Development	Mouse, oral, NOAEL = 300 mg/kg-day (only dose tested)	Colomina et al., 1994	Abstract only
Prenatal Development	Rat, oral, NOAEL = 768 mg/kg-day (highest dose tested)	Gomez et al., 1990	Abstract only
Prenatal Development	Rat, oral, NOAEL = 384 mg/kg-day (only dose tested)	Llobet et al., 1990	Abstract only

As taken from US EPA, 2014a.

“Published reproductive and developmental toxicity studies with aluminium compounds (aluminium sulphate, chloride, hydroxide and nitrate) were reviewed and evaluated by the EFSA AFC Panel in a previous opinion on the safety of aluminium from dietary intake (EFSA, 2008). The conclusions were as follows:

‘Several studies have been performed on the reproductive and developmental toxicity of aluminium compounds. Two studies in male mice using either intraperitoneal or subcutaneous administration of aluminium nitrate or chloride clearly demonstrated the ability of aluminium to produce testicular toxicity, decreased sperm quality and reduced fertility in male mice. However, no effects on male fertility were observed in one rat study where aluminium nitrate was administered by gavage. Unfortunately no data were reported on histological examination of testes, as it is well known that male rats maintain fertility even after severe testicular lesions. This also means that they may be less sensitive to this effect than humans. Reduced testicular weight and impaired semen quality have also been observed in male rabbits after daily administration by gavage of 34 mg/kg bw of aluminium chloride (corresponding to 6.4 mg aluminium/kg bw/day), the only dose applied, for 16 weeks. In male beagle dogs, dietary administration for 26 weeks of basic sodium aluminium phosphate (SALP), at a level corresponding to 75 mg aluminium/kg bw/day produced a decrease of testicular weight and degeneration of germinal epithelium. The NOAEL was 27 mg aluminium/kg bw/day. Only two studies are available on reproductive toxicity in females. No effects on female fertility was seen in rats after exposure for two weeks before mating and during gestation to aluminium nitrate by gavage or dissolved in drinking water. None of the aluminium compounds authorised as food additives in the EU have been tested for reproductive toxicity. However, the Panel noted that when SALP, acidic, was tested in dogs using a protocol similar to that used for SALP, basic, no testicular effects were reported after doses up to 88 mg aluminium/kg bw/day for 26 weeks. The potential of aluminium to produce embryotoxicity and teratogenicity has been demonstrated in rats given intraperitoneal injections of 0, 75, 100, or 200 mg aluminium chloride/kg bw/day on days 9 -13 or 14 -18 of pregnancy, corresponding to 15, 20, or 40 mg Al/kg bw/day. However, after oral administration, only one study has reported congenital malformations (cleft palate) in mice after gavage exposure to 627 mg aluminium lactate/kg bw/day. In this study 166 mg aluminium hydroxide/kg bw per day had no effect. In general, high doses of aluminium nitrate, chloride or lactate given by gavage were able to induce some signs of embryotoxicity in mice and rats, in particular, reduced fetal body weight or pup weight at birth and delayed ossification. The lowest LOAEL was reported for aluminium nitrate at a daily dose corresponding to 13 mg aluminium/kg bw/day in the rat. After dietary exposure of rats to aluminium chloride and lactate the lowest NOAEL was 100 mg aluminium/kg bw/day, respectively. Gavage administration of aluminium hydroxide at doses providing up to 264 mg aluminium/kg bw/day was without embryotoxic effects in rats’.”

“Gavage administration of aluminium hydroxide up to 264 mg Al/kg bw per day from GD 6 to GD 15 did not induce developmental effects in rats.”

As taken from EFSA, 2018

“Gavage administration of aluminium hydroxide at doses providing up to 103 and 264 mg Al/kg bw/day was without embryotoxic effects in mice and rats, respectively (EFSA, 2008).”

As taken from RIVM, 2020.

5.4. Mutagenicity

“Aluminium compounds have been evaluated as non-mutagenic by most standard methods of mutagenic assays.”

As taken from European Commission, 2011.

“...Metallic Al, its oxides, and common Al salts have not been shown to be either genotoxic or carcinogenic....” As taken from Willhite CC et al. 2014. Crit. Rev. Toxicol. 44 Suppl. 4, 1-80. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25233067>

Property Endpoint /	Data	Reference	Data quality
Gene Mutation in vitro	Negative in mouse lymphoma cells with and without metabolic activation	ECHA, 2013	Adequate, performed in accordance with OECD guidelines and GLP.
Chromosomal Aberrations in vivo	Negative for induction of micronuclei in polychromatic erythrocytes of bone marrow in Sprague-Dawley rats	ECHA, 2013	Adequate, performed in accordance with OECD guidelines and GLP.

As taken from US EPA, 2014a.

“Aluminium has been found in feline vaccine-associated sarcomas. In this study, we investigated the potential for aluminium to contribute directly to tumourigenesis. Our results indicated that an aluminium hydroxide adjuvant preparation was cytotoxic and mutagenic in human-Chinese hamster ovary (CHO) hybrid cells in vitro. Moreover, CHO cells deficient in DNA double strand break (DSB), but not single-strand break (SSB), repair, were particularly sensitive to aluminium exposure compared with repair proficient cells, suggesting that aluminium is associated with DSBs. In contrast to CHO cells, primary feline skin fibroblasts were resistant to the cytotoxic effects of aluminium compounds and exposure to an aluminium chloride salt promoted cell growth and cell cycle progression at concentrations much less than those measured in particular feline rabies vaccines. These findings suggest that aluminium exposure may contribute, theoretically, to both initiation and promotion of tumours in the absence of an inflammatory response.” As taken from AbdelMageed MA et al. 2018. Vet. Comp. Oncol. 16(1), E130-E143. PubMed, 2018 available at: <https://www.ncbi.nlm.nih.gov/pubmed/28960714>

“Published genotoxicity studies with aluminium compounds (aluminium sulphate, chloride, hydroxide and nitrate) were reviewed and evaluated by the EFSA AFC Panel in a previous opinion on the safety of aluminium from dietary intake (EFSA, 2008). The conclusions concerning genotoxicity were as follows: ‘Aluminium compounds were non-mutagenic in bacterial and mammalian cell systems, but some produced DNA damage and effects on chromosome integrity and segregation in vitro. Clastogenic effects were also observed in vivo when aluminium sulphate was administered at high doses by gavage or by the intraperitoneal route. Several indirect mechanisms have been proposed to explain the variety of genotoxic effects elicited by aluminium salts in experimental systems. Cross-linking of DNA with chromosomal proteins, interaction with

microtubule assembly and mitotic spindle functioning, induction of oxidative damage, damage of lysosomal membranes with liberation of DNAase, have been suggested to explain the induction of structural chromosomal aberrations, sister chromatid exchanges, chromosome loss and formation of oxidised bases in experimental systems. The Panel noted that these indirect mechanisms of genotoxicity, occurring at relatively high levels of exposure, are unlikely to be of relevance for humans exposed to aluminium via the diet'. The Panel noted that the conclusions on genotoxicity of aluminium in the Scientific Committee on Consumer Safety (SCCS 2014) and the European Commission and its Scientific Committee on Health, Environmental and Emerging Risks opinion (SCHEER, 2017) are in agreement with the EFSA (2008) evaluation."

As taken from EFSA, 2018

5.5. Cytotoxicity

"This study evaluated different dosage forms of aluminum adjuvant in generating allergic rhinitis animal models. Forty female BALB/c mice were assigned to four groups, including three dosage forms of aluminum adjuvant [powder, gel, and hydrosolvent of aluminum hydroxide, $\text{Al}(\text{OH})_3$] mixed with ovalbumin to simulate the symptoms of allergic rhinitis and one control group. Although the aluminum adjuvants were in different dosage forms, the content was 5 mg after conversion in all groups. The fourth group was given normal saline instead as a control. Mice of the powder group displayed typical symptoms of allergic rhinitis. We also found discrete eosinophils in the nasal mucosa of mice from the hydrosolvent group; however, no eosinophils were found in the gel group. These two groups both displayed cytotoxic symptoms and foreign body granuloma. Aluminum adjuvant used in producing animal models can induce foreign body granuloma and other untoward reactions, which are associated with the dosage level and form." As taken from Xi L et al. 2014. Genet. Mol. Res. 13(3), 5173-81. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25061742>

5.6. Carcinogenicity

A4: Not classifiable as a human carcinogen. /Aluminum metal and insoluble compound/ [American Conference of Governmental Industrial Hygienists TLVs and BEIs. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH, 2008, p. 11]**QC REVIEWED**

"/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Aluminium hydroxide was not carcinogenic after daily ip administration to mice for 4 months at dosages up to about 200 mg aluminium/kg/day". [Joint FAO/WHO Expert Committee on Food Additives; WHO Food Additives Ser 24: Aluminum (1989). Available from, as of June 4, 2004: <http://www.inchem.org/documents/jecfa/jecmono/v024je07.htm>]

"/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ /Aluminum hydrate was administered by intratracheal injection/... by 240 days /fibrosis of lungs corresponded/ to grade IV /fibrosis/, and from 270-365 days lesions were cellular and wholly collagenous (grade V). [Browning, E. Toxicity of Industrial Metals". 2nd ed. New York: Appleton-Century-Crofts, 1969., p. 8]**PEER REVIEWED**

"/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ The effects of aluminum on renal function and phosphate handling were studied using clearance techniques in chronically-intoxicated rats. Rats were given aluminum hydroxide (80 mg/kg bw, ip), 3 times/wk during 6 months. The phosphate tubular transport capacity was evaluated by determining the maximum tubular transport (TmRPI) and the fractional excretion of phosphate ($\text{FE\% Pi}$) during the infusion of phosphate solutions with increasing concentrations (0, 9, 18, 33 mM). Parathyroid gland function was studied using indirect methods: calcemia recovery after EDTA administration and the nephrogenic excretion of cAMP as indicative of renal PTH actions, by RIA. The systemic acid base status was determined

and food intake and rat growth were controlled in both groups. No changes were observed in the renal function. Pi reabsorption values per mL glomerular filtration rate (TRPi/GFR ug/mL) for different Pi plasmatic concentrations were distributed following a saturation curve compatible with a saturation kinetics. Aluminum increased TmR_{PI}/GFR in treated animals (T) 76+/-4 as compared with control animals (C) 57+/-7 ug/mL, without a statistical modification in the apparent affinity. The FE% Pi and FE% Na were significantly lower in treated animals than in control animals. There were neither systemic variations in the acid-base balance nor in the Ca and Pi concentrations in plasma. The calcemia recovery following a hypocalcemic stimulus and the nephrogenic excretion of cAMP (T: 44+/-4; C: 91+/-7 pmol/min) were diminished". [Mahieu S, Calvo ML; Toxicol Lett 94 (1): 47-56 (1998)]**PEER REVIEWED**

/OTHER TOXICITY INFORMATION/ The effect of intramuscular injection of 40 mg/2 mL aluminium hydroxide in the neck of pigs was examined in a number of ways. The investigation followed repeated slaughterhouse reports, according to which 64.8% of pigs from one particular farm were found at slaughter to have one or more nodules in the muscles of the neck (group slaughtered). The pigs had been injected with a vaccine containing 40 mg/2 mL dose of aluminium hydroxide as adjuvant. Research consisted of two phases: first, an epidemiological study was carried out, aimed at determining the risk factors for the granulomas. The results indicated that the vaccine was to be held responsible for the formation of granulomas. A clinical trial was then performed to further substantiate the initial hypothesis, by comparing pigs, which were aseptically inoculated twice with either the original vaccine or the adjuvant alone (groups vaccine and adjuvant) to pigs inoculated twice with apyrogenic bi-distilled water (group water) and to pigs inoculated once with the adjuvant and once with apyrogenic bi-distilled water (group adjuvant/water). Both studies agreed in their conclusions, which indicate that the high amount of aluminium hydroxide was the cause of the granulomas. [Valtulini S et al; Vaccine 23 (30): 3999-4004 (2005)].

As taken from HSDB, 2013.

"No studies were identified regarding cancer effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminium. An increase in cancer was not observed in male and female Wistar rats exposed via whole-body inhalation to atmospheres containing 2.18–2.45 mg Al/m³ as alumina fibers (≈96% aluminium oxide) for 86 weeks."

As taken from European Commission, 2011.

"....Neither is there clear evidence to show use of Al-containing underarm antiperspirants or cosmetics increases the risk of AD or breast cancer. Metallic Al, its oxides, and common Al salts have not been shown to be either genotoxic or carcinogenic....." As taken from Willhite CC et al. 2014. Crit. Rev. Toxicol. 44(Suppl. 4), 1-80. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25233067>

"Aluminum hydroxide is estimated to be of low hazard for carcinogenicity based on professional judgment and comparison to analogous aluminum compounds."

As taken from US EPA, 2014a.

"Aluminium has been found in feline vaccine-associated sarcomas. In this study, we investigated the potential for aluminium to contribute directly to tumourigenesis. Our results indicated that an aluminium hydroxide adjuvant preparation was cytotoxic and mutagenic in human-Chinese hamster ovary (CHO) hybrid cells in vitro. Moreover, CHO cells deficient in DNA double strand break (DSB), but not single-strand break (SSB), repair, were particularly sensitive to aluminium exposure compared with repair proficient cells, suggesting that aluminium is associated with DSBs. In contrast to CHO cells, primary feline skin fibroblasts were resistant to the cytotoxic effects of aluminium compounds and exposure to an aluminium chloride salt promoted cell growth and cell cycle progression at concentrations much less than those measured in particular feline rabies vaccines. These findings suggest that aluminium exposure may contribute, theoretically, to both

initiation and promotion of tumours in the absence of an inflammatory response.” As taken from AbdelMageed MA et al. 2018. Vet. Comp. Oncol. 16(1), E130-E143. PubMed, 2018 available at: <https://www.ncbi.nlm.nih.gov/pubmed/28960714>

5.7. Irritation/immunotoxicity

Skin, Eye and Respiratory Irritations:

“Irritation of the eyes has been noted in patients who have been exposed /to aluminum alkyls/. /Aluminum alkyls/ ” [Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 73]**PEER REVIEWED**

As taken from HSDB, 2013.

“Skin: Not a skin irritant (ECB, 1996) (cited from Stuer-Lauridsen et al., 2000). Aluminium hydroxide (powder) was not irritating on rabbit skin (Martinswerk GmbH, 1989) (cited from ECB, 2000).

Eye: One study indicates that aluminium hydroxide is not an eye irritant (ECB, 1996) (cited from Stuer-Lauridsen et al., 2000) (Martinswerk GmbH, 1989) (cited from ECB, 2000).

Sensitisation: No data available. However, aluminium hydroxide and other aluminium compounds have a wide dispersive use as additive in cosmetic products (e.g. as antiperspirants). Thus, skin sensitising properties can safely be excluded.”

As taken from European Commission, 2011.

“Low potential for skin sensitization (estimated based on professional judgment and comparison to analogous aluminum compounds).”

Property / Endpoint	Data	Reference	Data quality
Eye Irritation	Not irritating, rabbits	ECHA, 2013	Reported in a secondary source; conducted in accordance with OECD guidelines and GLP.
Skin Sensitization	Not sensitizing to guinea pigs in an in vivo maximization test	ECHA, 2013	Reported in a secondary source; conducted in accordance with OECD guidelines and GLP.

As taken from US EPA, 2014a.

The current influenza pandemic calls for a safe and effective vaccine. We assessed the safety and immunogenicity of eight formulations of 2009 pandemic influenza A H1N1 vaccine produced by ten Chinese manufacturers. METHODS: In this multicentre, double-blind, randomised trial, 12 691 people aged 3 years or older were recruited in ten centres in China. In each centre, participants were stratified by age and randomly assigned by a random number table to receive one of several vaccine formulations or placebo. The study assessed eight formulations: split-virion formulation containing 7.5 microg, 15 microg, or 30 microg haemagglutinin per dose, with or without aluminium hydroxide adjuvant, and whole-virion formulation containing 5 microg or 10 microg haemagglutinin per dose, with adjuvant. All formulations were produced from the reassortant strain X-179A (A/California/07/2009-A/PR/8/34). We analysed the safety (adverse events), immunogenicity (geometric mean titre [GMT] of haemagglutination inhibition antibody), and seroprotection (GMT $\geq$ 1:40) of the formulations. Analysis was by per protocol. Two sites registered their trial with ClinicalTrials.gov, numbers NCT00956111 and NCT00975572. The other eight studies were registered with the State Food and Drug Administration of China. FINDINGS: 12 691 participants received the first dose on day 0, and 12 348 participants received the second dose on day 21. The seroprotection rate 21 days after the first dose of vaccine ranged from 69.5% (95% CI 65.9-72.8)

for the 7.5 microg adjuvant split-virion formulation to 92.8% (91.9-93.6) for the 30 microg non-adjuvant split-virion formulation. The seroprotection rate was 86.5% (796 of 920; 84.1-88.7) in recipients of one dose of the 7.5 microg non-adjuvant split-virion vaccine compared with 9.8% (140 of 1432; 8.3-11.4) in recipients of placebo ($p < 0.0001$). One dose of the 7.5 microg non-adjuvant split-virion vaccine induced seroprotection in 178 of 232 children (aged 3 years to < 12 years; 76.7%, 70.7-82.0), 211 of 218 adolescents (12 years to < 18 years; 96.8%, 93.5-98.7), 289 of 323 adults (18-60 years; 89.5%, 85.6-92.6), and 118 of 147 adults older than 60 years (80.3%, 72.9-86.4), meeting the European Union's licensure criteria for seroprotection in all age-groups. In children, a second dose of the 7.5 microg formulation increased the seroprotection rate to 97.7% (215 of 220, 94.8-99.3). Adverse reactions were mostly mild or moderate, and self-limited. Severe adverse effects occurred in 69 (0.6%, 0.5-0.8) recipients of vaccine compared with one recipient (0.1%, 0-0.2) of placebo. The most common severe adverse reaction was fever, which occurred in 25 (0.22%; 0.14-0.33) recipients of vaccine after the first dose and four (0.04%; 0.01-0.09) recipients of vaccine after the second dose compared with no recipients of placebo after either dose. INTERPRETATION: One dose of non-adjuvant split-virion vaccine containing 7.5 microg haemagglutinin could be promoted as the formulation of choice against 2009 pandemic influenza A H1N1 for people aged 12 years or older. In children (aged < 12 years), two 7.5 mug doses might be needed. FUNDING: Sinovac Biotech, Hualan Biological Bacterin, China National Biotech Group, Beijing Tiantan Biological Products, Changchun Institute of Biological Products, Changchun Changsheng Life Sciences, Jiangsu Yanshen Biological Technology Stock, Zhejiang Tianyuan Bio-Pharmaceutical, Lanzhou Institute of Biological Products, Shanghai Institute of Biological Products, and Dalian Aleph Biomedical. Liang XF; Wang HQ; Wang JZ; Fang HH; Wu J; Zhu FC; Li RC; Xia SL; Zhao YL; Li FJ; Yan SH; Yin WD; An K; Feng DJ; Cui XL; Qi FC; Ju CJ; Zhang YH; Guo ZJ; Chen PY; Chen Z; Yan KM; Wang Y
Lancet. 2010, Jan 2; 375(9708):56-66. [Lancet] [PubMed]

Several case reports involving injections of vaccines in an aluminium-based vehicle showed local skin reactions/hypersensitivity to aluminium and aluminium hydroxide (insoluble). Although aluminium injected as hydroxide in an absorbed vaccine and antigen extracts can cause granulomas, the small number of reports of aluminium allergy from the aluminium industry indicated that epicutaneous application of aluminium is not strongly sensitising. Solutions of 10 % of aluminium chloride (soluble) and aluminium nitrate (soluble) induced skin damage in mice, rabbits and pigs, while aluminium sulphate (soluble), chlorohydrate (soluble), and hydroxide (insoluble) did not (NEG DECOS, 2011).

"Twenty patients referred for suspected allergic contact dermatitis to the Department of Occupational and Environmental Dermatology, Skane University Hospital, Malmo served as controls. They were patch tested with.....aluminium hydroxide at 6.5%...in pet.....aluminium hydroxide.....gave positive reactions in 2 of 21 patients..." As taken from Siemund I et al. 2012. Contact Dermatitis 67(3), 162-70. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22594839>

Immunotoxicity:

"Aluminum hydroxide (alum) is the most widely used adjuvant in human vaccines. Nevertheless, it is virtually unknown whether alum acts on B cells. In the present study, we explored the direct effect of alum on Ig expression by murine B cells in vitro. LPS-activated mouse spleen B cells were cultured with alum, and the level of isotype-specific Ig secretion, IgG1 secreting cell numbers, and Ig germ-line transcripts (GLT) were measured using ELISA, ELISPOT, and RT-PCR, respectively. Alum consistently enhanced total IgG1 production, numbers of IgG1 secreting cells, and GLTy1 expression. These results demonstrate that alum can directly cause IgG1 isotype switching leading

to IgG1 production.” As taken from Jin BR et al. 2013. Immune Netw. 13(1), 10-5. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/23559895>

“Aluminum-containing adjuvants are widely used in preventive vaccines against infectious diseases and in preparations for allergy immunotherapy. The mechanism by which they enhance the immune response remains poorly understood. Aluminum adjuvants selectively stimulate a Th2 immune response upon injection of mice and a mixed response in human beings. They support activation of CD8 T cells, but these cells do not undergo terminal differentiation to cytotoxic T cells. Adsorption of antigens to aluminum adjuvants enhances the immune response by facilitating phagocytosis and slowing the diffusion of antigens from the injection site which allows time for inflammatory cells to accumulate. The adsorptive strength is important as high affinity interactions interfere with the immune response. Adsorption can also affect the physical and chemical stability of antigens. Aluminum adjuvants activate dendritic cells via direct and indirect mechanisms. Phagocytosis of aluminum adjuvants followed by disruption of the phagolysosome activates NLRP3-inflammasomes resulting in the release of active IL-1 β and IL-18. Aluminum adjuvants also activate dendritic cells by binding to membrane lipid rafts. Injection of aluminum-adjuvanted vaccines causes the release of uric acid, DNA, and ATP from damaged cells which in turn activate dendritic cells. The use of aluminum adjuvant is limited by weak stimulation of cell-mediated immunity. This can be enhanced by addition of other immunomodulatory molecules. Adsorption of these molecules is determined by the same mechanisms that control adsorption of antigens and can affect the efficacy of such combination adjuvants. The widespread use of aluminum adjuvants can be attributed in part to the excellent safety record based on a 70-year history of use. They cause local inflammation at the injection site, but also reduce the severity of systemic and local reactions by binding biologically active molecules in vaccines.” As taken from Hogenesch H. 2013. Front. Immunol. 3, 406. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/23335921>

“Sub-cutaneous immunotherapy is an effective treatment for allergy. It works by helping to modify or re-balance an individual's immune response to allergens and its efficacy is greatly improved by the use of adjuvants, most commonly, aluminium hydroxide. Aluminium salts have been used in allergy therapy for many decades and are assumed to be safe with few established side-effects. This assumption belies their potency as adjuvants and their potential for biological reactivity both at injection sites and elsewhere in the body. There are very few data purporting to the safety of aluminium adjuvants in allergy immunotherapy and particularly so in relation to longer term health effects. There are, if only few, published reports of adverse events following allergy immunotherapy and aluminium adjuvants are the prime suspects in the majority of such incidents. Aluminium adjuvants are clearly capable of initiating unwanted side effects in recipients of immunotherapy and while there is as yet no evidence that such are commonplace it is complacent to consider aluminium salts as harmless constituents of allergy therapies. Future research should establish the safety of the use of aluminium adjuvants in sub-cutaneous allergy immunotherapy.” As taken from Exley C. 2014. Allergy Asthma Clin. Immunol. 10(1), 4. PubMed, 2014 available at <http://www.ncbi.nlm.nih.gov/pubmed/24444186>

“The design of more powerful adjuvants is a tool of crucial interest to ameliorate vaccination strategies to reduce injections and/or dose of antigen, induce local immunity and obtain better protection. Effective anti-infectious vaccines should elicit protective TH1 responses, cytotoxic CD8+ cells and antibody-forming cells. However, cytokine microenvironment is a key point also in targeted therapeutic vaccinations, such as allergen-specific immunotherapy, where the interference with an already-existing but inappropriate immunity is required. In this case, safe, appropriately conditioning and potentially orally available adjuvants together with delivery to appropriate subsets of dendritic cells would be highly appreciated to properly boost innate immune cells. In fact, aluminium hydroxide, although safe, has been classically associated with the induction of a TH2 response to co-formulated antigens. Thus, detoxified lipopolysaccharide (MPL-A), CpG oligonucleotides, imidazoquinolines and adenine derivatives acting via innate sensors may represent improvements in therapeutic vaccinations for allergy as able to interfere with pathogenic

TH2 cells with eventual induction of TH1 differentiation.” As taken from Fili L et al. 2014. Immunol. Lett. 161(2), 207-10. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/24361819>

“Allergen-specific immunotherapy (SIT) is a clinically effective therapy for immunoglobulin (Ig)E-mediated allergic diseases. To reduce the risk of IgE-mediated side effects, chemically modified allergoids have been introduced. Furthermore, adsorbance of allergens to aluminium hydroxide (alum) is widely used to enhance the immune response. The mechanisms behind the adjuvant effect of alum are still not completely understood. In the present study we analysed the effects of alum-adsorbed allergens and allergoids on their immunogenicity in vitro and in vivo and their ability to activate basophils of allergic donors. Human monocyte derived dendritic cells (DC) were incubated with native *Phleum pratense* or *Betula verrucosa* allergen extract or formaldehyde- or glutaraldehyde-modified allergoids, adsorbed or unadsorbed to alum. After maturation, DC were co-cultivated with autologous CD4(+) T cells. Allergenicity was tested by leukotriene and histamine release of human basophils. Finally, in-vivo immunogenicity was analysed by IgG production of immunized mice. T cell proliferation as well as interleukin (IL)-4, IL-13, IL-10 and interferon (IFN)- γ production were strongly decreased using glutaraldehyde-modified allergoids, but did not differ between alum-adsorbed allergens or allergoids and the corresponding unadsorbed preparations. Glutaraldehyde modification also led to a decreased leukotriene and histamine release compared to native allergens, being further decreased by adsorption to alum. In vivo, immunogenicity was reduced for allergoids which could be partly restored by adsorption to alum. Our results suggest that adsorption of native allergens or modified allergoids to alum had no consistent adjuvant effect but led to a reduced allergenicity in vitro, while we observed an adjuvant effect regarding IgG production in vivo.” As taken from Heydenreich B et al. 2014. Clin. Exp. Immunol. 176(3), 310-9. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/24528247>

“Aluminum hydroxide is used as a vaccine adjuvant in various human vaccines. Unfortunately, despite its favorable safety profile, aluminum hydroxide can only weakly or moderately potentiate antigen-specific antibody responses. When dispersed in an aqueous solution, aluminum hydroxide forms particulates of 1-20 μ m. There is increasing evidence that nanoparticles around or less than 200nm as vaccine or antigen carriers have a more potent adjuvant activity than large microparticles. In the present study, we synthesized aluminum hydroxide nanoparticles of 112nm. Using ovalbumin and *Bacillus anthracis* protective antigen protein as model antigens, we showed that protein antigens adsorbed on the aluminum hydroxide nanoparticles induced a stronger antigen-specific antibody response than the same protein antigens adsorbed on the traditional aluminum hydroxide microparticles of around 9.3 μ m. The potent adjuvant activity of the aluminum hydroxide nanoparticles was likely related to their ability to more effectively facilitate the uptake of the antigens adsorbed on them by antigen-presenting cells. Finally, the local inflammation induced by aluminum hydroxide nanoparticles in the injection sites was milder than that induced by microparticles. Simply reducing the particle size of the traditional aluminum hydroxide adjuvant into nanometers represents a novel and effective approach to improve its adjuvanticity.” As taken from Li X et al. 2014. J. Control. Release 173, 148-57. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/24188959>

“OBJECTIVE: To investigate the influence of aluminum hydroxide adjuvant on a murine model of allergic rhinitis (AR) and to confirm an appropriate method of establishing a mouse model of AR. METHOD: Establishing two types of BALB/c mice models of AR, one was identified as Local group which was characterized through intranasal sensitization and challenge using ovalbumin (OVA), and the other Systemic group which was made by intraperitoneal sensitization with OVA plus aluminum hydroxide and intranasal challenge through OVA. Then the numbers of sneezing and nasal rubbing were counted after the last challenge and the eosinophils in the nasal mucosa of mice models were observed and counted through Luna stain. Furthermore, morphological hyperplasia was examined in intraepithelial goblet cells and submucosal glands with HE stain. In addition, interleukin (IL) -4, IL-5, OVA specific IgE (sIgE) and interferon (IFN)-gamma in nasal lavage fluid (NLF) and serum of mice were examined using enzyme linked immunosorbent assay (ELISA). RESULT: The counts of sneezing and nasal rubbing in local group were more than those in

systemic group and eosinophilia in the nasal mucosa of former group was greater than that in the latter one. Morphological hyperplasia was stronger in intraepithelial goblet cells and submucosal glands in local group compared with that in systemic group. Furthermore, the contents of IL-4, IL-5 and IgE increased in the NLF and serum of mice of local group compared to those of systemic one. However, the production of IFN-gamma of mice in local group decreased when compared with that in Systemic group. CONCLUSION: OVA plus aluminum hydroxide adjuvant may promote Th1 type immune response as well as Th2 response. OVA intranasal sensitization and challenge locally is an appropriate way in the establishment of AR mice models.” As taken from Lin L et al. 2014. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 28(11), 780-4. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25219201>

“This study evaluated different dosage forms of aluminum adjuvant in generating allergic rhinitis animal models. Forty female BALB/c mice were assigned to four groups, including three dosage forms of aluminum adjuvant [powder, gel, and hydrosolvent of aluminum hydroxide, Al(OH)₃] mixed with ovalbumin to simulate the symptoms of allergic rhinitis and one control group. Although the aluminum adjuvants were in different dosage forms, the content was 5 mg after conversion in all groups. The fourth group was given normal saline instead as a control. Mice of the powder group displayed typical symptoms of allergic rhinitis. We also found discrete eosinophils in the nasal mucosa of mice from the hydrosolvent group; however, no eosinophils were found in the gel group. These two groups both displayed cytotoxic symptoms and foreign body granuloma. Aluminum adjuvant used in producing animal models can induce foreign body granuloma and other untoward reactions, which are associated with the dosage level and form.” As taken from Xi L et al. 2014. Genet. Mol. Res. 13(3), 5173-81. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25061742>

“.....recent controlled trials found that the immunologic response to certain vaccines with Al adjuvants was no greater, and in some cases less than, that after identical vaccination without Al adjuvants....” As taken from Willhite CC et al. 2014. Crit. Rev. Toxicol. 44(Suppl. 4), 1-80. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25233067>

“Aluminum hydroxide is estimated to have potential for immunotoxicity based on professional judgment and comparison to analogous aluminum compounds.”

Property / Endpoint	Data	Reference	Data quality
Repeated Dose Effects	6-Week human, oral, LOAEL = 25 mg Al/kg-day (Reduction in primed cytotoxic T-cells, only dose tested)	ATSDR, 2008	Reported in a secondary source.

As taken from US EPA, 2014a.

“In the past few decades, hundreds of materials have been tried as adjuvant; however, only aluminum-based adjuvants continue to be used widely in the world. Aluminum hydroxide, aluminum phosphate and alum constitute the main forms of aluminum used as adjuvants. Among these, aluminum hydroxide is the most commonly used chemical as adjuvant. In spite of its wide spread use, surprisingly, the mechanism of how aluminum hydroxide-based adjuvants exert their beneficial effects is still not fully understood. Current explanations for the mode of action of aluminum hydroxide-based adjuvants include, among others, the repository effect, pro-phagocytic effect, and activation of the pro-inflammatory NLRP3 pathway. These collectively galvanize innate as well as acquired immune responses and activate the complement system. Factors that have a profound influence on responses evoked by aluminum hydroxide-based adjuvant applications include adsorption rate, strength of the adsorption, size and uniformity of aluminum hydroxide particles, dosage of adjuvant, and the nature of antigens. Although vaccines containing aluminum hydroxide-based adjuvants are beneficial, sometimes they cause adverse reactions. Further, these vaccines

cannot be stored frozen. Until recently, aluminum hydroxide-based adjuvants were known to preferentially prime Th2-type immune responses. However, results of more recent studies show that depending on the vaccination route, aluminum hydroxide-based adjuvants can enhance both Th1 as well as Th2 cellular responses. Advances in systems biology have opened up new avenues for studying mechanisms of aluminum hydroxide-based adjuvants. These will assist in scaling new frontiers in aluminum hydroxide-based adjuvant research that include improvement of formulations, use of nanoparticles of aluminum hydroxide and development of composite adjuvants.” As taken from He P et al. 2015. Hum. Vaccin. Immunother. 11, 477-88. PubMed, 2016 available at <http://www.ncbi.nlm.nih.gov/pubmed/25692535>

“Of a total of 76,000 children 645 (0.85%) developed persisting itching nodules around the injection site (subcutaneous or intramuscular) after vaccination with aluminium hydroxide-adsorbed vaccines. The symptoms appeared 2 weeks to 5 years (median 3 months) after the vaccination and were prolonged (months, years). Of the children who developed itchy nodules 77% were patch test positive for aluminium (11) which according to the authors was an unexpectedly high incidence (Bergfors E et al. 2003).”

As taken from Swedish Criteria Group for Occupational Standards, 2017

“Intradermal (i.d.) application of vaccine is promising way how to induce specific immune response against particular pathogens. Adjuvants, substances added into vaccination dose with the aim to increase immunogenicity, play important role in activation of dendritic cells with subsequent activation of lymphocytes. They can, however, induce unwanted local reactions. The aim of the study was to determine the effect of i.d. administration of model antigen keyhole limped hemocyanine alone or with different adjuvants-aluminium hydroxide and oil-based adjuvants-on local histopathological reaction as well as dendritic cell activation at the site of administration and local cytokine and chemokine response. This was assessed at 4 and 24 hours after application. Selection of the adjuvants was based on the fact, that they differently enhance antibody or cell-mediated immunity. The results showed activation of dendritic cells and both Th1 and Th2 response stimulated by oil-based adjuvants. It was associated with higher expression of set of genes, incl. chemokine receptor CCR7 or Th1-associated chemokine CXCL10 and cytokine IFN γ . Application of the antigen with aluminium hydroxide induced higher expression of Th2-associated IL4 or IL13. On the other hand, both complete and incomplete Freund’s adjuvants provoked strong local reaction associated with influx of neutrophils. This was accompanied with high expression of proinflammatory IL1 or neutrophil chemoattractant CXCL8. Surprisingly, similarly strong local reaction was detected also after application of aluminium hydroxide-based adjuvant. The best balanced local reaction with sufficient activation of immune cells was detected after application of oil-based adjuvants Montanide and Emulsigen.” As taken from Oreskovic Z et al. 2019. PLoS One 14(2), e0211896. PubMed, 2019 available at <https://www.ncbi.nlm.nih.gov/pubmed/30742635>

“Reports detailing the acute formation of aluminum granulomas, which can cause persistent, intensely pruritic nodules secondary to the administration of aluminum-containing vaccines, are infrequently described in medical literature. To our knowledge, this is the first report describing the development of an aluminum granuloma causing a persistent, pruritic nodule at the injection site following the administration of the DTaP-IPV vaccine. We present the case of a 6-year-old girl who developed a severely pruritic subcutaneous nodule on her anterior right thigh at the injection site three weeks after the administration of the aluminum-containing DTaP-IPV (Kinrix) vaccine. The nodule was eventually excised 14 months after its initial appearance, after which her symptoms resolved. Histologic inspection demonstrated a dense, deep dermal and subcutaneous nodular mixed infiltrate of lymphocytes, histiocytes, and eosinophils, with germinal center formation. The bluish, amphophilic granular cytoplasm found in most of the histiocytes is a characteristic feature of “aluminum granulomas.” This adverse reaction should be considered in any patient presenting with similar findings in the weeks following a DTaP-IPV vaccination or other aluminum-containing vaccines. Furthermore, the self-limiting tendency of these nodules should not preclude affected patients from any future vaccinations, though vaccines without aluminum should be preferentially

selected when possible.” As taken from Haag CK et al. 2019. *Pediatr. Dermatol.* 36(1), e17-e19. PubMed, 2019 available at <https://www.ncbi.nlm.nih.gov/pubmed/30488642>.

“Skin damage has been observed in mice, rabbits, and pigs exposed to aluminium chloride or aluminium nitrate, but not following exposure to aluminium sulfate, aluminium hydroxide, aluminium acetate, or aluminium chlorohydrate (Lansdown, 1973).”

“Local dermal effects have been observed when aluminium compounds (10% w/v chloride, nitrate) have been applied to the skin of mice, rabbits and pigs over five-day periods (once per day) including epidermal damage, hyperkeratosis, acanthosis and microabscesses (Lansdown, 1973). In this study, these effects were not seen with aluminium acetate, hydroxide or chlorohydrate compounds.”

As taken from SCCS, 2022

“The objectives were to characterize the kinetics of acute phase proteins (APPs) α -2 macroglobulin (A2M), α -1 acid glycoprotein (A1AGP), and fibrinogen (FIB), and injection site macroscopic and microscopic findings following intramuscular administration of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (TDaP; Adacel); adjuvants (aluminum phosphate [AlPO₄]; aluminum hydroxide, Al(OH)₃; CpG/Al(OH)₃; or Quillaja saponaria 21 [QS-21]); or saline to female Wistar Han rats. Intravascular lipopolysaccharide (LPS) was a positive control. Injection sites and lymph nodes were evaluated microscopically, using hematoxylin and eosin (H&E) stained sections, 48 hours postdose (HPD) and compared with APP concentrations; A2M and A1AGP were measured using Meso Scale Discovery analyzer. Fibrinogen was measured on STA Compact analyzer. In a time-course study, APP peaked at 24 or 48 HPD. In a subsequent study at 48 HPD, injection site microscopic changes included inflammation and muscle degeneration/necrosis, which was different in severity/nature between groups. The APPs were not increased in rats administered saline, Al(OH)₃, or AlPO₄. Fibrinogen and A1AGP increased in rats administered CpG/Al(OH)₃, QS-21, or TDaP; and A2M increased in rats administered QS-21. Fibrinogen, A2M, and A1AGP increased after LPS administration. Acute phase proteins can be used to monitor inflammatory responses to adjuvants; however, some adjuvants may induce inflammation without higher APPs.” As taken from Reagan WJ et al. 2020. *Toxicol. Pathol.* 48(7), 845-856. PubMed, 2021 available at <https://pubmed.ncbi.nlm.nih.gov/33043819/>

“Aluminium salts have been used in vaccines for decades. However, the mechanisms underlying their adjuvant effect are still unclear. Neutrophils, the first immune cells at the injection site, can release cellular DNA together with granular material, so-called neutrophil extracellular traps (NETs). In mice, NETs apparently play a role in aluminium hydroxide (alum)-adjuvant immune response to vaccines. Although no experimental data exist, this effect is assumed to be operative also in humans. As a first step to verify this knowledge in humans, we demonstrate that the injection of alum particles into human skin biopsies *ex vivo* leads to similar tissue infiltration of neutrophils and NET-formation. Moreover, we characterized the mechanism leading to alum-induced NET-release in human neutrophils as rapid, NADPH oxidase-independent process involving charge, phagocytosis, phagolysosomal rupture, Ca²⁺ -flux, hyperpolarization of the mitochondrial membrane, and mitochondrial ROS. Extracellular flow and inhibition experiments suggested that no additional energy from oxidative phosphorylation or glycolysis is required for NET-release. This study suggests a so far unappreciated role for neutrophils in the initial phase of immune responses to alum-containing vaccines in humans and provides novel insights into bioenergetic requirements of NET-formation.” As taken from Reithofer M et al. 2020. *FASEB J.* 34(10), 14024-14041. PubMed, 2021 available at <https://pubmed.ncbi.nlm.nih.gov/32860638/>

“Purpose: Aluminum is the third most abundant metal in the earth's crust and is widely used in industry. Chronic contact with aluminum results in a reduction in the activity of electron transport chain complexes, leading to excessive production of reactive oxygen species (ROS) and oxidative stress. This study aimed to evaluate the effects of short-term exposure of aluminum hydroxide on oxidative stress and pulmonary inflammatory response. Materials and methods: Male BALB/c mice

were divided into three groups: control group (CG); phosphate buffered saline group (PBSG) and aluminum hydroxide group (AHG). CG was exposed to ambient air, while PBSG and AHG were exposed to PBS or aluminum hydroxide solutions via nebulization, three times per day for five consecutive days. Twenty-four hours after the last exposure, all animals were euthanized for subsequent analysis. Results: Exposure to aluminum hydroxide in the blood resulted in lower platelet levels, higher neutrophils, and lower monocytes compared to CG and PBSG. Aluminum hydroxide promoted the recruitment of inflammatory cells to the lung. Macrophage, neutrophil and lymphocyte counts were higher in AHG compared to CG and PBSG. Protein oxidation and superoxide dismutase activity were higher, while catalase activity and reduced and oxidized glutathione ratio in AHG were lower compared to CG and PBSG. Furthermore, there was an increase in the inflammatory markers CCL2 and IFN- γ in AHG compared to CG and PBSG. Conclusion: In conclusion, short-term nebulization with aluminum hydroxide induces the influx of inflammatory cells and oxidative stress in adult BALB/c mice." As taken from Kozima ET et al. 2020. Exp. Lung Res. 46(3-4), 64-74. PubMed, 2021 available at <https://pubmed.ncbi.nlm.nih.gov/32067522/>

5.8. All other relevant types of toxicity

“/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ Rats fed 6-10 mg aluminum (as aluminum hydroxide) daily showed significant impairment of growth at 3-4 wk. Rachitic changes occurred in bones; addition of phosphate in diet prevented these changes”. [Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978., p. 108]**PEER REVIEWED**

/HUMAN EXPOSURE STUDIES/ ... Eighteen healthy volunteers (mean age 42, 28-57 yr) were divided into a test group (9 females, 4 males) and a referent group (3 females, 2 males). Over 6 weeks, the test subjects ingested 10 mL of antacid (aluminum hydroxide, 59 mg Al/mL) three times daily. Aluminum was analyzed in urine before and during the exposure period (ICP-MS). Blood samples were used for analysis of lymphocyte subpopulations, mitogen-induced lymphocyte proliferation and in vitro production and circulating plasma concentrations of immunoglobulin (Ig) A, IgG, IgM, interleukin (IL) -2 and IL-4. Urinary Al concentration in the test subjects was approximately 10- to 20-fold higher than in the referent group during exposure. This indicates that ingestion of an Al-containing antacid is associated with an Al absorption far above that originating from food and drinking water. In both referents and test subjects the lymphocyte subpopulations, lymphocyte proliferation and the in vitro Ig and IL production showed similar, time-dependent changes before as well as during the exposure period. No major differences were seen between the referent and test groups regarding the immune parameters, except for a slightly smaller CD8+CD45R0+ population (primed cytotoxic T-cells), in the exposed individuals as compared to the referents. [Graske A et al; Biometals 13 (2): 123-133 (2000)]

/CASE REPORTS/ Macrophagic myofasciitis (MMF) is an emerging condition of unknown cause, detected in patients with diffuse arthromyalgias and fatigue, and characterized by muscle infiltration by granular periodic acid-Schiff's reagent-positive macrophages and lymphocytes. Intracytoplasmic inclusions have been observed in macrophages of some patients. To assess their significance, electron microscopy was performed in 40 consecutive cases and chemical analysis was done by microanalysis and atomic absorption spectrometry. Inclusions were constantly detected and corresponded to aluminium hydroxide, an immunostimulatory compound frequently used as a vaccine adjuvant. A lymphocytic component was constantly observed in MMF lesions. Serological tests were compatible with exposure to aluminium hydroxide-containing vaccines. History analysis revealed that 50 out of 50 patients had received vaccines against hepatitis B virus (86%), hepatitis A virus (19%) or tetanus toxoid (58%), 3-96 months (median 36 months) before biopsy. Diffuse myalgias were more frequent in patients with than without an MMF lesion at deltoid muscle biopsy ($P < 0.0001$). Myalgia onset was subsequent to the vaccination (median 11 months) in 94% of patients. MMF lesion was experimentally reproduced in rats. /The authors/ conclude that the MMF

lesion is secondary to intramuscular injection of aluminium hydroxide-containing vaccines, shows both long-term persistence of aluminium hydroxide and an ongoing local immune reaction, and is detected in patients with systemic symptoms which appeared subsequently to vaccination. [Gherardi RK et al; Brain 124 (Pt 9): 1821-31 (2001)]

/OTHER TOXICITY INFORMATION/ Macrophagic myofasciitis is a condition first reported in 1998, which cause remained obscure until 2001. Over 200 definite cases have been identified in France, and isolated cases have been recorded in other countries. The condition manifests by diffuse myalgias and chronic fatigue, forming a syndrome that meets both Center for Disease Control and Oxford criteria for the so-called chronic fatigue syndrome in about half of patients. One third of patients develop an autoimmune disease, such as multiple sclerosis. Even in the absence of overt autoimmune disease they commonly show subtle signs of chronic immune stimulation, and most of them are of the HLAB*01 group, a phenotype at risk to develop polymyalgia rheumatica and rheumatoid arthritis. Macrophagic myofasciitis is characterized by a stereotyped and immunologically active lesion at deltoid muscle biopsy. Electron microscopy, microanalytical studies, experimental procedures, and an epidemiological study recently demonstrated that the lesion is due to persistence for years at site of injection of an aluminum adjuvant used in vaccines against hepatitis B virus, hepatitis A virus, and tetanus toxoid. Aluminum hydroxide is known to potently stimulate the immune system and to shift immune responses towards a Th-2 profile. It is plausible that persistent systemic immune activation that fails to switch off represents the pathophysiologic basis of chronic fatigue syndrome associated with macrophagic myofasciitis, similarly to what happens in patients with post-infectious chronic fatigue and possibly idiopathic chronic fatigue syndrome. Therefore, the WHO recommended an epidemiological survey, currently conducted by the French agency AFSSAPS, aimed at substantiating the possible link between the focal macrophagic myofasciitis lesion (or previous immunization with aluminium-containing vaccines) and systemic symptoms. Interestingly, special emphasis has been put on Th-2 biased immune responses as a possible explanation of chronic fatigue and associated manifestations known as the Gulf war syndrome. Results concerning macrophagic myofasciitis may well open new avenues for etiologic investigation of this syndrome. Indeed, both type and structure of symptoms are strikingly similar in Gulf war veterans and patients with macrophagic myofasciitis. Multiple vaccinations performed over a short period of time in the Persian gulf area have been recognized as the main risk factor for Gulf War syndrome. Moreover, the war vaccine against anthrax, which is administered in a 6-shot regimen and seems to be crucially involved, is adjuvanted by aluminium hydroxide and, possibly, squalene, another Th-2 adjuvant... [Gherardi RK; Rev Neurol (Paris) 159 (2): 162-4 (2003)]

/LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Aluminium hydroxide and aluminium phosphate have been widely used as vaccine adjuvants with a good safety record for several decades. The recent observation in human deltoid muscle of macrophage aggregates containing aluminium hydroxide spicules and termed Macrophagic Myofasciitis (MMF) has encouraged research on aluminium salts. This study was conducted in order to further investigate the clearance of aluminium at the vaccine injection site and the features of induced histopathological lesions. Two groups of 12 monkeys were immunised in the quadriceps muscle with Diphtheria-Tetanus vaccines, which were adjuvanted with either aluminium hydroxide or aluminium phosphate. Three, six or twelve months after vaccination, four monkeys from each group were sacrificed and histopathological examination and aluminium assays were performed on quadriceps muscle sections. Histopathological lesions, similar to the MMF described in humans, were observed and were still present 3 months after aluminium phosphate and 12 months after aluminium hydroxide adjuvanted vaccine administration. An increase in aluminium concentration, more marked in the area of the lesions, was also observed at the 3- and 6-month time points. These findings were localised at the injection site and no similar changes were observed in the distal or proximal muscle fragments. /Investigators/ conclude from this study that aluminium adjuvanted vaccines administered by the intramuscular route trigger histopathological changes

restricted to the area around the injection site which persist for several months but are not associated with abnormal clinical signs. [Verdier F et al; Vaccine. 23 (11): 1359-67 (2005)]

/LABORATORY ANIMALS: Neurotoxicity/ Gulf War Syndrome is a multi-system disorder afflicting many veterans of Western armies in the 1990-1991 Gulf War. A number of those afflicted may show neurological deficits including various cognitive dysfunctions and motor neuron disease, the latter expression virtually indistinguishable from classical amyotrophic lateral sclerosis (ALS) except for the age of onset. This ALS cluster represents the second such ALS cluster described in the literature to date. Possible causes of GWS include several of the adjuvants in the anthrax vaccine and others. The most likely culprit appears to be aluminum hydroxide. In an initial series of experiments, we examined the potential toxicity of aluminum hydroxide in male, outbred CD-1 mice injected subcutaneously in two equivalent-to-human doses. After sacrifice, spinal cord and motor cortex samples were examined by immunohistochemistry. Aluminum-treated mice showed significantly increased apoptosis of motor neurons and increases in reactive astrocytes and microglial proliferation within the spinal cord and cortex. Morin stain detected the presence of aluminum in the cytoplasm of motor neurons with some neurons also testing positive for the presence of hyper-phosphorylated tau protein, a pathological hallmark of various neurological diseases, including Alzheimer's disease and frontotemporal dementia. A second series of experiments was conducted on mice injected with six doses of aluminum hydroxide. Behavioural analyses in these mice revealed significant impairments in a number of motor functions as well as diminished spatial memory capacity. [Shaw CA, Petrik MS.; J Inorg Biochem. 103 (11): 1555-62 (2009)]

/CASE REPORTS/ The well-described long-term effects of sustained exposure to aluminium in patients with end-stage renal failure (ESRF) are a result of uptake and storage of aluminium, leading to cellular toxicity. A case is presented suggesting that this aluminium may be mobilizable, and indicating the consequence of such release. A patient on hemodialysis (HD) presented acutely with infection, a raised CRP, decreased conscious level, impaired cognition and agitation. Subsequent neurological recovery over six to seven days appeared to follow the return of markedly elevated plasma aluminium concentrations to basal (i.e. from 25.2 $\mu\text{mol/L}$ to 2.5 $\mu\text{mol/L}$; reference range < 0.5 $\mu\text{mol/L}$), coupled with a resolution of the infection. The patient was on long-term aludrox therapy 3 g/day, and showed relative resistance to the exogenous hormone erythropoietin, resulting in a refractory anemia and suggesting aluminium toxicity. A series of HD patients (n = 5) presenting with bacteremia, not on aludrox, showed no appreciable rise in the plasma aluminium mean of 1.3 $\mu\text{mol/L}$ (SD 0.9; range 0.6-2.0 $\mu\text{mol/L}$). We suggest that infection can result in release of tissue aluminium, leading to acutely elevated plasma aluminium concentrations and signs of neurotoxicity. The amount of tissue storage and resultant aluminium release seemed to be related to the use of aluminium hydroxide as a phosphate binder. [Fenwick S et al; Ann Clin Biochem. 42 (Pt 2): 149-52 (2005)]

/CASE REPORTS/ Brain aluminum concentration has been found significantly higher in patients dying with dialysis encephalopathy than in uremic patients without this syndrome. Uremic boy with high brain aluminum concentration showed symptoms of severe encephalopathy after treatment with oral aluminum hydroxide. [Nathan E, Pedersen SE; Acta Paediatr Scand 69 (6): 793 (1980)]

/CASE REPORTS/ ... An 8-month-old white boy was brought to the emergency department due to irritability and pain with movement. Upon examination, the infant was irritable, unable to bear weight, had palpable clavicular bony lesions, point tenderness of the hips, and poor head control. The infant had lost several developmental milestones over the past 4 months (eg, ability to roll over) and had decreased appetite and minimal weight gain. Skeletal survey revealed multiple rib fractures, osteoporosis, and Ricketts. Hypophosphatemia (2.3 mg/dL; normal 3.2-6.3) and an elevated serum aluminum level (14 microg/L, normal 0-9) were noted. Past medical history was positive for gastroesophageal reflux. He had been started on ranitidine and aluminum hydroxide (1/2 teaspoonful per 6-ounce bottle) at 2 months of age. The infant's formula contained elevated aluminum levels. Further investigation showed that 1/2 tablespoonful instead of 1/2 teaspoonful of

antacid had been added to each 6-ounce formula bottle for the prior 6 months; only 1 month of antacid therapy had been recommended. An objective causality assessment revealed a probable adverse drug event. [Robinson RF et al; Ann Pharmacother 38 (2): 265-268 (2004)]

/BIOMONITORING/ The effect of five antacids on urinary pH /was studied/ in 11 subjects. ... Aluminum hydroxide suspension (Amphojel) and dihydroxyaluminum glycinate (Robalate) had no effect on urine pH. ... /While/ aluminum and magnesium hydroxide suspension (Maalox) increased urinary pH by almost one unit. Zinn also found an increase in urine pH in subjects receiving an aluminum and magnesium hydroxide-containing tablet (Mylanta). ... [Hansten P.D. Drug Interactions. 5th ed. Philadelphia: Lea and Febiger, 1985., p. 16]

/ENDOCRINE MODULATION/ Decrease in plasma parathyroid hormone levels following aluminum hydroxide therapy in patients with chronic renal failure appears to be indirect effect of aluminum intoxication ... Binding of aluminum with plasma inorganic phosphorus increases plasma calcium level with proportionate fall in parathyroid hormone. [Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978., p. 110]

Long-term administration of aluminum antacids in patients with renal failure or chronic renal failure may result in hyperaluminemia since small amounts of aluminum are absorbed from the GI tract and excretion of aluminum is decreased in patients with renal failure... aluminum may then accumulate in bones, lungs, and nerve tissue. Aluminum accumulation in the CNS may be the cause of dialysis encephalopathy... Dialysis dementia also may occur in patients with renal failure receiving long-term aluminum antacid therapy for hyperphosphatemia... Aluminum intoxication with severe osteomalacia and extensive aluminum deposition at the junction between calcified and noncalcified bone has been reported in several young children who were receiving large dosages of aluminum hydroxide for the management of hyperphosphatemia associated with azotemia; the children were not undergoing hemodialysis during aluminum hydroxide therapy. /Aluminum antacids/ [American Society of Health-System Pharmacists 2012; Drug Information 2012. Bethesda, MD. 2012, p. 2933]

Excessive doses, or even normal doses in patients with low-phosphate diets, may lead to phosphate depletion accompanied by increased resorption and urinary excretion of calcium with the risk of renal rickets in the young or osteomalacia in older patients. Increases in plasma concentrations of aluminum are a toxic hazard of aluminium hydroxide mixture given to patients with poor renal function, or to those on dialysis, and encephalopathy and dementia have occurred. /Aluminum hydroxide/ [Reynolds, J.E.F., Prasad, A.B. (eds.) Martindale-The Extra Pharmacopoeia. 28th ed. London: The Pharmaceutical Press, 1982., p. 72]

Aluminum salts may cause phosphorus depletion which is generally negligible. However, with prolonged administration or large doses, hypophosphatemia may occur, especially in patients with inadequate dietary intake of phosphorus; hypercalciuria secondary to bone resorption and increased intestinal absorption of calcium results. This phosphorus depletion syndrome is characterized by anorexia, malaise, and muscle weakness, and prolonged aluminum antacid therapy may cause urinary calculi, osteomalacia, and osteoporosis. ... /Antacids/ [McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2004. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2004 (Plus Supplements)., p. 2757]

/OTHER TOXICITY INFORMATION/ Aluminium hydroxide toxicity is predominantly seen in uraemic animals after i.p. injection and is manifested by symptoms of lethargy, periorbital bleeding, anorexia, and subsequently death... [Krewski D et al; J Toxicol Environ Health B Crit Rev 10 (Suppl 1): 1-269 (2007)]

Effects of both chronic aluminum (Al) exposure and partial hepatectomy on iron (Fe) homeostasis were studied. Male Wistar rats were intraperitoneally administered either 27 mg Al/kg body weight (as aluminum hydroxide) or the vehicle saline, three times a week for 3 months. After this time, half of the rats of each group was sham operated (SH) and the other half was partially hepatectomized (PH). Animals of the four experimental groups (vehicle+SH [SH]; Al+SH; vehicle+PH [PH], and

Al+PH) were killed 48 hr after the surgical procedure. Serum, hepatic, and intestinal Al levels were found to be increased both for Al+SH and Al+PH. The serum Fe concentration and transferrin saturation percentage were significantly diminished in the rats of the Al+PH group, thus showing interaction between Al administration and PH. The (59)Fe mucosal-to-serosal transport, studied in the intestinal loop in situ, was not affected by Al or PH. The malregulation of intestinal Fe absorption in Al exposure and/or PH when the serum Fe concentration was diminished could be the result of the increased lipid peroxidation (thiobarbituric acid-reactive substances [TBARS]) observed in this tissue. Mucosal TBARS were increased by Al exposure (+26%) and PH (+37%) and interaction between Al and PH was observed (+44%). These results show that when liver surgery is performed after prolonged Al exposure, it leads to impairment of Fe homeostasis. /The study/ underline the importance of the exposure to Al, a potentially toxic element, in the study of risk assessment in patients who must be submitted to major liver resection. [Contini Mdel C et al; Biol Trace Elem Res. 115 (1): 31-45 (2007)]

/The authors/ have shown that aluminum (Al) induces cholestasis associated with multiple alterations in hepatocellular transporters involved in bile secretory function, like Mrp2. This work aims to investigate whether these harmful effects are mediated by the oxidative stress caused by the metal. For this purpose, the capability of the antioxidant agent, vitamin E, to counteract these alterations was studied in male Wistar rats. Aluminum hydroxide (or saline in controls) was administered ip (27 mg/kg body weight, three times a week, for 90 d). Vitamin E (600 mg/kg body weight) was coadministered, sc. Al increased lipid peroxidation (+50%) and decreased hepatic glutation levels (-43%) and the activity of glutation peroxidase (-50%) and catalase (-88%). Vitamin E counteracted these effects total or partially. Both plasma and hepatic Al levels reached at the end of the treatment were significantly reduced by vitamin E (-40% and -44%, respectively; $p < 0.05$). Al increased 4 times the hepatic apoptotic index, and this effect was fully counteracted by vitamin E. Bile flow was decreased in Al treated rats (-37%) and restored to normality by vitamin E. The antioxidant normalized the hepatic handling of the Mrp2 substrates, rose bengal, and dinitrophenyl-S-glutathione, which was causally associated with restoration of Mrp2 expression. /These/ data indicate that oxidative stress has a crucial role in cholestasis, apoptotic/necrotic hepatocellular damage, and the impairment in liver transport function induced by Al and that vitamin E counteracts these harmful effects not only by preventing free-radical formation but also by favoring Al disposal. [Gonzalez MA et al; Biol Trace Elem Res. 116 (3): 329-48 (2007)]

As taken from HSDB, 2013.

“Aluminium hydroxide is used as an effective adjuvant in a wide range of vaccines for enhancing immune response to the antigen. The pathogenic role of aluminium hydroxide is now recognized by the presence of chronic fatigue syndrome, macrophagic myofasciitis and subcutaneous pseudolymphoma, linked to intramuscular injection of aluminium hydroxide-containing vaccines. The aim of this study is to verify if the subcutaneous pseudolymphoma observed in this patient in the site of vaccine injection is linked to an aluminium overload. Many years after vaccination, a subcutaneous nodule was discovered in a 45-year-old woman with subcutaneous pseudolymphoma. In skin biopsy at the injection site for vaccines, aluminium (Al) deposits are assessed by Morin stain and quantification of Al is performed by Zeeman Electrothermal Atomic Absorption Spectrophotometry. Morin stain shows Al deposits in the macrophages, and Al assays (in $\mu\text{g/g}$, dry weight) were 768.10 ± 18 for the patient compared with the two control patients, 5.61 ± 0.59 and 9.13 ± 0.057 . Given the pathology of this patient and the high Al concentration in skin biopsy, the authors wish to draw attention when using the Al salts known to be particularly effective as adjuvants in single or repeated vaccinations. The possible release of Al may induce other pathologies ascribed to the well-known toxicity of this metal.” As taken from Guillard O et al. 2012. J. Trace Elem. Med. Biol. 26(4), 291-3. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22425036>

“Macrophagic myofasciitis (MMF) is an immune-mediated condition first reported in 1998. MMF is characterized by post-vaccination systemic manifestations as well as local-stereotyped and

immunologically active lesion in the site of inoculation (deltoid muscle). MMF systemic symptoms included myalgias, arthralgias, marked asthenia, muscle weakness, chronic fatigue, and fever. Recently, studies demonstrated that the local lesion is due to persistence for years at site of injection of an aluminum (Al(OH)₃) adjuvant commonly used in human vaccines. Time elapsed from last immunization with an Al(OH)₃-containing vaccine to muscle biopsy range from 3 months to 8 years; in rare cases, MMF may be diagnosed even 10 years post-vaccination. The discrepancy between the wide applications of aluminum hydroxide-containing vaccines and the very limited number of MMF cases reported may be resolved by observations suggesting that aluminum-containing vaccinations may trigger MMF in genetically susceptible subjects carrying the HLA-DRB1*01. Thus, MMF may be defined as an emerging novel condition that may be triggered by exposure to alum-containing vaccines, in patients with a specific genetic background, and this temporal association may be exhibited from a few months up to 10 years.” As taken from Israeli E et al. 2011. Clin. Rev. Allergy Immunol. 41(2), 163-8. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/20882368>

“Macrophagic myofasciitis (MMF) is characterized by specific muscle lesions assessing long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization. Affected patients are middle-aged adults, mainly presenting with diffuse arthromyalgias, chronic fatigue, and cognitive dysfunction. Representative features of MMF-associated cognitive dysfunction (MACD) include (i) dysexecutive syndrome; (i) visual memory; (iii) left ear extinction at dichotic listening test. In present study we retrospectively evaluated the progression of MACD in 30 MMF patients. Most patients fulfilled criteria for non-amnestic/dysexecutive mild cognitive impairment, even if some cognitive deficits seemed unusually severe. MACD remained stable over time, although dysexecutive syndrome tended to worsen. Long-term follow-up of a subset of patients with 3 or 4 consecutive neuropsychological evaluations confirmed the stability of MACD with time, despite marked fluctuations.” As taken from Passeri E et al. 2011. J. Inorg. Biochem. 105(11), 1457-63. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22099155?dopt=AbstractPlus>

“.....Recently, a new syndrome was introduced, autoimmune/inflammatory syndrome induced by adjuvants (ASIA), that includes postvaccination phenomena, macrophagic myofasciitis, Gulf War syndrome and siliconosis. This syndrome is characterized by nonspecific and specific manifestations of autoimmune disease. The main substances associated with ASIA are squalene (Gulf War syndrome), aluminum hydroxide (postvaccination phenomena, macrophagic myofasciitis) and silicone with siliconosis.....The following review describes the wide clinical spectrum and pathogenesis of ASIA including defined autoimmune diseases and nonspecific autoimmune manifestations, as well as the outlook of future research in this field.” As taken from Vera-Lastra O et al. 2013. Expert Rev. Clin. Immunol. 9(4), 361-73. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/23557271>

“Aluminum is a ubiquitous element that is released naturally into the environment via volcanic activity and the breakdown of rocks on the earth's surface. Exposure of the general population to aluminum occurs primarily through the consumption of food, antacids, and buffered analgesics. Exposure to aluminum in the general population can also occur through vaccination, since vaccines often contain aluminum salts (frequently aluminum hydroxide or aluminum phosphate) as adjuvants. Because concerns have been expressed by the public that aluminum in vaccines may pose a risk to infants, we developed an up-to-date analysis of the safety of aluminum adjuvants. Keith et al. [1] previously analyzed the pharmacokinetics of aluminum for infant dietary and vaccine exposures and compared the resulting body burdens to those based on the minimal risk levels (MRLs) established by the Agency for Toxic Substances and Disease Registry. We updated the analysis of Keith et al. [1] with a current pediatric vaccination schedule [2]; baseline aluminum levels at birth; an aluminum retention function that reflects changing glomerular filtration rates in infants; an adjustment for the kinetics of aluminum efflux at the site of injection; contemporaneous MRLs; and the most recent infant body weight data for children 0-60 months of age [3]. Using these updated parameters we found that the body burden of aluminum from vaccines and diet throughout

an infant's first year of life is significantly less than the corresponding safe body burden of aluminum modeled using the regulatory MRL. We conclude that episodic exposures to vaccines that contain aluminum adjuvant continue to be extremely low risk to infants and that the benefits of using vaccines containing aluminum adjuvant outweigh any theoretical concerns." As taken from Mitkus RJ et al. 2011. Vaccine 29(51), 9538-43. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22001122>

"Renal stone disease is characterized by the differences depending on the age, gender, and the geographic location of the patients. Seventy-five percent of the renal stone components is the calcium (Ca). The most common type of the stones is the Ca oxalate stones, while Ca phosphate, uric acid, struvite, and sistine stones are more rarely reported. Other than these types, triamterene, adenosine, silica, indinavir, and ephedrine stones are also reported in the literature as case reports. However, to the best of our knowledge, aluminum hydroxide stones was not reported reported before. Herein we will report a 38-years-old woman with the history of recurrent renal colic disease whose renal stone was determined as aluminum hydroxide stone in type. Aluminum mineral may be considered in the formation of kidney stones as it is widely used in the field of healthcare and cosmetics." As taken from Cakiroglu B et al. 2014. Case Rep. Urol. 2014, 2122314. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25013740>

"...Trivalent Al reacts with water to produce bidentate superoxide coordination spheres $[Al(O_2)(H_2O_4)]^{+2}$ and $[Al(H_2O)_6]^{+3}$ that after complexation with $O_2^{\bullet-}$, generate Al superoxides $[Al(O_2^{\bullet})(H_2O_5)]^{+2}$. Semireduced $AlO_2^{\bullet}$ radicals deplete mitochondrial Fe and promote generation of H_2O_2 , $O_2^{\bullet-}$ and $OH^{\bullet}$. Thus, it is the Al^{+3} -induced formation of oxygen radicals that accounts for the oxidative damage that leads to intrinsic apoptosis. In contrast, the toxicity of the insoluble Al oxides depends primarily on their behavior as particulates....Adverse effects to vaccines with Al adjuvants have occurred; however, recent controlled trials found that the immunologic response to certain vaccines with Al adjuvants was no greater, and in some cases less than, that after identical vaccination without Al adjuvants...." As taken from Willhite CC et al. 2014. Crit. Rev. Toxicol. 44(Suppl. 4), 1-80. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25233067>

"It....inhibits the action of pepsin by increasing the pH and via adsorption."

As taken from PubChem.

6. Functional effects on

6.1. Broncho/pulmonary system

"/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ ...Aluminum hydrate... caused rapid and massive fibrosis of lungs /intratracheal injection/; after 25 days there was dense network of coarse reticulin fibers and a few collagen fibers (grade II fibrosis); from 60th-210th day reticulin was replaced by collagen and appearances corresponded to grade III..."[Browning, E. Toxicity of Industrial Metals. 2nd ed. New York: Appleton-Century-Crofts, 1969., p. 8]**PEER REVIEWED**

"/LABORATORY ANIMALS: Subchronic or Prechronic Exposure/ ...Saline (2 mL) or aluminum hydroxide [2 mL (0.15 g/mL)] was instilled intrapleurally in anesthetized male rats. The animals were studied 7 or 30 days after the instillation. Respiratory system, lung, and chest wall elastic, resistive, and viscoelastic/inhomogeneous pressures were measured by the end-inflation occlusion method. We studied the pleural remodeling process by means of semiquantitative analysis of the induced inflammation and quantitative analysis of the collagen extracellular matrix component. The effects on the underlying lung were analyzed morphometrically. Chest wall elastic and viscoelastic pressures increased after aluminum hydroxide instillation independent of time after instillation. Pleural inflammation was observed 7 days after instillation, while pleural adherence with a marked increase in the type I/type III collagen ratio was present 30 days after instillation. Histological

examination demonstrated no differences in lung parenchyma among the groups". [Albuquerque DA et al; Lung 179 (5): 293-303 (2001)]**PEER REVIEWED**

As taken from HSDB, 2013.

6.2. Cardiovascular system

No data available to us at this time.

6.3. Nervous system

"/LABORATORY ANIMALS: Neurotoxicity/ ...Changes /progressive encephalopathy, dementia and convulsions, neurofibrillary degeneration/ were observed when hydrated oxides of aluminum were applied to surface of brain or injected into cerebral cortex or Cisterna magna in apes and monkeys... subsequently... severe recurrent epilepsy". /Hydrated aluminum oxides/ [Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978., p. 111]**PEER REVIEWED**

"/LABORATORY ANIMALS: Neurotoxicity/ ...Focal epilepsy was produced in male cats by unilateral injection of aluminum hydroxide into either the basolateral amygdala (temporal lobe group) or anterior sigmoid gyrus (motor cortex group). Weekly sex testing trials with estrous females were conducted prior to and after aluminum hydroxide injection, and mating performance scores were compared with those of normal, unoperated cats (normal control group). All animals receiving aluminum hydroxide developed EEG and behavioral manifestations of epilepsy; i.e., interictal EEG spiking and partial or generalized seizures. Cats in the temporal lobe group exhibited a dramatic and complete suppression of sexual behavior at periods from 6-26 weeks after aluminum hydroxide injection. The duration of the hyposexuality varied between individual animals and returned to normal as suddenly as the onset occurred, despite the use of AEDs to prevent or control generalized seizure activity. Interictal EEG epileptiform spiking in the amygdala preceded the onset of hyposexuality by 1-12 weeks. By contrast, cats in the motor cortex and normal control groups showed no sign of sexual dysfunction throughout the experimental period, independent of seizure activity and/or antiepileptic drug (AED) treatment. [Feeney DM et al; Epilepsia 39 (2): 140-149 (1998)]**PEER REVIEWED**

/LABORATORY ANIMALS: Neurotoxicity/ Gulf War Syndrome is a multi-system disorder afflicting many veterans of Western armies in the 1990-1991 Gulf War. A number of those afflicted may show neurological deficits including various cognitive dysfunctions and motor neuron disease, the latter expression virtually indistinguishable from classical amyotrophic lateral sclerosis (ALS) except for the age of onset. This ALS cluster represents the second such ALS cluster described in the literature to date. Possible causes of GWS include several of the adjuvants in the anthrax vaccine and others. The most likely culprit appears to be aluminum hydroxide. In an initial series of experiments, we examined the potential toxicity of aluminum hydroxide in male, outbred CD-1 mice injected subcutaneously in two equivalent-to-human doses. After sacrifice, spinal cord and motor cortex samples were examined by immunohistochemistry. Aluminum-treated mice showed significantly increased apoptosis of motor neurons and increases in reactive astrocytes and microglial proliferation within the spinal cord and cortex. Morin stain detected the presence of aluminum in the cytoplasm of motor neurons with some neurons also testing positive for the presence of hyper-phosphorylated tau protein, a pathological hallmark of various neurological diseases, including Alzheimer's disease and frontotemporal dementia. A second series of experiments was conducted on mice injected with six doses of aluminum hydroxide. Behavioural analyses in these mice revealed significant impairments in a number of motor functions as well as diminished spatial memory capacity. [Shaw CA, Petrik MS.; J Inorg Biochem. 103 (11): 1555-62 (2009)]

Aluminum accumulation in the CNS may be the cause of dialysis encephalopathy... Dialysis dementia also may occur in patients with renal failure receiving long-term aluminum antacid therapy for hyperphosphatemia... /Aluminum antacids/ [American Society of Health-System Pharmacists 2012; Drug Information 2012. Bethesda, MD. 2012, p. 2933]

/OTHER TOXICITY INFORMATION/ Dialysis dementia is a progressive and usually fatal neurologic syndrome occurring in patients on chronic hemodialysis. These patients may also have elevated levels of aluminum (Al+3) in the cerebral cortex. Possible relations between brain Al+3, increased Al+3 intake, and dementia were evaluated. Studies were done in seven groups of patients and five groups of experimental animals. In both normal dogs and rats and those with renal failure, oral Al+3 loading (Al[OH]3), resulted in significant increases of brain Al+3 (P less than 0.01). In patients with renal failure, who were neither demented nor treated with dialysis, brain Al+3 was more than seven times normal (P less than 0.01), whereas in patients with dialysis dementia, mean brain Al+3 was more than 15 times normal. However, the two groups were not significantly different. Brain Al+3 was also significantly elevated in patients who had either metastatic cancer or hepatic coma. Apparently brain Al+3 can be elevated as a consequence of Al+3 loading, renal failure, and abnormalities of the blood-brain barrier. It is most likely that dialysis dementia has multifactorial causation and is probably not caused by elevated brain content of Al+3 alone. [Arieff Al et al; Ann Intern Med. 90 (5): 741-7 (1979)]

/BEHAVIORAL STUDIES/ Long Evans rats were treated for 90 days with water-soluble, insoluble or chelated aluminium compounds. The daily treatments given were as follows: controls, NaCl (100 mg/kg body weight) plus citric acid (30 mg/kg); AlCl3 (30 or 100 mg/kg); Al(OH)3 (100 mg/kg) plus citric acid (30 mg/kg); Al(OH)3 (300 mg/kg). Their learning ability was determined in the labyrinth test at day 90, and the choline-acetyltransferase, acetylcholinesterase activity and aluminium content of the brains were measured. Soluble and chelated aluminium compounds seriously worsened the learning ability, and the aluminium content of the brain was elevated. Acetylcholinesterase activity increased and choline-acetyltransferase activity decreased, resulting in a diminished cholinergic activity, which is a characteristic of Alzheimer's disease. [Bilkei-Gorzo A et al; Food Chem Toxicol 31 (5): 357-61 (1993)]

/BEHAVIORAL STUDIES/ A variety of behaviors was measured in adult Long-Evans male rats fed ground rat chow containing either no added aluminum, low aluminum (1500 mg/kg), moderate aluminum (2500 mg/kg), or high aluminum (3500 mg/kg). There were no effects of aluminum on either body weight or mouse killing. There was an inverse relationship between brain aluminum and open-field activity. Elevated brain aluminum was correlated with relatively poor performance on a single-trial passive-avoidance task and on a visual discrimination with reversal task. [Thorne BM et al; Physiol Behav. 36 (1): 63-7 (1986)]

As taken from HSDB, 2013.

“.....Signs of Al toxicity in the central nervous system (speech difficulty to total mutism to facial grimacing to multifacial seizures and dyspraxia) are related to Al accumulation in the brain and these symptoms can progress to frank encephalopathy.....A number of studies of Al exposure in relation to memory in rodents have been published, but the results are inconsistent. At present, there is no evidence to substantiate the hypothesis that the pathogenesis of Alzheimer's Disease is caused by Al found in food and drinking water at the levels consumed by people living in North America and Western Europe.....” As taken from Willhite CC et al. 2012. Crit. Rev. Toxicol. 42(5), 358-442. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22512666>

“....Aluminum has been held responsible for human morbidity and mortality, but there is no consistent and convincing evidence to associate the Al found in food and drinking water at the doses and chemical forms presently consumed by people living in North America and Western Europe with increased risk for Alzheimer's disease (AD). Neither is there clear evidence to show use of Al-containing underarm antiperspirants or cosmetics increases the risk of AD or breast cancer.....Aluminum exposures during neonatal and pediatric parenteral nutrition (PN) can impair

bone mineralization and delay neurological development....” As taken from Willhite CC et al. 2014. Crit. Rev. Toxicol. 44(Suppl. 4), 1-80. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25233067>

Property / Endpoint	Data	Reference	Data quality
Neurotoxicity Screening Battery (Adult)	30-day Rat, oral diet, no significant effects noted, NOAEL = 1,252 mg Al/kg-day	Thorne et al. 1986, 1987 (as described in ATSDR, 2008)	Reported in a secondary source.
Neurotoxicity Screening Battery (Adult)	90-day Rat, oral gavage, impaired learning in a labyrinth maze test NOAEL = Not established LOAEL = 35 mg Al/kg-day as aluminum hydroxide with citric acid (only dose tested)	Bilkei-Gorzo, 1993 (as described in ATSDR, 2008)	Reported in a secondary source; dose reported as 35 mg/kg-day as aluminum hydroxide with citric acid; citric acid was added to increase absorption; it is not proven that negative effects only related to aluminum hydroxide and not based on citric acid; also, the background aluminum content of the diet fed to rats was not reported; only one dose tested.

As taken from US EPA, 2014a.

“ BACKGROUND: Our group has shown that significant correlations exist between rates of Autism Spectrum Disorder (ASD) and total aluminum adjuvants given to children through vaccines in several Western countries. These correlations satisfied eight out of nine Hill criteria for causality. Experimental studies have demonstrated a range of behavioural abnormalities in young mice after postnatal exposure to aluminium. To build on our previous work, the current study will investigate the effect of aluminium adjuvants on social behaviour in mice. Anomalies in social interaction are a key characteristic of those with ASD. METHODS: Neonatal CD-1 mice pups were injected with either a total of 550µg of aluminum hydroxide gel (experimental group) or saline (control) spread out during the first two weeks of postnatal life. The mice were then subjected to behavioural tests for social interest and social novelty at postnatal week 8, 17 and 29. p-Values were calculated using the Mann-Whitney and Kruskal Wallis tests. RESULTS: Aluminum injected mice showed diminished social interest compared to controls at week 8 (p=0.016) and 17 (p=0.012). They also demonstrated abnormal social novelty from controls at week 8 (p=0.002) and week 29 (p=0.042). CONCLUSION: This is the first experimental study, to our knowledge, to demonstrate that aluminum adjuvants can impair social behaviour if applied in the early period of postnatal development. The study, however, is insufficient to make any assertive claims about the link between aluminium adjuvants and ASD in humans.” As taken from Sheth SKS et al. 2018. J. Inorg. Biochem. 181, 96-103. PubMed, 2019 available at: <https://www.ncbi.nlm.nih.gov/pubmed/29221615>

“Published neurotoxicity and developmental neurotoxicity studies with aluminium compounds (aluminium sulphate, chloride, hydroxide and nitrate) were reviewed and evaluated by the EFSA AFC Panel in a previous opinion on the safety of aluminium from dietary intake (EFSA, 2008). The conclusions concerning neurotoxicity were as follows: ‘In humans neurotoxicity was observed in patients undergoing dialysis due to the use of unpurified water containing high concentrations of aluminium. Furthermore, aluminium was associated with Alzheimer’s disease. However, the Panel and also the German Federal Institute for Risk Assessment (BfR, 2007) and the French Food Safety Agency (AFSSA, 2003) concluded that there is no scientific prove and that in addition the aluminium content of the diets was not taken into account. Aluminium is considered as a neurotoxicant in experimental animals (mice, rats), however, most of the studies showed limitations. Behavioural impairment (passive and conditioned avoidance responses) has been observed in the absence of overt encephalopathy or neurohistopathology in rats and mice exposed to soluble

aluminium salts (e.g. lactate, chloride) in the diet or drinking water generally at doses of 200 mg aluminium/kg bw per day or higher. Effects recorded in more than one study in immature animals included impaired performance of reflexes and simple behaviours. Reduced grip strength and startle responsiveness were found to persist up to 150 days of age. There was no effect on reactions to the light avoidance task in rats after gestational or postnatal exposure. In these studies, LOAELs were identified that ranged from maternal doses of 50 to 500 mg aluminium/kg bw per day. From the study in mice where the lowest LOAEL of 50 mg aluminium/kg bw per day, given as lactate, was reported for neurodevelopmental effects in the offspring, NOAELs of 10 mg aluminium/kg bw per day in the mother during pregnancy and 42 mg/kg bw per day during lactation could also be identified. However, it should be noted that, in another study performed by the same group of researchers, with administration of aluminium lactate from conception throughout the whole lifespan at 100 mg/kg bw/day no clear signs of neurotoxicity were observed in the same strain of mice’.”

As taken from EFSA, 2018

Introduction: Aluminium exposure is associated with bone disease (an elevated bone content of aluminium and reduced bone formation on bone biopsy) and neurotoxicity (features of altered brain functions and/or typical spike and slow wave waveforms on electroencephalogram) in patients with elevated blood aluminium concentrations.

Objectives: To critically analyse the literature to determine the dose-toxicity relationships between aluminium exposure and related bone disease and aluminium neurotoxicity.

Methods: A systematic review of the literature with collation and analysis of individual data of human cases of aluminium exposure was conducted between 1 January 1966 and 30 December 2020. Embase, MEDLINE (OVID MEDLINE), PubMed and TOXNET were searched with the following strategies: "*Aluminium AND toxicity OR aluminium AND poisoning OR aluminium AND dialysis OR aluminium AND chronic renal failure OR aluminium AND intravenous*" limited to "(human)". Inclusion criteria required individual data relating to aluminium exposure in humans. Papers in which features of aluminium toxicity and analytical confirmation of aluminium exposure could not be determined in individual patients were excluded.

Results: Thirty-seven papers were identified, which included data on 179 individuals exposed to aluminium. The sources of aluminium exposure (median duration of exposure) were: dialysis fluid (48 months) in 110 cases; oral aluminium hydroxide (20 months) in 20 cases; plasma exchange (2 months) in 16 cases; infant formula feed (minimal duration of 2 weeks) in 14 cases; intravesical exposures (2 days) in 13 oncology patients and potable water exposure in six cases.

Exposure to dialysis fluid: Of the 110 patients exposed to dialysis fluid, 99 were adults and 11 children, who were analysed separated. Of the adults, 50 with aluminium neurotoxicity had a median aluminium concentration of 467 µg/L (IQR 230 - 752), 28 with aluminium bone disease had a median aluminium concentration of 142 µg/L (IQR 46-309) and 21 with asymptomatic aluminium overload had a median aluminium concentration of 35 µg/L (IQR 26-51). Median aluminium concentrations were significantly greater in patients with aluminium neurotoxicity compared to those with aluminium bone disease ($p < 0.0001$) or asymptomatic aluminium overload ($p < 0.0001$).

Oral aluminium hydroxide: Of the 20 cases, 11 were adults and nine were children. Of the 11 adults, eight with aluminium neurotoxicity had a median aluminium concentration of 682 µg/L (IQR 438-770) and three with aluminium bone disease had a median aluminium concentration of 100 µg/L (IQR 62-138) ($p = 0.007$). Of the nine children, five had aluminium neurotoxicity with a median aluminium concentration of 335 µg/L (IQR 229-601), one had aluminium bone disease and an aluminium concentration of 1030 µg/L and three had asymptomatic aluminium overload with a median aluminium concentration 98 µg/L (IQR 65-365).

Plasma exchange: Three patients with stage 5 chronic kidney disease developed aluminium bone disease during plasma exchange; their median blood or serum aluminium concentration was 73 µg/L (IQR 59-81). Asymptomatic aluminium overload was reported in six patients receiving outpatient plasma exchange who had a median creatinine clearance of 71 mL/min (IQR 40-106) and a median aluminium concentration of 49 µg/L (IQR 34-116), and in seven intensive care

patients with acute kidney injury whose median aluminium concentration was 30 µg/L (IQR 17-35); ($p = 0.02$).

Intravesical exposures: All 13 intravesical exposures developed aluminium neurotoxicity and had a median aluminium concentration of 157 µg/L (IQR 45-276).

Potable water: All six patients developed aluminium bone disease and their median blood aluminium concentration was 17 µg/L (IQR 13-100).

Conclusions: Toxic aluminium exposure can result in neurotoxicity and bone disease, especially in patients with chronic kidney disease. Adults with stage 5 chronic kidney disease chronically exposed to aluminium developed aluminium neurotoxicity at higher concentrations than those with aluminium bone disease or with asymptomatic aluminium overload. Aluminium neurotoxicity was reported at lower concentrations following acute exposure to intravesical aluminium. Extrapolating the relevance of these concentrations to the general population is problematic in that the data were derived from oncology patients, however, the possibility that aluminium neurotoxicity may occur at concentrations lower than those reported historically in patients with stage 5 chronic kidney disease cannot be excluded. As taken from Coulson J.M. et al. (2022). Dose-response relationships in aluminium toxicity in humans. Pages 415-428 | Received 17 Jun 2020, Accepted 11 Jan 2022. PubMed, 2022 available at: <https://pubmed.ncbi.nlm.nih.gov/35179097>

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

The most frequent adverse effect of aluminum antacids is constipation. Decreased bowel motility, dehydration, or fluid restriction may predispose patients to intestinal obstruction. Hemorrhoids and fissures, or fecal impaction may occur. long-term administration of aluminum antacids In patients with renal failure or chronic renal failure may result in hyperaluminemia since small amounts of aluminum are absorbed from the GI tract and excretion of aluminum is decreased in patients with renal failure... aluminum may then accumulate in bones, lungs, and nerve tissue.... /Aluminum antacids/ [American Society of Health-System Pharmacists 2012; Drug Information 2012. Bethesda, MD. 2012, p. 2933]

Aluminum hydroxide mixture in common with other aluminum compounds is astringent and may cause nausea, vomiting, and constipation. Large doses can cause intestinal obstruction. /Aluminum hydroxide/ [Reynolds, J.E.F., Prasad, A.B. (eds.) Martindale-The Extra Pharmacopoeia. 28th ed. London: The Pharmaceutical Press, 1982., p. 72]

/The authors/ have shown that aluminum (Al) induces cholestasis associated with multiple alterations in hepatocellular transporters involved in bile secretory function, like Mrp2. This work aims to investigate whether these harmful effects are mediated by the oxidative stress caused by the metal. For this purpose, the capability of the antioxidant agent, vitamin E, to counteract these alterations was studied in male Wistar rats. Aluminum hydroxide (or saline in controls) was administered ip (27 mg/kg body weight, three times a week, for 90 d). Vitamin E (600 mg/kg body weight) was coadministered, sc. Al increased lipid peroxidation (+50%) and decreased hepatic glutathione levels (-43%) and the activity of glutathione peroxidase (-50%) and catalase (-88%). Vitamin E counteracted these effects total or partially. Both plasma and hepatic Al levels reached at the end of the treatment were significantly reduced by vitamin E (-40% and -44%, respectively; $p < 0.05$). Al increased 4 times the hepatic apoptotic index, and this effect was fully counteracted by vitamin E. Bile flow was decreased in Al treated rats (-37%) and restored to normality by vitamin E. The antioxidant normalized the hepatic handling of the Mrp2 substrates, rose bengal, and dinitrophenyl-S-glutathione, which was causally associated with restoration of Mrp2 expression. /These/ data indicate that oxidative stress has a crucial role in cholestasis, apoptotic/necrotic hepatocellular damage, and the impairment in liver transport function induced by Al and that vitamin E counteracts these harmful effects not only by preventing free-radical formation but also by favoring Al disposal. [Gonzalez MA et al; Biol Trace Elem Res. 116 (3): 329-48 (2007)]

Antacids affect bowel habits. Aluminum hydroxide causes constipation in rough proportion to the dose. The effect is greater in elderly patients. Aluminum compounds have caused ileus and colonic

perforation, possibly as extensions of the constipating effect. Obstruction from bezoars formed from masses of aluminum hydroxide and blood or other intestinal contents have also been reported. [Gilman, A.G., L.S.Goodman, and A. Gilman. (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 7th ed. New York: Macmillan Publishing Co., Inc., 1985., p. 983]

As taken from HSDB, 2013.

"Aluminum-containing adjuvants are widely used in preventive vaccines against infectious diseases and in preparations for allergy immunotherapy. The mechanism by which they enhance the immune response remains poorly understood. Aluminum adjuvants selectively stimulate a Th2 immune response upon injection of mice and a mixed response in human beings. They support activation of CD8 T cells, but these cells do not undergo terminal differentiation to cytotoxic T cells. Adsorption of antigens to aluminum adjuvants enhances the immune response by facilitating phagocytosis and slowing the diffusion of antigens from the injection site which allows time for inflammatory cells to accumulate. The adsorptive strength is important as high affinity interactions interfere with the immune response. Adsorption can also affect the physical and chemical stability of antigens. Aluminum adjuvants activate dendritic cells via direct and indirect mechanisms. Phagocytosis of aluminum adjuvants followed by disruption of the phagolysosome activates NLRP3-inflammasomes resulting in the release of active IL-1 β and IL-18. Aluminum adjuvants also activate dendritic cells by binding to membrane lipid rafts. Injection of aluminum-adjuvanted vaccines causes the release of uric acid, DNA, and ATP from damaged cells which in turn activate dendritic cells. The use of aluminum adjuvant is limited by weak stimulation of cell-mediated immunity. This can be enhanced by addition of other immunomodulatory molecules. Adsorption of these molecules is determined by the same mechanisms that control adsorption of antigens and can affect the efficacy of such combination adjuvants. The widespread use of aluminum adjuvants can be attributed in part to the excellent safety record based on a 70-year history of use. They cause local inflammation at the injection site, but also reduce the severity of systemic and local reactions by binding biologically active molecules in vaccines." As taken from Hogenesch H. 2012. Front. Immunol. 3, 406. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/23335921>

"Signs of chronic Al toxicity in the musculoskeletal system include a vitamin D-resistant osteomalacia (deranged membranous bone formation characterized by accumulation of the osteoid matrix and reduced mineralization, reduced numbers of osteoblasts and osteoclasts, decreased lamellar and osteoid bands with elevated Al concentrations) presenting as bone pain and proximal myopathy. Aluminum-induced bone disease can progress to stress fractures of the ribs, femur, vertebrae, humerus and metatarsals. Serum Al ≥ 100 $\mu\text{g/L}$ has a 75-88% positive predictive value for Al bone disease. Chronic Al toxicity is also manifest in the hematopoietic system as an erythropoietin-resistant microcytic hypochromic anemia." As taken from Willhite CC et al. 2012. Crit. Rev. Toxicol. 42(5), 358-442. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/22512666>

"....Aluminum exposures during neonatal and pediatric parenteral nutrition (PN) can impair bone mineralization...." As taken from Willhite CC et al. 2014. Crit. Rev. Toxicol. 44(Suppl. 4), 1-80. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25233067>

"Delayed gastric emptying and impaired gastric accommodation (decreased gastric compliance) play important roles in functional dyspepsia (FD). Here we screen for a clinically used drug with an ability to improve delayed gastric emptying in rats. Oral administration of aldioxa (dihydroxyaluminum allantoinate) partially improved clonidine- or restraint stress-induced delayed gastric emptying. Administration of allantoin, but not aluminium hydroxide, restored the gastric emptying. Both aldioxa and allantoin inhibited clonidine binding to the α -2 adrenergic receptor, suggesting that antagonistic activity of the allantoin moiety of aldioxa on this receptor is involved in the restoration of gastric emptying activity. Aldioxa or aluminium hydroxide but not allantoin restored gastric compliance with restraint stress, suggesting that aluminium hydroxide moiety is involved in this restoration. We propose that aldioxa is a candidate drug for FD, because its safety in humans has already been confirmed and its ameliorating effect on both of delayed gastric

emptying and impaired gastric compliance are confirmed here.” As taken from Asano T et al. 2015. Sci. Rep. 5, 17519. PubMed, 2016 available at <http://www.ncbi.nlm.nih.gov/pubmed/26620883>

“Macrophagic myofasciitis (MMF) is a rare muscle disease that is mainly manifested by diffuse muscle pain.”

“The reviews of Krewski et al. (2007), Willhite et al. (2014), Morris et al. (2017) and Principi and Esposito (2018) also reflected on a possible link between aluminium adjuvants and MMF. The hypothesis behind this association is aluminium hydroxide adjuvant from a vaccine remains embedded in the tissue and causes a steady immune reaction leading to MMF (WHO, 1999; Authier et al., 2001; Gherardi and Authier, 2012; Gherardi et al., 2016; Crépeaux et al., 2017a). Nevertheless, as Krewski et al. (2007) stated, due to the invasiveness of the biopsy procedure, cases of MMF have not been compared with asymptomatic controls (with reference to Netterlid et al., 2004) and the mechanisms through which aluminium might induce this disorder are currently unknown (with reference to Authier et al., 2001).”

“Exposure to aluminium adjuvant per se does not appear to cause the muscle disease MMF for the vast majority of patients. A proportion of patients who suffer from MMF may be susceptible to aluminium adjuvants administered by intramuscular injection. For this group, vaccination may have acted as either a cause or a co-factor for MMF.”

As taken from RIVM, 2020

7. Addiction

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

8. Burnt ingredient toxicity

Tobacco smoke condensates from cigarettes containing Aluminium Hydroxide 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 Aluminium Hydroxide. Table below provides tested level(s) and specific endpoint(s).

JTI NTM Study Report(s)

Endpoint	Tested level (ppm)	Reference
Smoke chemistry	-	JTI NTM Study Report(s)
In vitro genotoxicity	-	JTI NTM Study Report(s)
In vitro cytotoxicity	-	JTI NTM Study Report(s)

9. Heated/vapor emissions toxicity

Aerosol from heated tobacco stick(s) containing Aluminium Hydroxide 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	3.10	Labstat International Inc. (2021a)
In vitro genotoxicity	3.10	Labstat International Inc. (2021b)
In vitro cytotoxicity	3.10	Labstat International Inc. (2021b)

10. Ecotoxicity

10.1. Environmental fate

Environmental Fate:

“AQUATIC FATE: The trivalent aluminum ion is the predominant form at pH levels below 4(1). Between pH 5 and 6, the predominant hydrolysis products are $\text{Al}(\text{OH})_3$ and $\text{Al}(\text{OH})_2^+$ while the solid $\text{Al}(\text{OH})_3$ is most prevalent between pH 5.2 and 8.8(1). The soluble species $\text{Al}(\text{OH})_4^-$ is the predominant species above pH 9, and is the only species present above pH 10(2). Polymeric aluminum hydroxides appear between pH 4.7 and 10.5 and increase in size until they are transformed into colloidal particles of amorphous $\text{Al}(\text{OH})_3$ which crystallize to gibbsite in acid waters(3). [(1) Martell AE, Morteikaitis RJ; in Environmental chemistry and toxicology of aluminum. Lewis TE, ed. Chelsea, MI: Lewis Pub, Inc (1989) (2) Brusewitz S; Aluminum Vol 203. Stockholm, Sweden: University of Stockholm, Inst Theor Phys. p. 138 (1984) (3) Bodek I et al, eds; Environmental inorganic chemistry. NY, NY: Pergamon Press, pp. 6.7-1 to 6.7-9 (1988)]**PEER REVIEWED**

As taken from HSDB, 2013.

“Although the behavior of aluminum salts under environmental conditions is dependent on the characteristics of the local environment (predominately pH), transport of the aluminum (III) species is anticipated to be dominated by leaching through soil; runoff to aqueous environments; adsorption and/or precipitation of the metal ion onto soil or sediment; and wet and dry deposition dust particulates in air to land or surface water. Volatilization of this ionic compound from either wet or dry surfaces is not expected to be an important fate process. Under acidic pHs typically encountered in the environment, it may form insoluble polymeric aluminum hydroxide colloids while under basic conditions; anionic aluminum hydroxide is expected to predominate. Other factors influencing its behavior include the presence of dissolved organic matter, the extent of absorption on suspended particles, and the presence of other aluminum species.

As an inorganic material, aluminum hydroxide is not expected to biodegrade or oxidize under typical environmental conditions. Aluminum hydroxide does not absorb light at environmentally relevant wavelengths and is not expected to photolyze. No degradation processes for aluminum hydroxide under typical environmental conditions were identified.”

Property / Endpoint	Data	Reference	Data quality
Henry's Law Constant (atm-m ³ /mole)	<10 ⁻⁸ (Estimated)	Professional judgment	Cutoff value for non-volatile compounds
Sediment/ Soil Adsorption/ Desorption Coefficient – K _{oc}	>30,000 (Estimated)	Professional judgment; EPA, 2005	Cutoff value for non-volatile compounds
Water - Aerobic Biodegradation	Recalcitrant (Estimated)	Professional judgment	Substance is or contains inorganic elements, such as metal ions or oxides, that are expected to be found in the environment >180 days after release.
Water - Volatilization Half-life for Model River	>1 year (Estimated)	Professional judgment	Based on the magnitude of the estimated Henry's Law constant.
Water - Volatilization Half-life for Model Lake	>1 year (Estimated)	Professional judgment	Based on the magnitude of the estimated Henry's Law constant.

Soil - Aerobic Biodegradation	Recalcitrant (Estimated)	Professional judgment	Substance contains inorganic elements
Soil - Anaerobic Biodegradation	Recalcitrant (Estimated)	Professional judgment	Substance contains inorganic elements
Air - Atmospheric Half-life	>1 year (Estimated)	Professional judgment	Substance contains inorganic elements
Reactivity Photolysis -	Not a significant fate process (Estimated)	Professional judgment	Aluminum hydroxide does not absorb UV light at environmentally relevant wavelengths and is not expected to undergo photolysis.
Reactivity Hydrolysis -			Dissociation of aluminum hydroxide in environmental waters is dependent both on the pH and the local concentration of other aluminum species; dissociation will not occur unless in highly acidic waters, e.g., pH 3.

As taken from US EPA, 2014a.

EPISuite provides the following data:

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:

***WARNING: Inorganic Compound (Outside Estimation Domain)**

***WARNING: Estimation NOT VALID**

Bond Method :	Incomplete
Group Method:	Incomplete
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:	HLC: 5.957E-026 atm-m3/mole (6.036E-021 Pa-m3/mole) VP: 9.71E-020 mm Hg (source: MPBPVP) WS: 1.67E+005 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:

Can Not Estimate (can not calculate HenryLC)

Probability of Rapid Biodegradation (BIOWIN v4.10):

Biowin1 (Linear Model):	0.7104
Biowin2 (Non-Linear Model) :	0.8700
Biowin3 (Ultimate Survey Model):	3.0268 (weeks)
Biowin4 (Primary Survey Model) :	3.7352 (days-weeks)
Biowin5 (MITI Linear Model) :	0.4801
Biowin6 (MITI Non-Linear Model):	0.5680
Biowin7 (Anaerobic Linear Model):	0.8361
Ready Biodegradability Prediction:	NO

Hydrocarbon Biodegradation (BioHCwin v1.01):

Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:

Vapor pressure (liquid/subcooled):	1.05E-014 Pa (7.85E-017 mm Hg)
Log Koa (Koawin est):	not available
Kp (particle/gas partition coef. (m3/ug)):	2.87E+008
Mackay model:	not available
Octanol/air (Koa) model:	

Fraction sorbed to airborne particulates (phi):

Junge-Pankow model:	1
Mackay model:	1
Octanol/air (Koa) model:	not available

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:

WARNING: Inorganic Compound (Outside Estimation Domain)

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant =	0.4200 E-12 cm3/molecule-sec
Half-Life =	25.467 Days (12-hr day; 1.5E6 OH/cm3)
Ozone Reaction:	No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi): 1 (Junge-Pankow, Mackay avg) not available (Koa method) Note: the sorbed fraction may be resistant to atmospheric oxidation	

Soil Adsorption Coefficient (KOCWIN v2.00):

***WARNING: Inorganic Compound (Outside Estimation Domain)**

Koc :	31.82 L/kg (MCI method)
Log Koc:	1.503 (MCI method)
Koc :	0.7861 L/kg (Kow method)
Log Koc:	-0.105 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:

Rate constants can NOT be estimated for this structure!

Volatilization from Water:

Henry LC: 5.96E-026 atm-m3/mole (calculated from VP/WS)

Half-Life from Model River:	8.681E+021 hours (3.617E+020 days)

Half-Life from Model Lake:	9.47E+022 hours (3.946E+021 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	2.76e-008	611	1000
Water	24.1	360	1000
Soil	75.9	720	1000
Sediment	0.076	3.24e+003	0

Persistence Time: 697 hr

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that aluminum hydroxide is persistent in the environment.

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

10.2. Aquatic toxicity

Acute Toxicity to Fish

Type: semistatic

Species: Salmo trutta (Fish, fresh water, marine)

Exposure period: 96 hour(s)

Unit: mg/l

NOEC: > 100

Method: OECD Guide—line 203 "Fish, Acute Toxicity Test"

Year: 1992

GLP: yes

Aluminium hydroxide in powder form

Source: Test substance is aluminium hydroxide in powder form

Reference: (10)

Type: static

Species: Leuciscus idus (Fish, fresh water)

Year: 1989

Result : No influence

Test substance : as prescribed, saturated solution.

Purity : 99 %

Method: DIN 38412 L12

Source: Martinswerk GmbH Bergheim

Reference: (11)

Acute Toxicity to Aquatic Invertebrates

Species: *Daphnia magna* (Crustacea)

Exposure period: 48 hour(s)

Method: OECD Guide—line 202, part 1 "Daphnia sp., Acute Immobilisation Test"

GLP: Yes

Year: 1992

Source: Pechiney Paris

Reference: (12)

Test substance: as prescribed, saturated solution

Method: DIN 38412 L11

Year: 1989

Source: Martinswerk GmbH Bergheim

Reference: (13)

Toxicity to Aquatic Plants e.g. Algae

Species: *Selenastrum capricornutum* (Algae)

Exposure period: 72 hour(s)

Analytical monitoring: yes

Method: OECD Guide—line 201 "Algae, Growth Inhibition Test"

Endpoint: Growth inhibition

Test method: OECD guideline 201, with reduced Fe—EDTA

Source: Pechiney Paris

Reference: (14)

As taken from IUCLID Data sheet: Aluminium hydroxide (21645-51-2).

"Grahm (1980) reported two fish kills in lakes Ransjön and Ämten, two pristine acid lakes in Sweden, during 1978 and 1979. In 1978 the main part of the ciscoe (*Coregonus albula*) population was wiped out. One week later the pH was found to be 5.4 at the surface and 4.9 at the bottom, with maximum aluminium levels of 0.91 mg/litre in groundwater and 0.31 mg/litre in stream water. One year later a similar incident occurred when the pH was 6.0 in surface water and 5.4 in bottom water. Total aluminium concentrations ranged from 0.36 to 0.52 mg/litre. Analysis of fish gills revealed that aluminium concentrations were at least 6 to 7 times higher than those found in fish gills from reference lakes in the area. The authors conclude that weather patterns caused an increase in phytoplankton, which in turn increased pH levels near the surface. Aluminium hydroxide

was precipitated out in the epilimnion water. Ciscoes migrate to the surface to feed where the flocculated aluminium hydroxide caused fish gills to clog and fish to die of suffocation". As taken from INCHEM at <http://www.inchem.org/documents/ehc/ehc/ehc194.htm#SectionNumber:1.1>]

Species: *Pseudomonas putida*

GLP:

Method : DEV L8, modified

Result : no influence

Purity : > 99 %

Reference: (11)

As taken from IUCLID Data sheet: Aluminium hydroxide (21645-51-2).

"Aluminum hydroxide is estimated to be of moderate hazard for acute aquatic toxicity based on potential for dissolved aluminum species to cause adverse effects in aquatic species, as described in the EPA New Chemical Categories document which includes inorganic salts of aluminum (Professional judgment; EPA, 2010). Additional studies for acute toxicity to daphnia and algae are ongoing; the results of these studies may affect the acute aquatic hazard designation.

Aluminum hydroxide is estimated to be of moderate hazard for chronic aquatic toxicity based on potential for dissolved aluminum species to cause adverse effects in aquatic species, as described in the EPA Chemical Categories document which includes inorganic salts of aluminum (Professional judgment; EPA, 2010). An additional study for chronic toxicity to daphnia is ongoing; the results of this study may affect the chronic aquatic hazard designation."

Property / Endpoint	Data	Reference	Data quality
Daphnid LC50	Daphnia magna 48-hour NOEC >0.135 mg/L (Experimental)	ECHA, 2013	Study conducted with aluminum powder.
Green Algae EC50	Pseudokirchnerella subcapitata 96-hr EC50 = 0.46 mg/L (Experimental)	ECHA, 2013	Reported in a secondary source. EC50 range: 0.57 mg/L at pH of 7.6 and 0.46 mg/L at pH of 8.2. The water solubility of aluminum hydroxide under basic pH conditions is not available; experimental details are not sufficient to address the confidence limits of these data points.
Green Algae EC50	Pseudokirchnerella subcapitata 72-hour NOEC = 0.004 – 0.052 mg/L (Experimental)	ECHA, 2013	Reported in a secondary source. DfE criteria are based on LC and EC50 values; therefore a NOEC value is not sufficient to determine a hazard designation

As taken from US EPA, 2014a.

/AQUATIC SPECIES/ Algal assays are often carried out in culture media containing high concentrations of nutrients, including phosphate. These nutrients ameliorate the toxicity of aluminium, and limit the application of the results to natural waters. For example, in culture medium the green alga *Chlorella pyrenoidosa* successfully grew at concentrations of up to 12 mg total aluminium/L at pH 4.6, but an aluminium concentration of 24 mg/L was toxic. By selecting those algae which tolerated high levels of aluminium, the authors were able to develop algal cultures that grew at up to 48 mg/L. However, /another study/ found that maximum toxicity of aluminium to algal growth was achieved at pH 5.8 to 6.2, 5 µg labile Al/L significantly inhibiting the growth of the alga

Chlorella pyrenoidosa in a synthetic hard water. The assay showed that toxicity is a function of the labile, rather than the total, aluminium. It was found that $\text{Al}(\text{OH})_2^+$ was the aluminium species most toxic to the alga. [WHO; Environ Health Criteria 194: Aluminum (1997). Available from, as of June 3, 2004: <http://www.inchem.org/documents/ehc/ehc/ehc194.htm#SectionNumber:1.1>

/AQUATIC SPECIES/ Sensitivities of bluegill (*Lepomis macrochins*), channel catfish (*Ictalurus punctatus*) and fathead minnow (*Pimephales promelas*) to pH and aluminum were compared during 96 hr acute toxicity tests in the laboratory. Juveniles were exposed to four HCl (pH 4.5, 5.5, 6.5, 7.5 nominal) and five AlCl_3 (0, 50, 100, 200, 400 $\mu\text{g/L}$ nominal) treatments in moderately soft fresh water (total hardness, 20 to 25 mg/L CaCO_3) under continuous flow-through conditions. The ranking of species sensitivities to acid alone was fathead minnow (most sensitive), followed by channel catfish and bluegill (about equally sensitive). Aluminum was not toxic to these species at pH 6.5 and 7.5. The ranking of sensitivities to Al at pH 4.5 and 5.5 showed clearer species differences. Fathead minnow were most sensitive and died in all Al treatments. Bluegill were least sensitive and died only in the highest Al concentration at pH 5.5. The sensitivity of channel catfish to Al was intermediate, but was most similar to that of fathead minnow. Aluminum, predominantly as hydroxide species, appeared to be most toxic to bluegill at pH 5.5. Free and hydroxy Al species were apparently toxic to fathead minnow and channel catfish at pH 4.5 and 5.5. [Palmer RE et al; Environ Toxicol Chem 7 (6): 505-16 (1988)]

As taken from HSDB, 2013.

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that aluminum hydroxide is not inherently toxic to aquatic organisms.

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

“Adjuvants are substances added to vaccines to enhance the immune response of a given antigen. Most of the adjuvants are toxic at certain doses, and toxicity varies in different species. Moreover, there are no standard dosage limits set for adjuvant use in fish vaccines. We evaluated the acute toxicity, serum enzymes (AST/ALT) indicating hepatic injury and histopathological changes due to intra-peritoneal administration of different concentrations of a panel of adjuvants including quillaja saponin, aluminum hydroxide, squalene emulsion and Freund's incomplete adjuvant (FIA) with a dose ranging study of saponin (500, 160, 50, 16 and $5\mu\text{gfish}^{-1}$), aluminum hydroxide (5000, 1600, 500, 160 and $50\mu\text{gfish}^{-1}$), squalene emulsion (20, 10 and 5%), and FIA to determine the acceptable dosage for vaccination in olive flounder (*Paralichthys olivaceus*) fingerlings measuring $4.66\pm0.41\text{g}$, $8.47\pm0.42\text{cm}$ Aluminum hydroxide was toxic at $5000\mu\text{gfish}^{-1}$ and was acceptable at dose below $1600\mu\text{gfish}^{-1}$ with moderate histology and AST/ALT levels similar with control.....” As taken from Vinay TN et al. 2014. Vet. Immunol. Immunopathol. 158(1-2), 73-85. PubMed, 2014 available at <http://www.ncbi.nlm.nih.gov/pubmed/23570990>

“Metal risk assessment of industrialized harbors and coastal marine waters requires the application of robust water quality guidelines to determine the likelihood of biological impacts. Currently there is no such guideline available for aluminium in marine waters. A water quality guideline of 24 μg total Al/L has been developed for aluminium in marine waters based on chronic 10% inhibition or effect concentrations (IC10 or EC10) and no-observed-effect concentrations (NOECs) from 11 species (2 literature values and 9 species tested including temperate and tropical species) representing 6 taxonomic groups. The 3 most sensitive species tested were a diatom *Ceratoneis closterium* (formerly *Nitzschia closterium*; IC10 = 18 μg Al/L, 72-h growth rate inhibition) < mussel *Mytilus edulis planulatus* (EC10 = 250 μg Al/L, 72-h embryo development) < oyster *Saccostrea echinata* (EC10 = 410 μg Al/L, 48-h embryo development). Toxicity to these species was the result of the dissolved aluminium forms of aluminate ($\text{Al}(\text{OH})_4^-$) and aluminium hydroxide ($\text{Al}(\text{OH})_3$ (0)) although both dissolved, and particulate aluminium contributed to toxicity in the diatom *Minutocellus polymorphus* and green alga *Dunaliella tertiolecta*. In contrast, aluminium toxicity to the green flagellate alga *Tetraselmis* sp. was the result of particulate aluminium only. Four species, a brown

macroalga (*Hormosira banksii*), sea urchin embryo (*Heliocidaris tuberculata*), and 2 juvenile fish species (*Lates calcarifer* and *Acanthochromis polyacanthus*), were not adversely affected at the highest test concentration used.” As taken from Golding LA et al. 2015. *Environ. Toxicol. Chem.* 34(1), 141-51. PubMed, 2015 available at <http://www.ncbi.nlm.nih.gov/pubmed/25318392>

Record for aluminum hydroxide (Al(OH)₃) (CAS RN 21645-51-2)

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. Type Conc. (Std) Appl. Rate	Stat. Signif.
Paralichthys olivaceus Hirame, Flounder	IP U	SW LAB	7 d	NR-ZERO	NEF 0	MOR MORT	T 1.6 mg/kg bdwt	
Paralichthys olivaceus Hirame, Flounder	IP U	SW LAB	SR (8 - 15) d		CHG	ENZ GENZ/	T (0.05-5) mg/kg bdwt	
Paralichthys olivaceus Hirame, Flounder	IP U	SW LAB	MUL/ (8 - 15) d		CHG	HIS GHIS/	T (0.05-5) mg/kg bdwt	
Paralichthys olivaceus Hirame, Flounder	IP U	SW LAB	7 d		INC 10	MOR MORT	T 5 mg/kg bdwt	

As taken from EPA ECOTOX database

10.3. Sediment toxicity

No data available to us at this time.

10.4. Terrestrial toxicity

“Blume & Brümmer (1991) studied the influence of soil acidity on aluminium binding in sandy soils with a low humus content (< 2%). Binding was found to decrease steadily from very strong at pH 5.5-7.0 to very weak at pH 2.5. The binding of aluminium was found to be increased by increasing the organic matter content. In loam or clay soils binding was increased compared with sandy soils at all levels of pH. Driscoll et al. (1989) studied the chemistry and transfer of aluminium in a

forested watershed of the Adirondack region, New York, USA. The drainage waters from the watershed were highly acidic due to elevated inputs of both sulfuric and nitric acids compared with the release of basic cations. The conditions facilitated the mobilization of aluminium. Alumino-organic solutes were mainly released from the soil organic horizon with inorganic monomeric aluminium derived predominantly from the mineral soil and to a lesser extent from the soil organic horizon. Inorganic monomeric aluminium predominated in the drainage water. The deposition of organic monomeric aluminium in the stream bed coincided with the dissolved organic content retention whilst the deposition of inorganic monomeric aluminium appeared to be facilitated by nitrate retention. Nilsson & Bergkvist (1983) studied soil acidification and aluminium chemistry in three adjacent catchments on the Swedish west coast. The concentration of organic aluminium was linearly correlated with concentrations of carbon. The percentage of organic species in the dissolved aluminium decreased with increasing depth from > 90% in the upper layers to < 10% below 55 cm. The average concentration of total aluminium increased with increasing depth from 3.3 to 9.8 $\mu\text{mole/litre}$ at 5 cm to 95.3 to 115 $\mu\text{mole/litre}$ below 55 cm. Atmospheric acid inputs have a strong impact on the aluminium chemistry of acidic sandy soils with low concentrations of basic cations. The base saturation of such soils is low and the rate of basic cation weathering does not increase with rate of acid input. Any additional acidic deposition is neutralized by aluminium. Dissolution of aluminium is the major acid sink in such soils, neutralizing 30% to 95% of the total acid load (Mulder et al., 1989). Bergkvist (1987) studied the leaching of aluminium in a brown forest soil and a podzol with adjacent stands of spruce, beech and an open regeneration area in South Sweden using lysimeter techniques. The leaching of aluminium was greatest from the podzol. The solubility of aluminium increased suddenly within a small pH range (4.5-4.0) in the B horizon (15 to 55 cm). The concentration of aluminium in soil solution increased from 2 to 10 mg/litre when the pH decreased from 4.4 to 4.2. Berggren et al. (1990) reported that forest soils of south Sweden are losing base cations, such as aluminium, owing to increased leaching rates following soil acidification. The processes controlling the mobilization of aluminium in podzols and cambisols of southern Sweden were investigated by Berggren (1992). Podzols in spruce and beech stands had a high release of organic compounds from the upper 5 to 7 cm (O/Ah horizons), which resulted in high organic complexation of aluminium in soil solution at a depth of 15 cm (E horizon). Organic complexes were mainly adsorbed or precipitated at 20 to 40 cm (upper Bh horizon) and the overall transport of aluminium at 50 cm was governed by a pH-dependent dissolution of solid-phase aluminium. In the cambisols inorganic aluminium predominated at both 15 cm and 50 cm with solubility being closely related to solution pH. The results indicate that the relatively large organically bound solid-phase aluminium pools in both soil types give rise to the measured solution aluminium activities. The authors also found that aluminium in solution efficiently competed for exchange sites and played an important role in the mobilization of cadmium in these soils. In laboratory studies simulating snow melt leaching of forest soils, nitric acid leached more aluminium than did sulfuric acid from soil columns representative of high elevation forest soils and watersheds thought to be sensitive to acidification by acid precipitation. Increasing the nitric acid concentration 100-fold (pH 5 to 3) increased the total aluminium concentration in the leachate from 0.70 to 0.85 mmol/litre, while increasing the sulfuric acid had no effect. Similar experiments with albic and ochric mineral soil horizons revealed no difference between the acids and no effect of increasing acid concentrations (James & Riha, 1989). The acidity produced by soil nitrification is buffered by exchange with base cations. In acidified soils aluminium will be dissolved or the pH of the soil will decrease. Aluminium release from soil is also dependent on the sulfate supply and the capacity of the soil to provide aluminium hydroxides. The molar ratio between aluminium and nitrate is important in evaluating the effects of nitrification. During dry summers the release of aluminium ions may be entirely controlled by the acidification caused by nitrification (Gundersen & Rasmussen, 1990). As taken from INCHEM at: <http://www.inchem.org/documents/ehc/ehc/ehc194.htm#SectionNumber:1.1> "Mineral sunscreen nanocomposites, based on a nano-TiO(2) core, coated with aluminium hydroxide and dimethicone films, were submitted to an artificial ageing process. The resulting Altered TiO(2) Nanocomposites (ATN) were then tested in the liquid phase on the plant model *Vicia faba*, which was exposed 48 h

to three nominal concentrations: 5, 25 and 50 mg ATN/L. Plant growth, photosystem II maximum quantum yield, genotoxicity (micronucleus test) and phytochelatin levels showed no change compared to controls. Oxidative stress biomarkers remained unchanged in shoots while in roots, glutathione reductase activity decreased at 50 mg ATN/L and ascorbate peroxidase activity decreased for 5 and 25 mg ATN/L. Nevertheless, despite the weak response of biological endpoints, ICP-MS measurements revealed high Ti and Al concentrations in roots.....Eventual long-term effects on plants may occur.” As taken from Foltete AS et al. 2011. Environ. Pollut. 159(10), 2515-22. PubMed, 2013 available at <http://www.ncbi.nlm.nih.gov/pubmed/21802804>

10.5. All other relevant types of ecotoxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that the bioaccumulative potential of aluminium hydroxide in the environment has not been determined.

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

Property Endpoint /	Data	Reference	Data quality
Bioaccumulation - Fish BCF - BAF	<100 (Estimated)	Professional judgement	Aluminum hydroxide is an inorganic compound and is not anticipated to bioaccumulate or bioconcentrate. This inorganic compound is not amenable to available quantitative structure activity relationship models.

As taken from US EPA, 2014a.

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):	-1.7743 days (HL = 0.01682 days)
Log BCF Arnot-Gobas method (upper trophic):	-0.034 (BCF = 0.9254)
Log BAF Arnot-Gobas method (upper trophic):	-0.034 (BAF = 0.9254)
log Kow used:	-0.12 (estimated)

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13. Last audited

February 2023

I U C L I D

D a t a s e t

Existing Chemical	Substance ID: 21645-51-2
CAS No.	21645-51-2
EINECS Name	aluminium hydroxide
EINECS No.	244-492-7
Molecular Formula	AlH3O3

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.

The data have not undergone any evaluation by the European Commission.

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European Chemicals Bureau

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Town: 90441 Nürnberg
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Telefax: 00499114233643

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Name: ALUMINIUM PECHINEY
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Name: Aluminium Ranshofen Walzwerk Ges.m.b.H.
Street: Postach 32
Town: 5282 Ranshofen
Country: Austria

Name: BASF AG
Street: Karl-Bosch-Str
Town: 67056 Ludwigshafen
Country: Germany

1. General Information

date: 18-FEB-2000
Substance ID: 21645-51-2

Name: Ciba Specialty Chemicals Inc.
Town: 4002 Basel
Country: Switzerland

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Phone: +32-3-543.1211
Telefax: +32-3-542.0119
Telex: 33 924

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Telefax: +49.23.51.151.283

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Country: Germany
Phone: +49402375-0
Telefax: +49402375-90
Telex: 2170150

Name: Helm Austria GesmbH
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Town: 1010 Wien
Country: Austria
Phone: 513 38 10
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Name: Henkel KGaA
Street: Henkelstr. 67
Town: 40589 Duesseldorf
Country: Germany

Name: Honsel-Guss GmbH
Street: Fritz-Honsel-Str.
Town: 59872 Meschede
Country: Germany
Phone: 0291-291681
Telefax: 0291-291517

1. General Information

date: 18-FEB-2000
Substance ID: 21645-51-2

Name: Hydro Aluminium Uphusen GmbH
Street: Uphuser Heerstr. 7
Town: 28832 Achim
Country: Germany
Phone: +49.4202.57274
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Name: INCEMIN AG
Street: Schachen 82
Town: 5113 Holderbank
Country: Switzerland
Phone: +41(0)62 893 26 27
Telefax: +41(0)62 893 20 17

Name: Krems Chemie AG
Street: Hafenstrasse 77
Town: A-3500 Krems
Country: Austria

Name: Martinswerk GmbH
Street: Kölner Strasse 110, Postfach 1209
Town: 5010 Bergheim
Country: Germany

Name: Omya AB
Street: Kalendegatan 18
Town: 21135 Malmö
Country: Sweden
Phone: +46-40-72755
Telefax: +46-40-236519

Name: Pechiney
Town: Paris
Country: France

Name: Quantum Chemical Europe B.V.
Street: Lange Bunder 7
Town: 4854 MB Bavel
Country: Netherlands
Phone: 01613-6600
Telefax: 01613-3500
Telex: S4382QCE

Name: REHEIS IRELAND
Street: KILBARRACK ROAD
Town: 5 DUBLIN
Country: Ireland
Phone: +353 1 8322621
Telefax: +353 1 8392205
Telex: 32532REHI EI

Name: Rhone-Poulenc Italia SpA
Street: Via L del Vinci 3/7
Town: 57100 Livorno
Country: Italy
Phone: 39 586 425 155
Telefax: 39 586 425 255

Name: RWE-DEA Aktiengesellschaft für Mineraloel und Chemie
Street: Ueberseering 40
Town: 22297 Hamburg
Country: Germany
Phone: 040-6375-0
Telefax: 040-6375-3496
Telex: 21151320

Name: Shell Nederland Chemie B.V.
Street: Vondelingenweg 601
Town: 3196 KK Rotterdam
Country: Netherlands

Name: Star Maling og Lakkfabrikk A/S
Street: P.box 593
Town: 3412 Lierstranda
Country: Norway
Phone: +47 32857380
Telefax: +47 32857495

1.0.2 Location of Production Site

-

1.0.3 Identity of Recipients

-

1.1 General Substance Information

Substance type: inorganic
Physical status: liquid

Substance type: inorganic
Physical status: solid

Substance type: organometallic
Physical status: liquid

1.1.1 Spectra

-

1.2 Synonyms

AC 450

Source: BASF AG Ludwigshafen

AC 714KC

Source: BASF AG Ludwigshafen

AF 260

Source: BASF AG Ludwigshafen

AKP-DA

Source: BASF AG LudwigshafenAl(OH)₃**Source:** INCEMIN AG Holderbank
Henkel KGaA Duesseldorf

Alcoa 331

Source: BASF AG Ludwigshafen

Alcoa 710

Source: BASF AG Ludwigshafen

Alcoa AS 301

Source: BASF AG Ludwigshafen

Alcoa C 30BF

Source: BASF AG Ludwigshafen

Alcoa C 31

Source: BASF AG Ludwigshafen

Alcoa C 33

Source: BASF AG Ludwigshafen

Alcoa C 330

Source: BASF AG Ludwigshafen

Alcoa C 331

Source: BASF AG Ludwigshafen

Alcoa C 333

Source: BASF AG Ludwigshafen

Alcoa C 385

Source: BASF AG Ludwigshafen

Alcoa H 65

Source: BASF AG Ludwigshafen

Alhydrogel

Source: BASF AG Ludwigshafen

Alolt 8

Source: BASF AG Ludwigshafen

1. General Information

date: 18-FEB-2000
Substance ID: 21645-51-2

Alolt 80

Source: BASF AG Ludwigshafen

Alolt 90

Source: BASF AG Ludwigshafen

Alternagel

Source: BASF AG Ludwigshafen

Alugel

Source: BASF AG Ludwigshafen

Alugelibys

Source: BASF AG Ludwigshafen

Alumigel

Source: BASF AG Ludwigshafen

Alumina hydrate

Source: Rhone-Poulenc Italia SpA Livorno

Alumina trihydrat,

Source: Omya AB Malmö

Alumina trihydrate

Source: Rhone-Poulenc Italia SpA Livorno

BASF AG Ludwigshafen

Aluminic acid (H₃AlO₃)

Source: BASF AG Ludwigshafen

Aluminium hydrate

Source: Du Pont de Nemours International S.A. Antwerpen

Aluminium Hydroxide

Source: INCEMIN AG Holderbank

aluminium hydroxide

Source: Star Maling og Lakkfabrikk A/S Lierstranda

Aluminium oxide hydrate

Source: Rhone-Poulenc Italia SpA Livorno

Aluminium oxide trihydrate

Source: Rhone-Poulenc Italia SpA Livorno

Aluminium trihydrate

Source: Rhone-Poulenc Italia SpA Livorno

Aluminium trihydroxide

Source: Du Pont de Nemours International S.A. Antwerpen

Aluminiumhydroxid

Source: Henkel KGaA Duesseldorf

Aluminiumhydroxid, Filterkuchen, Aluminium-Beizschlamm

Source: Honsel-Guss GmbH Meschede

Aluminiumtrihydroxide

Source: INCEMIN AG Holderbank

Aluminum hydroxide (6CI, 8CI)

Source: BASF AG Ludwigshafen

Aluminum hydroxide (Al(OH)₃) (9CI)

Source: BASF AG Ludwigshafen

Aluminum hydroxide (INCI)

Source: Henkel KGaA Duesseldorf

Aluminum oxide (Al₂O₃), trihydrate

Source: BASF AG Ludwigshafen

Aluminum oxide trihydrate

Source: BASF AG Ludwigshafen

Aluminum trihydroxide

Source: BASF AG Ludwigshafen

Alusal

Source: BASF AG Ludwigshafen

Amberol ST 140F

Source: BASF AG Ludwigshafen

Amphogel

Source: BASF AG Ludwigshafen

Amphojel

Source: BASF AG Ludwigshafen

Apyral 120

Source: BASF AG Ludwigshafen

Apyral 120VAW

Source: BASF AG Ludwigshafen

Apyral 15

Source: BASF AG Ludwigshafen

Apyral 2

Source: BASF AG Ludwigshafen

Apyral 24

Source: BASF AG Ludwigshafen

Apyral 4

Source: BASF AG Ludwigshafen

Apyral 40

Source: BASF AG Ludwigshafen

Apyral 60

Source: BASF AG Ludwigshafen

Apyral 8

Source: BASF AG Ludwigshafen

Apyral 90

Source: BASF AG Ludwigshafen

Apyral B

Source: BASF AG Ludwigshafen

Apyral B 2

Source: BASF AG Ludwigshafen

Apyral B 60

Source: BASF AG Ludwigshafen

Apyral B 90

Source: BASF AG Ludwigshafen

AQUEOUS CONCENTRATE OF ALUMINIUM HYDROXIDE ,LIQUIGEL.

Source: REHEIS IRELAND DUBLIN

ATH

Source: INCEMIN AG Holderbank

B 103

Source: BASF AG Ludwigshafen

B 103 (hydroxide)

Source: BASF AG Ludwigshafen

B 1403

Source: BASF AG Ludwigshafen

B 1403S

Source: BASF AG Ludwigshafen

B 153

Source: BASF AG Ludwigshafen

B 303

Source: BASF AG Ludwigshafen

B 700

Source: BASF AG Ludwigshafen

B 703

Source: BASF AG Ludwigshafen

Baco AF 230

Source: BASF AG Ludwigshafen

Baco AF 260

Source: BASF AG Ludwigshafen

Baco FRF 20

Source: BASF AG Ludwigshafen

Baco FRF 40

Source: BASF AG Ludwigshafen

Baco FRF 80

Source: BASF AG Ludwigshafen

Baco FRF 80S5

Source: BASF AG Ludwigshafen

Baco FRF 85

Source: BASF AG Ludwigshafen

Baco FRF-LV 1S5

Source: BASF AG Ludwigshafen

Baco SF 7S3A

Source: BASF AG Ludwigshafen

Bayerit

Source: RWE-DEA Aktiengesellschaft für Mineraloel und Chemie Hamburg

BMZ

Source: BASF AG Ludwigshafen

BW 103

Source: BASF AG Ludwigshafen

BW 53

Source: BASF AG Ludwigshafen

C 12

Source: BASF AG Ludwigshafen

C 301

Source: BASF AG Ludwigshafen

C 301 (hydroxide)

Source: BASF AG Ludwigshafen

C 303

Source: BASF AG Ludwigshafen

C 303 (hydroxide)

Source: BASF AG Ludwigshafen

C 303H

Source: BASF AG Ludwigshafen

C 308

Source: BASF AG Ludwigshafen

C 308 (hydroxide)

Source: BASF AG Ludwigshafen

1. General Information

date: 18-FEB-2000
Substance ID: 21645-51-2

C 31		
Source:	BASF AG	Ludwigshafen
C 315		
Source:	BASF AG	Ludwigshafen
C 315H		
Source:	BASF AG	Ludwigshafen
C 31C		
Source:	BASF AG	Ludwigshafen
C 31F		
Source:	BASF AG	Ludwigshafen
C 325		
Source:	BASF AG	Ludwigshafen
C 325 (hydroxide)		
Source:	BASF AG	Ludwigshafen
C 33		
Source:	BASF AG	Ludwigshafen
C 333		
Source:	BASF AG	Ludwigshafen
C 4D		
Source:	BASF AG	Ludwigshafen
Calmogastrin		
Source:	BASF AG	Ludwigshafen
Catapal B		
Source:	BASF AG	Ludwigshafen
CE 30E		
Source:	BASF AG	Ludwigshafen
CHP 340S		
Source:	BASF AG	Ludwigshafen
CL 303		
Source:	BASF AG	Ludwigshafen
CL 310		
Source:	BASF AG	Ludwigshafen
CL 310 (hydroxide)		
Source:	BASF AG	Ludwigshafen
CW 308		
Source:	BASF AG	Ludwigshafen
CW 325		
Source:	BASF AG	Ludwigshafen

CW 380S

Source: BASF AG Ludwigshafen

DHT 4A (3)

Source: Shell Nederland Chemie B.V. Rotterdam

DT 079

Source: BASF AG Ludwigshafen

F 1000

Source: BASF AG Ludwigshafen

F 2000

Source: BASF AG Ludwigshafen

FM

Source: BASF AG Ludwigshafen

FM (filler)

Source: BASF AG Ludwigshafen

GHA 131

Source: BASF AG Ludwigshafen

GHA 331

Source: BASF AG Ludwigshafen

GHA 332

Source: BASF AG Ludwigshafen

GHA 431

Source: BASF AG Ludwigshafen

GHA 731

Source: BASF AG Ludwigshafen

H 21

Source: BASF AG Ludwigshafen

H 30C

Source: BASF AG Ludwigshafen

H 31

Source: BASF AG Ludwigshafen

H 310ST

Source: BASF AG Ludwigshafen

H 32

Source: BASF AG Ludwigshafen

H 34L

Source: BASF AG Ludwigshafen

H 42

Source: BASF AG Ludwigshafen

H 42ST		
Source:	BASF AG	Ludwigshafen
H 46		
Source:	BASF AG	Ludwigshafen
H3A103		
Source:	INCEMIN AG	Holderbank
HAL 42		
Source:	BASF AG	Ludwigshafen
HAL 43		
Source:	BASF AG	Ludwigshafen
Highlite H 43		
Source:	BASF AG	Ludwigshafen
Higilite		
Source:	BASF AG	Ludwigshafen
Higilite 42M		
Source:	BASF AG	Ludwigshafen
Higilite 42S		
Source:	BASF AG	Ludwigshafen
Higilite H		
Source:	BASF AG	Ludwigshafen
Higilite H 10		
Source:	BASF AG	Ludwigshafen
Higilite H 100		
Source:	BASF AG	Ludwigshafen
Higilite H 10C		
Source:	BASF AG	Ludwigshafen
Higilite H 141		
Source:	BASF AG	Ludwigshafen
Higilite H 21		
Source:	BASF AG	Ludwigshafen
Higilite H 210		
Source:	BASF AG	Ludwigshafen
Higilite H 30		
Source:	BASF AG	Ludwigshafen
Higilite H 31		
Source:	BASF AG	Ludwigshafen
Higilite H 310		
Source:	BASF AG	Ludwigshafen

Higilite H 311		
Source:	BASF AG	Ludwigshafen
Higilite H 31S		
Source:	BASF AG	Ludwigshafen
Higilite H 32		
Source:	BASF AG	Ludwigshafen
Higilite H 320		
Source:	BASF AG	Ludwigshafen
Higilite H 320ST		
Source:	BASF AG	Ludwigshafen
Higilite H 32I		
Source:	BASF AG	Ludwigshafen
Higilite H 32IX		
Source:	BASF AG	Ludwigshafen
Higilite H 32S		
Source:	BASF AG	Ludwigshafen
Higilite H 32ST		
Source:	BASF AG	Ludwigshafen
Higilite H 32TX		
Source:	BASF AG	Ludwigshafen
Higilite H 34		
Source:	BASF AG	Ludwigshafen
Higilite H 34HL		
Source:	BASF AG	Ludwigshafen
Higilite H 40		
Source:	BASF AG	Ludwigshafen
Higilite H 41		
Source:	BASF AG	Ludwigshafen
Higilite H 42		
Source:	BASF AG	Ludwigshafen
Higilite H 42H		
Source:	BASF AG	Ludwigshafen
Higilite H 42M		
Source:	BASF AG	Ludwigshafen
Higilite H 42S		
Source:	BASF AG	Ludwigshafen
Higilite H 43M		
Source:	BASF AG	Ludwigshafen

Higilite H 43S

Source: BASF AG Ludwigshafen

Higilite HBT 320

Source: BASF AG Ludwigshafen

Higilite HS 320ST

Source: BASF AG Ludwigshafen

Higilite HWC

Source: BASF AG Ludwigshafen

HWC

Source: BASF AG Ludwigshafen

Hychol 705

Source: BASF AG Ludwigshafen

Hydrafil

Source: BASF AG Ludwigshafen

Hydral 700

Source: BASF AG Ludwigshafen

Hydral 705

Source: BASF AG Ludwigshafen

Hydral 710

Source: BASF AG Ludwigshafen

Hydral 710B

Source: BASF AG Ludwigshafen

Hydral 710W

Source: BASF AG Ludwigshafen

Hydral PGA

Source: BASF AG Ludwigshafen

Hydrated alumina

Source: Rhone-Poulenc Italia SpA Livorno
BASF AG Ludwigshafen

Hydrated alumina

Source: Du Pont de Nemours International S.A. Antwerpen

Hydroxal

Source: BASF AG Ludwigshafen

Kyowaad 200S

Source: BASF AG Ludwigshafen

LA

Source: BASF AG Ludwigshafen

LA (filler)

Source: BASF AG Ludwigshafen

LA 5

Source: BASF AG Ludwigshafen

Liquigel

Source: BASF AG Ludwigshafen

Martifin

Source: BASF AG Ludwigshafen

Martinal A

Source: BASF AG Ludwigshafen

Martinal A/S

Source: BASF AG Ludwigshafen

Martinal BM 2

Source: BASF AG Ludwigshafen

Martinal C

Source: BASF AG Ludwigshafen

Martinal E

Source: BASF AG Ludwigshafen

Martinal F

Source: BASF AG Ludwigshafen

Martinal F-a

Source: BASF AG Ludwigshafen

Martinal OL 104

Source: BASF AG Ludwigshafen

Martinal OL 104C

Source: BASF AG Ludwigshafen

Martinal OL 107

Source: BASF AG Ludwigshafen

Martinal OL 111

Source: BASF AG Ludwigshafen

Martinal ON 310

Source: BASF AG Ludwigshafen

Martinal ON 313

Source: BASF AG Ludwigshafen

Martinal ON 320

Source: BASF AG Ludwigshafen

Martinal VPF 8907

Source: BASF AG Ludwigshafen

1. General Information

date: 18-FEB-2000
Substance ID: 21645-51-2

Martinal X		
Source:	BASF AG	Ludwigshafen
Micral 855		
Source:	BASF AG	Ludwigshafen
Micral 916		
Source:	BASF AG	Ludwigshafen
Micral 932		
Source:	BASF AG	Ludwigshafen
Mucogel		
Source:	BASF AG	Ludwigshafen
P 30BF		
Source:	BASF AG	Ludwigshafen
Paperad		
Source:	BASF AG	Ludwigshafen
Pepsamar		
Source:	BASF AG	Ludwigshafen
Reheis F 1000		
Source:	BASF AG	Ludwigshafen
RH 31F		
Source:	BASF AG	Ludwigshafen
RH 730		
Source:	BASF AG	Ludwigshafen
S 100		
Source:	BASF AG	Ludwigshafen
S 100 (filler)		
Source:	BASF AG	Ludwigshafen
SB 136		
Source:	BASF AG	Ludwigshafen
SB 432		
Source:	BASF AG	Ludwigshafen
SB 632		
Source:	BASF AG	Ludwigshafen
Securoc A		
Source:	INCEMIN AG	Holderbank
SF 11		
Source:	BASF AG	Ludwigshafen
SF 7		
Source:	BASF AG	Ludwigshafen

SpaceRite S 11ATH

Source: BASF AG Ludwigshafen

SpaceRite S 3ATH

Source: BASF AG Ludwigshafen

Spheralite 509A

Source: BASF AG Ludwigshafen

Tomix AD 220

Source: BASF AG Ludwigshafen

Tonerdehydrat

Source: Krems Chemie AG Krems

Trihyde OL 104

Source: BASF AG Ludwigshafen

Trihydroxyaluminum

Source: BASF AG Ludwigshafen

Trikup 710B

Source: BASF AG Ludwigshafen

UF 35E

Source: BASF AG Ludwigshafen

Ultrafine 15E

Source: BASF AG Ludwigshafen

Ultrafine 25E

Source: BASF AG Ludwigshafen

Ultrafine 35E

Source: BASF AG Ludwigshafen

White hydrate

Source: Du Pont de Nemours International S.A. Antwerpen**1.3 Impurities**

-

1.4 Additives

-

1.5 Quantity**Quantity**

more than 1 000 000 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:	Electrical/electronic engineering industry
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:	Polymers industry
Type:	industrial
Category:	Textile processing industry
Type:	use
Category:	Colouring agents
Type:	use
Category:	Construction materials additives
Type:	use
Category:	Cosmetics
Type:	use
Category:	Fillers
Type:	use
Category:	Flame retardants and fire preventing agents

Type: use
Category: Intermediates

Type: use
Category: Laboratory chemicals

Type: use
Category: Pharmaceuticals

Type: use
Category: Stabilizers

Type: use
Category: other: pigment

Type: use
Category: other: see RM

1.7.1 Technology Production/Use

-

1.8 Occupational Exposure Limit Values

Type of limit: MAK (DE)
Limit value: 6 mg/m³
Source: Du Pont de Nemours International S.A. Antwerpen
Ciba Specialty Chemicals Inc. Basel
Honsel-Guss GmbH Meschede

Type of limit: MAK (DE)
Limit value: 6 mg/m³
Remark: Fine dust value < 5 µm.
Source: Alumina Espanola S.A Madrid

Type of limit: MAK (DE)
Limit value: 6 mg/m³
Remark: Fine Dust Concentration
Source: INCEMIN AG Holderbank

Type of limit: MAK (DE)
Limit value: 6 mg/m³
Remark: Unspecific value for fine dust.
Source: Henkel KGaA Duesseldorf

(1)

Type of limit: MAK (DE)
Limit value: 6 mg/m³
Remark: Fine dust value < 5 µm
Source: Martinswerk GmbH Bergheim

1. General Information

date: 18-FEB-2000
Substance ID: 21645-51-2

Type of limit: MAK (DE)
Limit value: 6 mg/m³
Remark: Fine dust value < 5 µm
Source: Aluminium Oxid Stade GmbH Stade

Type of limit: MAK (DE)
Limit value: 6 mg/m³
Remark: Fine dust value < 5 µm
Source: Hydro Aluminium Uphusen GmbH Achim

Type of limit: MAK (DE)
Limit value: 6 mg/m³
Remark: Fine dust value < 5 µm.
Source: Eduard Hueck GmbH & Co. KG Lüdenscheid

Type of limit: OES (UK)
Limit value: 10 mg/m³
Remark: Total inhalable dust
EH 40/93 UK Health and Safety Executive
Source: Alcan Chemicals Ltd Gerrards Cross

Type of limit: OES (UK)
Limit value: 5 mg/m³
Remark: Respirable dust
EH 40/93 UK Health and Safety Executive
Source: Alcan Chemicals Ltd Gerrards Cross

Type of limit: TLV (US)
Limit value: 10 mg/m³
Remark: Considered a nuisance dust
Source: Rhone-Poulenc Italia SpA Livorno

(2)

Type of limit: other: NGV (Swe)
Limit value: 10 mg/m³
Remark: Continuous exposure during 8 h shift (NGV) due to AFS 1996.2
Source: Omya AB Malmö

Type of limit: other: VME
Limit value:
Remark: ACGIH VME (Al₂O₃) 10 mg/m³
Source: ALUMINIUM PECHINEY PARIS LA DEFENSE

1.9 Source of Exposure

Remark: Quantum Chemical Europe B.V. imports into the EU thermoplastic resin pellets which contain aluminum hydroxide as an encapsulated additive from Quantum's production plants in the United States. The material is either air freighted (via bag or box) or shipped (via bag, box or sea bulk/container) to the EU, then distributed within the EU by truck. Material is sold to plastic processors where it is converted into a variety of industrial and consumer products.

The typical loaded net weights per transport mode are as follows:

bags = 23 Kg
boxes = 360 - 680 Kg
containers = 17 - 20 mt

There are no special control measures during transport other than prescribed by the (inter)national regulations.

Source: Quantum Chemical Europe B.V. Bavel

Remark: Potential exposure by inhalation of dust when handling the product at workplace.

Source: Du Pont de Nemours International S.A. Antwerpen

Remark: Dust during production and handling (MAK-value 6 mg/m³)
Source: ALUMINIUM PECHINEY PARIS LA DEFENSE

(3)

Remark: Dust during production and handling (MAK-value 6 mg/m³)
Source: Alumina Espanola S.A Madrid

(4)

Remark: Sources of potential human exposure :
None

Source: Rhone-Poulenc Italia SpA Livorno

Remark: Production process :
Ground bauxite is digested in a caustic soda solution. The undissolved solids are removed by settling and filtration and disposed of in a landfill site. The caustic liquor is cooled and aluminium hydroxide precipitates. The hydroxide is separated from the liquor by filtration. The solids are dried and sent to storage. the filtrate is returned to the process to digest more bauxite.

Source: Rhone-Poulenc Italia SpA Livorno

Remark: Potential inhalation exposure during processing. Use good industrial hygiene practices.

Source: Ciba Specialty Chemicals Inc. Basel

Remark: Dust during production and handling (MAK-value 6 mg/m³)
Source: Alcan Chemicals Ltd Gerrards Cross

(3)

Remark: Dust during production and handling (MAK-value 6 mg/m3)
Source: Martinswerk GmbH Bergheim

(5)

Remark: Dust during production and handling (MAK-value 6 mg/m3)
Source: Aluminium Oxid Stade GmbH Stade

(6)

Remark: Dust during production and handling (MAK-value 6 mg/m3)
Source: Hydro Aluminium Uphusen GmbH Achim

(4)

Remark: Dust during production and handling (MAK-value 6 mg/m3)
Source: Eduard Hueck GmbH & Co. KG Lüdenscheid

(3)

Remark: siehe 1.10
Source: Honsel-Guss GmbH Meschede

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: other: industry self classification
Labelled by: other: industry self classification
Class of danger: 0 (generally not water polluting)
Source: Henkel KGaA Duesseldorf

(7)

1.14.2 Major Accident Hazards

Legislation:
Substance listed: no
Source: Henkel KGaA Duesseldorf

1.14.3 Air Pollution

-

1.15 Additional Remarks**Remark:** Waste disposal according to local regulations**Source:** ALUMINIUM PECHINEY PARIS LA DEFENSE
Alumina Espanola S.A Madrid
Alcan Chemicals Ltd Gerrards Cross
Martinswerk GmbH Bergheim
Aluminium Oxid Stade GmbH Stade
Hydro Aluminium Uphusen GmbH Achim**Remark:** Mode of transport : no special requirements**Source:** Disposal : collect in containers, bags or covered boxes.
Maybe disposed at an industrial secure landfill
Rhone-Poulenc Italia SpA Livorno**Source:** Henkel KGaA Duesseldorf**Remark:** In relation to the above-mentioned material it is endrained mud, which arises during the purification of sewage.**Source:** Waste disposal according to local regulations
Eduard Hueck GmbH & Co. KG Lüdenscheid**Remark:** C. Besondere Anmerkungen/Technische Information
C.1 Verbesserte DefinitionFilterkuchen aus der Al-Herstellung, bestehend aus ca.
27% Aluminiumhydroxid, 3% Chrom(III)hydroxid und
70% Wasser, entsteht in der Abwasserbehandlungsanlage bei
der Neutralisation von Al-Beizen.C.2 Exposition
Augen- und Hautkontakt vermeiden.C.3 Umweltaspekte
Auf Grund der Zusammensetzung wahrscheinlich
wassergefährdend.C.4 Verwendung, Wiederverwendung, Beseitigung
Aluminiumhydroxid wird im Prozeß zur Gewinnung von
Reinaluminium als Impfstoff in die Natriumaluminatlauge
verwendet, um zunächst Aluminiumoxid zu erhalten.**Source:** Honsel-Guss GmbH Meschede**Remark:** Aus galvanischer Oberflächenbehandlung**Source:** Alcan Deutschland Werk Nürnberg Nürnberg

1.16 Last Literature Search

-

1.17 Reviews

-

1.18 Listings e.g. Chemical Inventories

-

2.1 Melting Point

Value: ca. 200 degree C
Decomposition: yes
Remark: Decomposition into Aluminium Oxide and Water
Source: INCEMIN AG Holderbank

Value:
Decomposition: yes
Sublimation: no
Remark: At ca. 150-220 °C decomposition to Al₂O₃ and H₂O.
Source: Martinswerk GmbH Bergheim

2.2 Boiling Point

Value:
Remark: Not applicable
Source: Martinswerk GmbH Bergheim

2.3 Density

Type: density
Value: ca. 2.42 g/cm³ at 20 degree C
Source: INCEMIN AG Holderbank

Type: density
Value: 2.42 g/cm³ at 20 degree C
GLP: yes
Remark: JSO 787/10
Source: Martinswerk GmbH Bergheim

(8)

Type: relative density
Value: 1.01 - 1.25 at 25 degree C
Method: other
Source: REHEIS IRELAND DUBLIN

Type: density
Value: = 2.42 g/cm³
Source: Omya AB Malmö

2.3.1 Granulometry

-

2.4 Vapour Pressure

Value:
Remark: Not applicable
Source: Martinswerk GmbH Bergheim

2.5 Partition Coefficient

log Pow:

Method:

Year:

Remark: Not applicable

Source: Martinswerk GmbH Bergheim

2.6.1 Water Solubility

Value: ca. .0015 g/l at 20 degree C

pH: 7

Source: Martinswerk GmbH Bergheim

(9)

Value: ca. .015 mg/l at 20 degree C

Qualitative: not soluble

pH: ca. 8 - 9 and 20 degree C

Source: INCEMIN AG Holderbank

Qualitative: not soluble

Source: Omya AB Malmö

Value: <

pH: 5.8 - 6.8 at 40 g/l and 25 degree C

Source: REHEIS IRELAND DUBLIN

2.6.2 Surface Tension

-

2.7 Flash Point

Value:

Type:

Method:

Year:

Remark: Not applicable

Source: Martinswerk GmbH Bergheim

2.8 Auto Flammability

Value:

Remark: Not applicable

Source: Martinswerk GmbH Bergheim

2.9 Flammability

Result: non flammable

Source: REHEIS IRELAND DUBLIN

Result:
Remark: Not applicable
Source: Martinswerk GmbH Bergheim

2.10 Explosive Properties

Result: not explosive
Source: REHEIS IRELAND DUBLIN

Result:
Remark: Not applicable
Source: Martinswerk GmbH Bergheim

2.11 Oxidizing Properties

Result: no oxidizing properties
Source: REHEIS IRELAND DUBLIN

Result:
Remark: Not applicable
Source: Martinswerk GmbH Bergheim

2.12 Additional Remarks

-

3.1.1 Photodegradation

Type:

Method:

Year:

GLP:

Test substance:

Remark: Not applicable

Source: Martinswerk GmbH Bergheim

3.1.2 Stability in Water

Type:

Method:

Year:

GLP:

Test substance:

Remark: Not applicable

Source: Martinswerk GmbH Bergheim

3.1.3 Stability in Soil

Type:

Radiolabel:

Concentration:

Cation exch.

capac.

Microbial

biomass:

Method:

Year:

GLP:

Test substance:

Remark: Not applicable

Source: Martinswerk GmbH Bergheim

3.2 Monitoring Data (Environment)

Type of

measurement:

Medium:

Remark: Aluminium in the Environment

Aluminium is the most abundant metal and the third most abundant element, and composes approximately 8 % of the earth's crust. Its ubiquitous nature is understandable and if one reviews the considerable amount of literature available on Aluminium sources, transport, and fate in the environment, this becomes even more apparent.

Aluminium is everywhere; it is present in soils and clays, minerals and rocks and even in water, but not as a metal.

That is because Aluminium is a very chemically active element. Because of its chemical activity, and particularly its affinity for oxygen, Aluminium is not found in metallic state in nature; Aluminium is always found chemically combined with other elements, particularly oxygen.

Aluminium forms many inorganic and organic complexes in soil and surface waters.

Very little Aluminium ion is normally present in neutral waters, Aluminium hydroxide has a low solubility.

In the early part of this century, the phytotoxicity of Aluminium in agroecosystems was well known. Elaborate measures were taken to ameliorate Aluminium toxicity by lime application and by selection of Aluminium-tolerant species or cultivars. While some plant species are highly sensitive, others are capable of thriving in high-Aluminium soils.

The recent (last two decades) flurry in Aluminium research has focused on the effects of increased mobilization of Aluminium by acidic deposition. Increased Aluminium concentrations and corresponding reductions in fish populations have been attributed to the mobilization of Aluminium from the edaphic to the aquatic environment. Most of the research in aquatic ecosystems is contemporary, although much information on the terrestrial effects of Aluminium dates back to the early 1900's.

Another factor hindering progress in understanding the effects of Aluminium in the environment is the lack of analytical methods for determining the multitude of forms in which the element occurs. It is now well understood that the toxicity of Aluminium in aquatic and terrestrial systems is not well correlated with total Aluminium concentrations, but it a function of the concentration of the biologically active fraction of the total. In terms of acute toxicity, the inorganic monomeric form of Aluminium is believed to be the most toxic. However, organically bound species may be capable of crossing biological membranes and contribute to chronic bioaccumulation. In order to ascertain which species of Aluminium are acutely or chronically toxic, chemists must supply toxicologists with the necessary analytical tools. Existing methods are usually operationally defined (e.g., filterable, acid-extractable, nonexchangeable, labile, and nonlabile) and their biological relevance is not well known.

Source: Martinswerk GmbH Bergheim

3.3.1 Transport between Environmental Compartments

Type:

Media:

Method:

Year:

Remark: Not data available

Source: Martinswerk GmbH Bergheim

3.3.2 Distribution

Media:

Method:

Year:

Remark: No data available

Source: Martinswerk GmbH Bergheim

3.4 Mode of Degradation in Actual Use

Remark: No degradation

Source: Martinswerk GmbH Bergheim

3.5 Biodegradation

Type:

Inoculum:

Method:

Year:

GLP:

Test substance:

Remark: No data available

Source: Martinswerk GmbH Bergheim

3.6 BOD5, COD or BOD5/COD Ratio

Remark: Not applicable

Source: Martinswerk GmbH Bergheim

3.7 Bioaccumulation

Species:

Exposure period:

Concentration:

BCF:

Elimination:

Method:

Year:

GLP:

Test substance:

Remark: No data available

Source: Martinswerk GmbH Bergheim

3.8 Additional Remarks

-

AQUATIC ORGANISMS**4.1 Acute/Prolonged Toxicity to Fish**

Type: semistatic
Species: Salmo trutta (Fish, fresh water, marine)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: > 100
Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 1992 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Method: Test substance is aluminium hydroxide in powder form
Source: Pechiney Paris

(10)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: **Analytical monitoring:**
Method: other
Year: 1989 **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: Method : DIN 38412 L12
Result : No influence
Test substance : as prescribed, saturated solution. Purity : 99 %
Source: Martinswerk GmbH Bergheim

(11)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: > 100
Method: OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year: 1992 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Source: Pechiney Paris

(12)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: **Analytical monitoring:**
Method: other
Year: 1989 **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: Method : DIN 38412 L11
Result : No influence
Test substance : as prescribed, saturated solution
Source: Martinswerk GmbH Bergheim

(13)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: other
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: > 100
Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 1992 **GLP:** yes
Test substance: as prescribed by 1.1 - 1.4
Method: Endpoint: Growth inhibition
Testmethode: OECD guideline 201, with reduced Fe-EDTA
Source: Pechiney Paris

(14)

Species:
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: No data available
Source: Martinswerk GmbH Bergheim

4.4 Toxicity to Microorganisms e.g. Bacteria

Type:
Species: Pseudomonas putida (Bacteria)
Exposure period:
Unit: **Analytical monitoring:**
Method: other
Year: 1989 **GLP:**
Test substance: as prescribed by 1.1 - 1.4
Remark: Method : DEV L8, modified
Result : no influence
Test substance : as prescribed, saturated solution. Purity :
> 99 %
Source: Martinswerk GmbH Bergheim

(11)

4.5 Chronic Toxicity to Aquatic Organisms**4.5.1 Chronic Toxicity to Fish**

Species:
Endpoint:
Exposure period:
Unit: Analytical monitoring:
Method:
Year: GLP:
Test substance:
Remark: No data available
Source: Martinswerk GmbH Bergheim

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species:
Endpoint:
Exposure period:
Unit: Analytical monitoring:
Method:
Year: GLP:
Test substance:
Remark: No data available
Source: Martinswerk GmbH Bergheim

TERRESTRIAL ORGANISMS**4.6.1 Toxicity to Soil Dwelling Organisms**

Type:
Species:
Endpoint:
Exposure period:
Unit:
Method:
Year: GLP:
Test substance:
Remark: no data available
Source: Martinswerk GmbH Bergheim

4.6.2 Toxicity to Terrestrial Plants

Species:
Endpoint:
Expos. period:
Unit:
Method:
Year: GLP:
Test substance:
Remark: No data available
Source: Martinswerk GmbH Bergheim

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

-

4.7 Biological Effects Monitoring

Remark: No data available

Source: Martinswerk GmbH Bergheim

4.8 Biotransformation and Kinetics

Type:

Remark: No data available

Source: Martinswerk GmbH Bergheim

4.9 Additional Remarks

-

5.1 Acute Toxicity**5.1.1 Acute Oral Toxicity**

Type: LD50
Species: rat
Sex:
Number of
Animals:
Vehicle:
Value: > 5000 mg/kg bw
Method:
Year: GLP:
Test substance:
Source: Omya AB Malmö

Type: LD50
Species: rat
Sex:
Number of
Animals:
Vehicle:
Value: > 5000 mg/kg bw
Method: OECD Guide-line 401 "Acute Oral Toxicity"
Year: 1989 GLP:
Test substance:
Remark: Test substance : powder
Source: Martinswerk GmbH Bergheim

5.1.2 Acute Inhalation Toxicity

Type:
Species:
Sex:
Number of
Animals:
Vehicle:
Exposure time:
Value:
Method:
Year: GLP:
Test substance:
Remark: No data available
Source: Martinswerk GmbH Bergheim

5.1.3 Acute Dermal Toxicity

Type:
Species:
Sex:
Number of
Animals:
Vehicle:
Value:
Method:
Year: GLP:
Test substance:
Remark: No data available
Source: Martinswerk GmbH Bergheim

5.1.4 Acute Toxicity, other Routes

Type:
Species:
Sex:
Number of
Animals:
Vehicle:
Route of admin.:
Value:
Method:
Year: GLP:
Test substance:
Remark: No data available
Source: Martinswerk GmbH Bergheim

5.2 Corrosiveness and Irritation**5.2.1 Skin Irritation**

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of
Animals:
PDII:
Result:
EC classificat.:
Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year: 1989 GLP:
Test substance:
Remark: Not irritating according to EEC labelling regulations. No
symbol and risk phrases required.
Test substance : powder
Source: Martinswerk GmbH Bergheim

Species:**Concentration:****Exposure:****Exposure Time:****Number of
Animals:****PDII:****Result:** not irritating**EC classificat.:****Method:****Year:****GLP:****Test substance:****Source:** REHEIS IRELAND DUBLIN

5.2.2 Eye Irritation

Species: rabbit**Concentration:****Dose:****Exposure Time:****Comment:****Number of
Animals:****Result:****EC classificat.:****Method:** OECD Guide-line 405 "Acute Eye Irritation/Corrosion"**Year:**

1989

GLP:**Test substance:****Remark:** Not irritating to rabbit eye according to EEC labelling regulations.

No symbol and risk phrases required.

Test substance : powder

Source: Martinswerk GmbH Bergheim**Species:****Concentration:****Dose:****Exposure Time:****Comment:****Number of
Animals:****Result:****EC classificat.:** not irritating**Method:****Year:****GLP:****Test substance:****Source:** REHEIS IRELAND DUBLIN

5.3 Sensitization

Type:
Species:
Number of
Animals:
Vehicle:
Result:
Classification:
Method:
Year: GLP:
Test substance:
Remark: No data available
Source: Martinswerk GmbH Bergheim

Type:
Species:
Number of
Animals:
Vehicle:
Result:
Classification: not sensitizing
Method:
Year: GLP:
Test substance:
Source: REHEIS IRELAND DUBLIN

5.4 Repeated Dose Toxicity

Species: Sex:
Strain:
Route of admin.:
Exposure period:
Frequency of
treatment:
Post. obs.
period:
Doses:
Control Group:
Method:
Year: GLP:
Test substance:
Remark: No data available
Source: Martinswerk GmbH Bergheim

5.5 Genetic Toxicity 'in Vitro'

Type:

System of
testing:

Concentration:

Metabolic
activation:

Result:

Method:

Year:

GLP:

Test substance:

Remark: No data available

Source: Martinswerk GmbH Bergheim

5.6 Genetic Toxicity 'in Vivo'

Type:

Species:

Sex:

Strain:

Route of admin.:

Exposure period:

Doses:

Result:

Method:

Year:

GLP:

Test substance:

Remark: No data available

Source: Martinswerk GmbH Bergheim

5.7 Carcinogenicity

Species:

Sex:

Strain:

Route of admin.:

Exposure period:

Frequency of
treatment:Post. obs.
period:

Doses:

Result:

Control Group:

Method:

Year:

GLP:

Test substance:

Result: No carcinogenic effects

Source: Martinswerk GmbH Bergheim

(15)

5.8 Toxicity to Reproduction

Type:
Species: Sex:
Strain:
Route of admin.:
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: GLP:
Test substance:
Remark: No data available
Source: Martinswerk GmbH Bergheim

5.9 Developmental Toxicity/Teratogenicity

Species: mouse Sex:
Strain: Swiss
Route of admin.: gavage
Exposure period: days 6-15
Frequency of treatment: daily
Duration of test: gestation days 6-18
Doses: 0-66.5-133-266 mg/kg
Control Group: yes
Method:
Year: GLP:
Test substance: as prescribed by 1.1 - 1.4
Result: No evidence of material toxicity, embryo/fetal toxicity or teratogenicity
Source: Martinswerk GmbH Bergheim

(16)

5.10 Other Relevant Information

Type:
Source: Martinswerk GmbH Bergheim
(17) (18) (19) (20) (21) (22) (23) (24) (25) (26)

5.11 Experience with Human Exposure

Remark: There has been and there is still much dispute concerning the role of Aluminium and Health. Because Aluminium is so abundant in nature man is constantly exposed to large amount of it. But very little is actually found in human beings.

Allegation concerning neurological effects of Aluminium began appearing in the mid-1970's. It is now well established that patient in need of dialysis must not be treated with dialysis fluids containing high concentration

of Aluminium. Recent researches strongly question the presence of Aluminium Alzheimer structures in the brain and the role of aluminium in the actiology of Alzheimer disease. Present study focus on the possible role of the amyloid protein and the influence of genetic factors, possibly there are even mistakes in analytical methods.
Used as antacidans

Source: Martinswerk GmbH Bergheim

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7.1 Risk Assessment

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**Ministry of Environment
and Food of Denmark**
Environmental
Protection Agency

Environmental and health screening pro- files of phosphorous flame retardants

A LOUS follow-up project

Revision of October 2016

Environmental project
No. 1823

October 2016

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COWI A/S

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Sources must be acknowledged.

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Preface

Alternatives to halogenated flame retardants are to a large extent based on phosphorus chemistry. The Danish EPA has identified a lack of data on environmental and health effects of many of the phosphorous flame retardants and a lack of uniform data that can be used by companies who want to substitute phosphorous flame retardants for halogenated flame retardants.

This project compiles information about marketed phosphorous flame retardants, evaluates and modifies a screening tool for assessing flame retardants and other substances, and presents human health and environmental hazard screening profiles for a selected number of flame retardants in order to help companies to identify potential alternatives to halogenated flame retardants.

This revised version has been prepared in October 2016 in response to comments received from industry and Clean Productin Action to the report. The revision mainly concerns the description of the GreenScreen® method as well as the description of diethylphosphinate, aluminium salt (CAS No. 225789-38-8) and the description of polyphosphonate and phosphonate oligomers (both with CAS No. 68664-06-2).

Steering group

The project has been followed by a steering group consisting of:

- Toke Winther, Danish EPA (Chairman)
- Jesper Gruvmark, Danish EPA
- Carsten Lassen, COWI
- Jesper Kjølholt, COWI

Working group

The project has been carried out from July 2015 to November 2015 by a working group consisting of Carsten Lassen (Project Manager), Marlies Warming, Anna Brinch, Julie Zwicky Burkal, Jesper Kjølholt and Sonja Hagen Mikkelsen, COWI A/S, Denmark.

Summary and conclusion

Alternatives to halogenated flame retardants are to a large extent based on phosphorus chemistry. The Danish EPA has identified a lack of data on environmental and health effects of many of the phosphorous flame retardants and a lack of uniform data that can be used by companies who want to substitute phosphorous flame retardants for halogenated flame retardants.

The aim of this project has been to identify phosphorous flame retardants and develop screening level substance hazard profiles, to be used for substitution consideration in a European REACH context by companies using flame retardants.

The screening hazard profiles have been prepared based on a modified version of a method for hazard assessment of chemicals known as GreenScreen® for Safer Chemicals (GreenScreen®). GreenScreen® was developed based on the US EPA "Design for the Environment" (DfE) programme, as well as other international and national frameworks including Global Harmonized System of Classification and Labelling of Chemicals (GHS) and the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). It consists of a hazard profiling part and a "benchmarking" part aimed to assess the relevance of a substance for consideration in a substitution context. For some effect categories the GreenScreen® hazard criteria are different from the criteria used in the DfE assessments. For the purpose of the current project, the method was reviewed and modified taking into account a European regulatory context and the focus in this project on chemical hazard assessment in relation to consumer products.

Long list of phosphorous flame retardants

A gross list of 88 phosphorous flame retardant substances has been compiled based on literature and information on websites of manufacturers of flame retardants organised in the two trade associations EFRA (European Flame Retardants Association) and Pinfa (Phosphorus, Inorganic and Nitrogen Flame Retardants Association). Of these, approximately 50-60 different flame retardants substances are manufactured today. The two organisations represent all major manufacturers of flame retardants in Europe and the USA, and the list thereby is considered to include the main phosphorous flame retardants produced in this part of the world. The number cannot be estimated exactly as many of the flame retardants have proprietary (confidential) CAS numbers and chemical names. The substances are used in various flame retardant products (in combination with other constituents and other flame retardant substances), and the number of different flame retardant products is considerably higher than the number of substances.

The long list includes information on CAS No, chemical name, structural and general formula, phosphorous content, product and manufacturer names, and the tonnage registered under REACH.

Review and modification of the GreenScreen® methodology

A critical review of the GreenScreen® methodology was performed to evaluate its applicability for hazard assessment related to consumers and the environment in a European regulatory context. Based on this, the method was modified prior to use for hazard profiling in this report.

The EU applicability of the methodology has been addressed by critically reviewing the following main elements:

- i) the data sources to be used and their relative importance,
- ii) the hazard classification criteria, and
- iii) the alternatives assessment strategy and criteria for benchmarking of the substances.

The review revealed that the GreenScreen® methodology was developed using an internationally oriented approach with REACH and CLP/GHS criteria and guidance documents as key data for classifying the substances and recommends internationally recognized data sources. Thus, the approach was found to be in line also with Danish EPA and ECHA guidance documents for hazard identification. Consequently, the suggested adaptations of the hazard profiling part of the method are relatively minor and mainly concern the priority of some data sources, small adjustments of a few hazard classification limits, e.g. those for bioaccumulation, and omission of physical hazards from the hazard profiles (considered irrelevant in the consumer product context in the current project). A pilot test using the modified methodology was conducted on two substances, one previously assessed by the US EPA and one new substance. The modified screening profile of the substance previously evaluated by the US EPA differed from the earlier assessment only with regard to endocrine activity (not scored by US EPA) and bioaccumulation (score changed from "high" to "moderate" due to proposed changes in criteria limits for this endpoint).

As regards the benchmarking part of the GreenScreen® methodology, the only modification introduced is omission of criteria related to physical hazards, in consequence of the omission of these parameters in the hazard profiling part.

Selection of phosphorous flame retardants for screening

Besides a re-evaluation using the modified methodology of 23 flame retardant substances screened as part of the US EPA DfE programme, five flame retardants were selected for screening in this study. The five flame retardants were selected from the long list based on the following criteria: 1) The substance is already to some extent used as an alternative to halogenated flame retardants or marketed specifically as such; 2) the substance meets the applicable fire safety requirement for major applications of some halogenated flame retardants; 3) the substance is registered under REACH, or significant environmental and health data are available otherwise; and 4) the substance is not classified as a CMR substance in accordance with the CLP Regulation (Regulation (EC) No 1272/2008). The re-evaluation with the modified methodology was based on data provided by the US EPA DfE programme and no additional data has been used.

Applicability and screening profiles of manufactured phosphorous flame retardants

Using the modified screening method, screening profiles and overall hazard scores have been developed for 28 substances as summarised in Table 1. In the case where no modifications are suggested and where there are differences between the GreenScreen® hazard criteria and the criteria in the US EPA DfE programme, the criteria from the DfE programme have been used. The table furthermore includes screening profiles for some of the main halogenated flame retardants (more US EPA profiles shown in Appendix 1). Please note that the brominated flame retardants are typically used together with antimony trioxide, which has a harmonised classification as carcinogenic.

Besides the screening profiles, for each of the identified manufactured phosphorous flame retardants, information on the applicability of the flame retardants has been reviewed and summarised. The summarised information includes:

- Applicability for each of the substrates as indicated by Pinfa's Product Selector¹;
- Substrates (type of plastics, paint, textiles, etc.) as indicated by manufacturers;
- End applications (automotive, building sector, etc.) as indicated by manufacturers;
- Interaction with substrate (additive, reactive);
- Availability (recently introduced, widely applied, main flame retardant for the applications, etc.) to the extent data are available from manufacturers or the literature.
- Flame retardancy: Various information on the ability of the flame retardants in meeting different fire safety standards for relevant substrates as indicated in the literature, technical data sheets, etc. The description is built on the information readily available for each flame retardant.
- Halogen-containing flame retardants for the same application to the extent it is described in the literature or from the manufacturers' product selectors.

The review shows that phosphorous flame retardants are available for the major applications of halogenated flame retardants. The indications of applicability are mainly provided on an overall level. The list may be used to identify relevant alternative flame retardants. However, more specific information on applicability and price should be obtained from the listed manufacturers in a concrete substitution context.

Discussion of the applicability of the modified GreenScreen method

The hazard profiling methodology is assessed to be applicable to human health and environmental hazard profiling of chemical substances in a European context, not only for substances belonging to the group of flame retardants addressed in this project, but for hazard profiling of chemicals of possible concern in general. Flame retardant systems often consist of a mixture of several flame retardants and it should be noted that an assessment of a flame retardant system would include an assessment of each of the components. As an example the brominated flame retardants would often be used in combination with antimony trioxide so this substance should be included in the screening as well. The current GreenScreen Guidance does not provide any decision logic for deriving a single benchmark score for the mixture, but a practical approach would be to use the benchmark score for the component with the lowest score (i.e. highest hazard) as decisive for the total score of the mixture. Benchmark scoring is possible even if data are not available for all hazard endpoints. E.g. data on sensitization are not necessary in order to score at the second highest benchmark level (BM3), however scoring at the highest level (BM4) is only permissible for substances where data for all endpoints exist. If the aim of the assessment is to identify possible alternatives to a given chemical, it is recommended to start with a rough assessment based on the harmonised classification or the selfclassification in the ECHA C&L inventory before starting to prepare a full hazard profile for a substance.

It should be emphasized that hazard profiling using this screening tool must be performed by persons with solid professional capability and experience within toxicology/human health assessment and environmental assessment in order to obtain reliable, balanced substance profiles, not least when assessing substances with incomplete data sets or with conflicting data for the same effect parameter. Additionally, in some cases it may be necessary to generate/estimate data by use of QSAR modelling tools, which can require special expertise. For the substances assessed in this study, no new QSAR modelling has been carried out, however available QSAR-based data (e.g. from the Danish (Q)SAR Database) have been used, where relevant.

¹ <http://pinfa.org/index.php/product-selector>

As regards the benchmarking part of the methodology, i.e. an assessment of the relevance of substances in a substitution context, the exercise of scoring the 28 phosphorous substances revealed that the majority of the substances ended up in the second-lowest overall hazard category (2) and only three substances obtained a better score (i.e. 3 or 4). The highest scores are for ammonium polyphosphate, poly[phosphonate-co-carbonate] and phosphinic acid, aluminium salt (3:1), whereas the aryl phosphates in general scores low (1). Thus, the differentiation between the substances appears to be too low to be operational in a substitution situation. This outcome was, at least to some extent, caused by a "gap" between two benchmark criteria levels (BM1 and BM2) in the GreenScreen® method, resulting in some substances obtaining a benchmark score that do not appear to fully reflect their hazard potential (i.e. a too high score). Hence, an additional benchmark level ("BM1½") could in principle be relevant to introduce for future occasions. However, neither BM1½ nor BM2 are probably substances being very relevant to consider as possible alternatives in the long.

Finally, it should be noted that in a substitution decision-making situation, the hazard profile of a substance cannot stand alone but must be complemented by exposure considerations for relevant use scenarios. This could e.g. result in placing more weight on some endpoints than others for a specific use scenario. E.g. in many consumer product contexts (i.e. product where possible release will take over time), "acute toxicity" will not be relevant because acute concentrations are not likely to occur in reality and, hence, this endpoint could either be omitted or be given lower weight than chronic endpoints.

Furthermore, the mobility of the substance in the polymer matrix should be taken into account. Reactive flame retardants, are chemically bound to the polymer matrix, and are consequently expected to have lower mobility and volatility than additive flame retardants and would result in lower exposure levels especially in the use phase of the product life cycle. Polymeric flame retardants would likewise be expected to have lower mobility and volatility, resulting in lower exposure levels during the use phase.

TABLE 1

HAZARD PROFILES AND OVERALL HAZARD SCORES BASED ON THE MODIFIED GREENSCREEN METHOD FOR SELECTED HALOGENATED AND PHOSPHOROUS FLAME RETARDANTS.

Chemical name	CAS No.	Group I Human					Group II and II* Human								Ecotox		Fate		Overall hazard score		
		C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P		B	
								single	repeat*	single	repeat*										
Organophosphorous compounds																					
9,10-Dihydro-9-oxa-10-phosphaphenanthren-10-oxide (DOPO) *[Re]	35948-25-5	M	L	L	M	DG	L	DG	L	DG	M	M	DG	L	M	L	M	H	VL	2	
N,N-bis-(2-hydroxyethyl) aminomethane phosphonic acid diethyl ester	2781-11-5	M	M	L	L	DG	L	DG	M	DG	M	M	DG	L	L	M	L	H	L	2	
Poly(m-phenylene methylphosphonate) *[Re]	63747-58-0	L	L	M	M	H	L	DG	M	DG	M	L	DG	L	L	H	H	VH	H	1	
Phosphonate oligomers (reactive) *[Re]	68664-06-2	M	L	L	L	DG	L	L	L	M	M	L	DG	M	M	L	H	VH	H	2	
Poly[phosphonate-co-carbonate]	77226-90-5	L	L	L	L	L	L	L	L	L	L	L	DG	L	L	L	L	VH	L	3	
Phosphoric acid, mixed esters with [1,1'-bisphenyl-4,4'-diol] and phenol	1003300-73-9	M	L	L	L	DG	L	DG	L	DG	L	L	DG	L	L	H	H	H	L	2	
Oligomerisk phosphonate polyol *[Re]	363626-50-0	M	M	L	M	DG	L	L	L	M	M	L	DG	L	L	L	M	M	L	2	
Organophosphates (phosphate esters) – Aryl phosphates																					
Triphenyl phosphate	115-86-6	M	L	L	L	H	L	DG	H	DG	L	L	DG	L	L	VH	VH	L	L	1	
Tricresyl phosphate	1330-78-5	L	L	H	M	DG	M	DG	H	DG	M	M	DG	L	L	VH	H	M	H	1	
Cresyl diphenyl phosphate	26444-49-5	L	L	H	M	DG	M	DG	H	DG	M	M	DG	L	L	VH	H	M	H	1	
Phosphoric acid, bis(methylphenyl) phenyl ester	26446-73-1	L	L	H	M	DG	M	DG	H	DG	M	M	DG	L	L	VH	H	M	H	1	
Resorcinol bis-diphenyl phosphate	57583-54-7 / 125997-21-9	M	L	L	M	H	L	DG	M	DG	M	L	DG	L	L	VH	VH	M	H	1	
Bisphenol A bis(diphenyl phosphate)	5945-33-5 / 181028-79-5	M	L	DG	L	DG	L	DG	L	DG	L	L	DG	L	L	L	L	H	M	2	
Organophosphates (phosphate esters) – Alkyl phosphates																					

Chemical name	CAS No.	Group I Human					Group II and II* Human								Ecotox		Fate		Overall hazard score	
		C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P		B
								single	repeat*	single	repeat*									
Oligomeric ethyl ethylene phosphate	184538-58-7	L	M	L	L	DG	L	DG	L	DG	M	L	DG	L	M	L	L	VH	L	2
Organophosphates (phosphate esters) – Aryl alkyl phosphates																				
Isopropyl phenyl phosphate	68937-41-7	M	L	H	M	DG	L	DG	H	H	H	L	DG	L	L	VH	VH	M	VH	1
Tris (p-t-butylphenyl) phosphate	78-33-1	M	L	M	L	DG	L	DG	H	DG	M	M	DG	M	L	VH	VH	M	H	2
Phenol, isobutyleneated, phosphate (3:1); Reaction mass of 4-tert-butylphenyl diphenyl phosphate and bis(4-tertbutylphenyl) phenyl phosphate and triphenyl phosphate **	68937-40-6	DG	L	L	L	DG	L	DG	M	M	M	L	DG	M	M	VH	VH	L	M	2
Melamine-derived and other organic phosphates (not being esters)																				
Melamine pyrophosphate	15541-60-3	M	M	L	L	DG	L	DG	M	L	L	L	DG	L	L	L	L	H	L	2
Diphosphoric acid, compd. with piperazine , and substituted amine phosphate	66034-17-1 and confid.	M	M	M	M	DG	H	DG	M	DG	DG	L	M	L	M	M	L	H	L	2
Melamine phosphate **	41583-09-9	M	L	L	L	DG	L	DG	M	DG	DG	L	DG	L	DG	L	L	VH	VL	2
Ethylenediamine-o-phosphate **	14852-17-6	L	L	L	M	DG		DG	M	DG	DG	H	H	VH	L	M	H	VL	VL	2
Inorganic phosphorous compounds																				
Ammonium polyphosphate	68333-79-9	L	L	L	L	L	L	L	L	L	L	L	DG	L	L	L	L	(VH)	L	4
Red phosphorus	7723-14-0	L	M	L	L	DG	L	L	L	L	L	L	DG	M	M	L	L	H	L	2
Phosphinic acid, aluminium salt (3:1)**	7784-22-7	DG	L	L	L	DG	L	DG	M	DG	DG	L	DG	L	M	M	M	(VH)	L	3
Other phosphorous and non-categorised substances																				
Diethylphosphinate, aluminium	225789-38-8	L	L	L	M	DG	L	M	M	DG	M	L	DG	VL	L	M	M	H	L	2
Confidential halogen-free flame retardant, Emerald Innovation™ NH-1	Confidential	M	L	M	L	H	H	DG	H	DG	M	M	DG	M	M	VH	VH	M	H	1
Fyrol™ HF-5 **	Confidential	M	M	L	M	H	L	DG	M	DG	M	L	DG	L	M	VH	VH	VH	M	1
6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide **	848820-98-4	DG	DG	DG	DG	DG	L	DG	DG	DG	DG	L	DG	H	DG	M	M	H	L	2

Chemical name	CAS No.	Group I Human					Group II and II* Human								Ecotox		Fate		Overall hazard score	
		C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P		B
								single	repeat*	single	repeat*									
Halogenated flame retardants (examples)																				
Decabrominated diphenyl ether (decaBDE)	1163-19-5	M	L	L	H	H	L	DG	M	DG	L	L	DG	L	L	L	L	VH	H	1
Tetrabromobisphenol A (TBBPA) *[Re] (also used additive)	79-94-7	M	L	L	M	H	L	DG	L	L	L	L	DG	L	M	VH	H	H	M	1
Hexabromocyclododecane (HBCDD)	25637-99-4	M	L	M	H	H	L	DG	M	M	M	L	DG	L	L	VH	VH	H	VH	1
Tris (1-chloro-2-propyl) phosphate (TCCP)	13674-84-5	M	L	H	H	M	L	DG	M	M	M	L	DG	L	L	M	M	H	L	1

*[Re]: Reactive flame retardants; **: Hazard profiles prepared as part of this study, whereas the remainder are based on US EPA (2014 a, 2014 b, 2015)

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation AA = Acute aquatic toxicity N = Neurotoxicity	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation	VL Very Low hazard L Low hazard M Moderate hazard H High hazard VH Very High hazard () Indicate specific assessments for inorganic substances for which the standard scoring criteria are not valid.	DG : Data Gap (on a white background) means that due to lack of data no hazard score has been assigned Bold font : hazard score is based on measured/empirical data Normal font : the hazard score is based on estimated/predicted values (e.g. QSAR) or on read-across and/or other expert judgement

Sammenfatning og konklusion

Alternativer til halogenerede flammehæmmere er i vid udstrækning baseret på fosforkemi. Miljøstyrelsen har identificeret en mangel på data vedrørende miljø- og sundhedsmæssige effekter af mange af de fosforbaserede flammehæmmere samt en mangel på ensartede data, der kan bruges af virksomheder, der ønsker at erstatte halogenerede flammehæmmere med fosforbaserede flammehæmmere.

Formålet med dette projekt er at identificere fosforbaserede flammehæmmere og udvikle fareprofiler på screeningsniveau for de enkelte stoffer, som i europæisk REACH sammenhæng skal kunne bruges af virksomheder der anvender flammehæmmere.

Farescreeningsprofilerne er blevet udviklet på baggrund af en modificeret metode, der er kendt som GreenScreen® for Safer Chemicals (GreenScreen®). GreenScreen® er baseret på den amerikanske miljøstyrelses "Design for the Environment" (DfE) program samt på internationale og nationale reguleringer, herunder Global Harmonized System of Classification and Labelling of Chemicals (GHS) og EU's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Metoden anvendes til at opstille fareprofiler og tildele Benchmark Scores, som medvirker til at vurdere et givent kemisk stof i en substitutionskontekst. For nogle effektkategorier adskiller GreenScreen® kriterierne sig fra kriterierne anvendt i DfE vurderingerne. Metodens anvendelighed som beslutningsværktøj, der kan bruges af virksomheder i deres bestræbelser på at erstatte farlige stoffer i produkter, er blevet evalueret i en europæisk lovgivningsmæssig kontekst og på baggrund af dette projekts fokus på farevurdering af kemikalier i relation til forbrugerprodukter.

Bruttolisten af fosforbaserede flammehæmmere

En bruttoliste på 88 fosforbaserede flammehæmmere er blevet udarbejdet på grundlag af en litteraturgennemgang og information fra hjemmesider af producenter af flammehæmmere, som er medlemmer i brancheforeningerne EFRA (European Flame Retardants Association) og Pinfa (Phosphorus, Inorganic and Nitrogen Flame Retardants Association).

På bruttolisten er der 50-60 forskellige flammehæmmere, som fremstilles i dag. Tallet kan ikke angives præcist, for mange af flammehæmmerne har fortrolige CAS-numre og fortrolige kemiske navne. De to organisationer repræsenterer alle større producenter af flammehæmmere i Europa og USA, og listen vurderes dermed at omfatte de væsentligste fosforbaserede flammehæmmere, som produceres i denne del af verden. Stofferne anvendes i forskellige flammehæmmende produkter (i kombination med andre komponenter og andre flammehæmmende stoffer), og antallet af flammehæmmende produkter er betydeligt højere end antallet af stoffer. Bruttolisten indeholder oplysninger om CAS-nr., kemisk navn, strukturformel, sumformel, fosforindhold, produktnavne og producentnavne, og den registrerede tonnage i henhold til REACH.

Gennemgang og modificering af GreenScreen® metodologien

En kritisk gennemgang af GreenScreen® metoden er blevet udført i dette projekt med henblik på vurdering af metodens anvendelighed til farevurdering relateret til forbrugerprodukter og miljø i en europæisk kontekst. Metoden blev således modificeret inden den blev anvendt til farescreening i nærværende rapport.

Anvendeligheden af metoden er blevet behandlet ved at gennemgå følgende hovedelementer:

- i) hvilke datakilder, der skal anvendes til screeningen, og deres relative betydning,
- ii) kriterier for fareklassificeringen, og
- iii) vurderingsstrategien for alternativer og kriterier for "benchmarking" af stofferne.

Gennemgangen viste, at GreenScreen® metoden er blevet udviklet med en international tilgang, hvori REACH og CLP/GHS kriterier og vejledninger indgår som centrale datakilder til vurderingen af stofferne. Derudover anbefales brugen af internationalt anerkendte datakilder i metoden. Tilgangen er derfor også i overensstemmelse med Miljøstyrelsens og ECHAs vejledninger om fareidentifikation. De foreslåede tilpasninger af farescreeningen i metoden er derfor relativt små. Den største tilpasning gælder prioriteringen af nogle datakilder, små justeringer af enkelte grænseværdier i scoringskriterierne, f.eks. for bioakkumulering, og udeladelse af fysiske farer fra screeningsprofilerne (anses som irrelevant i forbrugerkontekst i nærværende projekt). Den modificerede metode er blevet testet på to stoffer, ét som tidligere er blevet vurderet af den amerikanske miljøstyrelse og ét nyt stof. Screeningsprofilen af det stof, som er blevet vurderet før, afveg kun på hormonforstyrrende aktivitet (som ikke vurderes af den amerikanske miljøstyrelse) og bioakkumulering (score blev ændret fra "high" til "moderate" baseret på foreslået ændring af grænseværdierne i kriteriet for bioakkumulering) fra den tidligere vurdering.

Med hensyn til Benchmark-delen af GreenScreen® metoden, er udeladelse af kriterier vedrørende fysiske farer den eneste ændring. Denne ændring følger af udeladelsen af disse parametre i farescreeningen.

Udvælgelse af fosforbaserede flammehæmmere til screening

Ud over en revurdering med den modificerede metode af 23 flammehæmmende stoffer, som blev screenet som en del af den amerikanske miljøstyrelses DfE program, blev fem flammehæmmere udvalgt til farescreening i denne undersøgelse. De fem flammehæmmere blev udvalgt fra bruttolisten ud fra følgende kriterier: 1) Stoffet anvendes allerede i et vist omfang som alternativ til halogenerede flammehæmmere eller bliver markedsført specifikt som sådan; 2) stoffet opfylder de foreskrevne brandkrav til hovedanvendelser af nogle af de halogenerede flammehæmmere; 3) stoffet er registreret i henhold til REACH, eller væsentlige miljø- og sundhedsmæssige data er tilgængelige på anden måde; og 4) stoffet er ikke klassificeret som et CMR-stof i henhold til CLP-forordningen (forordning (EF) nr. 1272/2008). Revurderingen med den modificerede metode var baseret på data fra den amerikanske miljøstyrelses DfE program, og der er ikke benyttet yderligere data.

Anvendelsesområde og screening profiler af fosforbaserede flammehæmmere

Screeningsprofiler og overordnede fare scores er blevet udviklet til 28 stoffer med den modificerede screeningsmetode som vist i Tabel 1. I de tilfælde, hvor ingen modificeringer er foreslået, og hvor der er forskelle mellem GreenScreen® kriterierne og de kriterier, som anvendes i DfE programmet, er kriterierne fra DfE programmet brugt. Tabellen viser derudover screeningsprofiler for nogle af de mest anvendte halogenerede flammehæmmere (flere profiler fra DfE programmet er vist i bilag 1).

For hver af de identificerede fosforbaserede flammehæmmere er oplysninger om anvendeligheden gennemgået og sammenfattet. Disse oplysninger omfatter:

- Anvendelighed til forskellige substrater, som de er angivet i Pinfa's Product Selector²;
- Substrater (type plast, maling, tekstiler mm) som angivet af producenterne;
- Slutanvendelser (bilindustrien, byggesektoren, etc.), som angivet af producenterne;
- Interaktion med substratet (additiv, reaktiv);
- Tilgængelighed (for nyligt indført, udbredt anvendelse, vigtigste flammehæmmere for bestemte anvendelser) i det omfang som data er tilgængelige fra producenterne eller litteratur;
- Flammehæmning: Oplysninger om hvorvidt flammehæmmerne møder de forskellige brandsikkerhedskrav for relevante substrater som angivet i litteraturen, i tekniske datablade mv.; Beskrivelsen bygger på de umiddelbart tilgængelige oplysninger.
- Halogenerede flammehæmmere for samme anvendelse i det omfang, som det er beskrevet i litteraturen eller fra producenterne produktvælgere.

Gennemgangen viser, at fosforbaserede flammehæmmere er tilgængelige for de fleste anvendelser af halogenerede flammehæmmere, men informationer om anvendelighed er hovedsageligt på et overordnet niveau. Listen kan bruges til at identificere relevante flammehæmmere. I en konkret substitutionssituation skal yderligere oplysninger om anvendelsesområde og pris indhentes fra de anførte producenter.

Diskussion af anvendeligheden af den modificerede GreenScreen-metode

Screeningsmetoden vurderes at kunne anvendes til sundheds- og miljøfare screening af kemiske stoffer i en europæisk sammenhæng. Dette gælder ikke kun stoffer, som tilhører gruppen af flammehæmmere, men også andre mulige problematiske stoffer. Flammehæmmersystemer består ofte af en blanding af forskellige flammehæmmere, og det skal bemærkes, at en screening af et flammehæmmersystem vil bestå af en screening af alle komponenter. Eksempelvis anvendes bromerede flammehæmmere i kombination med antimon trioxid, så dette stof vil også skulle indgå i screeningen. Gældende retningslinjer for GreenScreen[®] oplyser ikke, hvordan man får en benchmark score for en blanding, men en praktisk tilgang ville være at bruge benchmark scoren for den komponent, som får den laveste score (dvs. med den højeste risiko), som udslagsgivende for den samlede score af blandingen. Det er muligt at udarbejde en benchmark score, selv om der ikke er tilgængelige data for alle endpoints. Eksempelvis vil data vedrørende sensibilisering ikke være nødvendige for at kunne opnå en benchmark score på det næsthøjeste niveau (BM3), men det er kun muligt at opnå den højeste score (BM4), hvis der findes data for alle endpoints. Hvis formålet med vurderingen er, at identificere mulige alternativer for et givent stof, anbefales det, at begynde med en overordnet benchmark vurdering baseret på den harmoniserede klassificering eller selvklassificeringen angivet i REACH C&L inventory, før der udarbejdes et fuldstændigt fareprofil for et stof.

Det skal understreges, at farescreening med dette screeningsværktøj skal udføres af personer med solid faglig baggrund og erfaring inden for toksikologi/sundheds- og miljøvurdering for at opnå pålidelige stofprofiler. Dette er især vigtigt ved vurderingen af stoffer med ufuldstændigt datasæt eller ved modstridende data for samme effekt-parameter. Derudover kan det i nogle tilfælde være nødvendigt at generere data ved hjælp af QSAR modellerings-værktøjer, hvilket kræver særlig ekspertise. For de stoffer, der er vurderet i denne undersøgelse, er der ikke udarbejdet nye QSAR modelleringer, men tilgængelige QSAR-baserede data (f.eks. fra den danske (Q)SAR Database) er anvendt, hvor det har været relevant.

² <http://pinfa.org/index.php/product-selector>

Med hensyn til tildeling af de overordnede fare scores, som afspejler en vurdering af, hvor relevant et stof er med henblik på substitution, viser scoringen af de 28 fosforbaserede flammehæmmere, at de fleste stoffer endte i en overordnet fare kategori 2. Kun tre stoffer opnåede en bedre score (dvs. 3 eller 4). Den højeste score blev opnået for ammonium polyfosfat, poly[fosfonat-co-carbonat] og fosfinsyre, aluminium salt (3:1), hvor i mod alyfosfaterne generelt fik en lav score (1). Differentieringen mellem stofferne lader derfor til at være for lav for at kunne anvendes operationelt i en substitutionssituation. Dette skyldes til dels et "gab" mellem to af benchmark niveauerne (BM1 og BM2) i GreenScreen® metoden, som resulterer i, at nogle stoffer får en benchmark score, som ikke helt reflekterer deres farepotentiale (dvs. de får for høj en score). Det kunne i princippet - for fremtidige anvendelser af metoden -være relevant at indføre et ekstra benchmark niveau (BM1½). Det er dog også således, at det på langt sigt næppe vil være relevant at overveje, hverken stoffer som opnår BM1½ eller BM2 som mulige alternativer.

Endelig skal det bemærkes, at farescreeningen af et stof ikke kan stå alene i en beslutningsproces om substitution, men skal suppleres med eksponeringsovervejelser i relevante anvendelsesscenarier. Screeningsresultatet kunne f.eks. påvirkes af, at der lægges mere vægt på nogle effektparametre, som er særlig relevante for et bestemt anvendelsesscenarie. I sammenhæng med mange forbrugerprodukter vil "akut toksicitet" eksempelvis ikke være en relevant parameter, fordi koncentrationer, som er så høje, at de ville kunne medføre akutte effekter, aldrig vil forekomme i forbrugerprodukter. Derfor kunne denne parameter enten udelades eller i det mindste tildeles lavere vægt end de kroniske parametre.

Derudover bør der tages hensyn til mobilitet af stoffet i polymermatricen. Reaktive flammehæmmere er bundet i polymermatricen, og må derfor forventes at have en lavere mobilitet og flygtighed end additive flammehæmmere. Lavere mobilitet og flygtighed vil resultere i lavere eksponeringsniveauer, især i produktets brugsfase. Polymere flammehæmmere vil ligeledes forventes at have lavere mobilitet og flygtighed, hvilket resulterer i lavere eksponeringsniveauer i brugsfasen.

TABEL 1

FAREPROFILER OG OVERORDNEDE FARE SCORES BASEREDE PÅ DEN MODIFICEREDE GREENSCREEN METODE FOR UDVALGTE HALOGENEREDE OG FOSFORBASEREDE FLAMMEHÆMMERE.

Kemisk navn	CAS Nr.	Gruppe I Human					Gruppe II og II* Human								Økotoxici- tet		Skæbne		Over- ordnet fare score	
		C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P		B
								enkelt	gen- tagen*	enkelt	gentag- en*									
Organofosforforbindelser																				
9,10-Dihydro-9-oxa-10-fosfophenanthren-10-oxid (DOPO) *[Re]	35948-25-5	M	L	L	M	DG	L	DG	L	DG	M	M	DG	L	M	L	M	H	VL	2
N,N-bis-(2-hydroxyethyl) aminomethan fosforsyre diethylester	2781-11-5	M	M	L	L	DG	L	DG	M	DG	M	M	DG	L	L	M	L	H	L	2
Poly(m-phenylen methylfosfonat) **	63747-58-0	L	L	M	M	H	L	DG	M	DG	M	L	DG	L	L	H	H	VH	H	1
Fosfonat oligomerer (reaktive) [Re]	68664-06-2	M	L	L	L	DG	L	L	L	M	M	L	DG	M	M	L	H	VH	H	2
Poly[fosfonat-co-karbonat] **	77226-90-5	L	L	L	L	L	L	L	L	L	L	L	DG	L	L	L	L	VH	L	3
Fosforsyre, blandende estre med [1,1'-bisphenyl-4,4'-diol] og fenol	1003300-73-9	M	L	L	L	DG	L	DG	L	DG	L	L	DG	L	L	H	H	H	L	2
Oligomeric fosfonatepolyol *[Re]	363626-50-0	M	M	L	M	DG	L	L	L	M	M	L	DG	L	L	L	M	M	L	2
Organofosfater (fosfat ester) – Aryl fosfater																				
Triphenylfosfat	115-86-6	M	L	L	L	H	L	DG	H	DG	L	L	DG	L	L	VH	VH	L	L	1
Tricresylfosfat	1330-78-5	L	L	H	M	DG	M	DG	H	DG	M	M	DG	L	L	VH	H	M	H	1
Cresyl diphenylfosfat	26444-49-5	L	L	H	M	DG	M	DG	H	DG	M	M	DG	L	L	VH	H	M	H	1
Fosforsyre, bis(methylphenyl) phenyl ester	26446-73-1	L	L	H	M	DG	M	DG	H	DG	M	M	DG	L	L	VH	H	M	H	1
Resorcinol bis-diphenylfosfat **	57583-54-7 / 125997-21-9	M	L	L	M	H	L	DG	M	DG	M	L	DG	L	L	VH	VH	M	H	1
Bisphenol A bis(diphenylfosfat)	5945-33-5 / 181028-79-5	M	L	DG	L	DG	L	DG	L	DG	L	L	DG	L	L	L	L	H	M	2
Organofosfater (fosfat ester)– Alkyl fosfater																				
Oligomeric ethyl ethylenfosfat	184538-58-7	L	M	L	L	DG	L	DG	L	DG	M	L	DG	L	M	L	L	VH	L	2
Organofosfater (fosfat ester) – Aryl alkyl fosfater																				

Kemisk navn	CAS Nr.	Gruppe I Human					Gruppe II og II* Human								Økotoxici- tiet		Skæbne		Over- ordnet fare score	
		C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P		B
								enkelt	gen- tagen*	enkelt	gentag- en*									
Isopropyl phenylfosfate	68937-41-7	M	L	H	M	DG	L	DG	H	H	H	L	DG	L	L	VH	VH	M	VH	1
Tris (p-t-butylphenyl)fosfate	78-33-1	M	L	M	L	DG	L	DG	H	DG	M	M	DG	M	L	VH	VH	M	H	2
Phenol, isobutylenated, fosfat (3:1); Reakti- onsprodukt af 4-tert-butylphenyl diphenyl- fosfat og bis(4-tertbutylphenyl) phenylfosfat og triphenylfosfat	68937-40-6	DG	L	L	L	DG	L	DG	M	M	M	L	DG	M	M	VH	VH	L	M	2
Melamin-afledte og andre organiske fosfater (ikke ester)																				
Melamin pyrofosfat	15541-60-3	M	M	L	L	DG	L	DG	M	L	L	L	DG	L	L	L	L	H	L	2
Difosforsyre, forbindelser med piperazin , og substitueret aminfosfat	66034-17-1 and confid.	M	M	M	M	DG	H	DG	M	DG	DG	L	M	L	M	M	L	H	L	2
Melaminfosfat	41583-09-9	M	L	L	L	DG	L	DG	M	DG	DG	L	DG	L	DG	L	L	VH	VL	2
Ethylendiamin-o-fosfat	14852-17-6	L	L	L	M	DG		DG	M	DG	DG	H	H	VH	L	M	H	VL	VL	2
Uorganiske fosfatforbindelser																				
Ammonium polyfosfat **	68333-79-9	L	L	L	L	L	L	L	L	L	L	L	DG	L	L	L	L	(VH)	L	4
Rød fosfor	7723-14-0	L	M	L	L	DG	L	L	L	L	L	L	DG	M	M	L	L	H	L	2
Fosfinsyre, aluminium salt (3:1)	7784-22-7	DG	L	L	L	DG	L	DG	M	DG	DG	L	DG	L	M	M	M	(VH)	L	3
Andre fosforforbindelser og ikke kategoriserede forbindelser																				
Diethylfosfinat, aluminium salt	225789-38-8	L	L	L	M	DG	L	M	M	DG	M	L	DG	VL	L	M	M	H	L	2
Fortrolig halogen-fri flammehæmmer, Eme- rald Innovation™ NH-1	Confid.	M	L	M	L	H	H	DG	H	DG	M	M	DG	M	M	VH	VH	M	H	1
Fyrol™ HF-5 **	Confid.	M	M	L	M	H	L	DG	M	DG	M	L	DG	L	M	VH	VH	VH	M	1
6H-Dibenz[c,e][1,2]oxafosforin-6- propansyre, butyl ester, 6-oxid	848820-98-4	DG	DG	DG	DG	DG	L	DG	DG	DG	DG	L	DG	H	DG	M	M	H	L	2

Kemisk navn	CAS Nr.	Gruppe I Human					Gruppe II og II* Human								Økotoksi citet		Skæbne		Over-ordnet fare score	
		C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P		B
								enkelt	gen-tagen*	enkelt	gentag-en*									
Halogenerede flammehæmmere (eksempler)																				
Decabromineret diphenyl ether (decaBDE)	1163-19-5	M	L	L	H	H	L	DG	M	DG	L	L	DG	L	L	L	L	VH	H	1
Tetrabromobisphenol A (TBBPA) *[Re] (også brugt additivt)	79-94-7	M	L	L	M	H	L	DG	L	L	L	L	DG	L	M	VH	H	H	M	1
Hexabromocyclododecan (HBCDD)	25637-99-4	M	L	M	H	H	L	DG	M	M	M	L	DG	L	L	VH	VH	H	VH	1
Tris (1-chloro-2-propyl) fosfat (TCCP)	13674-84-5	M	L	H	H	M	L	DG	M	M	M	L	DG	L	L	M	M	H	L	1

*[Re]: Reative flammehæmmere; **: Fareprofiler udarbejdet i denne undersøgelse; de øvrige er baseret på US EPA (2014a, 2014 b; 2015).

C = Kræftfremkaldende M = Mutagenicitet R = Reproduktionstoksicitet D = Udviklingstoksicitet E = Hormonforstyrrende aktivitet AT = Akut toksicitet for pattedyr	ST = Systemisk toksicitet N = Neurotoksicitet SnS = Hudsensibilisering SNR = Respiratorisk sensibilisering IRS = Hudirritation Ire = Øjenirritation AA = Akut toksicitet for vandmiljøet N = Neurotoksicitet	AA = Akut toksicitet for vandmiljøet CA = Kronisk toksicitet for vandmiljøet P = Persistens B = Bioakkumulering	VL Meget lav fare L Lav fare M Moderat fare H Høj fare VH Meget høj fare () Angiver specifikke vurderinger for uorganiske stoffer, hvor standard scoring kriterierne ikke er gyldige.	DG: Data mangel (på hvid baggrund) betyder, at ingen fare score kunne blive tildelt på grund af manglende data. Fed skrift: Fare score er baseret på målte/ empiriske data. Normal skrift: Fare score er baseret på estimerede data (f.eks. QSAR) eller på analogislutninger og/eller ekspertvurderinger

1. Introduction

1.1 Background

The Danish Environmental Protection Agency (Danish EPA) has during the period 2012 to 2015 prepared surveys of 40 substances and substance groups on the agency's List of Undesirable Substances (LOUS). Two LOUS surveys - of brominated flame retardants (Lassen et al., 2014) and the chlorinated flame retardant TCCP (Larsen et al., 2014), respectively - identified a lack of information on relevant alternatives to these halogenated flame retardants.

A number of tools to assess chemical alternatives exist. One of the tools is the GreenScreen® for Safer Chemicals developed by the American NGO "Clean Production Action", which is based in part on an assessment method originally developed by the US Environmental Protection Agency (US EPA) as part of the programme "Design for the Environment" (DfE). The method is a transparent tool for evaluating and differentiating among chemicals based on their human health and environmental hazards. Screening profiles exist for a large number of phosphorous flame retardants from US EPA's DfE programme. It should be noted that the GreenScreen® criteria for some effects are different from the criteria used in the DfE programme and, hence, hazard profiles developed by the use of the GreenScreen method may be slightly different than the profiles developed in the DfE programme.

1.2 Objectives

The project has the following objectives:

- to present data on the technical and fire safety properties of marketed phosphorous flame retardants
- to evaluate and modify the GreenScreen® method with respect to compatibility in a European context in order to develop a screening tool, which can be used by companies who want to replace halogenated flame retardants
- to develop screening profiles for selected flame retardants according to the modified GreenScreen® method.

1.3 Activities

The following activities have been conducted within the project:

1.3.1 Compilation of the 'Long list of phosphorous flame retardants'

Based on literature search comprising information from manufacturers, reports on flame retardants, papers and other relevant literature, a long list of identified phosphorous flame retardants has been compiled. The list presents an overview of potentially relevant flame retardants (see chapter 2). Twenty eight substances from this list were selected according to criteria described in chapter 2 for evaluation according to the modified GreenScreen® method.

1.3.2 Evaluation and modification of the GreenScreen® method

The GreenScreen® method is a tool for evaluating and differentiating among chemicals based on their human health and environmental hazards. The method has been developed in the USA, therefore its applicability in a European context has been analysed.

Chapter 0 presents the original GreenScreen® method and suggest modifications according to a European context. Furthermore, the applicability of the method on flame retardants, which are potential alternatives to halogenated flame retardants, is tested on two examples substances.

1.3.3 Technical descriptions and development of hazard profiles for selected flame retardants

Hazard profiles based on the modified GreenScreen® method were developed for 28 marketed phosphorous flame retardants which have been selected from the long list of identified flame retardants and which may be used as alternatives for halogenated flame retardants. For the sake of comparison, screening profiles for four of the main halogenated flame retardants are also included.

In the case where no modifications are suggested and where there are differences between the GreenScreen® hazard criteria and the criteria in the US EPA DfE programme, the criteria from the DfE programme have been used.

In combination with a technical description of the flame retardants, the hazard profiles provide companies with a quick overview of the properties of potential alternatives.

In the light of substitution, development of smoke and hazardous substances from flame retardants in case of fire, are also an important parameter. Available information on this topic is presented in chapter 5.

2. Long list of phosphorous flame retardants

A long list of identified phosphorous flame retardants has been developed and is shown in Table 1. The list consists of phosphorous flame retardants identified from the following data sources:

- Websites of manufacturers organised in the two trade associations EFRA (European Flame Retardants Association) and Pinfa (Phosphorus, Inorganic and Nitrogen Flame Retardants Association).
- Reports developed under the US EPA Design for the Environment Programme (US EPA, 2014a,b,c, 2015).
- The Non-Halogenated Flame Retardant Handbook (Morgan and Wilkie, 2014).
- Two papers listing relevant phosphorus flame retardants (Bergman et al., 2012; van der Veen and de Boer, 2012).
- Other relevant literature identified in the project (SFT, 2009, Lassen et al., 1999, Lassen et al., 2006; Kemi, 2004, 2005; Arcadis, 2011)

For flame retardants marketed today, the information in Table 2 is supplemented with further information in chapter 3 and Appendix 10.

Reference

For flame retardants manufactured today, the names of the flame retardant products and the manufacturers are indicated. Some of the flame retardant products may contain more flame retardant substances in combination. For other flame retardants, a reference to the literature where the flame retardant is listed is indicated.

Registered volume

For substances registered under REACH, the registered volume is indicated. For non-polymeric substances it gives an indication of the total market volume, but it should be noted that several of the flame retardants are polymers, which are consequently not registered under REACH. For non-polymeric flame retardants, which are indicated as pre-registered but not registered, the total market volume is below 100 t/y per manufacturer/importer of these substances (limit volume for the latest registration deadline).

Availability of US EPA environmental and health screening profile

Furthermore, the table indicates whether an environmental and health screening profile is available in the four reports from the US EPA Design for Environment (DfE) programs on alternatives to decaBDE, HBCDD brominated flame retardants in printed circuit boards (printed CB), or pentaBDE in polyurethane foams (PUR). Substances, for which profiles have been developed as part of the current study, are indicated by "this study".

Substrate

The substrate column indicates in which substrates (plastic types, textiles, mixtures) the flame retardants are applied as indicated in technical data sheets and other information at the websites of the manufacturers. This information is supplemented with information from the branch organisation PINFA's Product Selector and information from the literature in section 2.2.

TABLE 2
IDENTIFIED PHOSPHOROUS FLAME RETARDANTS

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
Organophosphorous compounds										
35948-25-5	252-813-7	9,10-Dihydro-9-oxa-10-phosphaphenanthren-10-oxide	DOPO	KCCS DO11 EVERFOS DOPO	Metadynea Everkem	1,000 – 10,000	Printed CB	ABS, flexible polyurethane, unsaturated polyester, epoxy resin, phenolics resin, coating (paint), textile (back coating)		56
2781-11-5	220-482-8	N,N-(bis)-hydroxyethyl-aminomethane phosphonic acid diethyl ester		Levagard 4090 N Fyrol™ 6	Lanxess ICL-IP Europe	Pre-registered	PUR	Rigid PUR foams, PF, EP and UP resins		58
63747-58-0	*613-366-7	Poly(m-phenylene methylphosphonate)	DEEP	Fyrol PMP	ICL-IP Europe	Pre-registered	Printed CB	Epoxy resins		60
68664-06-2	Not available	Phosphonate oligomers (reactive) (Mn <10,000)		NOFIA™ OL1001 NOFIA™ OL3001	FRX Polymers	Not reg/pre-reg	Deca	Unsaturated Polyesters, Epoxy, Polyurethane and Polyurea		62
68664-06-2	Not available	Polyphosphonates (Mn >10,000)		Nofia HM1100	FRX Polymers	Not reg/pre-reg	Deca	Unsaturated Polyesters, Epoxy, Polyurethane and Polyurea		255
77226-90-5	Not available	Poly[phosphonate-co-carbonate]		NOFIA™ CO3000 NOFIA™ CO6000	FRX Polymers	Not reg/pre-reg	Deca	HIPS/PPO, PC/ABS, Polycarbonate (PC)		64
1003300-73-9	Not available	Phosphoric acid, mixed esters with [1,1'-bisphenyl-4,4'-diol] and phenol	BPBP	ADK STAB FP-800	Adeka Palmarole	Not reg/pre-reg	Deca	Polycarbonates and polyesters, polymer blends such as PC/ABS and PC/HIPS.		66
363626-50-0	Not available	Oligomeric phosphonate polyol		Exolit® OP 560 Exolit® OP 550	Clariant	Not reg/pre-reg	PUR	Flexible polyurethane foams		68
20120-33-6	243-528-9	Dimethyl {3-[(hydroxymethyl)amino]-3-oxopropyl}phosphonate		EVERFOS CP	Everkem	100 – 1,000		Cotton textile		234
18755-43-6	242-555-3	Dimethyl propyl phosphonate	DMPP	Levagard DMPP	Lanxess	100 – 1,000		PIR/PUR rigid foams and thermosets		235

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
Not identified	Not identified	Phosphine oxide diol and triol		Not identified		Not reg/pre-reg		PUR, PET, epoxy resins	SFT 2009	
78-38-6	201-111-9	Diethyl ethylphosphonate		Aflammit® PLF 822	THOR	Pre-registered		Rigid PUR and PIR foams, epoxy, unsaturated polyesters		236
15827-60-8	239-931-4	Diethylenetriamine-penta(methylene phosphonic acid)				1,000 – 10,000			www.flame-retardant-material.com	
Organophosphates (phosphate esters)										
<i>Aryl phosphates</i>										
115-86-6	204-112-2	Triphenyl phosphate	TPHP	EVERFOS TP (TPP) Disflamoll TP Disflamoll TP liquid	Everkem Lanxess Lanxess	1,000 – 10,000	De-ca/PUR	PP, PE, PDM, PVC, HIPS, PC/ABS (alloys), PPO/HIPS (alloys), rigid and flexible polyurethane, TPU, Epoxy resin, phenolics resin, PC, textile (back coating), adhesive, rubbers, cellulose acetate, cellulose acetate butyrate and vinyl copolymer, PPE/HIPS		70
26967-76-0	248-147-1	Tri(4-isopropylphenyl) phosphate	TIBPP			Pre-registered			European Commission 2011; KEMI 2005, 2009	
68937-40-6	273-065-8 / 700-990-0	Phenol, isobutylated, phosphate (3:1); Reaction mass of 4-tert-		Reofos® LF-50; Disflamoll TP LXS	Green Lake Solutions Lanxess	1,000 – 10,000	This study	PVC, flexible polyurethanes, cellulosic resins, and synthetic rubber. Flame retard-		72

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
		butylphenyl diphenyl phosphate and bis(4-tertbutylphenyl) phenyl phosphate and triphenyl phosphate		51092				ant processing aid for engineering resins, such as modified PPO, polycarbonate and polycarbonate blends		
1330-78-5	215-548-8	Tricresyl phosphate	TMPP	EVERFOS TCP Kronitex® TCP Disflamoll TKP Disflamoll TKP-P	Everkem Great lake solutions Lanxess Lanxess	1,000 – 10,000	PUR	PVC, PVC flexible, polyester, phenolics resin, Nitrocellulose lacquers and coatings and processing aid for natural and synthetic rubbers (NBR and SBR)		74
28109-00-4	248-849-8	Bis-(isopropylphenyl) phenyl phosphate				Pre-registered			European Commission 2011	
28777-70-0	249-209-0	Tris-(tert-butylphenyl) phosphate	TBDP			Pre-registered			European Commission 2011	
26444-49-5	247-693-8	Cresyl diphenyl phosphate	CDP	EVERFOS CDP Kronitex® CDP Disflamoll DPK	Everkem Great Lakes Solutions Lanxess	Pre-registered	PUR (in the assessment of 1330-78-5)	PVC, flexible polyurethane, epoxy resin, phenolics resin, PC/ABS blends, TPU compounds, PUR-foams (rigid and flexible) and rubbers		76
26446-73-1	247-708-8	Phosphoric acid, bis(methylphenyl) phenyl ester	MEHP; Methylated triphenyl phosphates; Bis(methylphenyl) phenyl phosphate			Pre-registered	PUR (part of assessment of 1330-78-5)		USEPA 2015	76
57583-54-7 (sometimes 125997-21-9 is used inter-	260-830-6	Resorcinol bis-diphenyl phosphate	PBDPP	EVERFOS RDP Fyrolflex RDP AFLAMMIT® PLF 280	Everkem ICL-IP Europe THOR	1,000 – 10,000	Deca	EPDM, HIPS, PC/ABS (alloys), PPE/HIPS (alloys), TPU, epoxy resin, PC, modified PPO,		79

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
chageably)										
5945-33-5 (sometimes 181028-79-5 is used interchangeably)	425-220-8	Bisphenol A bis(diphenyl phosphate)	BPA-BDPP, BDP	ADK STAB FP-600 EVERFOS BP (BDP) Fyrolflex BDP	Adeka Palmarole Everkem ICL-IP Europe	1,000-10,000	Deca	EPDM, HIPS, PC/ABS (alloys), PPE/HIPS (alloys), TPU, epoxy resin, PC, HIPS/PPO		81
25155-23-1	246-677-8	Trixylyl phosphate	TXP	EVERFOS TXP	Everkem	100 – 1,000		EPDM, PVC, PC/ABS (alloys), rigid and flexible polyurethane, phenolics resin, Coating (paint), textile (back coating), adhesive		237
65652-41-7	265-859-8	Bis-(tert-butylphenyl)phenyl phosphate				Pre-registered		PVC	European Commission 2011	
78-33-1	201-106-1	Tris-(p-tert-butylphenyl) phosphate	TBPP			Pre-registered	PUR		European Commission 2011	87
1330-78-5, 78-32-0, 78-30-8 and 25155-23-1		Tri(m,p-cresyl) phosphate mixture		Lindol	ICL-IP Europe	1330-78-5: 1,000-10,000; 25155-23-1: 100-1,000 and 78-32-0 and 78-30-8: Pre-registered		PVC flexible, Cellulosic Plastic Composite		
Proprietary		Proprietary aromatic phosphate		Fyrolflex Sol-DP	ICL-IP Europe			HIPS/PPO, PC/PC ABS		
Proprietary		Proprietary halogen-free phosphorus ester		Fyrol A710	ICL-IP Europe			Flexible Polyurethane foams		

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
Proprietary		Proprietary		Emerald Innovation™ NH-1	Great Lake Solutions		PUR	Furniture and automotive flexible polyurethane foam applications.		106
Alkyl phosphates										
184538-58-7	*606-033-2	Oligomeric ethyl ethylene phosphate		Fyrol PNX Fyrol PNX-LE AFLAMMIT® PLF 140	ICL-IP Europe THOR	Pre-registered	PUR	Flexible and rigid polyurethane foams, cellulosic plastic composite		83
78-40-0	201-114-5	Triethyl phosphate	TEP	Levagard TEP-Z	Lanxess	1,000 – 10,000		PIR / PUR rigid foams and thermosets		241
126-73-8	204-800-2	Tributyl phosphate	TNBP	Phosflex 4	ICL-IP Europe	1,000 – 10,000		PVC flexible, latex/adhesives, cellulosic plastic composite		242
1806-54-8	217-305-1	Trioctyl phosphate				Preregistered			KEMI 2005	
Not identified	Not identified	Neoalkoxy tri (dioctyl phosphate) titanate							KEMI 2005	
78-42-2	201-116-6	Tris-(2-ethylhexyl) phosphate	TEHP	Disflamoll TOF	Lanxess	1,000 – 10,000		Many types of polymers including PVC flexible, PUR, NBR, SBR and EPDM.		243
78-51-3	201-122-9	Tris(2-butoxyethyl) phosphate	TBOEP	Phosflex T-BEP	ICL-IP Europe	1,000 – 10,000		Rubbers/elastomers, latex/adhesives		244
5301-78-0	*610-937-2	Pentaerythritol phosphate alcohol				Pre-registered			KEMI 2004	
Aryl alkyl phosphates										
68937-41-7	273-066-3	Isopropyl phenyl phosphate		EVERFOS 1350 - 1950 series Reofos® 35 - 95 series	Everkem Great lake solutions	10,000-100,000	PUR	PVC, cellulosic resins, and synthetic rubber, EPDM, HIPS, PC/ABS (alloys), PPO/HIPS (alloys), rigid and flexible polyurethane, TPU, epoxyresin, phenolics		85

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
				Phosflex 31L Phosflex 41L	ICL-IP Europe			resin, PC, Coating (paint), textile (back coating), adhesive, rubbers.		
1241-94-7	214-987-2	Diphenyl (2-ethylhexyl) phosphate	DPO	Disflamoll DPO Phosflex 362	Lanxess ICL-IP Europe	1,000 – 10,000		PVC, thermoplastic polyurethane, nitrile butadiene rubber, cellulose nitrate, cellulose acetate		245
28108-99-8	248-848-2	Diphenyl isopropyl phosphate				Pre-registered			European Commission 2011	
29761-21-5	249-828-6	Isodecyl diphenyl phosphate		Phosflex 390	ICL-IP Europe	1,000 – 10,000		PVC flexible		246
56803-37-3	260-391-0	tert-butylphenyl diphenyl phosphate				Pre-registered			European Commission 2011	
56803-37-3; 65652-41-7; 78-33-1 and 115-86-6	260-391-0, 265-859-8, 201-106-1, and 204-112-2	t-Butylated triphenyl phosphate mixture		Phosflex 71B	ICL-IP Europe	Substances are pre-registered individually, except 115-86-6: 1,000 – 10,000		HIPS/PPO, PC/PC ABS, PVC flexible		247
27460-02-2 and 142474-86-0		Linear alkyl diphenyl phosphate	Phosphoric acid, dodecyl diphenyl ester	Phosflex 418	ICL-IP Europe	27460-02-2 is Pre-registered		PVC flexible		
		Octyl diphenyl phosphate							KEMI 2005	
Organophosphites										

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
7789-79-9	232-190-8	Calcium phosphinate		Phoslite IP-C	Italmatch	Pre-registered		PC/ABS, polycarbonate PC, Rubbers/elastomers, PVC flexible	PINFA, 2015	
868-85-9	212-783-8	Dimethyl phosphonate	DMHP			1,000 – 10,000			SFT 2009	
756-79-9	Not identified	Dimethyl methyl phosphonate	DMMP			Not reg/pre-reg			Pinfa 2015	
Melamine-derived and other organic phosphates (not being esters)										
15541-60-3	239-590-1	Melamine pyrophosphate		EVERFLAM MPP-2 AFLAMMIT® PMN 370	Everkem THOR	Pre-registered	Deca, printed CB	Coating (paint), textile (back coating)		89
218768-84-4	*606-855-1	Melamine polyphosphate	MPP	Melapur® 200 range BUDIT 3141 AFLAMMIT® PMN 200	BASF Budenheim THOR	Not reg/pre-registered				248
20208-95-1	243-601-5	Melamine polyphosphate		EVERFLAM MPP-1	Everkem	Pre-registered		Polyester, PA		249
41583-09-9	255-449-7	Melamine phosphate		Melapur MP Budit 312 Melagard MP MPT11 AFLAMMIT® PMN 185	BASF Budenheim Italmatch Metadynea Austria THOR	1,000 – 10,000		Thermoplastics, polyolefins, elastomers, engineering resins, paints, intumescent fire retardant coating		91
1271168-40-1	Not available	Melamine-poly(aluminium phosphate)		Safire® 200	Floridienne Chimie s.a. (patent belongs to Catena additives)	Not reg/pre-reg		PA, Nylon, PBT, PE, PP, PS, HIPS, PPE		250
1271172-98-5	Not available	Melamine-poly(zinc phos-		Safire® 400		Not reg/pre-		EVA, PA, Nylon, PBT, PE,		251

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
	ble	phate)				reg		PUR, PVC flexible, TPE and TPV		
Not identified	Not identified	Melamine-poly(magnesium phosphate)		Safire® 600				PBT PA, Nylon		252
Not identified	Not identified	Melamine orthophosphate		BUDIT 310	Budenheim					
94031-26-2	Not available	1,3,5-Triazine-2,4,6-triaminephosphate	Flame retardant P	PPP111	Metadynea Austria GmbH	Not reg/pre-reg		Intumescent flame retardant systems		253
66034-17-1	457-330-7	Diphosphoric acid, compd. with piperazine		ADK STAB FP-2100J ADK STAB FP-2200	Adeka Palmarole	10 – 100	Deca			93
Inorganic phosphorous compounds										
68333-79-9	269-789-9	Ammonium polyphosphate		BUDIT 3123 - 3178 series FR CROS 484 FR CROS C30 FR CROS C60 Exolit® AP series EVERFLAM APP AFLAMMIT® PCI 202 Preniphor EPFR-series	Budenheim Clariant Everkem Thor Presafer	10,000 - 100,000	PUR	Unsaturated polyester resin, acrylic resins, epoxy or phenolics. PP, PE, PP copolymers and PP blends, Rigid and flexible polyurethane, TPU, epoxy resin, coating (paint)		95
68333-79-9 and 14728-39-9	269-789-9 and not identified	Polyphosphoric acids, ammonium salts	APP			CAS No 14728-39-9 is not pre-	PUR		European Commission 2011;	See 95

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufac-turer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Refer-ence*	Page
						registered, See above for CAS No 68333-79-9			Stuer-Lauridsen et al. 2000; KemI 2004, 2005, 2009; UK HSE 2012; EFRA 2012	
		Based on ammonium polyphosphate		Phos-Chek ® LC95W Solution Phos-Chek ® LC95W FT936 / Fire-Trol 936 FT934 / Fire-Trol 934 FT931 / Fire-Trol 931 Phos-Chek ® LC95A-F BUDIT® IS 3001 AFLAMMIT® PPN series	BK Giulinibk-giulini GmbH Budenheim THOR					
7723-14-0	918-594-3	Red phosphorus		Red Phosphorus HB 801 Red Phosphorus PU 6580 Exolit® RP series MASTERET series	Clariant	1,000 – 10,000	Deca	Solid plastics, closed cell foams, polymer adhesives polyisocyanurate and polyurethane rigid foams plastics, polyurethanes, synthetic and natural rubber latex systems polyolefines articles,		98

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
					Italmatch			epoxy resins polypropylene articles and sometimes in PA.		
7722-76-1	231-764-5	Monoammonium phosphate				1,000,000-10,000,000			KEMI 2004	
7783-28-0	231-987-8	Diammonium phosphate		Phos-Chek 259-F	BK Giulini GmbH	1,000,000-10,000,000		Wildfire control		255
7722-76-1; 7783-28-0	231-764-5; 231-987-8	Monoammonium Phosphate, Diammonium Phosphate		PHOS-CHEK® MVP-F PHOS-CHEK® MVP-Fx	BK Giulini GmbH	1,000,000-10,000,000 (for the two substances, respectively)		Wildfire control		
7784-22-7	479-150-8	Phosphinic acid, aluminium salt (3:1)		Phoslite B-series	Italmatch	10-100		PBT, Polyamide (PA), Polypropylene (PP), Thermoplastic elastomers, XPS foam, Polypropylene foam (PP), Rubbers/Elastomers, Other textile fibers, Epoxy Resins, Unsaturated polyesters, PVC flexible, Polypropylene (PP), TPU, PE/EVA	PINFA, 2015	177
Not identified	Not identified	Aluminium phosphates		FR CROS 134 P FR CROS 134 T	Budenheim			Aluminium phosphates		257
Other phosphorous and non-categorised substances										
14852-17-6	238-914-9	Ethylenediamine-o-phosphate	EDAP	EP11 Aflammit® PCO 123/234	Metadynea Austria THOR	0-10		Polyolefins and in most thermoset applications. self-intumescent		102

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
225789-38-8	*607-114-5	Diethylphosphinate, aluminium salt		Exolit® OP series	Clariant	Pre-registered	Printed CB	High temperature polyamides , polyesters, reinforced polyamide (6 and 66)		104
4090-51-1	223-829-1	2,2'-oxybis[5,5-dimethyl-1,3,2-dioxaphosphorinane] 2,2'-disulphide		Exolit® 5060 PK	Clariant	100 – 1,000		Viscose fibres		258
1402947-09-4	Not available	Ammonium 6H-dibenzo[c,e][1,2]oxaphosphinin-6-olate 6-oxide		DXA 12	Metadynea Austria	Not reg/pre-reg				259
98165-92-5	Not available	Phosphoric acid, bis[3-[(diphenoxyphosphinyl)oxy]phenyl] phenyl ester				Not reg/pre-reg			Ecolabel 2014.	
83029-72-5	Not available	phosphoric acid, bis(4-(1-(4-(diphenoxyphosphinyl)oxy)phenyl)-1-methylethyl) phenyl ester							Ecolabel 2014.	
Proprietary		Proprietary (19.5%P, 17,5%N) New substance (REACH registered in Europe, TSCA listed in USA).		AFLAMMIT® PCO 700	THOR					
Proprietary		Proprietary (14%P, 37%N) New substance (REACH registered in Europe, TSCA listed in USA)		AFLAMMIT® PCO 800	THOR					
Proprietary		Proprietary (24%P)		AFLAMMIT® PCO 900 (ex TL 1260F) AFLAMMIT® PCO	THOR					

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
				960 (ex TL 1260)						
Not identified	Not identified	Isopropylated phosphate ester (8,3%P)		AFLAMMIT® PLF 150	THOR			PVC, rubber and flexible PUR foams. Can also be used as a processing aid in PC and PPO (and their respective blends)		
Not identified	Not identified	Cyclic phosphonate (19%P)		AFLAMMIT® PLF 710	THOR					
Proprietary		Substituted Amine Phosphate Mixture					Deca		US EPA 2015	93
Proprietary		Proprietary Phosphorus Ester Blend		Fyrol™ HF-5	ICL-IP Europe		PUR			108
Proprietary		Proprietary non-halogen phosphorus ester		Fyrol HF-4	ICL-IP Europe			Flexible Polyurethane foams		
Proprietary		Proprietary phosphorus ester		Fyrol® HF-10	ICL-IP Europe			Flexible Polyurethane foams		
Proprietary		Proprietary mixture of phosphate esters		Fyrol® HF-5HP	ICL-IP Europe			Flexible Polyurethane foams		
Proprietary		Proprietary		Fyrol® HF-9	ICL-IP Europe			Flexible Polyurethane foams		
Proprietary		Oligomeric phosphate ester		Levagard® TP LXS 51078	Lanxess			Flexible PUfoams		
848820-98-4	805-659-5	6H-Dibenz[c,e][1,2]oxaphosphotin-6-propanoic acid, butyl ester, 6-oxide	DOPO-AC4	DOB11 Levagard TP LXS 51114	Metadynea Austria Lanxess	10 – 100		Polyesters, PUR and epoxy-systems		
36240-31-0	Not available	10-Hydroxy-9,10-dihydro-9-oxa-10-	DOPO-OX, DOPO-OH	DX 11	Metadynea Austria	Not reg/pre-reg		polyesters, epoxy-systems, polyolefines		

CAS No	EC No	Chemical name	Abbreviation, trivial name	FR product	Manufacturer **	REACH registered tonnage, t/year	H/E Pro-file***	Substrate (as indicated by manufacturers)	Reference*	Page
		phosphaphenanthrene-10-oxide								

* For manufactured flame retardants reference is made to the web-sites of the manufacturers.

** If no indication of manufacturer, no flame retardants with the substance manufactured by companies that are members of EFRA and Pinfa have been identified

*** Profile refers to available US EPA profiles. Deca = US EPA 2014a, PUR = US EPA 2015, Printed CB = US EPA 2014b (see reference list)

An asterix before the EC number indicates that the substance has no EC number, but be the pre-registration or registration has been given a list number in the EC format.

3. Modification of the GreenScreen® methodology

In this chapter, a general level description of the original GreenScreen® method for hazard profiling and benchmarking for chemical alternatives assessment is given and adaptations/modifications for possible use of the method in a European regulatory context are presented based on a critical review of the original method combined with pilot testing on two substances. However, the intention has not been to provide a detailed review of all aspects of the methodology or to elaborate a use manual, merely to provide a foundation for the reader to understand the subsequent hazard profiling and scoring of 28 phosphorous-based flame retardants considered to be possible alternatives to a number of undesired brominated flame retardants. For full details on the basics of the methodology reference is made to the original description of GreenScreen® (Clean Production Action, 2013).

3.1 The GreenScreen® methodology

The GreenScreen® method was developed by the American NGO "Clean Production Action" and was first made publically available in 2011. The current version is V1.2 (Clean Production Action, 2013). GreenScreen® is based in part on an assessment method, "Alternatives Assessment Criteria for Hazard Evaluation", which was originally developed by the US Environmental Protection Agency (US EPA) as part of the programme "Design for the Environment" (DfE) as *"a transparent tool for evaluating and differentiating among chemicals based on their human health and environmental hazards"*. GreenScreen® was thus not specifically developed to assess flame retardants.

GreenScreen® is a systematic screening level approach to documenting and classifying human health and environmental hazards associated with chemicals. GreenScreen® can be used for identifying chemicals of high concern and safer alternatives. It is used to support product design and development, materials procurement, and as part of alternatives assessment based on internationally accepted classification criteria. A GreenScreen® assessment of a chemical results in a summary hazard profile, which can be used for risk assessment, and a so-called benchmark score, which can be used to assess the potential of the chemical when searching for safer alternatives. Benchmark scores are determined by analysing specific combinations of hazard classifications using a set of benchmarking criteria defined by GreenScreen®, which reflect hazard concerns established by governments nationally and internationally. The simplified procedure of a GreenScreen® assessment is shown below.

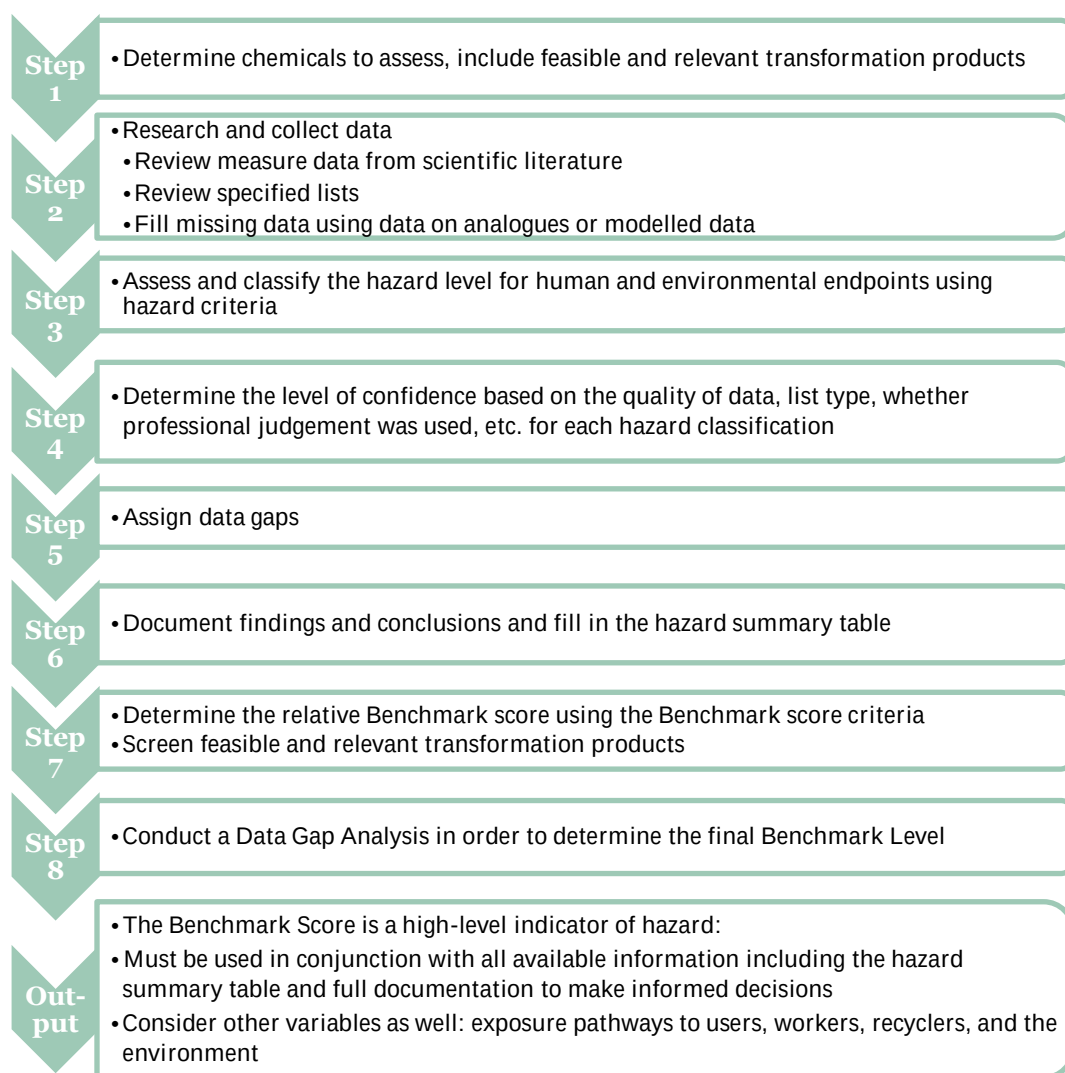


FIGURE 1
OVERVIEW OF THE GREENSCREEN® HAZARD ASSESSMENT PROCEDURE (REPRODUCED AND SIMPLIFIED FROM
CLEAN PRODUCTION ACTION, 2013)

Each relevant toxicological and environmental property of the chemical being evaluated is "translated" into a hazard level ("High", "Moderate", or "Low" and in some cases "very High" or "very Low") by applying one or more hazard criteria used by national (American) regulatory bodies, the European Union (REACH/CLP) or international organisations (e.g. OECD, IARC etc.).

Human health hazards are divided into Group I and Group II endpoints, where Group I covers hazards that can lead to chronic or life-threatening effects or adverse impacts that are potentially induced at low doses and transferred between generations, i.e. carcinogenicity, mutagenicity, genotoxicity, reproductive toxicity, developmental and neurodevelopmental toxicity, and endocrine activity. Group I endpoints have three hazard levels (H, M, L). Group II and II* cover systemic toxicity endpoints, sensitisation and skin and eye irritation. Group II endpoints (acute toxicity, systemic toxicity, neurotoxicity, and skin and eye irritation) are evaluated based on single exposure and are assigned one of four hazard levels (vH, H, M, L) whereas the Group II* endpoints (including systemic toxicity and neurotoxicity) are evaluated based on repeated exposure and are assigned one of three hazard levels (H, M, L). Group II* endpoints also include sensitisation.

Ecotoxicity, environmental fate and physical hazards endpoints are assigned four hazard levels except for persistence (P) and bioaccumulation (B) which are assigned five levels also including the “Very Low” (vL) level. Identified, relevant environmental transformation products should be taken into account in the hazard assessment of a substance.

An example GreenScreen® Hazard Summary Table is shown in Table 2.

TABLE 2
EXAMPLE OF A GREENSCREEN® HAZARD SUMMARY TABLE

Group I Human					Group II and II* Human										Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F	
						single	repeat*	single	repeat*											
DG	L	L	M	M	DG	L	L	M	M	L	L	L	L	L	L	vH	M	L	L	

Abbreviations:

C = Carcinogenicity M = Mutagenicity R = Reproductive Toxicity D = Developmental Toxicity E = Endocrine activity AT = Acute mammalian Toxicity	SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation AA = Acute aquatic toxicity ST = Systemic toxicity N = Neurotoxicity	SnS = Skin sensitization CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation Rx = Reactivity F = Flammability

An example of the criteria applied for the hazard profiling, which are based on classifications by various regulatory bodies or international organisations, is presented below by the original GreenScreen® set of criteria for carcinogenicity (Table 3).

TABLE 3
GREENSCREEN® HAZARD CRITERIA FOR CARCINOGENICITY

Carcinogenicity (C)	Information	Information	List type	High	Moderate	Low
	Data	GHS Criteria & Guidance		GHS Category 1A (Known) or 1B (Presumed) for any route of exposure	GHS Category 2 (Suspected) for any route of exposure	Adequate data available, and negative studies, no structural alerts, and GHS not classified.
	A lists	EU CMR *1	Authoritative	Category 1 or 2	Category 3	
		EU CMR *2	Authoritative	Carc 1A or 1B	Carc 2	
		EU H-	Authoritative	H350 or H350i	H351	
		EU R-phrases	Authoritative	R45 or R49	R40	
		EU SVHC	Authoritative	Reason for inclusion: Carcinogenic		
		IARC	Authoritative	Group 1 or 2A	Group 2B	Group 4
		MAK	Authoritative	Carcinogenic Group 1 or 2	Carcinogenic Group 3, 4, or 5	
		NIOSH-C	Authoritative	Occupational Cancer		
		NTP-RoC	Authoritative	Known or Reasonably Anticipated		
		Prop 65	Authoritative	Known to the state to cause cancer		
		EPA-C (1986)	Authoritative	Group A, B1 or B2	Group C	Group E
		EPA-C (1996)	Authoritative	Known or Likely		Not Likely
	B lists	EPA-C(1986)	Authoritative	Group D		
		EPA-C (1999)	Authoritative	Suggestive Evidence, but not sufficient to assess human carcinogenic potential		
		EPA-C (2005)	Authoritative	Suggestive evidence of carcinogenic potential		
		IARC	Authoritative	Group 3		

*1 Classification according to (DSD) Council Directive 67/548/EEC

*2 Classification according to (CLP) Regulation (EC) No 1272/2008

Following the hazard profiling of a substance, an assessment of its potential for being a possible alternative to an existing substance can, when relevant, be carried out using a stepwise so-called benchmarking approach as illustrated in Table 4 below.

Normally, the data identified in the hazard profiling process and the resulting scores in the summary hazard table are used for this purpose but a very rough, first assessment can be made based on substance classifications alone. Such a rough assessment will primarily serve to rapidly exclude substances without potential as alternatives before spending resources on a more in-depth identification and evaluation of specific data.

TABLE 4

GREENSCREEN® BENCHMARKS (BASED ON CLEAN PRODUCTION ACTION, 2013). CRITERIA MARKED WITH GREY ARE THOSE ORIGINAL GREENSCREEN® CRITERIA, WHICH ARE OMITTED IN THE PROPOSED MODIFIED METHODOLOGY (PHYSICAL HAZARDS).

Benchmark 1 (Avoid – Chemical of high concern)
a. PBT = High P + High B + [very High T (Ecotoxicity, Group II Human or High T (Group I and II* Human)] b. vPvB = very High P + very High B c. vPT = very High P + [very High T (Ecotoxicity, Group II Human) or High T (Group I and II* Human)] d. vBT = very High B + [very High T (Ecotoxicity, Group II Human) or High T (Group I and II* Human)] e. High T (Group I Human)
Benchmark 2 (Use but search for safer substitutes)
a. Moderate P + Moderate B + Moderate T (Ecotoxicity, Group I, II and II* Human) b. High P + High B c. High P + Moderate T (Ecotoxicity, Group I, II and II* Human) d. High B + Moderate T (Ecotoxicity, Group I, II and II* Human) e. Moderate T (Group I Human) f. Very High T (Ecotoxicity or Group II Human) or High T (Group II* Human) g. High Flammability or High Reactivity
Benchmark 3 (Use but still opportunity for improvement)
a. Moderate P or Moderate B b. Moderate Ecotoxicity c. Moderate T (Group II or II* Human) d. Moderate Flammability or Moderate Reactivity
Benchmark 4 (Prefer – safer chemical)
Low P + Low B + Low T (Ecotoxicity, Group I, II and II* Human) + Low Physical Hazards (Flammability and Reactivity) + Low (additional ecotoxicity endpoints when available)

As demonstrated by the illustration, the Benchmark 1 hazard criteria align to a large extent with the definition of a substance of very high concern (SVHC) under REACH, and a chemical may be assigned this score based on one endpoint only or a combination of endpoints. As an example a substance classified under GHS/CLP in category 1 for carcinogenicity will be assigned the benchmark 1 score as well a substance fulfilling the PBT criteria. Benchmark scores 2 and 3 are assigned based on either an individual criterion or a combination of criteria and the evaluation of a minimum data set for chemicals not achieving Benchmark 1, and Benchmark 4 is assigned to chemicals based on data for all 18 hazard endpoints when the resulting hazard levels are all in the low category.

3.2 Adaptation of the methodology to a European context

A critical review of the GreenScreen® methodology was performed to evaluate its applicability for hazard assessment related to consumers and the environment in a European regulatory context.

This evaluation of the methodology has focussed on the hazard classification/scoring criteria, the required data and the recommended documentation sources to ensure that the methodology reflects the principles and criteria in the current European chemical regulation (REACH and CLP) and also meets the Danish EPA's requirements to hazard assessment of chemical substances in consumer product projects. Also the procedure and criteria for the subsequent benchmark scoring

for assessment of the potential of a chemical as an alternative to existing chemicals have been reviewed critically.

To address this, the methodology has been critically reviewed with regard to the following:

- i) data collection,
- ii) criteria for hazard profiling,
- iii) benchmarking procedure,
- iv) criteria for alternatives assessment

The reviewed elements of the methodology have been compared to the information sources and perceived validity of health and environmental data recommended by the Danish EPA and/or ECHA for hazard assessment of chemicals, and the classifications and specific hazard criteria applied in Denmark and/or the EU. Subsequently, relevant modifications or adaptations of the methodology to the European context have been made. The evaluation and suggestions for adaptations are described in the sub-sections below.

The suggested modifications to the methodology and criteria are relatively minor as the review process confirmed that the GreenScreen® method was developed using already to a significant extent an internationally oriented approach with REACH and CLP/GHS criteria and guidance as key data for classifying the substances, and considering and incorporating internationally recognised data sources, including those recommended or requested by ECHA and the Danish EPA, in addition to specific North American lists of data sources. The details will be presented in the following sections.

When applying the modified method in this report it has to be noted that, in the case where no modifications are suggested and where there are differences between the GreenScreen® hazard criteria and the criteria in the US EPA DfE programme, the criteria from the DfE programme have been used.

3.2.1 Evaluation and adaptation of data sources

The list of information sources included in the GreenScreen® methodology was reviewed and found to comprise many of the same sources (factual and bibliographic databases/portals, homepages, model tools) that are commonly used also in Denmark when performing hazard and risk assessments of chemicals in consumer products (and of chemical substances in general). GreenScreen for Safer Chemicals Version 1.2 Information Sources document is intended to provide support for performing GreenScreen Assessments but is not intended to serve as an exhaustive and ordered list of all information sources that should be used to perform a hazard assessment on a chemical.

However, some bias towards US information sources was noted and, additionally, a few data sources were considered to address issues at a too detailed level for a screening assessment. Based on these considerations, a few information sources are suggested to be omitted and a few new ones proposed to be included. Also, fee-based databases have generally been omitted. Further, the order of appearance of the data sources has been changed partly to reflect the "European view", partly to organise the information sources a bit more systematically, i.e. in the following three main categories:

- 1) Classification databases,
- 2) factual databases and homepages (i.e. including review reports) and
- 3) model tool homepages and databases.

In the adapted data source list, the following data sources are omitted from the GreenScreen® list of information sources (version 1.2):

- CHE database (database which summarises links between chemical contaminants and approximately 180 human diseases or conditions. Omitted as the relevant information is expected to be covered by other sources)
- GHS (Substituted with CLP criteria)
- EPA RED (No additional relevant information provided)
- UM-BBD (Not accessible)
- RTECS (fee-based)
- LOLI (fee-based)
- Ariel (fee-based)
- ISSCAN (this model is expected to be covered by other included models)

The following data sources are added to the adapted GreenScreen® list of information sources (version 1.2):

- CLP (Substitutes GHS criteria)
- CLP advisory list for self-classification (added, Danish QSAR predictions)
- Gestis (Substance database from the German Social Accident Insurance containing information about approx. 9400 substances)

The list of information sources for a screening assessment with proposed modifications for a European context is shown in Table 5. For practical reasons, entries targeting several information sources, e.g. database portals such as eChemPortal and Toxnet, have been split up to show the direct links to the most relevant databases comprised by the portal, which are not already covered by an individual entry, as this supports a more systematic data search. These entries have been given a greyish shading.

TABLE 5

LIST OF INFORMATION SOURCES FOR GREENSCREEN® ASSESSMENT, MODIFIED TO A EUROPEAN CONTEXT. GREY-SHADED ENTRIES UNDER A DATABASE PORTAL ARE THOSE CONSIDERED MOST RELEVANT, AND WHICH DO NOT HAVE AN INDIVIDUAL ENTRY ALREADY.

ID	Abbreviation	Information Type	Information Source	URL and/or Reference
1	CLP	CLP Classifications and Substance Data	European Chemicals Agency, ECHA	http://echa.europa.eu/information-on-chemicals/cl-inventory-database
2	CLP advisory list for self-classification	Database with QSAR predictions for classification	Danish Environmental Protection Agency	http://mst.dk/virksomhed-myndighed/kemikalier/stoflister-og-databaser/vejledende-liste-til-selvklassificering-af-farlige-stoffer/clp/
3	REACH	Database (substance registration dossiers)	European Chemicals Agency, ECHA	http://echa.europa.eu/information-on-chemicals/registered-substances
4	eChemPortal	Database Portal	The Organisation for Economic Co-operation and Development eChemPortal	http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en

ID	Abbreviation	Information Type	Information Source	URL and/or Reference
	EnviChem	Database	SYKE, Data Bank of Environmental Properties of Chemicals	http://www.ymparisto.fi/en-US/Maps_and_statistics/Data_systems/Data_bank_of_Environmental_Properties_of(30591)
	OECD HPV	Database	Organisation for Economic Cooperation and Development (OECD) Existing Chemicals Database	http://webnet.oecd.org/hpv/ui/Default.aspx
	GSBL	Database	Joint Substance Data Pool of the German Federal Government and the German Federal States	http://en.gsbl.de/gsblweb30/main.do?sessionId=B029017C653833915C6451110B0BCC6E
5	INCHEM	Database Portal	Chemical Safety Information from Intergovernmental Organizations (IPCS, WHO, CCOHS, IOMC)	http://www.inchem.org/
	CICADs	Database	Concise International Chemical Assessment Documents	http://www.inchem.org/pages/cicads.html
	EHC	Database	Environmental Health Criteria Monographs	http://www.inchem.org/pages/ehc.html
	IARC	Database	International Agency for Research on Cancer (IARC) Monographs on the Evaluation of carcinogenic Risks to Humans	http://monographs.iarc.fr/
	JECFA	Database	Joint Expert Committee on Food Additives (JECFA) - Monographs and Evaluations	http://www.inchem.org/pages/jecfa.html
	SIDS	Database	OECD Screening Information Data Set (SIDS) High Production Volume Chemicals	http://www.inchem.org/pages/sids.html
	UKPID	Database	UK Poison Information Documents	http://www.inchem.org/pages/ukpids.html

ID	Abbreviation	Information Type	Information Source	URL and/or Reference
6	IRIS	Database	US Environmental Protection Agency (EPA), National Center for Environmental Assessment, Integrated Risk Information System (IRIS) Database	http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList
7	NIOSH/OSHA	Pocket Guide/Database	NIOSH Pocket Guide	http://www.cdc.gov/niosh/npg/
8	TOXNET	Database Portal	The Toxicology Data Network	http://toxnet.nlm.nih.gov/index.html
	HSDB	Database	The Toxicology Data Network	http://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm
	TOXLINE	Database	The Toxicology Data Network	http://toxnet.nlm.nih.gov/newtoxnet/toxline.htm
	DART	Database	The Toxicology Data Network	http://toxnet.nlm.nih.gov/newtoxnet/dart.htm
	GENE-TOX	Database	The Toxicology Data Network	http://toxnet.nlm.nih.gov/newtoxnet/genetox.htm
9	ACToR	Database Portal	Aggregated Computational Toxicology Resource	http://actor.epa.gov/actor/faces/AC-ToRHome.jsp;jsessionid=3EDA0C36597CBD1945389C18D05A7E4
10	ECOTOX	Database	The ECOTOXicology Database (US EPA)	http://cfpub.epa.gov/ecotox/
11	Gestis	Database	Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA)	http://gestis.itrust.de/nxt/gateway.dll/gestis_de/000000.xml?f=templates\$fn=default.htm\$3.0
12	Scorecard	Database	Scorecard Chemical Profiles	http://scorecard.goodguide.com/chemical---profiles/
13	PubChem	Database	PubChem	http://pubchem.ncbi.nlm.nih.gov/
14	ASTDR	Database	US Department of Health and Human Services, Agency for Toxic Substance & Disease Registry	http://www.atsdr.cdc.gov/az/a.html

ID	Abbreviation	Information Type	Information Source	URL and/or Reference
15	ToxRefDB	Database	US EPA Toxicity Reference Database (ToxRefDB), which captures thousands of in vivo animal toxicity studies on hundreds of chemicals.	http://www.epa.gov/comptox/toxrefdb/
16	FDA - ED	Database	US Food and Drug Administration (FDA) Endocrine Disruptor Knowledge Base (EDKB)	http://www.fda.gov/scienceresearch/bioinformaticstools/endocrinedisruptorknowledge-base/default.htm
17	CHIRP	Database	Japan National Institute of Technology and Evaluation (NITE) Chemical Risk Information Platform (CHIRP)	http://www.safe.nite.go.jp/english/db.html
18	PAN	Database	Pesticide Action Network Pesticide Database	http://www.pesticideinfo.org/Search_Chemicals.jsp
19	SIN List and SIN similarity tool	Database	ChemSec, the International Chemical Secretariat	http://sinlist.chemsec.org/
20	EPI Suite	Model tool	US EPA EPI (Estimation Programs Interface) Suite™	http://www.epa.gov/oppt/exposure/pubs/episuite.htm
21	PBT Profiler	Model tool	US EPA PBT Profiler	http://www.pbtprofiler.net/
22	(Q)SAR	Model tool	Danish (Q)SAR Database	http://qsar.food.dtu.dk/
23	OECD Toolbox	Model tool	The Organisation for Economic Co-operation and Development (OECD)	http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm
24	OncoLogic™	Model tool	US EPA, Sustainable Futures	http://www.epa.gov/oppt/sf/pubs/oncologic.htm

In addition to the above table with information sources, Appendix 3 contains the modified version of GreenScreen's so-called "Specified List", which is a table with a collection of lists with e.g. human health and environmental classifications of chemicals according to defined hazard criteria. The list indicates whether the individual lists originate from authoritative (reliable) sources (see definitions at start of the appendix) or are of a screening level type of information (lower degree of validation).

Finally, GreenScreen's "List Translator" (see Appendix 4) should be mentioned. This is based on the same classification lists as mentioned above, however here with a further sub-division into hazard classification parameters and categories to which benchmark scores are assigned. This simple benchmarking approach can be used for a first, rough assessment of a chemical as to whether it has any potential at all for being considered in an alternatives assessment, and thereby whether it is worthwhile to use the required efforts and resources to develop a full, documented hazard profile for the substance. No modifications of this list have been suggested.

3.2.2 Evaluation and adaptation of criteria for hazard profiling

Overall, GreenScreen's categories for hazard profiling are found to reflect well the classification categories used in REACH and CLP (GHS). The classification criteria in some other countries such as Canada and a number of signatories to the GHS system under United Nations as part of the GreenScreen® methodology were during this review found to be irrelevant for assessments in a European context and have therefore been deleted in the proposed adapted criteria table.

Further, physical hazard parameters such as flammability and reactivity, which are included in the profiling according to the GreenScreen® methodology, were also considered of marginal relevance in the current context focusing on protection of consumers and the environment. In the situations where exposure of consumers and/or the environment can occur, it was based on expert judgement assessed that the chemical substances will not be present in sufficient amounts and concentrations for such physical hazards to be expressed. They were therefore omitted from the hazard profiling and subsequent benchmarking procedures.

The same argument could in many cases also apply to other hazard endpoints, such as acute toxicity in Group II Human and acute ecotoxicity. It is, however, not considered justifiable to generalize in the same way for these endpoints as for the physical hazards and therefore these endpoints are suggested to be evaluated specifically on a case-by-case basis. In this report no modifications with regard to these hazard endpoints have been introduced.

Specific needs for adaptation of human health and environmental and hazard criteria in a European context are described in the following.

A table with the full set of adapted criteria and associated information sources is included as Appendix 2 to this report, while other tables comprising human health and environmental classification lists and their assigned scores for benchmarking (i.e. scoring for alternatives assessment) are included as Appendix 3 and Appendix 4, respectively. In order not to confuse the modified version with the original GreenScreen® method, "hazard profile" is used instead of "modified GreenScreen® profile" for the hazard profiles developed in this report.

Human health hazard criteria

The GreenScreen® health hazard criteria are largely based on GHS criteria which correspond to the criteria implemented with CLP. For some hazard classes the criteria however include more categories than those implemented with CLP. This is the case for acute mammalian toxicity and for skin and eye irritation where the GreenScreen® method includes category 5 for acute toxicity, category 3 for skin irritation, and category 2B for eye irritation, which are not included in CLP.

Furthermore, the GreenScreen® method has singled out neurotoxicity from the systemic toxicity/organ effects using US EPA Guidance to define applicable neurotoxic effects and otherwise weight of evidence-based criteria to categorise the effects. As neurotoxicity is a relevant endpoint for organophosphorus compounds, it is suggested to keep this endpoint as an individual hazard class in the modified approach.

In addition to the specific classification criteria, a number of authoritative lists and screening lists are included. Some of these lists are developed in the US at a federal or state level, such as the Prop 65 List (California Proposition 65) administered by the California EPA and including chemicals known to the state to cause cancer or reproductive toxicity. Evaluations not developed at a federal level such as Prop 65 are removed from the modified approach. In general, if applying data/entries from these lists, it is important to be aware that they may be developed with very different purposes and evidence behind the listing.

Endocrine activity/disruption does not have a specific classification category under the CLP/GHS Regulation. Substances demonstrating endocrine activity/disruption are therefore only classified if they fulfil the criteria for classification of other endpoints covered by the Regulation, e.g. effects on fertility or developmental effects, which result in a classification for reproductive toxicity.

The GreenScreen® method for identifying endocrine activity/disruption is therefore list-based with a number of screening lists and SVHC substances, which have been included in the REACH Candidate List based on endocrine activity (equivalent level of concern) as the only authoritative list. With regard to lists developed by the EU, the priority list of chemicals developed within the EU-Strategy for Endocrine Disruptors is included as a screening list. The Endocrine Active Substances Information System (EASIS) is under development to update the existing EU database hosted by Directorate General (DG) for Environment. This list is suggested to be added to the methodology when finalised. Under the modified method if a substance has not been included in any of the mentioned lists, but experimental data are available, the substance's endocrine activity potential is scored according to the criteria for the EU priority list based on the data levels as specified in the OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupting Chemicals (see Appendix 2; ECETOC, 2009). If no experimental data are available, the endpoint is marked as a data gap (DG) corresponding to category 3b (no data available) of the EU priority list. Apart from these comments, the human health assessment part of the current GreenScreen® method is considered appropriate and is not modified.

The following specific adaptations of the list of health categories and information sources were made:

Data:

- GHS is substituted with CLP

Lists added:

- CLP classifications by industry are added as a B-list
- ADR (substitute for DOT)

"A Lists" removed:

- Other country-specific GHS implementations
- DOT
- Prop 65
- NTP-RoC (Considered covered by IARC)
- NTP OHAAAT (includes currently very few substances)

"B Lists" removed:

- EPA AMT
- G&L
- Boyes-N
- OSPAR
- WHMIS
- DOT

Environmental hazard criteria

The GreenScreen® environmental hazard criteria comprise only a few hazard categories: Acute aquatic toxicity, chronic aquatic toxicity, persistence and bioaccumulation. The translation of classification categories (or data based ranges) into GreenScreen® hazard profile categories ("High" - "Moderate" - "Low", in some cases complemented by "Very High" and "Very Low") is found to be highly inspired by REACH and CLP/GHS hazard classification, either using the different levels of hazard categories or hazard phrases/statements or the numerical intervals of the hazard data un-

derlying the classifications. In particular for the persistence and bioaccumulation categories, the profiling categories are directly inspired by the PBT and vPvB criteria in REACH.

The following specific adaptations of the environmental categories were made:

- EU H-statements for acute and chronic aquatic toxicity: Missing categories have been added;
- EU R-phrases for acute and chronic aquatic toxicity: Small corrections and addition of missing categories;
- CLP classifications by industry regarding acute and chronic aquatic toxicity added as a B-list (non-authoritative info);
- Persistence in air: Half-life <2 days changed to be a combined moderate-low category;
- Categories of High and Moderate Bioaccumulation potential as represented by BCF changed from >1000-5000 and >500-1000, respectively, to >2000-5000 and >500-2000, to reflect more correctly the EU PBT and vPvB category delimitations;
- Low and Very Low bioaccumulation potential as reflected by Log Kow changed to include an interval for "Low" (>3.0 to 4.0) and reducing "Very Low" to Log Kow <3.
- Adaptations of sources of criteria: As above for health criteria sources. Additionally, DSL is suggested to be removed from the list of sources of environmental criteria.

Hazard profile presentation

The colour codes and symbols/abbreviations used by GreenScreen® for presenting the substance hazard profiles in the summary hazard tables are suggested to be modified slightly in the context of this report as they were found to be, albeit stringent, somewhat overloaded with information and also contained more information on this form than the US EPA summary hazard profiles to be reviewed. E.g. it was found that assessment and comments on data quality and validity could be more adequately addressed in an accompanying short text than on tabular form.

Hence, the summary tables in the current report (using the modified approach) apply the following colour codes, symbols and abbreviations for presentation of the substance hazard profiles:

TABLE 6
OVERVIEW OF COLOUR CODES, SYMBOLS AND ABBREVIATIONS USED IN THE CURRENT REPORT FOR PRESENTATION OF SUBSTANCE HAZARD PROFILES IN SUMMARY HAZARD TABLES.

Colour code or symbol	Explanation
VL	Very Low hazard
L	Low hazard
M	Moderate hazard
H	High hazard
VH	Very High hazard
DG	DG = Data Gap (on a white background) means that due to lack of data no hazard score has been assigned
Bold	" Bold " font means that the hazard score is based on measured/empirical data
Normal	"Normal" font mean that the hazard score is based on estimated/predicted values (e.g. QSAR) or on read-across and/or other expert judgement
()	Parentheses are used to indicate specific assessments for inorganic substances, in particular of persistence for which the standard scoring criteria are not valid.

3.2.3 Evaluation and adaptation of benchmarking criteria and procedure

The procedure and criteria for benchmarking of substances in a substitution context is basically considered to be useful and applicable for a screening level assessment in its current form (see Table 4 for definition of BM levels). However, as explained in the preceding section, in a European context, the modified GreenScreen® methodology is anticipated only to be used to assess hazards of chemical substances to consumers and/or the environment.

The physical hazards (flammability and reactivity) included in the original GreenScreen® benchmarking criteria are considered to be of marginal relevance within the scope for the current project (see section 3.2.2). Flammability and reactivity are mainly of relevance in the application of the flame retardants for manufacture of flame retarded products and the hazard criteria for these parameters are therefore suggested to be omitted from the benchmarking procedure as applied here (Benchmark levels 2 (2.g), 3 (3.d) and 4).

We have found it less evident to make a similar general distinction between the endpoints in Group II Human and have therefore adopted the full set of endpoints as defined in the original procedure. In order not to confuse the modified version with the original GreenScreen® method, “overall hazard score” is used instead of “benchmark score” for the hazard profiles developed in this report.

3.3 Pilot test of the modified methodology

Two phosphorous substances were selected for testing the modified GreenScreen® methodology; one substance that has already been screened by the US EPA, CAS no. 115-86-6, triphenyl phosphate, and one “new”, i.e. not previously screened, substance: CAS no. 68937-40-6, phenol, isobutyleneated, phosphate.

3.3.1 Triphenyl phosphate, CAS No 115-86-6

The screening of triphenyl phosphate by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives to the flame retardant decaBDE (US EPA, 2014a).

The comparison of the result – the summary hazard table – with the original hazard summary table by US EPA (US EPA 2014a) is shown in Table 7 and Table 8, respectively. The US EPA's presentation of the results slightly deviates from the original GreenScreen® summary table format and it was therefore found necessary to slightly adapt the presentation for the purpose of the current project. The US EPA does not include endocrine activity in the hazard comparison because of limited data for evaluation and lack of robust tools for modelling endocrine activity. Nonetheless, the US EPA lists studies on endocrine activity, if such data were available. In addition, the US EPA includes a category for repeated dose toxicity but not “systemic toxicity from single exposure” as it is the case in GreenScreen®. With regard to neurotoxicity the US EPA has one category whereas the GreenScreen® method differentiates between neurotoxicity from single and repeated exposure, respectively.

TABLE 7
US EPA SCREENING RESULT FOR TRIPHENYL PHOSPHATE (FORMAT SLIGHTLY MODIFIED TO FIT INTO CURRENT GREENSCREEN® FORMAT)

Group I Human						Group II and II* Human								Ecotox		Fate	
C	M	R	D	E ¹	AT	ST		N		SnS*	SnR* ³	IrS	IrE	AA	CA	P	B
						single ²	repeat*	single ²	repeat*								
M	L	L	L		L	DG	H	DG	L	L		VL	L	VH	VH	L	M

1 Endpoint not evaluated with a score by the US EPA

2 No systemic toxicity or neurotoxicity based on single exposure reported by US EPA

3 No data located by US EPA

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

TABLE 8
SCORING OF TRIPHENYL PHOSPHATE USING THE PROPOSED MODIFIED ASSESSMENT/CLASSIFICATION METHODOLOGY

Group I Human						Group II and II* Human								Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	L	L	L	H	L	DG	H	DG	L	L	DG	L	L	VH	VH	L	L	1

Comments to hazard profile scores

As appears by comparison of the two tables, the two screening results for triphenyl phosphate are identical with the exception of the results for endocrine activity, bioaccumulation potential and skin irritation.

Several primary studies and a few secondary sources listed in the US EPA report (2014a) demonstrate effects on endocrine activity *in vitro* as well as *in vivo*. We have therefore assigned the score "High" to this endpoint (US EPA only presents data on endocrine activity, when available, but has not included scoring of this effect parameter)

Bioaccumulation was scored as "M" ("Moderate") by US EPA (2014a). However, based on the data presented this score is considered to be incorrect as none of the presented BCF's exceed a value of 500, which is the upper limit for a score as "Low". COWI therefore scores bioaccumulation potential as "L" based on the same data.

This result is in agreement with the evaluation and suggested small modifications of the GreenScreen® methodology to adapt it to a European context, which, with the exception of "Bioaccumulation", has led to only minor modifications of the original criteria limits and a moderate revision of the priority information sources to be used in the screening (as described in section 2.2).

For the particular example triphenyl phosphate, the mentioned modification of the "Bioaccumulation" criteria would not have had any impact on the hazard scoring anyway while use of the modified priority data sources (instead as the original data set, which was used here) theoretically could have affected the result slightly.

Overall hazard scoring

The US EPA substance profiles do not include an overall hazard score assessment as the GreenScreen® method does. Such a column is included in the modified substance summary table above to provide the full overview of the outcome of the substance assessment in one table. In the case of triphenyl phosphate, an overall hazard score = 1 is assigned because the substance meets criterion e) High T (Group I Human) by scoring "High" for endocrine activity.

3.3.2 Phenol, isobutyleneated, phosphate (3:1), CAS No 68937-40-6

Isobutyleneated phenol phosphate was used to test a new substance, i.e. a substance not previously assessed by the US EPA, using the modified GreenScreen® procedure.

The overall result of the data evaluation, i.e. the summary hazard table, is shown below while the full data set from the data collection including justification of the scoring based on the retrieved data is enclosed as Appendix 5 to this report.

TABLE 9

SCORING OF ISOBUTYLENATED PHENOL PHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
DG	L	L	L	DG	H	DG	M	M	M	L	DG	M	M	VH	VH	L	M	2

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Scoring of human health parameters are identical using the original GreenScreen® hazard criteria and the modified procedure for the endpoints where data have been identified. Information was not identified for carcinogenic properties, endocrine disruption, target organ toxicity from a single exposure, and respiratory sensitisation.

For the environmental parameters, only the scoring of Bioaccumulation potential would have been different if the original GreenScreen® hazard criteria had been applied as the BCFs in fish are in the interval from 1,000-2,000. The original GreenScreen® method has an upper limit of BCF = 1,000 for the "Moderate" criterion, and thus would have scored "High" for this substance, while the suggested modified method scores bioaccumulation potential as "Moderate" up to BCF = 2,000 (according to the lower limit for the B-criterion under REACH (PBT assessment)).

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not meet any of the criteria at Level 1 but meets criterion f) at Level 2 by scoring "very high" for ecotoxicity.

3.4 Applicability of the modified GreenScreen® methodology

The GreenScreen® methodology for screening hazard assessment of chemical substances was reviewed critically with the aim to assess whether the methodology could be of interest and would be possible to apply for such assessments in a European context, possibly with some modifications to be suggested.

The review revealed that despite having been developed in an American context, the GreenScreen® methodology is to a high degree aligned with both national and international regulations including the GHS and REACH, as well as national and international hazard lists and authoritative lists.

Therefore, the suggested modifications of the methodology to adapt it to a European context are relatively minor and relate mainly to the data sources to be used for documentation and the relative priority of these, and a few changes of hazard classification intervals.

The hazard profiling methodology is considered to be applicable to human health and environmental hazard profiling of chemical substances in a European context. This is the case, not only for substances belonging to the group of flame retardants addressed in this project, but also for hazard profiling of chemicals of possible concern in general, extending beyond consumer product projects with possible additional, minor modifications. If the aim of the assessment is to identify possible alternatives to a given chemical, it is recommended to start with a rough overall hazard scoring assessment based on the List Translator before starting to prepare a full hazard profile for a substance.

However, the authors of this report find that hazard profiling using this screening tool requires persons with solid professional capability and experience within toxicology/human health assessment and environmental assessment in order to obtain reliable, balanced substance profiles, not least when assessing substances with incomplete data sets or with conflicting data for the same effect parameter. Additionally, in some cases it may be necessary to generate estimate data by use of QSAR modelling tools, which can require special expertise.

As regards the benchmarking part of the methodology, the criteria at Benchmark 1 level (BM1, i.e. the "worst" substances) are found to be aligned to a large extent with REACH SVHC criteria, with the exception that also a "very high" score for toxicity in Group II Human or "high" score in Group II* Human in combination with vP or vB lead to BM =1 in the GreenScreen® methodology. This is considered a relevant addition to the REACH SVHC criteria when the focus is on consumer products. Whether this exception is covered by the REACH SVHC criteria regarding Equivalent Level of Concern has not been assessed.

Benchmark scoring is possible even if data are not available for all hazard endpoints. E.g. data on sensitization are not necessary in order to score at the second highest benchmark level (BM3), however scoring at the highest level (BM4, i.e. the "best" substances) is only permissible for substances where data for all endpoints exist.

The exercise of overall hazard scoring of the 28 substances (individual results presented in the following chapter) revealed that the majority of the substances ended up in the same category and, thus, the differentiation between the substances appear to be too low to be really operational in a substitution situation. The exercise further showed that this, at least to some extent, was caused by a "gap" between two criteria levels (BM1 and BM2, see Table 4 for definitions) resulting in some substances obtaining an overall hazard score that does not fully reflect the hazard potential. Hence, for future occasions an additional benchmark level ("BM1½") could in principle be relevant to introduce. However, neither BM1½ nor BM2 substances are in reality very relevant to consider as possible long-term alternatives due to the nature and magnitude of the hazards covered by these two categories.

Finally, it should be noted that in a substitution decision-making situation, the hazard profile of a substance cannot stand alone but must be complemented by exposure considerations for relevant use scenarios. This could result in considering that for a specific scenario more weight should be put on some endpoints than others. E.g. in most consumer product contexts "acute toxicity" will not be a relevant endpoint because such concentrations are not likely to occur in reality and, consequently, this endpoint should be evaluated on a case-by-case basis and possibly be neglected or at least be given lower weight than chronic endpoints. In other situations environmental endpoints could be assessed less relevant than human health endpoints for a particular scenario.

4. Hazard profiles and application data for flame retardants

This chapter presents hazard profiles for 28 marketed phosphorous flame retardants and five of the main halogenated flame retardants based on the modified GreenScreen® method.

Application profiles of marketed phosphorous flame retardants

The application profiles include for each of the marketed phosphorous flame retardants information on:

- CAS No, chemical name, structural formula, general formula, phosphorous content, abbreviations, product names, manufacturers, registered tonnage
- Applicability for each of the substrates as indicated in Pinfa's Product Selector (applicable, could be applied, etc.)
- Substrates (type of plastics, paint, textiles, etc.) as indicated by the manufacturers
- End applications (automotive, building, etc.) as indicated by manufacturers
- Interaction with substrate (additive, reactive)
- Environmental/health profiles: References to the US EPA DfE reports and screenings carried out in this project.
- Availability (recently introduced, widely applied, main flame retardant for the applications, etc.) to the extent data are available from manufacturers or the literature.
- Flame retardancy: Various information on the ability of the flame retardants in meeting different fire safety standards for relevant substrates as indicated in the literature, technical data sheets, etc. The description built on the information readily available for each flame retardant and is not systematically using the same methodology.
- Halogen-containing flame retardants for the same application to the extent it is described in the literature or in the manufacturer's product selectors. The list of halogen-containing flame retardants is not considered comprehensive, but includes examples identified.

The data are collected from technical data sheets and safety data sheets (SDSs) from the manufacturer's websites, as well as from literature with evaluations of flame retardants (references indicated in the tables).

Hazard profiles

Based on the methodology described in Chapter 3, modified GreenScreen profiles have been developed for 23 phosphorous flame retardants evaluated by the US EPA.

In addition to these, five "new" flame retardants (i.e. not previously evaluated by the US EPA) were selected for hazard screening as part of this study. The five flame retardants were selected from the long list based on the following criteria:

- The substance is already to some extent used as an alternative to halogenated flame retardants or marketed specifically as such.
- The substance meets the applicable fire safety requirement for major applications of the halogenated flame retardants
- The substance is registered under REACH, or significant environmental and health data are available otherwise

- The substance is not classified as a CMR substance in accordance with the CLP Regulation (Regulation (EC) No 1272/2008)

When available, information on environmental transformation products of the substances (or group of substances) has, in accordance with the GreenScreen® procedure, been taken into account when scoring the different endpoints to produce a hazard profile for one of the new substances. E.g. for melamine phosphate (CAS No. 41583-09-9), much of the data are based on tests with pure melamine and not the phosphate derivative. In the datasheet for melamine phosphate (Appendix 7), it is stated for each of the data provided when they are based on pure melamine rather than on the phosphate derivative.

The existing hazard profiles for the substances evaluated by US EPA mention transformation products where such have been identified, and where the hazards scores of these deviate from those of the parent compound. However, no full data sheets on transformation products are provided by US EPA and, hence, it has not been possible within the framework of the present study to fully evaluate a parameter such as endocrine disruption (ED), which is not included in the US EPA profile. However, where data indicate identification of transformation products, such as resorcinol in relation to RDP, these have been included in the screening.

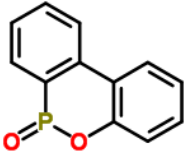
If also considering theoretical transformation products, such as bisphenol A in relation to BAPP, bisphenol A would score "high" for ED based on the adapted criteria. This would result in an overall hazard score 1 for flame retardants eventually resulting in transformation products such as bisphenol A, which is lower than the current scores.

In additions to the screening profiles, an overall hazard score has been calculated and is presented for each of the screened substances.

4.1 Organophosphorous compounds

4.1.1 DOPO, CAS No. 35948-25-5

Technical description

CAS No	35948-25-5
EC No	252-813-7
Chemical name	9,10-Dihydro-9-oxa-10-phosphaphenanthren-10-oxide
Structural formula	 Registration
General formula	C ₁₂ H ₉ O ₂ P
Phosphorous content	14.0 – 14.6 (Metadynea)
Abbreviation, synonyms	DOPO; 6H-dibenz[c,e][1,2]oxaphosphorin-6-oxide
FR products and manufacturers	KCCS DO11, Metadynea EVERFOS DOPO, Everkem Mileflame DOPO, MPI Chemie
Registered tonnage, t/year	1,000 - 10,000

Pinfa Product Selector	Group Thermosets	Substrate Epoxy resins	Applicability Applicable
Other information on substrate	Evrfoos: ABS, flexible PUR, unsaturated polyester, epoxy resin, phenolic resins Metadynea: "DO11 is especially suited for polyesters and epoxy-systems, where DO11 is used as intermediate. It is s most effective as flame retardant where a gas / vapour phase radical inhibitor is required"		
End applications	Electrical and electronic equipment (EEE), transportation, wire and cable building and construction.		
Reactive/additive	Reactive		
Health env. profiles	Alternatives to TBBPA in printed CB (US EPA 2014c)		
Availability	Available from several manufacturers		
Flame retardancy	DOPO has been used as a flame retardant for certain types of printed wiring boards (Morose, 2006). UL 94-V0 rating of printed wiring boards was reached with 1.6 - 2.2% P-loading depending on substrates (Rakotamala et al., 2010). DOPO is the first efficient halogen free flame retardant for novolac-based epoxy systems (Rakotamala et al., 2010).		
Halogen-containing flame retardants for the same application (ex-amples)	TBBPA used reactively		

Hazard profile

The screening of DOPO by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives to the halogenated flame retardant in printed circuit boards (US EPA, 2014c).

TABLE 10
SCORING DOPO USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human								Ecotox		Fate		Overall Hazard Score	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P		B
						single	repeat*	single	repeat*									
M	L	L	M	DG	L	DG	L	DG	M	M	DG	L	M	L	M	H	VL	2

Comments to hazard profile scores

The US EPA scores for Group I human toxicity are “moderate” for carcinogenicity and developmental toxicity due to an uncertain concern for adverse effects based on analogy with similar structures. Reproductive toxicity is scored as “low” based on analogy and professional judgement, and mutagenicity/genotoxicity is scored as “low” based on negative results from different *in vitro* studies. For Group II human toxicity systemic toxicity in one repeat dose study is available resulting in a “low” score based on the NOAEL established at the highest dose tested. The potential for neurotoxicity is scored as “moderate” based on structural alerts and professional judgement. No data is available for endocrine disruption and respiratory sensitization. Skin sensitization is scored a “moderate” due to limited data except for results from a local lymph node assay starting at 5%. Skin irritation was scored as “low” based on no skin reactions in an OECD test and eye irritation was scored as “moderate” based on moderate signs of eye irritation clearing in 7 days.

The US EPA score for persistence in the environment is "high" based on estimated data leading to an assessment of the half-life for ultimate degradation in soil of 75 days. However, the origin of this value is unclear as it is not included in the data table but only appears in the text justifying the

score. As, on the other hand, it is not obvious that the score for persistence should only be "moderate", the "high" score is maintained here.

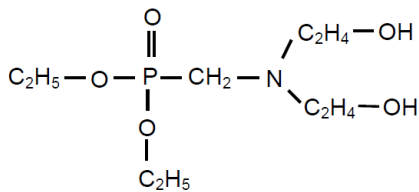
No changes have been made to the US EPA hazard scores except for skin irritation and bioaccumulation, where the US EPA score was changed from "very low" to "low" and "low" to "very low", respectively. This is not because of a different assessment of the data, but merely because of a different categorization of the criteria in the original and the modified methodology.

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind the overall hazard score = 1 but meets criterion e) for the overall hazard score = 2 by scoring "moderate" for both carcinogenicity and developmental effects in Group I Human.

4.1.2 N,N-bis-(2-hydroxyethyl) aminomethane phosphonic acid diethyl ester, CAS No. 2781-11-5

Technical description

CAS No	2781-11-5		
EC No	220-482-8		
Chemical name	N,N-bis-(2-hydroxyethyl) aminomethane phosphonic acid diethyl ester		
Structural formula	 Fyrol™ 6 datasheet		
General formula	C9H22NO5P		
Phosphorous content	12.1 % (Levagard 4090 N) 12.4 % (Fyrol™ 6)		
Abbreviation, synonyms	Diethyl bis(2-hydroxyethyl) aminomethylphosphonate		
FR products and manufacturers	Levagard 4090 N (Lanxess) Fyrol™ 6 (ICL-IP Europe)		
Registered tonnage, t/year	Pre-registered		
Pinfa Product Selector	Group: Foams Thermosets	Substrate: PUR rigid foam PUR flexible foams Phenolic resins	Applicability: Applicable Applicable Applicable
Other information on substrate	Rigid PUR foams, PF, EP and UP resins		
End applications	"Levagard® 4090 N is especially suitable as flame retardant for rigid PUR foams. The product can support a closed-cell foam structure and can be combined with other Levagard or Disflamoll products. Further applications are possible in PF, EP and UP resins" (Lanxess)		
Reactive/additive	Reactive phosphonate ester which is incorporated into the foam structure by reacting as a polyol		
Health env. profiles	alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).		
Availability	Available from several manufacturers. The product is mainly used in rigid		

	PUR foams. Only used in flexible PUR foam in niche applications at the moment (Lassen et al., 2015)
Flame retardancy	Can be formulated to provide flame retardancy in spray, froth, pour-in-place and quasi pre-polymer applications, as well as the flame lamination of fabric with flexible foams (ICL-IP Europe).
Halogen-containing flame retardants for the same application (examples)	TCDP, TCPP

Hazard profile

The screening of N,N-bis-(2-hydroxyethyl) aminomethane phosphonic acid diethyl ester by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).

TABLE 11

SCORING N,N-BIS-(2-HYDROXYLETHYL) AMINOMETHANE PHOSPHONIC ACID DIETHYL ESTER USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human										Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B		
						single	repeat*	single	repeat*										
M	M	L	L	DG	L	DG	M	DG	M	M	DG	L	L	M	L	H	L	2	

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Data for three structurally similar analogs indicate evidence of carcinogenicity in laboratory animals and the uncertainty based on lack of studies on the substance compound leads to a “moderate” hazard designation by the US EPA. Conflicting results in tests with the commercial product (positive/negative) lead to a “moderate” score for mutagenicity/genotoxicity.

For most of the human health and ecotoxicity endpoints, experimental data for a commercial product (Fyrol 6) are available in the US EPA report (2015). The evaluation of potential for neurotoxicity, repeated dose effects and skin sensitization were based on either structural alerts (organophosphates, amines) and/or professional judgement.

The evaluation of irritation of eye and skin is based on experimental data from rabbit studies.

No data were available for endocrine activity and respiratory sensitization.

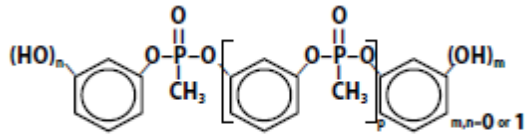
The bioaccumulation score is based on QSAR estimations.

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1 but meets criterion c) for Benchmark 2 by scoring “high” in persistence and “moderate” for several endpoints in Group I, II and II* Human.

4.1.3 Poly(m-phenylene methylphosphonate), CAS No. 63747-58-0

Technical description

CAS No	63747-58-0
EC No	*613-366-7
Chemical name	Poly(m-phenylene methylphosphonate)
Structural formula	 ICL-IP Europe product catalogue
General formula	(C ₁₃ H ₁₃ O ₃ P · C ₆ H ₆ O ₂) _x
Phosphorous content	17.5 % (Fyrol PMP)
Abbreviation, synonyms	DEEP
FR products and manufacturers	Fyrol PMP (ICL-IP Europe)
Registered tonnage, t/year	Pre-registered
Pinfa Product Selector	Not identified in PPS
Other information on substrate	Epoxy resins (ICL-IP Europe)
End applications	EEE
Reactive/additive	Reactive
Health env. profiles	Alternatives to the halogenated flame retardant in printed circuit boards (US EPA, 2014b)
Availability	Have been on the market for several years and applied for printed wiring boards.
Flame retardancy	FR-4 laminates with Fyrol PMP are marketed (Morose, 2006) When a novolac epoxy resin is cured with Fyrol PMP (20 wt %) in presence of ATH (35 wt %) a UL 94-V0 rating can be reached (Rakotamala et al., 2010).
Halogen-containing flame retardants for the same application (examples)	TBBPA (used reactively)

Hazard profile

The screening of Poly(m-phenylene methylphosphonate) by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives to the halogenated flame retardant in printed circuit boards (US EPA, 2014b).

TABLE 12
SCORING OF POLY(M-PHENYLENE METHYLPHOSPHONATE) USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
L	L	M	M	H	L	DG	M	DG	M	L	DG	L	L	H	H	VH	H	1

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

The US EPA scores for Group I human toxicity are “low” for carcinogenicity and genotoxicity based on analogy with similar structures and professional judgment. Reproductive toxicity as well as mutagenicity/genotoxicity are scored as “medium” based on data for a confidential analogue and professional judgement. The score for systemic toxicity is based on analogy to RDP (CASRN 125997-21-9), a confidential analogue and professional judgement.

There are no experimental data for endocrine activity in the report, however, resorcinol (CAS Nr 108-46-3), a metabolite of the analogue RDP and a starting material in Fyrol PMP synthesis, is listed as a Cat. 1 (Evidence for endocrine disruption in living organisms) substance on the priority list by the EU. COWI therefore assigns the score “high” to this endpoint.

With respect to neurotoxic effects, the “moderate” score is derived from extrapolation from a 28-day study for the analogue RDP (CASRN 125997-21-9). There is also potential for neurotoxicity based on the presence of the phenol and organophosphorus structural alerts.

No data were available for respiratory sensitization.

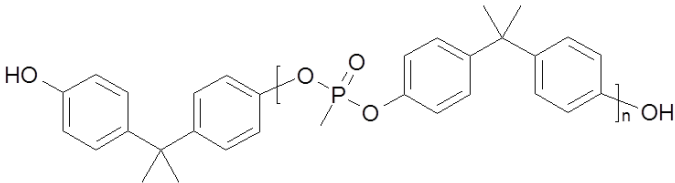
The high MW components with a MW>1,000 have low water solubility and are expected to have no effects at saturation. However, QSAR estimations for the ECOSAR class of phenols of the n = 1 oligomers result in LC50 values low enough to cause “high” aquatic toxicity scores. Since the n = 1 oligomer constitutes only a fraction of the polymer mixture (more exact data on polymer composition are not available) and the estimations are based on a compound class and not a specific compound, we regard the score as protective. Correspondingly, only two oligomers (n = 3 and 4) cause the bioaccumulation score “high”, while the other components of the polymer mixture have moderate or low potential to bioaccumulate.

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance scores “High” for the endpoints endocrine activity, acute and chronic aquatic toxicity, as well as for bioaccumulation. Furthermore, the substance scores “Very high” for persistence.

4.1.4 Phosphonate oligomers, CAS No. 68664-06-2

Technical description

CAS No	68664-06-2		
EC No	Not available		
Chemical name	Phosphonate oligomers		
Structural formula	 Representative structure (US EPA 2014a)		
General formula	C15H16O2(C16H17O3P)n		
Phosphorous content	8.5 % (NOFIA™ OL1001) 10 % (NOFIA™ OL3001)		
Abbreviation, synonyms			
FR products and manufacturers	NOFIA™ OL1001, NOFIA™ OL3001 (FRX Polymers)		
Registered tonnage, t/year	Not reg/pre-reg		
Pinfa Product Selector	Group:	Substrate:	Applicability:
	Solid thermoplastics	Thermoplastic elastomers	Applicable
	Foams	Rubbers/elastomers	Applicable
	Thermosets	Unsaturated polyesters	Applicable
		Epoxy resin	Applicable
	Wires and cables	TPU	Applicable
Other information on substrate	Unsaturated polyesters, epoxy, PUR and polyurea		
End applications	Decorative laminates, wall panels, copper clad laminates for printed circuit boards, protective sheets and coatings, adhesives (FRX Polymers)		
Reactive/additive	Reactive		
Health env. profiles	Alternatives for the flame retardant decaBDE (US EPA, 2014a)		
Availability	-		
Flame retardancy	-		
Halogen-containing flame retardants for the same application (examples)	DecaBDE, TBBPA		

Hazard profile

The screening of Phosphonate oligomers by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for the flame retardant decaBDE (US EPA, 2014a).

TABLE 13
SCORING PHOSPHONATE OLIGOMERS USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human										Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B		
						single	repeat*	single	repeat*										
M	L	L	L	DG	L	L	L	M	M	L	DG	M	M	L	H	VH	H	2	

C = Carcinogenicity
M = Mutagenicity
R = Reproductive toxicity
D = Developmental toxicity
E = Endocrine activity
AT = Acute mammalian toxicity

ST = Systemic toxicity
N = Neurotoxicity
SnS = Skin sensitization
SnR = Respiratory sensitization
IrS = Skin irritation
IrE = Eye irritation

AA = Acute aquatic toxicity
CA = Chronic aquatic toxicity
P = Persistence
B = Bioaccumulation

Comments to hazard profile scores

No data on carcinogenicity have been located in the US EPA report leading to the conclusion that carcinogenic effects cannot be ruled out. The US EPA estimates the potential for mutagenicity/genotoxicity of the phosphonate oligomer as low based on analogy to BAPP (CAS no. 181028-79-5)

Based on professional judgement, limited bioavailability and the absence of structural alerts, the potential for reproductive and developmental effects were estimated as low. The score (moderate) for neurotoxicity and irritation of skin and eye is based on the presence of the phenol structural alert.

With respect to endocrine activity and respiratory sensitization, no studies were available.

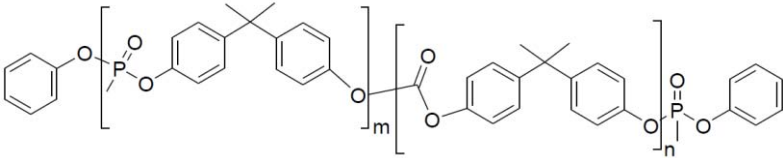
The scores for aquatic toxicity and persistence are based on professional judgement and QSAR estimations. The “high” score for chronic aquatic toxicity results from estimation on the n=1 and n=2 oligomers. Both measured and estimated data are available for the evaluation of bioaccumulation.

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1. However, since the overall hazard 2 criterion b) only requires high P and high B, while the substance scores “very high” in P and also “high” in T, the overall hazard score 2 does not fully reflect the hazard potential of the substance.

4.1.5 Poly[phosphonate-co-carbonate], CAS No. 77226-90-5

Technical description

CAS No	77226-90-5		
EC No	Not available		
Chemical name	Poly[phosphonate-co-carbonate]		
Structural formula	 Representative structure (US EPA 2014a)		
General formula	$C_{15}H_{16}O_2(C_{16}H_{14}O_3)_n(C_{16}H_{17}O_3P)_m$		
Phosphorous content	No data		
Abbreviation, synonyms	Carbonic acid, diphenyl ester, polymer with diphenyl P-methylphosphonate and 4,4'-(1-methylethylidene)bis[phenol]		
FR products and manufacturers	NOFIA™ CO6000 (FRX Polymers)		
Registered tonnage, t/year	Not reg/pre-reg		
Pinfa Product Selector	Group: Solid thermoplastics	Substrate: HIPS/PPO PC/ABS Polycarbonate (PC)	Applicability: Applicable Applicable Applicable
Other information on substrate	None		
End applications	"Thin, transparent, high flow molding EE&CE applications and extruded films and sheet for B&C applications" (FRX Polymers)		
Reactive/additive	Additive		
Health env. profiles	Alternatives for the flame retardant decaBDE (US EPA, 2014a)		
Availability	-		
Flame retardancy	UL 94 V0 grades of polycarbonate and polycarbonate blends		
Halogen-containing flame retardants for the same application (examples)	TBBPA, proprietary polymeric FR		

Hazard profile

The screening of poly[phosphonate-co-carbonate] by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for the flame retardant decaBDE (US EPA, 2014a).

TABLE 14
SCORING POLY[PHOSPHONATE-CO-CARBONATE] USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human						Group II and II* Human								Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
L	L	L	L	L	L	L	L	L	L	L	DG	L	L	L	L	VH	L	3

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Only very limited measured data are available in the US EPA report. However, because of the large size of the polymer (MW >1,000), it is expected to have limited bioavailability and metabolism in the human body. Therefore, the potential for human health effects is low based on professional judgement.

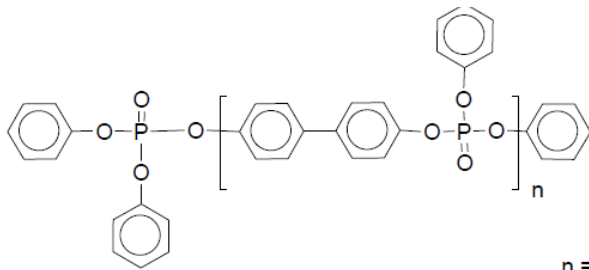
Correspondingly, the large MW, limited bioavailability and low water solubility suggest that there will be no effects on the aquatic environment at saturation. The polymer is not expected to be removed by biodegradation or other degradative processes under environmental conditions because of limited bioavailability, limited water solubility and limited partitioning to air.

Overall hazard scoring

An overall hazard score = 3 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1 or 2. However, since the overall hazard 3 criterion a) only requires moderate P or B, while the substance scores “very high” in P, the overall hazard score 3 does not fully reflect the hazard potential of the substance.

4.1.6 Phosphoric acid, mixed esters with [1,1'-bisphenyl-4,4'-diol] and phenol, CAS No. 1003300-73-9

Technical description

CAS No	1003300-73-9		
EC No	Not available		
Chemical name	Phosphoric acid, mixed esters with [1,1'-bisphenyl-4,4'-diol] and phenol		
Structural formula	 n = 1-4 US EPA 2014a		
General formula	C ₃₆ H ₂₈ O ₈ P ₂ (n = 1)		
Phosphorous content	No data		
Abbreviation, synonyms	BPBP		
FR products and manufacturers	ADK STAB FP-800 (Adeka Palmerole)		
Registered tonnage, t/year	Not reg/pre-reg		
Pinfa Product Selector	Group: Solid thermoplastics Textiles/paints/adhesives Wire and cables	Substrate: HIPS/PPO PC/ABS Polycarbonate (PC) Other textile fibers TPU	Applicability: Applicable Applicable Applicable Applicable Applicable
Other information on substrate	Polycarbonates and polyesters, polymer blends such as PC/ABS and PC/HIPS.		
End applications	-		
Reactive/additive	Additive		
Health env. profiles	Evaluated in this study (see below)		
Availability	-		
Flame retardancy	-		
Halogen-containing flame retardants for the same application (examples)	DecaBDE, TBBPA, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others		

Hazard profile

The screening of phosphoric acid, mixed esters with [1,1'-bisphenyl-4,4'-diol] and phenol (BPBP) by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for the flame retardant decaBDE (US EPA, 2014a).

TABLE 15

SCORING PHOSPHORIC ACID, MIXED ESTERS WITH [1,1'-BISPHENYL-4,4'-DIOL] AND PHENOL USING THE PROPOSED MODIFIED METHODOLOGY.

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	L	L	L	DG	L	DG	L	DG	L	L	DG	VL	VL	H	H	H	L	

C = Carcinogenicity

M = Mutagenicity

R = Reproductive toxicity

D = Developmental toxicity

E = Endocrine activity

AT = Acute mammalian toxicity

ST = Systemic toxicity

N = Neurotoxicity

SnS = Skin sensitization

SnR = Respiratory sensitization

IrS = Skin irritation

IrE = Eye irritation

AA = Acute aquatic toxicity

CA = Chronic aquatic toxicity

P = Persistence

B = Bioaccumulation

Comments to hazard profile scores

BPBP is a polymer mixture mainly consisting of the n = 1 oligomers (> 80% of the composition).

In the absence of experimental data, the carcinogenic potential of BPBP was precautionously scored as “moderate”, even though neither structural alerts nor read-across from an analogue indicate carcinogenicity. *In vitro* studies showed that BPBP is not mutagenic.

No data were available for the endpoints endocrine disruption and respiratory sensitization.

A single 28-day oral neurotoxicity screening study lead to the conclusion of low neurotoxic potential in the US EPA report. However, the authors also state that there is uncertainty due to lack of data on cholinesterase inhibition, which is an effect associated with phosphate esters.

With respect to aquatic toxicity, several experimental studies with BPBP report EC50/LC50 values above the water solubility limit without providing further study details, thus indicating no effects at saturation. QSAR estimations for the compound class of neutral organics yield very low LC50 values (< 0.01), but professional judgement indicates that this compound does not lie within the domain of the ECOSAR model. A single experimental study in algae with a structurally similar, but confidential analogue yields very low effect concentrations (EC50 value of <1.0 mg/L and NOEC < 0.1 mg/L), causing the assignment of the “high” score for the aquatic toxicity endpoints. Based on a conservative approach, the assessment is adopted in our evaluation.

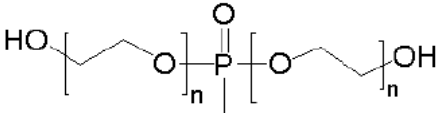
A single experimental study, QSAR estimations and professional judgement on biotic and abiotic degradation lead to the conclusion that the substance is not easily removed under environmental conditions. With respect to bioaccumulation, our score (low) deviates according to CLP criteria from the evaluation by the US EPA, who assigned the score “moderate” based on a QSAR-estimated BCF of 172.

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1. The overall hazard 2 criterion c) requires only high P and moderate T (Ecotoxicity or Group I, II or II* Human), while the substance scores “high” in T (ecotox.). However, considering the conservative approach in evaluating ecotoxicity, the Benchmark score 2 presumably reflects the hazard potential of the substance sufficiently.

4.1.7 Oligomeric phosphonate polyol, CAS No. 363626-50-0

Technical description

CAS No	363626-50-0
EC No	Not available
Chemical name	Oligomeric phosphonate polyol
Structural formula	 US EPA 2015
General formula	CH5O3P·(C2H4O)n·(C2H4O)n
Phosphorous content	10 - 13% (Exolit® OP 560)
Abbreviation, synonyms	
FR products and manufacturers	Exolit® OP 560, Exolit® OP 550 (Clariant)
Registered tonnage, t/year	Neither registered nor pre-registered
Pinfa Product Selector	Group: Substrate: Applicability:
Other information on substrate	Flexible polyurethane foams
End applications	Automotive industry
Reactive/additive	Reactive
Health env. profiles	Alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).
Availability	The product has been marketed for more than 10 years. The FR seems in particular to be used together with PUR foam with a "green" polyurethane foam technology partly based on biomass-derived natural oil polyols and according to the manufacturer, Exolit, OP types FRs are especially suited for these polyols
Flame retardancy	Reactive flame retardant (phosphor-based polyol) i.e. it is incorporated into a polymer backbone (e.g. polyurethane) by chemically bonding with raw materials during the polymerization process. The concentration of Exolit OP 560 is about 20% of the level of non-reactive FRs, which would normally be required to pass the Californian standard Cal 117 for furniture (Lassen et al., 2015) No data regarding meeting the UK Crib 5 test for furniture has been identified. Some informal information has indicated that with this FR it would be more challenging to develop foams that can pass the UK Crib 5 test as compared with the Cal 117 (Lassen et al. 2015).
Halogen-containing flame retardants for the same application (examples)	TCCP; TDCP in flexible PUR foams

Hazard profile

The screening of oligomeric phosphonate polyol by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).

TABLE 16
SCORING OF PHOSPHORUS POLYOL USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	M	L	M	DG	L	L	L	M	M	L	DG	L	L	L	M	M	L	2

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

There is uncertainty due to lack of experimental data on carcinogenicity and genotoxicity for this substance; those effects can therefore not be ruled out. The scoring of reproductive and developmental potential, neurotoxicity, repeated dose effects and skin sensitization is based on professional judgement and structural alerts (organophosphates).

No data were available for the endpoints endocrine disruption and respiratory sensitization.

Only few experimental data were available for aquatic toxicity; the evaluation is therefore supported by QSAR and professional judgement based on read-across.

The bioaccumulation score is based on solely QSAR estimations, while a few experimental studies also support the conclusion on persistence.

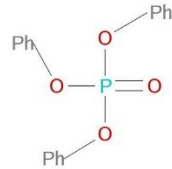
Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1 but meets criterion e) for Benchmark 2 by scoring “moderate” for several endpoints in Group I Human.

4.2 Organophosphates (phosphate esters) – Aryl phosphates

4.2.1 Triphenyl phosphate, CAS No. 115-86-6

Technical description

CAS No	115-86-6		
EC No	204-112-2		
Chemical name	Triphenyl phosphate		
Structural formula	 Registration		
General formula	C18H15O4P		
Phosphorous content	9.5% (EVERFOS TP (TPP); Disflamoll TP; Disflamoll TP Liquid)		
Abbreviation, synonyms	TPP, TPHP		
FR products and manufacturers	EVERFOS TP (TPP) (Everkem) Disflamoll TP, Disflamoll TP liquid (Lanxess)		
Registered tonnage, t/year	1,000 – 10,000		
Pinfa Product Selector	Group: Solid thermoplastics Thermosets	Substrate: HIPS/PPO PC/ABS Phenolic resins Epoxy resins	Applicability: Applicable Applicable Applicable Applicable
Other information on substrate	PP, PE, PVC, HIPS, PC/ABS (alloys), PPO/HIPS (alloys), rigid and flexible polyurethane, TPU, Epoxy resin, phenolics resin, PC, textile (back coating), adhesive, rubbers, cellulose acetate, cellulose acetate butyrate and vinyl copolymer, PPE/HIPS		
End applications	Moulding applications, coatings, EEE		
Reactive/additive	Additive		
Health env. profiles	Alternatives to decaBDE (US EPA, 2015); flame retardants to flexible PUR foams (US EPA, 2014b)		
Availability	Have been available for many years from several manufacturers		
Flame retardancy	When using phosphorous flame retardants to substitute for HIPS with decaBDE it has been necessary to replace the HIPS with the copolymers PC/ABS and HIPS/PPO in order to meet the requirements in casings of EEE (Lassen et al., 2007; Illinois EPA, 2007). Loading of 8-12% in PC/ABS in order to prepare V-0 grade PC/ABS for EEE (Lassen et al., 2006).		
Halogen-containing flame retardants for the same application (examples)	DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others		

Hazard profile

The screening of triphenyl phosphate by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives to the flame retardant decaBDE (US EPA, 2014a).

TABLE 17
SCORING OF TRIPHENYL PHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human						Group II and II* Human								Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	L	L	L	H	L	DG	H	DG	L	L	DG	L	L	VH	VH	L	L	1

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores.

Experimental data are available for all human toxicity endpoints apart from respiratory sensitization in the US EPA report, often referred from reliable secondary sources.

The US EPA does not assign a score on the endpoint of endocrine activity. However, several primary studies and a few secondary sources listed in the report demonstrate effects on endocrine activity *in vitro* as well as *in vivo*. We therefore assign the score "High" to this endpoint.

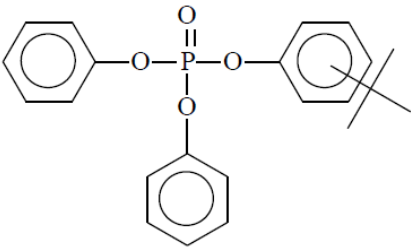
Bioaccumulation was scored as "M" ("Moderate") by US EPA (2014a). However, based on the data presented this is considered be incorrect as none of the presented BCF's exceed a value of 500, which is the upper limit for a score as "Low". COWI therefore scores bioaccumulation potential as "L" based on the same data.

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance meets criterion e) of Benchmark 1: High T (Group Human I).

4.2.2 Phenol, isobutyleneated, phosphate (3:1), CAS No. 68937-40-6

Technical description

CAS No	68937-40-6
EC No	273-065-8 / 700-990-0
Chemical name	Phenol, isobutyleneated, phosphate (3:1)
Structural formula	 Reofos® LF-50 data sheet
General formula	
Phosphorous content	8.4% (Reofos® LF-50)
Abbreviation, synonyms	Reaction mass of 4-tert-butylphenyl diphenyl phosphate and bis(4-tertbutylphenyl) phenyl phosphate and triphenyl phosphate
FR products and manufacturers	Reofos® LF-50 (Green Lake Solutions) Disflamoll TP LXS 51092 (Lanxess)
Registered tonnage, t/year	1,000 – 10,000
Pinfa Product Selector	Not identified in PPS
Other information on substrate	PVC, flexible polyurethanes, cellulosic resins, and synthetic rubber. Flame retardant processing aid for engineering resins, such as modified PPO, polycarbonate and polycarbonate blends
End applications	-
Reactive/additive	Additive
Health env. profiles	Screened as part of this study (see below)
Availability	-
Flame retardancy	-
Halogen-containing flame retardants for the same application (examples)	TCPP

Hazard profile

The screening of this alternative by the modified GreenScreen® methodology was based on information compiled according to the information sources described in 3.2.1. The full data set from the data collection including justification of the scoring is enclosed as Appendix 5 to this report.

TABLE 18
SCORING OF PHENOL, ISOBUTYLENATED, PHOSPHATE (3:1) USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Hazard Score
						single	repeat*	single	repeat*									
DG	L	L	L	DG	L	DG	M	M	M	L	DG	M	M	VH	VH	L	M	2

Comments to hazard profile scores

According to REACH registration, Phenol, isobutyleneated, phosphate is made up of four different constituents: p-t-butylphenyl diphenyl phosphate, bis(p-t-butylphenyl) phenyl phosphate, tris(p-tert-butylphenyl) phosphate and triphenyl phosphate. Furthermore, some tests were made with commercial products. Data on the components as well as on the commercial products are considered in the screening.

A notified classification is available for Phenol, isobutyleneated, phosphate (3:1); Aquatic Chronic 1 (H410; 1 notifier) and Aquatic Chronic 3 (H412; 1 notifier).

Information was not identified for carcinogenic properties, endocrine disruption, target organ toxicity from a single exposure, and respiratory sensitization. For all other human endpoints as well as aquatic toxicity, experimental data were available.

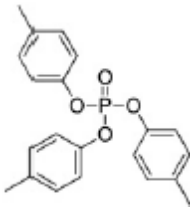
A single biodegradability study allowed for the evaluating of persistence while the scoring of bioaccumulation potential is based on both measured and estimated data.

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not meet any of the criteria at Level 1 but meets criterion f) at Level 2 by scoring "very high" for ecotoxicity.

4.2.3 Tricresyl phosphate, CAS No. 1330-78-5

Technical description

CAS No	1330-78-5		
EC No	215-548-8		
Chemical name	Tricresyl phosphate		
Structural formula	 Bergman et al. 2012		
General formula	C21H21O4P		
Phosphorous content	8.4% (Everfos TCP); Disflamoll TKP, Disflamoll TKP-P; Kronitex TCP)		
Abbreviation, synonyms	TMPP; Tris(methylphenyl) phosphate, TCP		
FR products and manufacturers	EVERFOS TCP (Everkem) Kronitex® TCP (Great Lake Solutions) Disflamoll TKP (Lanxess) Disflamoll TKP-P (Lanxess)		
Registered tonnage, t/year	1,000 – 10,000		
Pinfa Product Selector	Group: Wires and cables	Substrate: PVC flexible	Applicability: Applicable
Other information on substrate	PVC, PVC flexible, polyester, phenolics resin, nitrocellulose lacquers and coatings and processing aid for natural and synthetic rubbers (NBR and SBR)		
End applications	Wires and cables, building materials		
Reactive/additive	Additive		
Health env. profiles	Alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015)		
Availability	Available from manufacturers		
Flame retardancy	-		
Halogen-containing flame retardants for the same application (examples)	DBDPE, EBTEBPI, TCPP		

Hazard profile

The screening of tricresyl phosphate by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).

TABLE 19
SCORING TRICRESYL PHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
L	L	H	M	DG	M	DG	H	DG	M	M	DG	L	L	VH	H	M	H	1

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

The alternative tricresyl phosphate may contain a mixture of methylated triphenyl phosphate isomers with an unspecified degree of methyl substitution. Therefore, 12 closely related compounds were included in the assessment by the US EPA.

Experimental data for tricresyl phosphate are available for all human health endpoints apart from respiratory sensitization. Most conclusions on the respective endpoints are based on experiments with a commercial mixture of the substance.

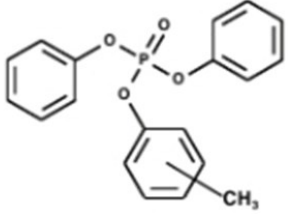
The evaluation of aquatic toxicity, persistence and bioaccumulation was based on experimental data supported by QSAR estimations. Ten out of the 11 available factors for bioconcentration/-accumulation do not exceed > 2000, which is the lower margin for the “high” according to CLP criteria. However, considering the available measured log Kow values (5.11, 5.9, 4.51, and 3.7) and a conservative approach, the “high” score assigned by the US EPA is also applied in our evaluation.

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance fulfils the criterion e) behind Benchmark 1; High T (Group I Human).

4.2.4 Cresyl diphenyl phosphate, CAS No. 26444-49-5

Technical description

CAS No	26444-49-5		
EC No	247-693-8		
Chemical name	Cresyl diphenyl phosphate		
Structural formula	 Everkem product brochure		
General formula	C ₂₁ H ₁₇ O ₄ P		
Phosphorous content	9.5% (EVERFOS CDP) 9.1% (Kronitex CDP; Disflamoll DPK)		
Abbreviation, synonyms	CDP		
FR products and manufacturers	EVERFOS CDP (Everkem) Kronitex® CDP (Great Lakes Solution) Disflamoll DPK (Lanxess)		
Registered tonnage, t/year	Pre-registered		
Pinfa Product Selector	Group:	Substrate:	Applicability:
	Solid thermoplastic	PC/ABS	Applicable
		HIPS/PPO	Applicable
		Thermoplastic elastomer	Applicable
	Foams	PVC/nitrile foam	Applicable
		PUR rigid foam	Could be applied
		Rubbers/elastomers	Applicable
	Textiles/paints/adhesives	Hot melts	Applicable
		Paints	Applicable
		Latex/adhesives	Applicable
	Thermosets	Phenolic resins	Applicable
	Wires and cables	PVC flexible	Applicable
		TPU	Applicable
		PE/EVA	Could be applied
Other information on substrate	PVC, flexible polyurethane, epoxy resin, phenolics resin, PC/ABS blends, TPU compounds, PUR- foams (rigid and flexible) and rubbers		
End applications	Electrical components, printed wiring board, building materials		
Reactive/additive	Additive		
Health env. profiles	Not included in US EPA screenings but a screening is prepared below based on an analogue substance		
Availability	Have been available for many years from several manufacturers		

Flame retardancy	Used in PC/ABS copolymers in casings for EEE (Lowell, 2005), but seems to be less used than other organophosphates (DBP, RDP, TPP) for this application.
Halogen-containing flame retardants for the same application (examples)	DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others may be used for some of the same applications. For the main application area in PVC application CDP is not used as an alternative to halogenated flame retardants.

Hazard profile

Cresyl diphenyl phosphate (CDP) is a structural analogue to and an impurity in TCP (CAS No. 1330-78-5, section 4.2.2), only differing in the methylation degree of the phenol moieties. Available substance data were included in the profile of TCP, and a separate screening of CDP is not available in the US EPA report (US EPA, 2015). We therefore suggest the same scoring for CDP as for TCP.

TABLE 20
SCORING OF CRESYL DIPHENYL PHOSPHATE BASED ON THE PROFILE FOR TCP.

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
L	L	H	M	DG	M	DG	H	DG	M	M	DG	L	L	VH	H	M	H	1

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

See section 4.2.2.

Overall hazard scoring

Overall hazard score 1, see section 4.2.2.

4.2.5 Phosphoric acid, bis(methylphenyl) phenyl ester, CAS No. 26446-73-1

Technical description

CAS No	26446-73-1
EC No	247-708-8
Chemical name	Phosphoric acid, bis(methylphenyl) phenyl ester
Structural formula	-
General formula	-
Phosphorous content	-
Abbreviation, synonyms	Bis-(methylphenyl) phenyl phosphate
FR products and manufacturers	Not identified as manufactured. The substance is a structural analogue to and a impurity in TCP

Hazard profile

Phosphoric acid, bis(methylphenyl) phenyl ester is a structural analogue to and a impurity in TCP (CAS No. 1330-78-5, section 4.2.2), only differing in the methylation degree of the phenol moieties. Available substance data were included in the profile of TCP, and a separate screening of phosphoric acid, bis(methylphenyl) phenyl ester is not available in the US EPA report (US EPA, 2015). We therefore suggest the same scoring for phosphoric acid, bis(methylphenyl) phenyl ester as for TCP.

TABLE 21

SCORING OF PHOSPHORIC ACID, BIS(METHYLPHENYL) PHENYL ESTER BASED ON THE PROFILE FOR TCP.

Group I Human						Group II and II* Human								Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
L	L	H	M	DG	M	DG	H	DG	M	M	DG	L	L	VH	H	M	H	1

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

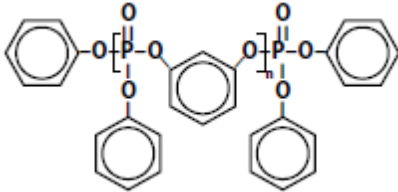
See section 4.2.2.

Overall hazard scoring

Overall hazard scorek 1, see section 4.2.2.

4.2.6 Resorcinol bis-diphenyl phosphate, CAS No. 57583-54-7

Technical description

CAS No	57583-54-7 (sometimes 125997-21-9 is used interchangeably)		
EC No	260-830-6		
Chemical name	Resorcinol bis-diphenyl phosphate		
Structural formula	 ICL-IP Europe product catalogue		
General formula	C ₃₀ H ₂₄ O ₈ P ₂		
Phosphorous content	10.8% (EVERFOS RDP) 10.7% Fyrolflex RDP		
Abbreviation, synonyms	RDP, tetraphenyl m-phenylene bis(phosphate), tetraphenyl resorcinol bis-diphenyl phosphate, PBDPP		
FR products and manufacturers	EVERFOS RDP (Everkem) Fyrolflex RDP (ICL-IP Europe) AFLAMMIT® PLF 280 (THOR)		
Registered tonnage, t/year	1,000 – 10,000		
Pinfa Product Selector	Group: Solid thermosplastic	Substrate: HIPS/PPO PC/ABS Polycarbonate (PC) Polyamide (PA) PBT PET	Applicability: Applicable Applicable Applicable Applicable Applicable Applicable
Other information on substrate	EPDM, HIPS, PC/ABS (alloys), PPE/HIPS (alloys), TPU, epoxy resin, PC, modified PPO,		
End applications	Automotive, EEE		
Reactive/additive	Additive		
Health env. profiles	Alternatives for the flame retardant decaBDE (US EPA, 2014a)		
Availability	Available from many manufacturers. RDP are widely used as flame retardant in casing of EEE made of the co-polymers PC/ABS and HIPS/PPO (Lassen et al., 2006)		
Flame retardancy	When using phosphorous flame retardants to substitute for HIPS with decaBDE it has been necessary to replace the HIPS with the copolymers PC/ABS and HIPS/PPO in order to meet the requirements in casings for EEE (Lassen et al., 2007; Illinois EPA, 2007). Loading 10-14% in order to prepare V-0 grade PC/ABS for EEE (Lassen et al., 2006)		
Halogen-containing flame retardants for the same application (examples)	DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others		

Hazard profile

The screening of resorcinol bis-diphenyl phosphate (RDP) by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for the flame retardant decaBDE (US EPA, 2014a).

TABLE 22

SCORING OF RESORCINOL BIS-DIPHENYL PHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Hazard Score
						single	repeat*	single	repeat*									
M	L	L	M	H	L	DG	M	DG	M	L	DG	L	L	VH	VH	M	H	1

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

The score on acute mammalian toxicity is based on experimental data with RDP. Data on carcinogenicity were not located by the US EPA, but the carcinogenic potential is estimated to be moderate based on professional judgement. In contrast, several experimental studies were available for mutagenicity and genotoxicity, resulting in a low score for this endpoint.

Experimental data for resorcinol bis-diphenylphosphate indicate no adverse effects on reproductive performance or fertility parameters at the doses tested. However, the US EPA states that there may be potential for reproductive toxicity based on analogy to confidential analogue.

Resorcinol (CAS No 108-46-3), a metabolite of RDP, is listed as a Cat. 1 (Evidence for endocrine disruption in living organisms) substance on the priority list by the EU. We have therefore assigned the score “high” to this endpoint. With respect to neurotoxic effects, the “moderate” score is derived from extrapolation from a 28-day study. There is also potential for neurotoxicity based on the presence of organophosphates structural alerts. RDP produced mild irritation in rabbit eyes; however, effects were reversible within 24 hours.

An experimental study with daphnids suggests that the EC50 does not exceed water solubility, leading to the designation of “very high” scores for aquatic toxicity.

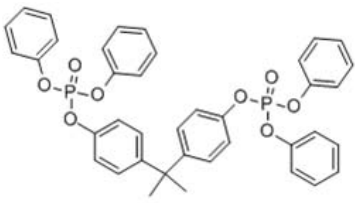
With respect to bioaccumulation, the US EPA assigns the score “high” based on a QSAR-estimated BCF of 1,300. This value would usually be regarded as “moderately” bioaccumulative according to CLP criteria. However, the Log Kow has been measured to 4.93 and 4.9 by two independent studies, thus triggering a “High” score for bioaccumulation. Since the US EPA report does not provide further details on whether the BCF QSAR estimate is based on measured or estimated log Kow values, we rely in our evaluation of bioaccumulation on the measured log Kow value, resulting in a “high” score.

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance fulfils criterion e) “high” T (Group I Human).

4.2.7 Bisphenol A bis(diphenyl phosphate), CAS No. 5945-33-5

Technical description

CAS No	5945-33-5 (sometimes 181028-79-5 is used interchangeable).		
EC No	425-220-8		
Chemical name	Bisphenol A bis(diphenyl phosphate)		
Structural formula	 Registration		
General formula	C ₃₉ H ₃₄ O ₈ P ₂ (n = 1; CAS No. 5945-33-5)		
Phosphorous content	8.9% (Everfos BP (BDP); Fyrolflex BDP; ADK STAB FP-600)		
Abbreviation, synonyms	BPA-BDPP, BDP, BAPP; (1-methylethylidene)di-4,1-phenylenetetraphenyl diphosphate		
FR products and manufacturers	ADK STAB FP-600 (Adeka Palmarole) EVERFOS BP (BDP) (Everkem) Fyrolflex BDP (ICL-IP Europe)		
Registered tonnage, t/year	1,000 – 10,000		
Pinfa Product Selector	Group: Solid thermoplastic Textiles/paints/adhesives Wires and cables	Substrate: HIPS/PPO PC/ABS Polycarbonate (PC) Other textile fibres TPU	Applicability: Applicable Applicable Applicable Applicable Applicable
Other information on substrate	EPDM, HIPS, PC/ABS (alloys), PPE/HIPS (alloys), TPU, epoxy resin, PC, HIPS/PPO		
End applications	EEE		
Reactive/additive	Additive		
Health env. profiles	Alternatives to decaBDE (US EPA, 2014a)		
Availability	Have been available from several manufacturers for many years. A major flame retardant for casings for EEE		
Flame retardancy	When using phosphorous flame retardants to substitute for HIPS with decaBDE it has been necessary to replace the HIPS with the copolymers PC/ABS and HIPS/PPO in order to meet the requirements in casings or EEE (Lassen et al., 2007; Illinois EPA, 2007). Loading 10-14% in order to obtain V-0 grade PC/ABS for EEE (Lassen et al., 2006)		
Halogen-containing flame retardants for the same application (examples)	Polybrominated styrenes/ brominated polystyrenes (main FR in PA), decaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others		

Hazard profile

The screening of bisphenol A bis(diphenyl phosphate) (BAPP) by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for the flame retardant decaBDE (US EPA, 2014a).

TABLE 23

SCORING OF BISPHENOL A BIS(DIPHENYL PHOSPHATE) USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Hazard Score
						single	repeat*	single	repeat*									
M	L	DG	L	DG	L	DG	L	DG	L	L	DG	L	L	L	L	H	M	2

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

The US EPA suggests that BAPP may have a low potential for carcinogenicity based on expert judgement and the absence of no structural alerts in the molecule. However, due to uncertainty caused by lack of data, the US EPA assigns a “moderate” score.

A single 28-day oral neurotoxicity screening study lead to the conclusion of low neurotoxic potential in the US EPA report. However, the authors also state that there is uncertainty due to lack of data on cholinesterase inhibition, which is an effect associated with phosphate esters.

With respect to reproductive effects, the US EPA report provides no data at all. The designation of “low” potential for reproductive effects is solely based on expert judgement without further justification. We have therefore marked this endpoint as data gap. Data are also lacking for the endpoints endocrine activity and respiratory sensitization. The potential for developmental effects is estimated to be low based on a structurally similar confidential analogue.

Experimental data indicate no effects on the aquatic environment at saturation. BAPP is neither readily biodegradable nor expected to be removed by abiotic degradation. With respect to bioaccumulation, our score (“moderate”) deviates according to CLP criteria from the evaluation by the US EPA, who assigned the score “high” based on a QSAR-estimated BAF of 1,100.

Bisphenol A was not identified as a transformation product of BAPP by US EPA as such, but was mentioned as a possible transformation product, which would score differently than the parent compound for reproductive effects, skin sensitization and dermal irritation (“moderate” versus “low” for BAPP). However, the hazards of the theoretical degradation products including bisphenol A were not considered in the hazard profile for BAPP in the US EPA report and therefore endocrine disruption related to this substance has not been considered here.

Overall hazard scoring

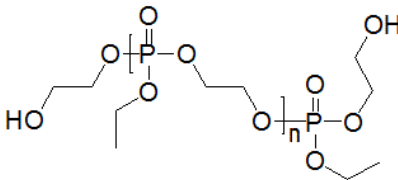
An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1, but meets criterion c) for Benchmark 2 by scoring "high" for persistence and "moderate" for carcinogenicity.

It is noted that inclusion of bisphenol A in the benchmarking would not have changed the assigned overall hazard score (2) (when not considering endocrine disruption properties for which data were not provided by US EPA).

4.3 Organophosphates (phosphate esters) – Alkyl phosphates

4.3.1 Oligomeric ethyl ethylene phosphate, CAS No. 184538-58-7

Technical description

CAS No	184538-58-7
EC No	*606-033-2
Chemical name	Oligomeric ethyl ethylene phosphate
Structural formula	 Representative structure (US EPA 2015)
General formula	$(C_6H_{15}O_4P \cdot C_2H_4O \cdot O_5P_2)_n$
Phosphorous content	19% (Fyrol PNX and Fyrol PNX-LE; Aflammit PLF 140)
Abbreviation, synonyms	Phosphoric acid, triethyl ester, polymer with oxirane and phosphorus oxide (P2O5)
FR products and manufacturers	Fyrol PNX (ICL-IP Europe) Fyrol PNX-LE (ICL-IP Europe) Aflammit PLF 140 (THOR)
Registered tonnage, t/year	Pre-registered
Pinfa Product Selector	Not identified in PPS
Other information on substrate	Flexible and rigid polyurethane foams, cellulosic plastic composite
End applications	Flexible foams in automotive, bedding and seating
Reactive/additive	Indicated as both additive and reactive
Health env. profiles	PUR, US EPA, 2015
Availability	This FR and FRs with similar chemistry are available from several manufacturers
Flame retardancy	It is indicated that the flame retardants is most suitable for MVSS 302 (motor vehicle standard) and Cal 117 type foams (California standard for resilient filling materials), but also applicable in UL94HF foams (for EEE). Its high molecular weight is another advantage in automotive foams because in suitable formulations it is low fogging and can give foams low in VOC emissions, passing the general automotive volatile requirements. No data on market penetration has been obtained. (Lassen et al., 2015)
Halogen-containing	TCPP, TDCP

flame retardants for the same application (examples)	

Hazard profile

The screening of oligomeric ethyl ethylene phosphate by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).

TABLE 24
SCORING OF OLIGOMERIC ETHYL ETHYLENE PHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
L	M	L	L	DG	L	DG	L	DG	M	L	DG	L	M	L	L	VH	L	2

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Limited data were available for the substance. The scores for carcinogenicity, genotoxicity, reproductive and developmental effects provided by the US EPA are based on estimations and expert judgement, the latter also taking the polymer's limited bioavailability and structural alerts into account.

The persistence designation "very high" for the polymer is based on experimental data and professional judgement for its higher MW components (MW >1,000).

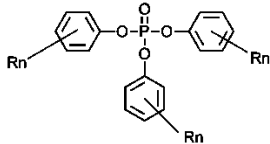
Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1, but meets criterion c) for Benchmark 2 by scoring "high" for persistence and "moderate" for carcinogenicity and irritation of the eye.

4.4 Organophosphates (phosphate esters) – Aryl alkyl phosphates

4.4.1 Isopropyl phenyl phosphate, CAS No. 68937-41-7

Technical description

CAS No	68937-41-7		
EC No	273-066-3		
Chemical name	Isopropyl phenyl phosphate		
Structural formula	 R = isopropyl; n = 0, 1, 2 or 3 Registration		
General formula			
Phosphorous content	8.3% (Phosflex 31L/41L; EVERFOS 1500; Reofos® 50; Reofos® 65) 8.6% (EVERFOS 1350; Reofos® 35) 8.1% (EVERFOS 1650) 7.6% (EVERFOS 1950) 7.5% (EVERFOS 4000)		
Abbreviation, synonyms	Phenol, isopropylated, phosphate (3:1), IPPP; ITP; IPTPP; TIPPP; Isopropylated triphenyl phosphate; Isopropylated phenol phosphate		
FR products and manufacturers	EVERFOS 1350, EVERFOS 1500, EVERFOS 1650, EVERFOS 1950, EVERFOS 4000 (Everkem) Reofos® 35, Reofos® 50, Reofos® 65, Reofos® 95 (Great lake solutions) Phosflex 31L, Phosflex 41L (ICL-IP Europe)		
Registered tonnage, t/year	10,000 – 100,000		
Pinfa Product Selector	Group:	Substrate:	Applicability:
	Solid thermoplastics	PC/ABS	Applicable
		HIPS/PPO	Applicable
		PUR flexible foam	Applicable
	Foams	PVC/nitrile foam	Applicable
		Rubbers/elastomers	Applicable
		Hot melts	Applicable
	Textile/paints/adhesives	Paints	Applicable
		Latex/adhesives	Applicable
		Phenolic resins	Applicable
	Thermosets	Phenolic resins	Applicable
	Wires and cables	PVC flexible	Applicable
		TPU	Applicable
Other information on substrate	PVC, cellulosic resins, and synthetic rubber, EPDM, HIPS, PC/ABS (alloys), PPO/HIPS (alloys), rigid and flexible polyurethane, TPU, epoxyresin, phenolics resin, PC, Coating (paint), textile (back coating), adhesive, rubbers.		
End applications	-		
Reactive/additive	Additive		
Health env. profiles	Flame retardants used in flexible polyurethane foam (US EPA, 2015).		
Availability	Available from many manufacturers, widely used for many years.		

Flame retardancy	-
Halogen-containing flame retardants for the same application (examples)	TCCP, DBDPE; EBTEBPI

Hazard profile

The screening of isopropylated triphenyl phosphate by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).

TABLE 25
SCORING OF ISOPROPYLATED TRIPHENYL PHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Hazard Score
						single	repeat*	single	repeat*									
M	L	H	M	DG	L	DG	H	H	H	L	DG	L	L	VH	VH	M	VH	1

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Commercial products of the alternative isopropylated triphenyl phosphate may contain a mixture consisting of isopropylated triphenyl phosphates with an unspecified degree of isopropylation. Therefore tris(isopropylphenyl) phosphate isomers and other related compounds have been included in the assessment.

Due to lack of data, the US EPA assesses the carcinogenic potential as uncertain and assigns the “moderate” score to this endpoint. Based on weight of evidence including negative results in gene mutation tests, mutagenicity/genotoxicity was scored as low.

The scores for reproductive, developmental, systemic and neuro-toxicity are based on experimental data. Furthermore, the potential for neurotoxicity is supported by the structural alert for organophosphates.

With respect to endocrine activity, no data were available for this substance. However, tests with commercial products containing analogues (components not further specified) indicate endocrine activity, but it is unclear which component or components of the mixture are driving the endocrine activity effects. We therefore mark this endpoint as data gap.

Numerous experimental studies, supported by QSAR estimations, lead to the “very high” scores for aquatic toxicity. Experimental studies with commercial products are also available for persistence and bioaccumulation. Nonetheless, the bioaccumulation designation “High” in the US EPA report is based on the estimated BAF values (estimations for representative structures for components of the mixture) being >1,000, and two of the six estimated values do also exceed 5000. The US EPA states lower confidence in the experimental BCF values because they are not consistent with the limited water solubility of the substances and because the studies were performed on commercial products consisting of mixtures of unquantified components. Using a conservative approach and considering

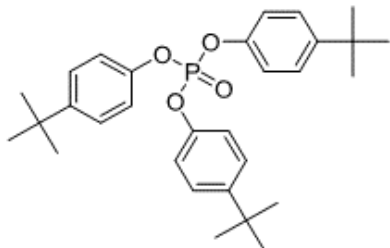
adequate measured log Kow values (4.92 to 5.17) for commercial products, we have assigned the score “very high” based on the estimated BAF values.

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance scores “Very high” for the endpoints acute and chronic aquatic toxicity, as well as for bioaccumulation, thus fulfilling criterion d) of Benchmark 1. Furthermore, the substance scores “High” for Group I and II* Human.

4.4.2 Tris (p-t-butylphenyl) phosphate, CAS No. 78-33-1

Technical description

CAS No	78-33-1
EC No	201-106-1
Chemical name	Tris (p-t-butylphenyl) phosphate
Structural formula	 US EPA, 2015
General formula	C30H39O4P
Phosphorous content	
Abbreviation, synonyms	Phenol, 4-(1,1-dimethylethyl)-, 1,1',1''-phosphate
FR products and manufacturers	Part of Phosflex 71B (ICL-IP Europe)
Registered tonnage, t/year	Not registered
Pinfa Product Selector	Not in PPS
Other information on substrate	HIPS/PPO, PC/PC ABS, flexible PVC
End applications	PVC & textile adhesive coatings
Reactive/additive	Additive
Health env. profiles	Flame retardants used in flexible polyurethane foam (US EPA, 2015).
Availability	-
Flame retardancy	UL94 V0/V1 grades of HIPS/PPO and PC/ABS
Halogen-containing flame retardants for the same application (examples)	DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others

Hazard profile

The screening of tris (p-t-butylphenyl) phosphate by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).

TABLE 26
SCORING OF TRIS (P-T-BUTYLPHENYL) PHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human								Ecotox		Fate		Overall	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Hazard Score
						single	repeat*	single	repeat*									
M	L	M	L	DG	L	DG	H	DG	M	M	DG	M	L	VH	VH	M	H	2

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Commercial products of the alternative TBPP may contain a mixture of t-butyl isomers and t-butyl substituted phenyl phosphate esters depending on the manufacturing, purification and processing of the compound. TBPP isomers and t-butyl substituted phenyl phosphate esters are anticipated to be present in commercial products and were therefore considered in the evaluation by the US EPA.

Due to lack of data, the US EPA assesses the carcinogenic potential as uncertain and assigns the score “moderate” score to this endpoint. Based on experimental studies yielding negative results in gene mutation tests, mutagenicity/genotoxicity was scored as low.

The scores for reproductive, developmental, systemic and neuro-toxicity are based on experimental data with mixture components of TBPP and in a few cases (reproductive and repeated dose effects) also individual isomers of TBPP.

With respect to endocrine activity, no data were available for this test substance. Tests with related compounds (hydraulic BTP: mixture of p-t-butylphenyl phenyl phosphates (84%), triphenyl phosphate, and m-t-phenyl phosphate), demonstrated changes in adrenal glands and ovaries. These test are, however, not sufficient for applying a score to this endpoint, we therefore mark endocrine activity as data gap.

Experimental data for mixture components of TBPP are available for skin sensitization and irritation of skin and eye, but no data are available for respiratory sensitization.

The hazard designations for aquatic toxicity are based on experimental data for mixture components of TBPP for fish and daphnia.

The persistence designation is derived from measured values for t-butylphenyl diphenyl phosphate (CASRN 56803-37-3). For the same substance, measured bioaccumulation values are available from non-guideline studies, which are used by the US EPA for hazard designation. The QSAR-estimated BAF for tris (p-t-butylphenyl) phosphate is 100,000, even though the authors note that the value may be overestimated given the limited water solubility. Using a conservative approach and considering measured and estimated log Kow values > 5, we have assigned the score “very high” based on the estimated BAF value.

Overall hazard scoring

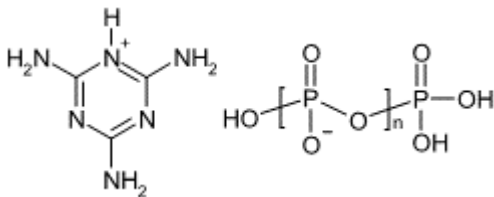
An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1. The overall hazard 2 criterion f) requires only “very high” (Ecotoxicity,

Group I, II or II* Human), while the substance also scores “high” in B and Group II and II* Human. Thus, the Benchmark score 2 does not fully reflect the hazard potential of the substance.

4.5 Melamine-derived and other organic phosphates (not being esters)

4.5.1 Melamine pyrophosphate, CAS No. 15541-60-3

Technical description

CAS No	15541-60-3
EC No	239-590-1
Chemical name	Melamine pyrophosphate
Structural formula	 US EPA, 2014a
General formula	C ₃ H ₁₀ N ₆ O ₇ P ₂
Phosphorous content	>14% (Everflam MPP-2)
Abbreviation, synonyms	Melamine polyphosphate (US EPA 2014a) diphosphoric acid, compound with 1,3,5-triazine-2,4,6-triamine
FR products and manufacturers	EVERFLAM MPP-2 (Everkem) AFLAMMIT® PMN 370 (THOR)
Registered tonnage, t/year	Pre-registered
Pinfa Product Selector	Not Coating (paint), textile (back coating) identified in PPS
Other information on substrate	Various fabrics, nylons, paints, paper and plastics; mainly used for coating/paint and textile backcoating (Everkem)
End applications	-
Reactive/additive	Additive
Health env. profiles	Alternatives to decaBDE (US EPA, 2014a)
Availability	-
Flame retardancy	-
Halogen-containing flame retardants for the same application (examples)	HBCDD

Hazard profile

The screening of melamine phosphate by the modified GreenScreen® methodology was based on information compiled according to the information sources described in 3.2.1.

TABLE 27
SCORING OF MELAMINE PHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Hazard Score
						single	repeat*	single	repeat*									
M	L	L	L	DG	L	DG	M	DG	DG	L	DG	L	DG	L	L	VH	VL	2

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Experimental studies with melamine phosphate are sparse. Therefore, the hazard designations are based on studies performed with melamine. The only exceptions are genotoxicity assays performed with melamine phosphate.

There is experimental evidence that oral melamine exposure causes carcinogenicity in animals; however, no data were located to support its carcinogenicity in humans. The experimental results on melamine, in accordance with the scoring of melamine polyphosphate (section 4.5.1), justify the moderate score. Genotoxicity tests with melamine phosphate yielded negative results.

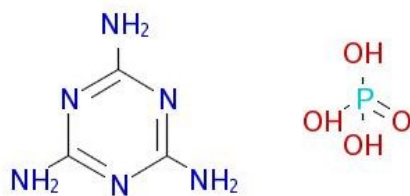
Experimental data on reproductive and developmental effects of melamine phosphate were not available. However, corresponding to the scoring of melamine polyphosphate (section 3.5.4) and read-across with melamine, a low hazard is assigned to these endpoints.

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1, but meets criterion c) for Benchmark 2 by scoring “very high” for persistence (only “high” is required for Benchmark 2) and “moderate” for carcinogenicity and systemic toxicity.

4.5.2 Melamine phosphate, CAS No. 41583-09-9

Technical description

CAS No	41583-09-9																								
EC No	255-449-7																								
Chemical name	1,3,5-triazine-2,4,6-triamine phosphate (pre-registration)																								
Structural formula	 REACH Registration data																								
General formula	C3H6N6.xH3O4P																								
Phosphorous content	10 - 13% (MPT11)																								
Abbreviation, synonyms	Melamine phosphate, reaction product of 1,3,5-triazine-2,4,6-triamine phosphate and orthophosphoric acid																								
FR products and manufacturers	Melapur MP (BASF) Melagard MP (Italmatch) MPT11 (Metadynea Austria GmbH) AFLAMMIT® PMN 185 (THOR) Budite 312 (Budenheim)																								
Registered tonnage, t/year	1,000 - 10,000																								
Pinfa Product Selector	<table><tr><td>Group:</td><td>Substrate:</td><td>Applicability:</td></tr><tr><td rowspan="3">Solid Thermoplastics</td><td>Polyethylene (PE)</td><td>Applicable</td></tr><tr><td>Polypropylene (PP)</td><td>Applicable</td></tr><tr><td>Textiles/Paints/Adhesives</td><td>Paints</td><td>Applicable</td></tr><tr><td rowspan="5">Thermosets</td><td>Intumescent Coatings</td><td>Applicable</td></tr><tr><td>Textile backcoating</td><td>Applicable</td></tr><tr><td>Unsaturated polyesters</td><td>Applicable</td></tr><tr><td>Phenolic Resins</td><td>Applicable</td></tr><tr><td>Epoxy Resins</td><td>Applicable</td></tr></table>			Group:	Substrate:	Applicability:	Solid Thermoplastics	Polyethylene (PE)	Applicable	Polypropylene (PP)	Applicable	Textiles/Paints/Adhesives	Paints	Applicable	Thermosets	Intumescent Coatings	Applicable	Textile backcoating	Applicable	Unsaturated polyesters	Applicable	Phenolic Resins	Applicable	Epoxy Resins	Applicable
Group:	Substrate:	Applicability:																							
Solid Thermoplastics	Polyethylene (PE)	Applicable																							
	Polypropylene (PP)	Applicable																							
	Textiles/Paints/Adhesives	Paints	Applicable																						
Thermosets	Intumescent Coatings	Applicable																							
	Textile backcoating	Applicable																							
	Unsaturated polyesters	Applicable																							
	Phenolic Resins	Applicable																							
	Epoxy Resins	Applicable																							
Other information on substrate	Thermoplastics, polyolefins, elastomers, engineering resins, paints, intumescent fire retardant coating.																								
End applications	-																								
Reactive/additive	Reactive																								
Health env. profiles	Screened as part of this study (see below)																								
Availability	Available for many years from many manufacturers																								
Flame retardancy	-																								
Halogen-containing flame retardants for the same application (examples)	DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others																								

Hazard profile

The screening of melamine phosphate by the modified GreenScreen® methodology was based on information compiled according to the information sources described in 3.2.1. The full data set from the data collection including justification of the scoring is enclosed as Appendix 7 to this report.

TABLE 28
SCORING OF MELAMINE PHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Hazard Score
						single	repeat*	single	repeat*									
M	L	L	L	DG	L	DG	M	DG	DG	L	DG	L	DG	L	L	VH	VL	2

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Experimental studies with melamine phosphate are sparse. Therefore, the hazard designations are based on studies performed with melamine. The only exceptions are genotoxicity assays performed with melamine phosphate.

There is experimental evidence that oral melamine exposure causes carcinogenicity in animals; however, no data were located to support its carcinogenicity in humans. The experimental results on melamine, in accordance with the scoring of melamine polyphosphate (section 4.5.1), justify the moderate score. Genotoxicity tests with melamine phosphate yielded negative results.

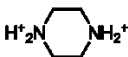
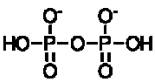
Experimental data on reproductive and developmental effects of melamine phosphate were not available. However, corresponding to the scoring of melamine polyphosphate (section 3.5.4) and read-across with melamine, a low hazard is assigned to these endpoints.

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1, but meets criterion c) for Benchmark 2 by scoring “very high” for persistence (only “high” is required for Benchmark 2) and “moderate” for carcinogenicity and systemic toxicity.

4.5.3 Diphosphoric acid, compd. with piperazine, CAS No. 66034-17-1, and substituted amine phosphate (confidential CAS No.)

Technical description

CAS No	66034-17-1		
EC No	457-330-7		
Chemical name	Diphosphoric acid, compd. with piperazine		
Structural formula	  Registration		
General formula	Not available		
Phosphorous content	55-65% (ADK STAB FP-2100J) 16-21% ADK STAB FP2200)		
Abbreviation, synonyms			
FR products and manufacturers	ADK STAB FP-2100J, ADK STAB FP-2200 (Adeka Palmarole)		
Registered tonnage, t/year	10 – 100		
Pinfa Product Selector	Group: Solid Thermoplastics Foams Textiles/Paints/Adhesives Thermosets Wire and cables	Substrate: Polypropylene (PP) Polyethylene (PE) Thermoplastic elastomers EVA-cop. Rubbers/Elastomers Textile backcoating Intumescent Coatings Latex/adhesives Hot melts Epoxy Resins Unsaturated polyesters Vinyl esters Acrylic resins TPU Polypropylene (PP) EPDM PE/EVA	Applicability: Applicable Applicable Applicable Applicable Could be applied Could be applied Applicable Could be applied Could be applied Could be applied Applicable Applicable Applicable Applicable Applicable Applicable Applicable Applicable Applicable
Other information on substrate	-		
End applications	-		

Reactive/additive	Additive
Health env. profiles	Alternatives for the flame retardant decaBDE (US EPA, 2014a)
Availability	-
Flame retardancy	-
Halogen-containing flame retardants for the same application (examples)	DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others

Hazard profile

The screening of the piperazine pyrophosphate and the substituted amine phosphate (confidential CAS no.) by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for the flame retardant decaBDE (US EPA, 2014a).

TABLE 29
SCORING OF DIPHOSPHORIC ACID, COMPD. WITH PIPERAZINE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	M	M	M	DG	H	DG	M	DG	DG	L	M	L	M	M	L	H	L	2

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Piperazine pyrophosphate constitutes approximately 50% of the commercial mixtures. The remaining 50% are made of a confidential substituted amine phosphate. For most endpoints, experimental studies on both piperazine and the substituted amine phosphate component are available.

The US EPA estimates the carcinogenicity hazard potential as moderate based several animal studies with the substituted amine phosphate component. Positive results in *in vitro* and *in vivo* studies with the substituted amine phosphate component lead to the conclusion on moderate mutagenicity/genotoxicity. Based on data for the piperazine moiety, the reproductive hazard potential was estimated to be moderate. Based on data for the piperazine moiety and professional judgement, the hazard potential for developmental effects and respiratory sensitization were likewise estimated to be moderate. With respect to neurotoxicity, no data were available.

In the only study available on endocrine activity, the substituted amine phosphate component did not exhibit estrogenic activity *in vitro* assay. The data are insufficient for an evaluation, we therefore mark the endpoint as DG (data gap).

Regarding persistence in the environment, the substituted amine phosphate mixture is estimated to show high persistence based on experimental data for the organic components. Low potential for bioaccumulation was based on both QSAR estimations and a confidential study of the amine phosphate component.

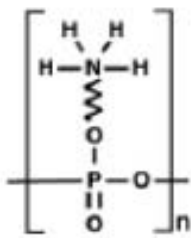
Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1. However, the Benchmark 2 criterion c) only requires “high” P and “moderate” T (Ecotoxicity, Group I, II or II* Human), while the substance scores “high” in P and T.

4.6 Inorganic phosphorous compounds

4.6.1 Ammonium polyphosphate, CAS No. 68333-79-9

Technical description

CAS No	68333-79-9
EC No	269-789-9
Chemical name	Ammonium polyphosphate
Structural formula	 Everkem product catalogue
General formula	NH ₄ PO ₃
Phosphorous content	12.5-13.5% (Exolit® AP 420) 17-19% (Exolit® AP 740 S) 18-20% (Exolit® AP 740 F, Exolit® AP 740) 19-21% (Exolit® AP 760) Approx. 20% (Exolit® AP 755) 20-22% (Exolit® AP 750) 21-23% (Exolit® AP 742) 23-25% (Exolit® AP 765 (TP), Exolit® AP 766 (TP)) 29-31% (Exolit® AP 462, Preniphor EPFR-APP241, Preniphor EPFR-APP262) 29.5-31.5% (Preniphor EPFR-APP231) 31-32% (Exolit® AP 423, Exolit® AP 422, EVERFLAM APP, Preniphor EPFR-APP222H, Preniphor EPFR-APP222, Preniphor EPFR-APP223, Preniphor EPFR-APP224, Preniphor EPFR-APP263)
Abbreviation, synonyms	APP; Ammonium polyphosphate (with synergists); Ammonium polyphosphate (coated); Polyphosphoric acids, ammonium salts
FR products and manufacturers	BUDIT 3123, BUDIT 3167, BUDIT 3168, BUDIT 3178, FR CROS 484, FR CROS C30, FR CROS C60, (Budenheim). Exolit® AP 740 F, Exolit® AP 462, Exolit® AP 423, Exolit® AP 742, Exolit® AP 750, Exolit® AP 422, Exolit® AP 420, Exolit® AP 760, Exolit® AP 755, Exolit® AP 740, Exolit® AP 740 S, Exolit® AP 765 (TP), Exolit® AP 766 (TP), (Clariant) EVERFLAM APP (Everkem) AFLAMMIT® PCI 202 (Thor) Preniphor EPFR-APP222H, Preniphor EPFR-APP222, Preniphor EPFR-APP223, Preniphor EPFR-APP224, Preniphor EPFR-APP231, Preniphor EPFR-APP241, Preniphor EPFR-APP262, Preniphor EPFR-APP263, (Presaf-er) Mileflame NP 1000 (MPI Chemie BV)

	Other product based on ammonium polyphosphate Phos-Chek ® LC95W Solution Phos-Chek ® LC95W FT936 / Fire-Trol 936 FT934 / Fire-Trol 934 FT931 / Fire-Trol 931 Phos-Chek ® LC95A-F BUDIT® IS 3001 AFLAMMIT® PPN series		
Registered tonnage, t/year	10,000 - 100,000		
Pinfa Product Selector	Group: Solid Thermoplastics Foams Textiles/Paints/Adhesives Thermosets Wire and cables Others	Substrate: Polypropylene (PP) Polyethylene (PE) Thermoplastic elastomers EVA-cop. Rubbers/Elastomers PUR flexible foam PUR Rigid foam Other textile fibres Intumescent Coatings Hot melts Latex/adhesives Textile backcoating Acrylic resins Epoxy Resins Phenolic Resins Unsaturated polyesters Vinyl esters PE/EVA Paper/Wood	Applicability: Applicable Applicable Could be applied Applicable Could be applied Applicable Applicable Could be applied Could be applied Could be applied Applicable Applicable Applicable Applicable Could be applied Applicable Could be applied
Other information on substrate	Unsaturated polyester resin, acrylic resins, epoxy or phenolics. PP, PE, PP copolymers and PP blends. Rigid and flexible polyurethane, TPU, epoxy resin, coating (paint)		
End applications	Building materials/Construction, transportation, EEE, furniture, wood, paper, textiles, intumescent coatings		
Reactive/additive	Additive		
Health env. profiles	Flame retardants used in flexible polyurethane foam (US EPA, 2015).		
Availability	Have been available for many years from many manufacturers		
Flame retardancy	V-0 grade PP and PE for EEE can be obtained by loadings of 26-30% and 30-35%, respectively, ammonium polyphosphate (Lassen et al., 2006) Alternative for decaBDE for natural synthetic fibres (Illinois EPA, 2007)		
Halogen-containing flame retardants for the same application (examples)	DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others		

Hazard profile

The screening of ammonium polyphosphate by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).

TABLE 30
SCORING OF AMMONIUM POLYPHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Hazard Score
						single	repeat*	single	repeat*									
L	L	L	L	L	L	L	L	L	L	L	DG	L	L	L	L	(VH)	L	4

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

No experimental data were located with respect to carcinogenicity, mutagenicity/genotoxicity, reproductive and developmental effects, endocrine activity, repeated dose effects and neurotoxicity. Therefore, professional judgement considering the polymer's molecular weight (MW >1,000) and limited bioavailability justify the scoring of these endpoints.

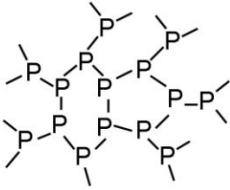
Several experimental studies are listed in the US EPA report concerning the endpoints acute aquatic toxicity and persistence. Furthermore, these endpoints as well as chronic aquatic toxicity and bioaccumulation are characterized by QSAR estimates.

Overall hazard scoring

The substance scores "low" for all endpoints, apart from persistence. However, since the substance is inorganic and persistence is not combined with chronic effects, a Benchmark 4 can be assigned.

4.6.2 Red phosphorus, CAS No. 7723-14-0

Technical description

CAS No	7723-14-0		
EC No	918-594-3		
Chemical name	Red phosphorus		
Structural formula	 Registration		
General formula	Not available		
Phosphorous content	43.0 - 48.0% (Exolit® RP 6520) 60.0 - 63.0% (Red Phosphorus PU 6580, Exolit® RP 607) 50% (MASTERET 70450, MASTERET 80450, MASTERET 20450) 60% (MASTERET 10460 B2XF, MASTERET 15460 B2XF, MASTERET 40460 B2XF, MASTERET 63460 B2XF) 70% (MASTERET 10170) >90% (Exolit® RP 614 presscake (TP)) >95.0% (Red Phosphorus HB 801)		
Abbreviation, synonyms	Red phosphorus, concentrates; Red phosphorus, dispersions		
FR products and manufacturers	Red Phosphorus HB 801, Red Phosphorus PU 6580, Exolit® RP 607, Exolit® RP 6520, Exolit® RP 614 presscake (TP), (Clariant) MASTERET 10170, MASTERET 63460 B2XF, MASTERET 70450, MASTERET 10460 B2XF, MASTERET 15460 B2XF, MASTERET 20450, MASTERET 40460 B2XF, MASTERET 80450 (Italmatch)		
Registered tonnage, t/year	1,000 - 10,000		
Pinfa Product Selector	Group: Solid Thermoplastics Foams Thermosets Textiles/Paints/Adhesives	Substrate: Polyamide (PA) Polypropylene (PP) Polyethylene (PE) Rubbers/Elastomers PUR Rigid foam Epoxy Resins Unsaturated polyesters Phenolic Resins Hot melts Latex/adhesives Other textile fibres	Applicability: Applicable Could be applied Could be applied Could be applied Applicable Applicable Could be applied Could be applied Applicable Applicable
Other information on substrate	Solid plastics, closed cell foams, polymer adhesives, polyisocyanurate and polyurethane rigid foams, plastics, polyurethanes, synthetic and natural rubber latex systems, polyolefines articles, epoxy resins, polypropylene articles and sometimes in PA.		
End applications	EEE, automotive applications		

Reactive/additive	Additive
Health env. profiles	Alternatives for decaBDE (US EPA, 2014a)
Availability	Available from many manufacturers. Account for a significant share of flame retarded polyamide in EEE (Lassen et al., 2006)
Flame retardancy	Vo grade glass reinforced polyamide (PA 66) for use in electrical and electronic equipment can be obtained with loadings of 10-13% red phosphorus (Lassen et al., 2006) Can be used for electronics applications and must be combined with aluminium hydroxide (Morose, 2006).
Halogen-containing flame retardants for the same application (examples)	DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others

Hazard profile

The screening of Red phosphorus by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for the flame retardant decaBDE (US EPA, 2014a).

TABLE 31
SCORING OF RED PHOSPHORUS USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human								Ecotox		Fate		Overall Hazard Score	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P		B
						single	repeat*	single	repeat*									
L	M	L	L	DG	L	L	L	L	L	DG	M	M	L	L	H	L	2	

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

The evaluation of carcinogenicity and reproductive effects is based on expert judgement. A single secondary source indicates weak mutagenic effects, due to uncertainty about this endpoint, the US EPA designates the score “moderate”. The evaluation of reproductive and developmental effects, systemic toxicity as well as neurotoxicity is based in expert judgement.

The authors of the report also refer to several animal studies on exposure to a pyrotechnic mixture containing red phosphorous (red phosphorus/butyl rubber aerosols or smoke), demonstrating immunotoxic, lethal and repeated dose effects. However, the toxicity reported could, according to the authors’ evaluation, not be attributed to any of the components of the mixture including red phosphorus.

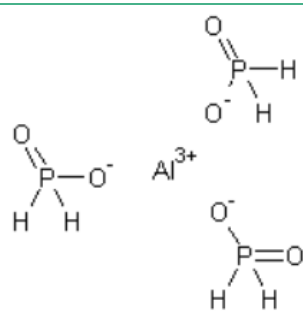
With respect to aquatic toxicity, several studies report effects at concentrations above the water solubility limit. Therefore, no effects at saturation can be assigned.

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1, but meets criterion c) for Benchmark 2 by scoring “high” for persistence and “moderate” for mutagenicity/genotoxicity as well as eye sensitization and irritation.

4.6.3 Phosphinic acid, aluminium salt (3:1), CAS no. 7784-22-7

Technical description

CAS No	7784-22-7																																				
Chemical name	Phosphinic acid, aluminium salt (3:1)																																				
Structural formula	 Registration data																																				
General formula	-																																				
Phosphorous content	-																																				
Abbreviation, synonyms	Hypophosphite, aluminium salt																																				
FR products and manufacturers	Phoslite IP-A (Italmatch)																																				
Registered tonnage, t/year	10 - 100																																				
Pinfa Product Selector	With synergist: <table><thead><tr><th>Group:</th><th>Substrate:</th><th>Applicability:</th></tr></thead><tbody><tr><td rowspan="4">Solid Thermoplastics</td><td>PBT</td><td>applicable</td></tr><tr><td>Polyamide (PA)</td><td>applicable</td></tr><tr><td>Polypropylene (PP)</td><td>applicable</td></tr><tr><td>Thermoplastic elastomers</td><td>applicable</td></tr><tr><td rowspan="3">Foams</td><td>XPS foam</td><td>applicable</td></tr><tr><td>Polypropylene foam (PP)</td><td>applicable</td></tr><tr><td>Rubbers/Elastomers</td><td>applicable</td></tr><tr><td>Textiles/Paints/Adhesives</td><td>Other textile fibres</td><td>applicable</td></tr><tr><td rowspan="2">Thermosets</td><td>Epoxy Resins</td><td>applicable</td></tr><tr><td>Unsaturated polyesters</td><td>applicable</td></tr><tr><td rowspan="4">Wire and cables</td><td>PVC flexible</td><td>applicable</td></tr><tr><td>Polypropylene (PP)</td><td>applicable</td></tr><tr><td>TPU</td><td>applicable</td></tr><tr><td>PE/EVA</td><td>applicable</td></tr></tbody></table>	Group:	Substrate:	Applicability:	Solid Thermoplastics	PBT	applicable	Polyamide (PA)	applicable	Polypropylene (PP)	applicable	Thermoplastic elastomers	applicable	Foams	XPS foam	applicable	Polypropylene foam (PP)	applicable	Rubbers/Elastomers	applicable	Textiles/Paints/Adhesives	Other textile fibres	applicable	Thermosets	Epoxy Resins	applicable	Unsaturated polyesters	applicable	Wire and cables	PVC flexible	applicable	Polypropylene (PP)	applicable	TPU	applicable	PE/EVA	applicable
Group:	Substrate:	Applicability:																																			
Solid Thermoplastics	PBT	applicable																																			
	Polyamide (PA)	applicable																																			
	Polypropylene (PP)	applicable																																			
	Thermoplastic elastomers	applicable																																			
Foams	XPS foam	applicable																																			
	Polypropylene foam (PP)	applicable																																			
	Rubbers/Elastomers	applicable																																			
Textiles/Paints/Adhesives	Other textile fibres	applicable																																			
Thermosets	Epoxy Resins	applicable																																			
	Unsaturated polyesters	applicable																																			
Wire and cables	PVC flexible	applicable																																			
	Polypropylene (PP)	applicable																																			
	TPU	applicable																																			
	PE/EVA	applicable																																			
Other information on substrate	It is a new family of white products intended to be used in polypropylene (PP) as well as in engineering polymers, in particular in polyamides, PBT, PC and PC Alloys, but also as antimony trioxide replacement (Italmatch)																																				
End applications	-																																				
Reactive/additive	Additive																																				
Health env. profiles	Screened as part of this study																																				
Availability	Recently introduced line of FR additives (Italmatch)																																				
Flame retardancy	Intended for polypropylene (PP) UL 94 V2 applications, PBT UL 94 V0, ABS, PVC, PC and PC Alloys																																				
Halogen-containing flame retardants for the same application (examples)	DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others																																				

Hazard profile

The screening of this alternative by the modified GreenScreen® methodology was based on information compiled according to the information sources described in 3.2.1. The full data set from the data collection including justification of the scoring is enclosed as Appendix 6 to this report.

TABLE 32

SCORING OF PHOSPHINIC ACID, ALUMINIUM SALT (3:1) USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Hazard Score
						single	repeat*	single	repeat*									
DG	L	L	L	DG	L	DG	M	DG	DG	L	DG	L	M	M	M	(VH)	L	3

Comments to hazard profile scores

Apart from the REACH registration data, no other data sources provide information on the substance. QSAR estimations are not applicable, because the substance is inorganic. Most of the scores, for which experimental data were available, are based on studies with a commercial product.

No studies were available for persistence and bioaccumulation, the scores of these endpoints are therefore based on read-across and professional judgement. Since the substance is inorganic, persistence is not considered a negative characteristic.

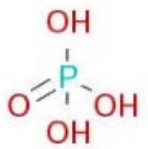
Overall hazard scoring

An overall hazard score = 3 has been assigned, even though the substance formally fulfils the criterion c) for Benchmark 2 by scoring “very high” for persistence (only “high” required for Benchmark 2) and “moderate” for several toxicity endpoints. However, the persistence score is exempted from the evaluation because the substance is inorganic. Thus criteria b) and c) behind overall hazard 3 are fulfilled (“moderate ecotoxicity” and “moderate T”, respectively).

4.7 Other phosphorous and non-categorised substances

4.7.1 Ethylenediamine-o-phosphate, CAS No. 14852-17-6

Technical description

CAS No	14852-17-6																																	
EC No	238-914-9																																	
Chemical name	ethylenediamine, salt with phosphoric acid																																	
Structural formula	  Reach registration data																																	
General formula	C2H8N2.xH3O4P																																	
Phosphorous content	18 – 21 (Metadynea, 2014)																																	
Abbreviation, synonyms	EDAP, EP11																																	
FR products and manufacturers	EP11 (Metadynea Austria GmbH) Aflammit® PCO 123/234 (THOR)																																	
Registered tonnage, t/year	0 - 10																																	
Pinfa Product Selector	<table><tr><td>Group:</td><td>Substrate:</td><td>Applicability:</td></tr><tr><td rowspan="4">Solid Thermoplastics</td><td>Polyethylene (PE)</td><td>Applicable</td></tr><tr><td>Polypropylene (PP)</td><td>Applicable</td></tr><tr><td>EVA-cop.</td><td>Applicable</td><td></td></tr><tr><td></td><td></td><td></td></tr><tr><td rowspan="5">Textiles/Paints/Adhesives</td><td>Paints</td><td>Applicable</td></tr><tr><td>Intumescent Coatings</td><td>Applicable</td></tr><tr><td>Hot melts</td><td>Could be applied</td></tr><tr><td>Textile backcoating</td><td>Applicable</td></tr><tr><td></td><td></td><td></td></tr><tr><td rowspan="2">Thermosets</td><td>Epoxy Resins</td><td>Could be applied</td></tr><tr><td>Unsaturated polyesters</td><td>Could be applied</td></tr></table>			Group:	Substrate:	Applicability:	Solid Thermoplastics	Polyethylene (PE)	Applicable	Polypropylene (PP)	Applicable	EVA-cop.	Applicable					Textiles/Paints/Adhesives	Paints	Applicable	Intumescent Coatings	Applicable	Hot melts	Could be applied	Textile backcoating	Applicable				Thermosets	Epoxy Resins	Could be applied	Unsaturated polyesters	Could be applied
Group:	Substrate:	Applicability:																																
Solid Thermoplastics	Polyethylene (PE)	Applicable																																
	Polypropylene (PP)	Applicable																																
	EVA-cop.	Applicable																																
Textiles/Paints/Adhesives	Paints	Applicable																																
	Intumescent Coatings	Applicable																																
	Hot melts	Could be applied																																
	Textile backcoating	Applicable																																
Thermosets	Epoxy Resins	Could be applied																																
	Unsaturated polyesters	Could be applied																																
Other information on substrate	Solid Thermoplastics																																	
End applications	Recommended for electronics and electricals, transportation, construction.(Thor)																																	
Reactive/additive	Additive																																	
Health env. profiles	Screened as part of this study (see below)																																	
Availability	-																																	
Flame retardancy	-																																	
Halogen-containing flame retardants for the same application (examples)	DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others																																	

Hazard profile

The screening of this alternative by the modified GreenScreen® methodology was based on information compiled according to the information sources described in 3.2.1. The full data set from the data collection including justification of the scoring is enclosed as Appendix 8 to this report.

TABLE 33
SCORING OF ETHYLENEDIAMINE PHOSPHATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Hazard Score
						single	repeat*	single	repeat*									
L	L	L	M	DG	L	DG	M	DG	DG	H	H	VH	L	M	H	VL	VL	2

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Ethylenediamine phosphate (CAS No. 14852-17-6) consist of a mixture of ethylenediamine and phosphoric acid. Only very limited data are available for ethylenediamine phosphate. Ethylenediamine (CAS No. 107-15-3) is therefore used as chemical surrogate in case of lack of data for ethylenediamine phosphate.

Ethylenediamine has a harmonised classification comprising the following health hazards: Acute Tox. 4 * (H302), Acute Tox. 4 * (H312), Skin Corr. 1B (H314), Skin Sens. 1 (H317), Resp. Sens. 1 (H334). Phosphoric acid (CAS No. 7664-38-2) also has a harmonised classification: Skin Corr. 1B (H314).

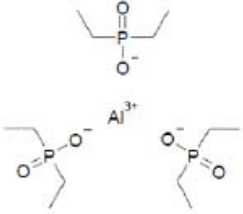
The human endpoints carcinogenicity, developmental and systemic toxicity as well as respiratory sensitization and dermal irritation are based read-across on data for ethylenediammonium dichloride, ethylenediamine and/or QSAR estimates. The same applies to the aquatic toxicity and fate endpoints.

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1, but meets criterion e) and f) for Benchmark 2 by scoring “Moderate” for developmental toxicity (Group I Human) and “Very high” and “High” for other endpoints in Group II Human and ecotoxicity.

4.7.2 Diethylphosphinate, aluminium salt, CAS No. 225789-38-8

Technical description

CAS No	225789-38-8		
EC No	*607-114-5		
Chemical name	Diethylphosphinate, aluminium salt		
Structural formula	 US EPA 2014b		
General formula	3 C ₄ H ₁₁ PO ₂ ·Al		
Phosphorous content	<i>Neat Al-diethylphosphinates:</i> 23.3 - 24.0% (Exolit® OP 930, Exolit® OP 935, Exolit® OP 1230, Exolit® OP 1240) Blends of Al-diethylphosphinate with one or more other substances (e.g. melamine polyphosphate (synergist)): 18.7 - 19.7% (Exolit® OP 1312) 19.7 - 20.7% (Exolit® OP 1311) 19.8 - 20.8% (Exolit® OP 1260 (TP)) 20.5 - 21.5% (Exolit® OP 1314) 24.5 - 25.5% (Exolit® OP 1400)		
Abbreviation, synonyms	Phosphinic acid, P,P-diethyl-, aluminium salt (3:1)		
FR products and manufacturers	Exolit® OP 930, Exolit® OP 935, Exolit® OP 1230, Exolit® OP 1240, Exolit® OP 1260 (TP), Exolit® OP 1311, Exolit® OP 1312, Exolit® OP 1314, Exolit® OP 1400 (Clariant)		
Registered tonnage, t/y	Pre-registered		
Pinfa Product Selector	Group:	Substrate:	Applicability:
	Solid Thermoplastics	Thermoplastic elastomers	Could be applied
		Polyamide (PA)	Could be applied
		PBT	Applicable
		PET	Applicable
	Textiles/Paints/Adhesives	Other textile fibres	Could be applied
	Thermosets	Acrylic resins	Could be applied
		Epoxy resins	Applicable
	Wire and cables	TPU	Applicable
Other information on substrate	High temperature polyamides , polyesters, reinforced polyamide (6 and 66)		
End applications	EEE, automotive		
Reactive/additive	Additive		
Health env. profiles	Alternatives to the halogenated flame retardant in printed circuit boards (US EPA, 2014b)		
Availability	Have been on the market for many years. Have mainly been applied for epoxy		

	resins, TBU and PBT/PET
Flame retardancy	Vo grade PBT for EEE can be obtained with loadings of about Exolit® OP 1312 while Vo grade PA can be obtained with loadings of 15-20% (Lassen et al., 2006) Aluminium diethyl phosphinates were originally developed for glass-fibre reinforced polyamides and polyester achieved UL 94-V0 rating in with ~40 wt % additive (Rakotamala, 2010). Vo grade phenol novolac epoxy resin can be obtained with about 10% aluminium diethylphosphinate-based flame retardants (Rakotamala, 2010) (other loadings in combination with other flame retardants). UL 94-V0 rating could be achieved with a combined flame retardant loading of 20 wt % aluminium diethylphosphinate and melamine cyanurate (Rakotamala, 2010). It has been reported that metal phosphinates are most effective in combination with a nitrogen synergist, such as melamine polyphosphate (Rakotamala, 2010).
Halogen-containing flame retardants for the same application (examples)	TBBPA (reactive and additive), decaBDE

Hazard profile

The screening of Aluminium Diethylphosphinate by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives to the halogenated flame retardant in printed circuit boards (US EPA, 2014b).

TABLE 34
SCORING OF ALUMINIUM DIETHYLPHOSPHINATE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
L	L	L	M	DG	L	M	M	DG	M	L	DG	L	L	M	M	H	L	2

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

Aluminium diethylphosphinate is estimated to be of low hazard for carcinogenicity based on comparison to analogous metal salts and professional judgement. The US EPA estimates the substance to be of moderate hazard for immunotoxicity due to the presence of a bioavailable aluminium and based on comparison to analogous metal salts and professional judgement.

According to professional judgement, neurodevelopmental effects may occur due to the presence of a phosphinate. Experimental studies specifically designed to evaluate the neurodevelopmental endpoint were not located, and the single available developmental toxicity screening study available did not show any adverse effects. Based on a conservative approach, the assessment by the US EPA is shared here. Aluminium diethylphosphinate is scored to be of “moderate” hazard for neurotoxicity based on analogy to aluminium hydroxide and professional judgement.

Estimates for the organic counter-ion indicate that the half-life for ultimate aerobic biodegradation in water is less than 60 days, corresponding to the moderate potential for persistence. The metal ion is recalcitrant to biodegradation or other typical environmental removal processes, resulting in a “High” score for persistence.

Overall hazard scoring

An overall hazard score = 2 has been assigned because the substance does not fulfil any of the criteria behind Benchmark 1 but meets criterion e) for Benchmark 2 by scoring “moderate” for toxicity in Group I.

4.7.3 Confidential halogen-free flame retardant, Emerald Innovation™ NH-1*

Technical description

CAS No	Confidential
EC No	-
Chemical name	Confidential
Structural formula	N.a.
General formula	N.a.
Phosphorous content	7.9 % (Emerald Innovation™ NH-1)
Abbreviation, synonyms	-
FR products and manufacturers	Emerald Innovation™ NH-1 (Great Lake Solutions)
Registered tonnage, t/year	-
Pinfa Product Selector	Not identified in PSS
Other information on substrate	Flexible Polyurethane foams
End applications	"Is an effective, halogen-free replacement for chlorinated phosphate esters in furniture and automotive flexible polyurethane foam applications" (Great Lake Solutions)
Reactive/additive	Additive
Health env. profiles	Flame retardants used in flexible polyurethane foam (US EPA, 2015)
Availability	-
Flame retardancy	Effective in meeting a variety of fire safety standards, including British Standard 5852 Crib V, California Technical Bulletin 117, FMVSS 302 and UL94 HF-1 (Great Lake Solutions)
Halogen-containing flame retardants for the same application (examples)	TCCP, TDCP

Hazard profile

The screening of this confidential flame retardant by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).

TABLE 35
SCORING OF THE CONFIDENTIAL HALOGEN-FREE FLAME RETARDANT USING THE PROPOSED MODIFIED METH-
ODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	L	M	L	H	H	DG	H	DG	M	M	DG	M	M	VH	VH	M	H	1

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

The confidential flame retardant Emerald Innovation™ NH-1* consists of 3 components (Confidential C, Confidential D and Confidential E), all with confidential CAS No. Experimental and measured data for the single compounds are listed in the US EPA report (2015), but are summarized in one hazard table here.

Carcinogenic effects cannot be ruled out, because there is uncertainty due to lack of data for Confidential C and E. A “moderate” hazard has been designated for reproductive effects based on uncertainty due to lack of more definite studies on Confidential C.

The designations for the other human endpoints are based on experimental data for the confidential components C, D, and E.

With respect to endocrine activity, studies were available for two of the components. Component D showed endocrine activity in some *in vitro* assays, impaired reproduction in zebra fish and a single study also suggests human health effects (decreased sperm count and altered hormone levels in men) related to exposure of component D. The actual exposure to component D is, however, unknown in the latter study. Based on a conservative approach, we assign the score “High” to the endpoint of endocrine activity.

Experimental data for component D and E trigger a “very high” hazard designation for aquatic toxicity and degradation studies for component E lead to the score “moderate” for persistence.

Measured BCF values for the components C and D do not exceed 364. The US EPA states that the bioaccumulation score “high” is based on a QSAR-estimated BAF of 18,000 for component E (usually values > 5000 trigger “very high”), but states also that the “estimated low BCF value [presumably for component E] is consistent with the limited water solubility estimates”. The Log Kow for component E has been estimated at 11, thus being greater than the methodology cut-off value of 10, and measured Log Kow values are not available. Being conservative, we assign the score “very high” based on the estimated BAF.

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance meets criterion e) for Benchmark 1 by scoring “high” for T (Group I Human).

4.7.4 Fyrol™ HF-5

Technical description

CAS No	Confidential
EC No	-
Chemical name	Proprietary Phosphorus Ester Blend
Structural formula	-
General formula	-
Phosphorous content	14% (Fyrol™ HF-5)
Abbreviation, synonyms	
FR products and manufacturers	Fyrol™ HF-5 (ICL-IP Europe)
Registered tonnage, t/year	-
Pinfa Product Selector	Not available
Other information on substrate	Flexible polyurethane foam. Its high molecular weight and low fogging potential is advantageous in demanding flexible foam applications where low VOC emissions are required.
End applications	Furniture, automotive
Reactive/additive	Additive
Health env. profiles	Flame retardants used in flexible polyurethane foam (US EPA, 2015)
Availability	-
Flame retardancy	It is highly effective in producing flame retardant flexible polyurethane foam meeting both Cal TB 117 and MVSS-302 criteria. (ICL-IP Europe)
Halogen-containing flame retardants for the same application (examples)	TCPP, TDCP

Hazard profile

The screening of Fyrol™ HF-5* by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).

TABLE 36
SCORING OF FYROL™ HF-5* USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	M	L	M	H	L	DG	M	DG	M	L	DG	L	M	VH	VH	VH	M	1

C = Carcinogenicity M = Mutagenicity R = Reproductive toxicity D = Developmental toxicity E = Endocrine activity AT = Acute mammalian toxicity	ST = Systemic toxicity N = Neurotoxicity SnS = Skin sensitization SnR = Respiratory sensitization IrS = Skin irritation IrE = Eye irritation	AA = Acute aquatic toxicity CA = Chronic aquatic toxicity P = Persistence B = Bioaccumulation

Comments to hazard profile scores

The flame retardant Fyrol™ HF-5* contains 2 confidential components (Confidential A, Confidential B), both with confidential CAS No. Experimental and measured data for the single compounds are listed in the US EPA report (2015), but are summarized in one hazard table here. The substance is a mixture that contains polymeric components, and both residual monomers, unreacted starting material and low MW oligomers are expected to be present in the product.

No experimental data were available for the endpoint carcinogenicity. However, Confidential B is estimated to have uncertain potential for carcinogenicity based on analogy to related chemicals and professional judgement, while confidential A is estimated to have low potential for carcinogenicity.

For all other human endpoints, experimental data are available for either one or even both components. In addition to experimental data for component B, a metabolite of the test substance is listed as a suspected endocrine disruptor by the EU. The potential for endocrine activity for Confidential A is uncertain. In accordance with the GreenScreen profiles of 4.1.3 Poly(m-phenylene methylphosphonate), CAS No. 63747-58-0), and 4.2.6 Resorcinol bis-diphenyl phosphate, CAS No. 57583-54-7), we have assigned the score “high” to endocrine activity, based on the metabolite.

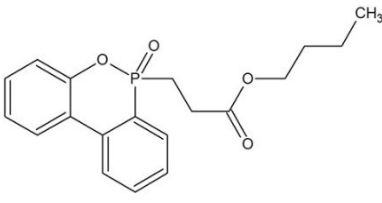
The evaluation of aquatic toxicity is based on experimental data. The persistence designation is based on experimental data with the higher MW components (MW >1,000). No experimental data are available on bioaccumulation, a QSAR-estimated fish BCF of 1,300 for the n=1 oligomer leads to the “moderate” score for bioaccumulation.

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance fulfils criterion c) “very high” for both P and T, as well as criterion e) “high” T (Group I Human).

**4.7.5 6H-Dibenz[c,e][1,2]oxa-phosphotin-6-propanoic acid, butyl ester, 6-oxide,
CAS No. 848820-98-4**

Technical description

CAS No	848820-98-4
EC No	805-659-5
Chemical name	6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide
Structural formula	 Metadynea
General formula	C ₁₉ H ₂₁ O ₄ P
Phosphorous content	Min. 8.5
Abbreviation, synonyms	DOB11
FR products and manufacturers	DOPO-AC4, DOB11, Metadynea Austria GmbH Levagard TP LXS 51114, Lanxess
Registered tonnage, t/year	10 – 100
Pinfa Product Selector	Not included in PPS
Other information on substrate	Polyesters, PUR and epoxy-systems
End applications	DOB11 is especially suited for polyesters, PUR and epoxy-systems intermediate (Metadynea, 2014a).
Reactive/additive	Additive
Health env. profiles	Screened as part of this study (see below)
Availability	Available from several manufacturers Product introduction into the flexible PUR market has just started; only lab experience is available (Lassen et al., 2015).
Flame retardancy	Gas phase inhibitor. Loading approx. twice the concentration of TDCP to pass the automotive MVSS 302 test (Lassen et al., 2015)
Halogen-containing flame retardants for the same application (examples)	TCPP, TDCP DecaBDE, DBDPE, EBTEBPI (all in combination with antimony trioxide) and others

Hazard profile

The screening of this alternative by the modified GreenScreen® methodology was based on information compiled according to the information sources described in 3.2.1. The full data set from the data collection including justification of the scoring is enclosed as Appendix 9 to this report.

TABLE 37

SCORING OF 6H-DIBENZ[C,E][1,2]OXAPHOSPHORIN-6-PROPANOIC ACID, BUTYL ESTER, 6-OXIDE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
DG	DG	DG	DG	DG	L	DG	DG	DG	DG	L	DG	H	DG	M	M	H	L	2

Comments to hazard profile scores

A notified classification is available for 6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide: Skin Irrit. 2 (H315; 29 notifiers), Aquatic Chronic 3 (H412; 28 notifiers).

Only very limited data are available for the substance. Experimental data lead to the scores of Group II Human, ecotoxicity and fate. Some of the endpoint scores are supported by QSAR estimates.

Overall hazard scoring

A Benchmark score = 2 has been assigned because the substance does not fulfil any criteria behind Benchmark 1, but meets criterion c) of Benchmark 2 by scoring “high” for persistence, “high” for an endpoint in Group II Human and “moderate” for ecotoxicity (only “moderate” toxicity scores are required for criterion c) of Benchmark 2).

4.8 Halogenated flame retardants

4.8.1 Decabrominated diphenyl ether (decaBDE), CAS No. 1163-19-5

Hazard profile

The screening of decaBDE by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for the flame retardant decabromodiphenyl ether (DecaBDE; US EPA, 2014b).

TABLE 38
SCORING OF DECABDE USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human						Group II and II* Human								Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	L	L	H	H	L	DG	M	DG	L	L	DG	L	L	L	L	VH	H	1

Comments to hazard profile scores

All endpoint scores, except neurotoxicity, aquatic toxicity and bioaccumulation are based on experimental data presented in the report (US EPA, 2014b).

With respect to endocrine activity, DecaBDE is listed as a Category 2 (Evidence of potential to cause endocrine disruption) on the EU priority list of substances. Moreover, some metabolites of decaBDE are known to produce estrogenic effects (US EPA, 2014b). We therefore assign the score “high” to this endpoint.

Given the low water solubility of the substance, no aquatic effects at saturation are expected (US EPA, 2014b).

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance meets criterion c) and e) for Benchmark 1 by scoring “high” for developmental toxicity (Group I Human) and “very high” for persistence.

4.8.2 Tetrabromobisphenol A (TBBPA), CAS No. 79-94-7

Hazard profile

The screening of TBBPA by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for halogenated flame retardant in printed circuit boards (US EPA, 2014c).

TABLE 39
SCORING OF TBBPA USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human					Group II and II* Human									Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	L	L	M	H	L	DG	L	L	L	L	DG	L	M	VH	H	H	M	1

Comments to hazard profile scores

All scores are based on experimental data. The scores of fate endpoints are further supported by estimated data.

The US EPA did not assign a score on endocrine activity, but listed > 20 studies relating to this endpoint. Both whole animal and *in vitro* studies indicate that TBBPA may exhibit endocrine activity.

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance meets criterion e) for Benchmark 1 by scoring "high" for T (Group I Human).

4.8.3 Hexabromocyclododecane (HBCDD), CAS No. 25637-99-4 and 3194-55-6

Hazard profile

The screening of HBCDD by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for hexabromocyclododecane (HBCDD) (US EPA, 2014c).

TABLE 40
SCORING OF HBCDD USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human						Group II and II* Human								Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	L	M	H	H	L	DG	M	M	M	L	DG	L	L	VH	VH	H	VH	1

Comments to hazard profile scores

There are 16 possible hexabromocyclododecane (HBCDD) isomers. CAS No. 25637-99-4 is assigned to a non-specific mixture of all HBCDD isomers and CASRN 3194-55-6 is assigned to the mixture of 1,2,5,6,9,10-HBCDD isomers. The US EPA report accounts for differences in the fate and behaviour in the environment, and the potential for toxic effects for individual HBCD isomers.

The carcinogenicity score is derived from an estimation and an insufficient, but indicative mouse study. The score for neurotoxicity is based on structural alert and professional judgment. For all other human health endpoints, sufficient experimental data have been available in the US EPA report. *In vitro* and *in vivo* studies demonstrated endocrine activity, thus we mark this endpoint with "High". Experimental data give rise to the environmental scores.

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance fulfils the criteria a), d) and e) by scoring "very high" for aquatic toxicity and bioaccumulation and "high" for toxicity (Group I Human).

4.8.4 Tris (1-chloro-2-propyl) phosphate (TCCP), CAS No. 13674-84-5

Hazard profile

The screening of TCCP by the modified GreenScreen® methodology was made using the data for the substance collected and presented by US EPA in its assessment of alternatives for flame retardants used in flexible polyurethane foam (US EPA, 2015).

TABLE 41
SCORING OF TCCP USING THE PROPOSED MODIFIED METHODOLOGY

Group I Human						Group II and II* Human								Ecotox		Fate		Overall Hazard Score
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	
						single	repeat*	single	repeat*									
M	L	H	H	M	L	DG	M	M	M	L	DG	L	L	M	M	H	L	1

Comments to hazard profile scores

There were no experimental data located for carcinogenicity; carcinogenic effects cannot be ruled out. The US EPA therefore applies the score “moderate” to this endpoint. The neurotoxicity scores are based on experimental data and supported by weight of evidence from structural alert for organophosphates. Endocrine activity was demonstrated in several cell assays.

Measured and estimated BCF and BAF values are < 100, corresponding to the “very low” bioaccumulation designation (the US EPA assigns “low” according to their bioaccumulation criterion). However, the authors also state that the designation is not consistent with results of biomonitoring studies, since TCCP has been detected in herring gull eggs and human breast milk (US EPA, 2015). Considering the measured log Kow (2.68, 2.59 and 3.33), we maintain the “low” hazard designation.

Overall hazard scoring

An overall hazard score = 1 has been assigned because the substance meets criterion e) by scoring “high” for T (Group I Human).

5. Phosphorous flame retardants and smoke by fire

5.1 Formation of particles and hazardous gases by fire

Most fire deaths are caused by inhalation of smoke. Often smoke incapacitates so quickly that people are overcome and cannot make it to an otherwise accessible exit. Synthetic materials being commonplace in buildings, construction and means of transport form especially dangerous smoke. As a fire grows it will often consume most of the available oxygen, slowing the burning process, and this “incomplete combustion” leads to the formation of toxic gases.

Smoke is made of components that can each be lethal in its own way (NFPA, 2015):

- **Particles:** Unburned, partially burned, and completely burned substances can be so small they penetrate the respiratory system’s protective filters, and lodge in the lungs. Some are actively toxic; others are irritating to the eyes and digestive system.
- **Vapours:** Foglike droplets of liquid can poison if inhaled or absorbed through the skin.
- **Toxic gases:** The most common, carbon monoxide (CO), can be deadly, even in small quantities, as it replaced oxygen in the bloodstream. Hydrogen cyanide results from the burning of plastics, such as PVC pipe, and interferes with cellular respiration. Phosgene is formed when household products, such as vinyl materials, are burned. At low levels, phosgene can cause itchy eyes and a sore throat; at higher levels it can cause pulmonary oedema and death.

Key toxic products in fires, as summarised by Purser (2009), are:

- Products threatening survival during and immediately after a fire:
 - **Asphyxiant gases:** CO, HCN, CO₂, low oxygen
 - **Irritants:**
 - ◆ acid gases – HCl, HBr, HF, COF₂, H₃PO₄, SO₂, NO_x
 - ◆ organic irritants - acrolein, formaldehyde, crotonaldehyde, phenol, styrene
 - **Particulates** (especially ultrafine particles)
- Products causing environmental contamination, with long term health implications for repeated exposure during firefighting or post-fire investigation
 - Benzene, isocyanates, PCBs, PAHs, dioxins and furans, aldehydes
 - Inhalable fibres: asbestos, ceramic, mineral, carbon fibre
 - Particulates, metals

The possible effects of the toxicants are different for the different fire zones as summarised by Purser (2009):

- **Zone 1:** Inside fire compartment. Exposure to effluent fire plume lethal within minutes (due to asphyxiant and irritant gases).
- **Zone 2:** Outside immediate fire compartment or building. Exposure to effluent plume with dilution factor of 50-100 times that inside fire (hazard from brief exposure to more concentrated “downwashed” smoke plumes) canteen.
- **Zone 3:** Surrounding area of city exposed to downwind plume) – Potential minor health hazards to large exposed population from much more diluted plume

Asphyxiant gases (carbon monoxide and hydrogen cyanide) are the main Zone 1 killers, but are relatively harmless at the 50-100 dilution levels in the smoke plume outside the immediate fire zone. Irritant gases and associated particulates are also lethal at Zone 1 concentrations, but still present significant health hazards at Zone 2 (and to some extent at Zone 3 concentrations). Irritant gases cause inflammation of eyes and respiratory tract (potential acute and chronic bronchitis, chronic obstructive lung diseases, such as fibrosis or emphysema, RADs (reactive airway dysfunction syndrome). Other exposures toxic at Zone 2 concentrations or during post-fire investigation are (Purser, 2009):

- Sensitizers including formaldehyde and isocyanates leading to asthma
- Organic carcinogens: PAHs, dioxins, dibenzofurans, metals
- Ceramic and asbestos fibres: lung fibrosis, pleural cancers
- Ultrafine particulates and CO: risk of angina and heart attacks

5.1.1 Flame retardant mechanism of phosphorous flame retardants

As described by Clariant Produkte (2015), flame retardants may slow down or even interrupt the combustion process by physical or chemical action in the solid, liquid or gas phase. They interfere during heating, decomposition, ignition or flame spread with the course of the fire. The most important processes are:

- **Physical action** by **cooling** (endothermic process of FR decomposition) or **dilution** of the substrate in the gas phase (i.e. formation of water) and the solid phase (alumina trihydrate and magnesium hydroxide), or by **coating** the substrate (shielding it against the attack of oxygen and heat) with phosphorous and nitrogen compounds.
- **Chemical action** in the gas phase interferes with the combustion processes by eliminating the high energy H and OH radicals by halogen halides from halogenated flame retardants, metal halogen compounds from antimony trioxide, and phosphorous-containing fragments from phosphorous flame retardants ("flame poisoning"). In the solid phase, the flame retardant forms a carbonaceous layer on the surface of the polymer by dehydration, formation of double bonds, thus initiating cyclization and cross-linking (phosphorous, nitrogen compounds, intumescent systems).

The benefit of fire retardant treatments is mainly to reduce the probability that a heat or ignition source will initiate a growing spreading fire (Purser, 2009). If the initial ignition resistance is overcome the presence of flame retardants may reduce the rate of fire growth. For some flame retardants mechanism in this phase the presence of flame retardants may also slow the burning process leading to the increased formation of toxic gases. With respect to toxic product yields the ideal fire retardant system according to Purser (2009) acts in the solid phase and minimises the release of organic fuel vapours and acid gases. Systems that lead to reduced organic emissions relative to the parent polymer include inert fillers, alumina trihydrate systems, char forming or layer forming systems locking up fuel carbon such as borax/boric acid and char forming nitrogen-phosphorus systems, and nano-clay systems (Purser, 2009).

Phosphorous-containing flame retardants are active mainly in the solid phase of the polymer and influence pyrolysis and char formation (Troitzsch, 2004). In the solid phase they form phosphoric and related acids by thermal degradation, and water is released from the substrate in the solid phase, which act as a "heat sink". They form a thin glassy coating, which is a barrier that lowers the evolution of combustible gases in the gas phase and limits the diffusion of oxygen and the heat transfer (Troitzsch, 2004). Specific phosphorus flame retardants such as the metal phosphinates may also act in the gas phase by the formation of P and PO radicals interrupting the radical chain mechanism of the combustion process (Clariant Produkte, 2014). Vapour phase flame inhibition is enhanced by the presence of nitrogen and halogens (Purser, 2014).

The mechanism of intumescent flame retardant systems which are typically a combination of phosphorus and nitrogen compounds is to form a isolating carbon layer which reduce smoke formation (Pinfa, 2011). In the event of fire the flame retardants react together as a result of the temperature increase to form a carbon foam. This foam attains a thickness of 10 to 100 times of the originally applied coating and insulates the substrate material through its low thermal conductivity. Intumescent coating systems are often used to protect steel from overheating, but can also be applied to timber surfaces, thereby acting as an FR coating, inhibiting ignition, surface spread of flame, and heat propagation. These coatings consist of a carbon supplier (starch, polyol, or pentaerythritol), ammonium polyphosphate, and melamine as an expanding agent (Turner, 2014).

5.2 The influence of phosphorous flame retardants on the formation of smoke and toxic gases

Depending upon the flame retardant system, as mentioned above, the phosphorous flame retardants acts partly in the solid phase by formation of a char and partly in the vapour phase. The influence of the phosphorous flame retardants on the formation of the toxic gases and other smoke components depends on the specific systems. A summary of fire performance of phosphorous flame retardants is shown in Table 42. Whereas non-halogenated phosphorous flame retardants in general reduce the yields of toxic combustion products compared to materials without flame retardants, phosphorous halogenated flame retardants increase the yields.

TABLE 42
SUMMARY OF FIRE PERFORMANCE OF PHOSPHOROUS FLAME RETARDANTS (BASED ON TURNER, 2014)

	Reduces fire probability	Reduces fire size	Yields of toxic combustion products	Yields of environmental toxic products
Phosphorous and phosphorous/nitrogen FRs	Yes	Yes, by char formation and in gas phase	Some reduced	Reduced
Phosphorous halogen	Yes	Yes, mainly gas phase	Increased	Increased
Ammonium polyphosphate	Yes	Yes, with char formation	Reduced	Reduced
Intumescent coatings	Yes	Yes	No	None

Char formation

The main feature of phosphorous flame retardants is char-forming activity, sometimes combined with foaming-up (intumescence), which then forms a protective top layer on the plastic surface. The advantage of such a solid-phase mechanism is that it causes less release of smoke and off-gases in a developing fire situation, thus keeping secondary fire damage as low as possible (Schmitt, 2007).

The main advantages of intumescent phosphor-based flame retardants in polyolefins (polyethylenes and polypropylenes) are as summarised by Schmitt (2007):

- Very low smoke density in the developing phase of a fire
- No corrosivity of the smoke/off gases, which is important for electronics
- Low heat-release rates, therefore reduced speed of fire spread.

The flame performance of phosphorous flame retardants as compared with halogenated flame retardants have been studied in several studies.

Molyneux et al. (2014 a,b) burned standard industry formulations of flame retarded aliphatic polyamides, meeting UL 94 V-0 under controlled conditions, and the yields of the major asphyxiants, carbon monoxide (CO) and hydrogen cyanide (HCN) was quantified. The study showed that in

aliphatic polyamides, brominated flame retardants with an antimony oxide synergist, which interfere with gas-phase free radical reactions, produce high yields of both carbon monoxide and hydrogen cyanide. In contrast, the aluminium phosphinate/melamine polyphosphate combination, which is believed to act in both gas and condensed phases, caused a significantly smaller increase in the yields of these two main asphyxiants. According to the authors it is crucial, in the context of the flame inhibition that the phosphorus system reduces the H and O radical concentrations without a corresponding decrease in the OH radical concentration. Moreover, while the phosphorus flame retardant is effective as an ignition suppressant at lower temperatures (corresponding to early flaming), this effect “switches off” at high temperatures, minimising the potential increase in fire toxicity, once the fire develops. The work furthermore showed that hydrogen cyanide (HCN) was the major contributor to the toxicity for all fire retarded PA materials reported in the study, even in well-ventilated conditions, although the contribution from CO from materials flame retarded with brominated flame retardants was also significant. By estimating the overall fire toxicity (using toxicity equivalency factors for the different toxic compounds), the study showed that the polyamide with the flame retardant containing bromine and antimony caused a significant increase in the fire toxicity, compared to the material flame retarded by the aluminium phosphinate/melamine polyphosphate blend. (Molyneux et al., 2014 a).

With the aims to develop halogen-free poly(1,4-butylene terephthalate) (PBT) composites with enhanced flame retardancy Yang et al. (2011) produced flame retarded PBT using aluminium hypophosphite (AHP) and melamine derivatives (melamine polyphosphate and melamine cyanurate). A loading of 20 wt % flame retardant mixture fulfilled the PBT composites high limited oxygen index (LOI) and V-0 classification in UL 94 testing. For the PBT composites with the incorporation of aluminium hypophosphite (AHP) and melamine derivatives, the heat release capacity (HRC), which is an indicator of a material fire hazard, was significantly reduced, and the intensities of a variety of combustible or toxic gases detected by TG-IR technique were remarkably decreased. (Yang et al., 2011)

Even the yield of smoke is lower when using phosphorous flame retardants as compared to halogenated flame retardants in some systems the addition of the flame retardants result in higher smoke formation than in the non-flame retarded system. Polyamide 6 (PA 6) and polypropylene (PP) containing fire retardants, nanofillers or a combination of both additives were tested under three different fire conditions, to determine the effect of additives on the soot production or toxic product yields. In all ventilation conditions the virgin polymer produces the least amount of soot, both the additives used (fire retardant and nanoclay) increase the amount of soot, mainly within 0.5–1.0 μm range, for each fire condition. (Rhodes et al. 2011).

An important consideration is the form in which the vapour phase phosphorus is released during fires. This has according to Purser (2014) been little studied, but in general phosphorus and organic phosphorous compounds are readily oxidized, so that the main product is P_2O_5 , which then hydrolyses to H_3PO_4 . This is moderately toxic, and may make some small contribution to overall toxicity of fire effluents from treated materials. Phosphine (PH_3) is another toxic compound detected in some fire effluents (a highly toxic substance causing lung oedema. Some traces of organophosphorus compounds have been detected in the combustion products from burning materials, but toxicity test protocols designed to detect neurotoxic compounds have not been used with combustion atmospheres. One serious exception is the finding that any phosphorus source when combined with a trimethylol polyol can produce a potent neurotoxic class of bicyclic phosphates in combustion products. In practice this has been a potential problem only with certain turbine lubricants containing trimethylol (Purser, 2014)

Low smoke, zero halogen cables have been growing strongly in Europe. According to EFRA (2015) bis-aryl phosphates (BDP, CDP) provide good low temperature flexibility in thermoplastic elastomers and rubbers such as EPDM, SBR, NBR or TPU, and are also recommended for low smoke

formulations. (EFRA, 2015). Even the phosphorous flame retardants result in lower smoke yield, mainly non-phosphorous inorganic flame retardants are used as smoke suppressants in flame retardants formulations. For wires and cables made of polyolefins like LDPE, LLDPE or PP, mineral flame retardants are often used – mainly finely precipitated aluminium tri-hydroxide (ATH) and magnesium dihydroxide (MDH). While relatively inexpensive, they usually require high loadings of up to 60% of the weight of the final material. Zinc borate can be used in combination with ATH and MDH to enhance smoke suppression (EFRA, 2015).

Abbreviations and acronyms

ABS	Acrylonitrile-butadiene-styrene
ACToR	Aggregated Computational Toxicology Resource
ADR	European Agreement concerning the International Carriage of Dangerous Goods by Road
ASTDR	Agency for Toxic Substance & Disease Registry
AHP	Aluminum hypophosphite
ATH	Aluminium trihydrate
ATO	Antimony trioxide, Sb ₂ O ₃
APP	Ammonium polyphosphate
BAF	Bioaccumulation factor
BAPP	Bisphenol A bis(diphenyl phosphate)
BCF	Bioconcentration factor
BPA-BDPP	Bisphenol A bis(diphenyl phosphate)
BPBP	Phosphoric acid, mixed esters with [1,1'-bisphenyl-4,4'-diol] and phenol
BM	Benchmark
C&L	Classification and labelling
CAS	Chemical Abstracts Service
CB	Circuit boards
CDP	Cresyl diphenyl phosphate
CHIRP	Chemical Risk Information Platform
CICAD	Concise International Chemical Assessment Documents
CLP	Classification, labelling and packaging
CMR	Carcinogenic, mutagenic and reprotoxic
CO	Carbon monoxide
CO ₂	Carbon dioxide
DBDPE	Decabromodiphenyl ethane
DBDPE	Ethane-1,2-bis(pentabromophenyl)
Deca-BDE	Decabromodiphenyl ether
DfE	Design for the Environment [programme]
DG	Data gap
DOT	US Department of Transportation Hazardous Materials Regulations
EBTEBPI	Ethylene bis(tetrabromophthalimide)
ECHA	European Chemicals Agency
ED	Endocrine disruption
EDAP	Ethylenediamine, salt with phosphoric acid
EEE	Electrical and electronic equipment
EFRA	European Flame Retardants Association
EHC	Environmental Health Criteria
EPA	Environmental Protection Agency
EPDM	Ethylene propylene diene monomer (M-class) rubber
EPI	Estimation Programs Interface
EPS	Expanded polystyrene
EVA	Ethylene-vinyl acetate
FDA - ED	US Food and Drug Administration - Endocrine Disruptor Knowledge Base
FR	Flame retarded or flame retardants
GHS	Global Harmonized System
HBCDD	Hexabromocyclododecane (same as HBCD)
HCL	Hydrochloric acid

HF	Hydrogen fluoride
HIPS	High impact polystyrene
HIPS/PPO	Copolymer of HIPS and PPO
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
INCHEM	Chemical Safety Information from Intergovernmental Organizations
IRIS	Integrated Risk Information System
JECFA	Joint Expert Committee on Food Additives
LC50	Lethal concentration which causes the death of 50% of a group of test animals
LOUS	List of Undesirable Substances
MAK	Maximum permissible concentration of a substance as a gas, vapour or aerosol in the air at the workplace (derived from German)
MDH	Magnesium dihydroxide
MW	Molecular weight
NGO	Non-governmental organisation
NIOSH	National Institute for Occupational Safety and Health
OECD	Organisation for Economic Co-operation and Development
PAH	Polyaromatic hydrocarbons
PAN	Pesticide Action Network Pesticide Database
PBT	Persistent, bioaccumulative and toxic
PBT	Polybutylene terephthalate
PC	Polycarbonate
PC/ABS	Copolymer of PC and ABS
PCB	Polychlorinated biphenyls
PE	Polyethylene
PDM	Poly
PET	Poly(ethylene terephthalate)
Pinfa	Phosphorus, Inorganic and Nitrogen Flame Retardants Association
PP	Polypropylene
PPO	Polyphenylene oxide
PPS	Pinfa Product Selector
PS	Polystyrene
PUR	Polyurethane
PVC	Polyvinyl chloride
QSAR	Quantitative structure–activity relationship
RDP	Resorcinol bis(diphenylphosphate)
REACH	Registration, Evaluation, Authorisation and Restriction .of Chemicals
SIDS	Screening Information Data Set
Stot	Specific target organ toxicity
SVHC	Substances of very high concern
TBBPA	Tetrabromobisphenol A
TBPP	Tris (p-t-butylphenyl) phosphate
TCP	Tricresyl phosphate
TCPP	Tris(2-chloro-1-methylethyl) phosphate
TDCP	Tris[2-chloro-1-(chloromethyl)ethyl] phosphate
TMPP	Tricresyl phosphate
ToxRefDB	US EPA Toxicity Reference Database
TPU	Thermoplastic polyurethane
UKPID	UK Poison Information Documents
UL 94	Underwriters Laboratories 94 standard
US EPA	United States Environmental Protection Agency
USA	United States of America
vPvB	Very persistent and very bioaccumulative
XPS	Extruded polystyrene

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Appendix 1 Summary hazard profiles from US EPA

The screening level hazard summary for flame retardants used in PUR foams as alternatives to penta-BDE prepared by the US EPA (2015) are shown in the following table. The table only contains information regarding the inherent hazards of flame retardant chemicals. Evaluation of risk considers both the hazard and exposure associated with substance including combustion and degradation by-products. The caveats listed in the legend and footnote sections must be taken into account when interpreting the hazard information in the table.

TABLE 43

SCREENING LEVEL HAZARD SUMMARY FOR SELECTED HALOGENATED AND NON-HALOGENATED PHOSPHOROUS FLAME RETARDANTS USED IN PUR FOAMS AS ALTERNATIVES TO PENTA-BDE (US EPA, 2015) *1

Chemical	CAS No	Human Health Effects											Aquatic Toxicity		Environ-mental Fate	
		Acute toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
Phosphorus flame retardants																
Ammonium polyphosphate (APP) ¥	68333-79-9	L	L	L	L	L	L	L ^d	L		VL	L	L	L	VH	L
Triphenyl phosphate (TPP) †	115-86-6	L	M	L	L	L	L	H	L		L	VL	VH	VH	L	M
Tricresyl phosphate (TCP) 1	1330-78-5	M	L	L	H	M	M	H	M		L	L	VH	VH	M	H
Isopropylated triphenyl phosphate (IPTPP) †	68937-41-7	L	M	L	H	H	H	H	L		L	L	VH	VH	M	H
Tris (p-t-butylphenyl) phosphate (TBPP)	78-33-1	L	M	L	M	L	M	H	M		L	M	VH	VH	M	H
Diethyl bis(2hydroxyethyl) ami-nomethylphosphonate	2781-11-5	L	M	M	L	L	M	M	M		L	VL	L	L	H	L
Oligomeric ethyl ethylene phosphate	184538-58-7	L	L	M	L	M	M	L ^d	L		M	L	L	L	VH	L
Oligomeric phosphonate polyol	363626-50-0	L	M	M	L	M	M	L	L		L	VL	L	L	M	L
New-to-Market Proprietary Mixtures																
Emerald Innovation™ NH-1	Proprietary	H	M	L	M	L	M	H	M		M	M	VH	VH	M	H
Confidential C	Confidential	H	M	L	M	VL	M	L	M		M	M	H	H	L	L
Confidential D	Confidential	L	M	L	L	L	L	H	L		L	VL	VH	VH	L	M
Confidential E	Confidential	L	M	L	L	L	M	M	M		VL	M	VH	VH	M	H
Fyrol™ HF-5	Proprietary	L	M\$	M	L	M	M\$	M ^d	L		M	L	VH	VH	VH	H‡
Confidential A	Confidential	L	L	M	L	L	M	L	L		M	L	L	L	VH	L
Confidential B	Confidential	L	M	L	L	M	M	M	L		L	VL	VH	VH	M	H
Halogenated Flame Retardants - Firemaster® 550 Components																

Firemaster® 550*	Mixture	L	M	M	H	H	H	H	M		L	L	VH	VH	H	H
Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester (TBB) ‡	183658-27-7	L	M	L	M	M	M	M	M		L	L	L	L	H	H
Di(2-ethylhexyl) tetrabromophthalate (TBPH) ^ ‡	26040-51-7	L	M	M	M	M	M	M	L		L	L	L	L	H	H
Isopropylated triphenyl phosphate (IPTPP) ^	68937-41-7	L	M	L	H	H	H	H	L		L	L	VH	VH	M	H
Triphenyl phosphate (TPP) ^	115-86-6	L	M	L	L	L	L	H	L		L	VL	VH	VH	L	M
Halogenated Flame Retardants - Chlorinated Phosphorus Alternatives																
Tris (2-chloroethyl) phosphate (TCEP)	115-96-8	H	H	M	M	H	M	M	L		L	L	H	H	M	L
Tris (2-chloro-1-methylethyl) phosphate (TCPP)	13674-84-5; 6145-73-9	L	M	L	H	H	M	M	L		L	L	M	H	H	L
Tris (1,3-dichloro-2-propyl) phosphate (TDCPP)	13674-87-8	L	H	M	H	M	L	H	L		L	L	H	H	H	L
Phosphoric acid, P,P'-[2,2-bis(chloromethyl)-1,3propanediyl] P,P,P',P'-tetrakis(2-chloroethyl) ester (V6)	38051-10-4	L	M	L	M	H	L	M	L		L	L	M	H	H	L

Notes from the cited report:

VL = Very Low hazard **L** = Low hazard **M** = Moderate hazard **H** = High hazard **VH** = Very High hazard –

Endpoints in coloured text (**VL**, **L**, **M**, **H**, and **VH**) were assigned based on empirical data.

Endpoints in black (**VL**, **L**, **M**, **H**, and **VH**) were assigned using values from predictive models and/or professional judgement.

* This mixture is made up of four components contained in the hazard summary table. Hazard designations in bold and colour are based on test data for the mixture, as summarized in the hazard profiles for the components. Hazard designations in italics are based on the most conservative results from one of the four components.

^ This component of Firemaster® 550 may be used alone or in other mixtures as an alternative.

‡ Aquatic toxicity: EPA/DFE criteria are based in large part upon water column exposures, which may not be adequate for poorly soluble substances such as many flame retardants that may partition to sediment and particulates.

1 This assessment also includes information for other methylated triphenyl phosphate isomers (phosphoric acid, bis(methylphenyl) phenyl ester (CASRN 26446-73-1) and phosphoric acid, methylphenyl diphenyl ester (CASRN 26444-49-5))

TABLE 44

SCREENING LEVEL HAZARD SUMMARY FOR decaBDE AND BROMINATED FLAME RETARDANT ALTERNATIVES (US EPA, 2014A) *1

THIS TABLE ONLY CONTAINS INFORMATION REGARDING THE INHERENT HAZARDS OF FLAME RETARDANT CHEMICALS. THE CAVEATS LISTED IN THE LEGEND AND FOOTNOTE SECTIONS MUST BE TAKEN INTO ACCOUNT WHEN INTERPRETING THE HAZARD INFORMATION IN THE TABLE.

Chemical	CAS No	Human Health Effects											Aquatic Toxicity		Environ-mental Fate	
		Acute toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
DecaBDE and discrete BFR alternatives																
Decabromodiphenyl ether, decaBDE	1163-19-5	L	M	L	L	H	H	M	L		L	L	L	L	VH	H
Bis(hexachlorocyclopentadieno) cy-clooctane,	13560-89-9	L	M ^s	M ^s	VL	VL	L	M	L		VL	L	L	L	VH	H
Decabromodiphenyl ethane, DBDPE	84852-53-9	L	M ^s	L	L	VL	H ^s	L	L		VL	VL	L	L	VH	H
Ethylene (bistetrabromophthalimide), EBTEBPI	32588-76-4	L	M ^s	L	L	L	M ^s	L	L		VL	VL	L	L	VH	H
Tetrabromobisphenol A bis (2,3-dibromopropyl) ether, TBBPA-BDBPE	21850-44-2	L	M	M	M	M	L	M	M		L	L	L	L	VH	H
Tris(tribromoneopentyl) phosphate, TTBNPP	19186-97-1	L	M	M	L	H	H	M	H		L	L	L	L	H	M
Tris(tribromophenoxy) triazine, TTBP-TAZ	25713-60-4	L	L	L	L	L	L	L	L		L	VL	L	L	VH	H
Polymeric BFRs																
Brominated epoxy resin end-capped with tribromophenol	135229-48-0	H	L	L	L	L	L	M ^d	L		L	VL	L	L	VH	L
Brominated polyacrylate	59447-57-3	L	L	L	L	L	L	M ^d	L		L	L	L	L	VH	L
Brominated polystyrene	88497-56-7	L	L	L	L	L	L	M ^d	L		L	L	L	L	VH	L
Confidential brominated epoxy polymer #1	Confidential	L	L	L	L	L	L	M ^d	L		L	L	L	L	VH	L
Confidential brominated epoxy polymer #2	Confidential	L	L [♦]	L [♦]	L [♦]	L [♦]	L	M ^{♦d}	L [♦]	♦	L	L	L [♦]	L [♦]	VH	L [♦]
Confidential brominated epoxy polymer Mixture	Confidential	L	L [♦]	L [♦]	L [♦]	L [♦]	L	M ^{♦d}	L [♦]	♦	L	L	L [♦]	L [♦]	VH	L [♦]

Chemical	CAS No	Human Health Effects											Aquatic Toxicity		Environmental Fate	
		Acute toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
Confidential brominated epoxy polymer Mixture	Confidential	<i>L</i>	<i>L</i> [♦]	<i>L</i> [♦]	<i>L</i> [♦]	<i>L</i> [♦]	<i>L</i>	<i>M</i> ^{♦d}	<i>L</i> [♦]	♦	<i>L</i>	<i>L</i>	<i>L</i> [♦]	<i>L</i> [♦]	<i>VH</i>	<i>L</i> [♦]
Confidential brominated polymer	Confidential	<i>L</i>	<i>L</i> ✕	<i>L</i>	<i>L</i> ✕	<i>L</i> ✕	<i>L</i> ✕	<i>L</i> ✕	<i>L</i>	<i>L</i>	<i>L</i>	<i>VL</i>	<i>L</i>	<i>M</i> ^{T✕}	<i>VH</i> ^T	<i>M</i> ^{T✕}
TBBPA glycidyl ether, TBBPA polymer	68928-70-1	<i>L</i>	<i>L</i> [♦]	<i>L</i> [♦]	<i>L</i> [♦]	<i>L</i> [♦]	<i>L</i>	<i>M</i> ^{♦d}	<i>L</i>	♦	<i>L</i>	<i>L</i>	<i>L</i> [♦]	<i>L</i> [♦]	<i>VH</i>	<i>L</i> [♦]
Organic phosphorus or nitrogen flame retardants (PFRs or NFRs) alternatives																
Substituted amine phosphate mixture	Confidential	<i>H</i>	<i>M</i>	<i>M</i>	<i>M</i>	<i>M</i>	<i>L</i>	<i>M</i>	<i>M</i>	<i>M</i> ^s	<i>M</i> ^s	<i>VH</i>	<i>M</i>	<i>L</i>	<i>H</i>	<i>L</i>
Triphenyl phosphate	115-86-6	<i>L</i>	<i>M</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>M</i>	<i>L</i>		<i>L</i>	<i>VL</i>	<i>VH</i>	<i>VH</i>	<i>L</i>	<i>M</i>
Bisphenol A bis-(diphenyl phosphate), BAPP	181028-79-5	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i> ^s	<i>L</i>	<i>L</i>	<i>L</i>		<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>H</i>	<i>H</i> ^o
Melamine cyanurate	37640-57-6	<i>L</i>	<i>M</i>	<i>M</i>	<i>M</i> ^s	<i>M</i> ^s	<i>L</i>	<i>H</i>	<i>L</i>		<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>VH</i>	<i>L</i>
Melamine polyphosphate	15541-60-3	<i>L</i>	<i>M</i>	<i>M</i>	<i>L</i> ^s	<i>L</i>	<i>L</i> ^s	<i>M</i>	<i>L</i>		<i>L</i>	<i>VL</i>	<i>L</i>	<i>L</i>	<i>H</i>	<i>L</i>
N-alkoxy hindered amine reaction products	191680-81-6	<i>L</i>	<i>M</i>	<i>L</i>	<i>H</i>	<i>H</i>	<i>L</i>	<i>H</i>	<i>L</i>		<i>L</i>	<i>VL</i>	<i>H</i>	<i>H</i>	<i>H</i>	<i>H</i> ⁺
Phosphonate oligomer	68664-06-2	<i>L</i>	<i>M</i>	<i>L</i> ^s	<i>L</i> [✕]	<i>L</i> [✕]	<i>M</i> ⁺	<i>L</i> ^{*s}	<i>L</i> ^{*s}		<i>M</i> ^{s+}	<i>M</i> ⁺	<i>L</i> [✕]	<i>H</i> ⁺	<i>VH</i>	<i>H</i> ⁺
Polyphosphonate	68664-06-2	<i>L</i>	✕	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>M</i> ^d	<i>L</i>		<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>VH</i>	<i>L</i>
Poly[phosphonate-co-carbonate]	77226-90-5	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>M</i> ^d	<i>L</i>		<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>VH</i>	<i>L</i>
Resorcinol bis-diphenylphosphate	125997-21-9	<i>L</i>	<i>M</i> ^s	<i>L</i>	<i>L</i>	<i>VL</i>	<i>M</i> ^s	<i>M</i>	<i>L</i>		<i>L</i>	<i>VL</i>	<i>VH</i>	<i>H</i> ⁺	<i>M</i>	<i>H</i> ⁺
Inorganic flame retardant alternatives																
Aluminium diethylphosphinate	225789-38-8	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>M</i>	<i>M</i>	<i>L</i>	<i>L</i>		<i>L</i>	<i>VL</i>	<i>M</i>	<i>M</i>	<i>H</i> ^R	<i>L</i>
Aluminium hydroxide	21645-51-2	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>M</i>	<i>L</i>	<i>L</i>		<i>VL</i>	<i>VL</i>	<i>M</i>	<i>M</i>	<i>H</i> ^R	<i>L</i>
Ammonium polyphosphate	68333-79-9	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>M</i> ^d	<i>L</i>		<i>VL</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>VH</i>	<i>L</i>
Antimony trioxide1	1309-64-4	<i>L</i>	<i>L</i> [*]	<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	<i>M</i>	<i>L</i>		<i>L</i>	<i>M</i>	<i>M</i>	<i>M</i>	<i>H</i> ^R	<i>L</i>

Chemical	CAS No	Human Health Effects											Aquatic Toxicity		Environmental Fate	
		Acute toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
Magnesium hydroxide	1309-42-8	L	L	L	L	L	L	L	L		M	M	L	L	H^R	L
Red phosphorus	7723-14-0	VH	L	M	L	L	L	L	L		M	H	L	L	H	L
Zinc borate	1332-07-6	L	L	H	M	M	H	L	L		L	L	H	H	H^R	L

*1 The cited report is a draft for public comment and the front page says "**Do not cite or quote**".

*2 Copied from US EPA, 2008

Notes from the cited report:

VL = Very Low hazard **L** = Low hazard **M** = Moderate hazard **H** = High hazard **VH** = Very High hazard –

Endpoints in coloured text (**VL**, **L**, **M**, **H**, and **VH**) were assigned based on empirical data.

Endpoints in black italics (*VL*, *L*, *M*, *H*, and *VH*) were assigned using values from predictive models and/or professional judgment.

§ Based on analogy to experimental data for a structurally similar compound.

d This hazard designation is driven by potential for lung overloading as a result of dust forming operations.

◆ Different formulations of the commercial product are available. One of these many formulations has an average MW of ~1,600 and contains significant amounts of lower MW components. These lower MW components are primarily unchanged starting materials that have hazard potentials different than the polymeric flame retardant, as follows: VERY HIGH- Estimated potential for bioaccumulation; HIGH-Experimental concern for acute aquatic toxicity; HIGH-Estimated potential for chronic aquatic toxicity; MODERATE Experimental concern for developmental; and MODERATE-Estimated potential for carcinogenicity, genotoxicity, repeated dose, reproductive, and skin and respiratory sensitization toxicity

□ This alternative may contain impurities. These impurities have hazard designations that differ from the flame retardant alternative, Confidential Brominated Polymer, as follows, based on experimental data: HIGH for human health, HIGH for aquatic toxicity, VERY HIGH for bioaccumulation, and VERY HIGH for persistence

T This chemical is subject to testing in an EPA consent order.

‡ The highest hazard designation of any of the oligomers with MW <1,000. 0 The highest hazard designation of a representative component of the oligomeric mixture with MWs <1,000.

¥ Phosphonate Oligomer, with a MW range of 1,000 to 5,000, may contain significant amounts of an impurity, depending on the final product preparation. This impurity has hazard designations that differ from the polymeric flame retardant, as follows: MODERATE-Experimental concern for repeated dose, skin sensitization and eye irritation; and HIGH-Experimental concern for reproductive, developmental, acute aquatic toxicity.

- R Recalcitrant: Substance is comprised of metallic species that will not degrade, but may change oxidation state or undergo complexation processes under environmental conditions.
- * Ongoing studies may result in a change in this endpoint

TABLE 45

SCREENING LEVEL HAZARD SUMMARY FOR NON-HALOGENATED PHOSPHOROUS FLAME RETARDANTS USED IN PRINTED CIRCUIT BOARDS (US EPA, 2014B) *1

Chemical	CAS No	Human Health Effects											Aquatic Toxicity		Environ-mental Fate	
		Acute toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
Reactive Flame-Retardant Chemicals																
Tetrabromobisphenol A	79-94-7	L	M	L	L♦	M	L	L	L♦		M	L♦	VH	H	H	M
DOPO	35948-25-5	L	M	L	L§	M	M	L	M		M	VL	L	M	H	L
Fyrol PMP	63747-58-0	L	L§	L§	M§	M§	M§	M§	L		L	L	H‡	H‡	VH	H‡
Reactive Flame-Retardant Resins																
D.E.R. 500 Series¥	26265-08-7	L	M	M	M	M	M	M	H		M‡	M‡	L	L	VH	H‡
Dow XZ-92547¥	Confidential	L	M‡	M§	M‡	M‡	M‡	M‡	H	M‡	VL	L	L	H	VH	H‡
Additive Flame-Retardant Chemicals																
Aluminum Diethylphosphinate ¥	225789-38-8	L	L§	L	L	M§	M§	M§	L		L	VL	M	M	HR	L
Aluminum Hydroxide ¥	21645-51-2	L	L§	L	L	M§	M§	M§	L		L	VL	M	M	HR	L
Magnesium Hydroxide ¥	1309-42-8	L	L§	L	L	M§	M§	M§	L		L	VL	M	M	HR	L
Melamine Polyphosphate 1 ¥	15541-60-3	L	M	M	H	M	M	M	L		L	VL	L	L	H	L
Silicon Dioxide (amorphous)	7631-86-9	L ^	L ^	L ^	L	L	L§	H ▫	L		L ^	VL	L	L	HR	L

Notes from the cited report:

VL = Very Low hazard L = Low hazard M = Moderate hazard H = High hazard VH = Very High hazard –

Endpoints in coloured text (VL, L, M, H, and VH) were assigned based on empirical data.

Endpoints in black (VL, L, M, H, and VH) were assigned using values from predictive models and/or professional judgement.

♦ TBBPA has been shown to degrade under anaerobic conditions to form bisphenol A (BPA; CASRN 80-05-7). BPA has hazard designations different than TBBPA, as follows: MODERATE (experimental) for reproductive, skin sensitization and dermal irritation.

R Recalcitrant: Substance is comprised of metallic species (or metalloids) that will not degrade, but may change oxidation state or undergo complexation processes under environmental conditions.

§ Based on analogy to experimental data for a structurally similar compound.

□ Concern linked to direct lung effects associated with the inhalation of poorly soluble particles less than 10 microns in diameter.

^ Depending on the grade or purity of amorphous silicon dioxide commercial products, the crystalline form of silicon dioxide may be present. The hazard designations for crystalline silicon dioxide differ from those of amorphous silicon dioxide, as follows: VERY HIGH (experimental) for carcinogenicity; HIGH (experimental) genotoxicity; MODERATE (experimental) for acute toxicity and eye irritation.

¥ Aquatic toxicity: EPA/DfE criteria are based in large part upon water column exposures which may not be adequate for poorly soluble substances such as many flame retardants that may partition to sediment and particulates.

Appendix 2

Modified GreenScreen® Criteria

TABLE 46
MODIFIED GREENSCREEN® CRITERIA FOR HUMAN HEALTH ENDPOINTS

End-point	Information Type	Information Source	List Type	High (H)	Moderate (M)	Low (L)
Carcinogenicity (C)	Data	CLP Criteria & Guidance		CLP Category 1A (Known) or 1B (Presumed) for any route of exposure	CLP Category 2 (Suspected) for any route of exposure or limited or marginal evidence of carcinogenicity in animals (See Guidance)	Adequate data available, and negative studies, no structural alerts, and CLP not classified.
	A Lists	EU CMR (1), harmonised	Authoritative	Category 1 or 2	Category 3	
		EU CMR (2)	Authoritative	Carc 1A or 1B	Carc 2	
		EU H-statements, harmonised	Authoritative	H350 or H350i	H351	
		EU R-phrases	Authoritative	R45 or R49	R40	
		EU SVHC	Authoritative	Reason for inclusion: Carcinogenic		
		IARC	Authoritative	Group 1 or 2A	Group 2B	Group 4
		MAK	Authoritative	Carcinogenic Group 1 or 2	Carcinogenic Group 3, 4, or 5	
		NIOSH-C	Authoritative	Occupational Cancer		
		NTP-RoC	Authoritative	Known or Reasonably Anticipated		
		EPA-C (1986)	Authoritative	Group A, B1 or B2	Group C	Group E
		EPA-C (1996, 1999, 2005)	Authoritative	Known or Likely		Not Likely
	B Lists	EPA-C(1986)	Authoritative	Group D		
		CLP, industry	Screening	Category 1 or 2	Category 3	
		EPA-C (1999)	Authoritative	Suggestive Evidence, but not sufficient to assess human carcinogenic potential		
		EPA-C (2005)	Authoritative	Suggestive evidence of carcinogenic potential		
		IARC	Authoritative	Group 3		

End-point	Information Type	Information Source	List Type	High (H)	Moderate (M)	Low (L)
Mutagenicity/ Genotoxicity (M)	Data	CLP Criteria & Guidance		CLP Category 1A (Known) or 1B (Presumed) for any route of exposure	CLP Category 2 (Suspected) for any route of exposure or limited or marginal evidence of mutagenicity in animals (See Guidance)	Adequate data available and negative studies for both chromosomal aberrations and gene mutations, no structural alerts, and CLP not classified.
	A Lists	EU CMR (1)	Authoritative	Category 1 or 2	Category 3	
		EU CMR (2)	Authoritative	Muta 1A or 1B	Muta 2	
		EU H-statements	Authoritative	H340	H341	
		EU R-phrases	Authoritative	R46	R68	
		EU SVHC	Authoritative	Reason for inclusion: Mutagenic		
	B Lists	MAK	Authoritative	Germ Cell Mutagen 1, 2, or 3a		
		MAK	Authoritative	Germ Cell Mutagen 3b or 5		
Reproductive Toxicity (R)	Data	CLP Criteria & Guidance <i>Note: CLP Reproductive Toxicity includes both reproductive and developmental effects, while the Green Screen separates them into two distinct hazard endpoints. This classification must be based on reproductive effects alone.</i>		CLP Category 1A (Known) or 1B (Presumed) for any route of exposure	CLP Category 2 (Suspected) for any route of exposure or limited or marginal evidence of reproductive toxicity in animals (See Guidance)	Adequate data available, and negative, no structural alerts, and CLP not classified.
	A Lists	EU H-statements	Authoritative	H360F, H360FD, H360Fd	H360Df, H361f, H361fd	
		EU R-phrases	Authoritative	R60	R62	
		NTP-OHAaT	Authoritative	Clear Evidence of Adverse Effects - Reproductive		Clear Evidence of No Adverse Effects - Reproductive
	B Lists	NTP-OHAaT	Authoritative	Limited Evidence of Adverse Effects - Reproductive or Some Evidence of Adverse Effects - Reproductive		
						Limited Evidence of No Adverse Effects - Reproductive or Some

End-point	Information Type	Information Source	List Type	High (H)	Moderate (M)	Low (L)
						Evidence of No Adverse Effects - Reproductive
				Insufficient Evidence for a Conclusion - Reproductive Toxicity		
Developmental Toxicity (D)	Data	CLP Criteria & Guidance <i>Note: CLP Reproductive Toxicity includes both reproductive and developmental effects, while the Green Screen separates them into two distinct hazard endpoints. This classification must be based on developmental effects alone.</i>		CLP Category 1A (Known) or 1B (Presumed) for any route of exposure	CLP Category 2 (Suspected) for any route of exposure or limited or marginal evidence of developmental toxicity in animals (See Guidance)	Adequate data available, and negative, no structural alerts, and CLP not classified.
	A Lists	EU H-statements	Authoritative	H360FD, H360D, H360Df, or H362	H360Fd, H361d, H361fd	
		EU R-phrases	Authoritative	R61 or R64	R63	
		NTP-OHAaT	Authoritative	Clear Evidence of Adverse Effects - Developmental		Clear Evidence of No Adverse Effects - Developmental
		MAK	Authoritative	Pregnancy Risk Group A or B		
						Pregnancy Risk Group C
				Pregnancy Risk Group D		
		NTP-OHAaT	Authoritative	Limited Evidence of Adverse Effects - Developmental or Some Evidence of Adverse Effects - Developmental		
						Limited Evidence of No Adverse Effects - Reproductive or Some Evidence of No Adverse Effects - Developmental
				Insufficient Evidence for a Conclusion - Developmental Toxicity		
Endocrine Activity (E)	Data	EU ED criteria for prioritisation		Evidence of endocrine disrupting activity in at least one species using intact animals (Category 1 criterion for classification on the EU ED priority list)	At least some in vitro evidence of biological activity related to endocrine disruption (Category 2 criterion for classification on EU ED priority list)	No evidence of endocrine disrupting activity (Category 3a criterion for classification on EU ED priority list)

End-point	Information Type	Information Source	List Type	High (H)	Moderate (M)	Low (L)
		OECD Conceptual Framework		Positive results in <i>in vivo</i> tests according to Level 3, 4 and 5 of OECD conceptual framework (ECETOC, 2009)	Positive results in <i>in vitro</i> tests according to Level 2 of OECD conceptual framework (ECETOC, 2009)	Negative results in <i>in vitro</i> tests according to Level 2 of OECD conceptual framework (ECETOC, 2009)
	A Lists	EU ED	Screening			Category 3a
		EU SVHC	Authoritative	Reason for Inclusion: Endocrine Activity		
	B Lists	EU ED	Screening	Category 1 or 2		
				Category 3b		
		SIN	Screening	Reason for Inclusion: Endocrine Disruptor		

1 Classification according to (DSD) Council Directive 67/548/EEC

2 Classification according to (CLP) Regulation (EC) No 1272/2008

End-point	Information Type	Information Source	List Type	Very High (vH)	High (H)	Moderate (M)	Low (L)
Acute Mammalian Toxicity (AT)	Data	CLP Criteria & Guidance		CLP Category 1 or 2 for any route of exposure	CLP Category 3 for any route of exposure	CLP Category 4 for any route of exposure	CLP Category 5 or adequate data available, and negative studies, no structural alerts, and CLP not classified.
		Guidance Values for Animal Data (see CLP for further information)	Oral LD50 (mg/kg)	≤50	>50-300	>300 - 2000	>2000
			Dermal LD50 (mg/kg)	≤200	>200-1000	>1000 - 2000	>2000
			Inhalation-Gas or Vapor LC50(mg/L)	≤2	>2-10	>10 - 20	>20
			Inhalation-Dust/Mist/Fumes LC50 (mg/L)	≤0.5	>0.5-1.0	>1 - 5	>5
	A Lists	EU H-statements	Authoritative	H300, H310, or H330	H301, H311, or H331	H302, H312, or H332	

End-point	Information Type	Information Source		List Type	Very High (vH)	High (H)	Moderate (M)	Low (L)
		EU R-phrases		Authoritative	R26, R27 or R28			
		EU R-phrases		Authoritative		R20, R21, or R22		
Systemic Toxicity/Organ Effects (ST)	Single Exposure	CLP Criteria & Guidance			CLP Category 1 Single Exposure for any route of exposure	CLP Category 2 Single Exposure for any route of exposure	CLP Category 3 Single Exposure for any route of exposure	Adequate data available, and negative studies, no structural alerts, and CLP not classified
		CLP Guidance Values for Animal Data (see CLP for further information)	Oral (mg/kg-bw)		≤300	>300-2000		
			Dermal (mg/kg-bw)		≤1000	>1000-2000		
			Inhalation-Gas or Vapor (mg/L/4h)		≤10	>10-20		
			Inhalation-Dust/Mist/Fumes (mg/L/4h)		≤1.0	>1.0-5.0		
	A Lists	EU H-statements		Authoritative	H370	H371	H335	
		EU R-phrases		Authoritative	R39, R39/23, R39/24, or R39/25, R39/26, R39/27, R39/28	R68/20, R68/21, or R68/22,	R37	
	Repeated* Exposure	CLP Criteria & Guidance				CLP Category 1 Repeated Exposure for any route of exposure	CLP Category 2 Repeated Exposure for any route of exposure	Adequate data available, and negative studies, no structural alerts, and CLP not classified
		CLP Guidance Values for Animal Data (see CLP for further information)	Oral (mg/kg-bw/day)			≤10	>10-100	>100
			Dermal (mg/kg-bw/day)			≤20	>20-200	>200
			Inhalation-Gas or Vapor (mg/L/6h/day)			≤0.2	>0.2-1.0	>1.0
			Inhalation-Dust/Mist/Fumes (mg/L/6h/day)			≤0.02	>0.02-0.2	>0.2
		EU H-statements		Authoritative		H372	H373	

End-point		Information Type	Information Source	List Type	Very High (vH)	High (H)	Moderate (M)	Low (L)	
		A Lists	EU R-phrases	Authoritative		R48/23, R48/24, R48/25	R48/20, R48/21, R48/22		
		B Lists	EU R-phrases	Authoritative		R48 "Danger of serious damage to health by prolonged exposure"			
Neurotoxicity	Single Exposure	Data	CLP Criteria Systemic Toxicity/Organ Effects using US EPA Risk Assessment Guidance to define applicable neurotoxic effects.		CLP Category 1 Single Exposure for any route of exposure	CLP Category 2 Single Exposure for any route of exposure	CLP Category 3 Single Exposure for any route of exposure	Adequate data available, and negative studies, no structural alerts, and CLP not classified	
		A-Lists	CLP, industry	Screening	Category 1	Category 2	Category 3	"Not Classified"	
	Repeated*	Data	CLP Criteria Systemic Toxicity/Organ Effects using US EPA Risk Assessment Guidance to define applicable neurotoxic effects.			CLP Category 1 Repeated Exposure for any route of exposure	CLP Category 2 Repeated Exposure for any route of exposure	Adequate data available, and negative studies, no structural alerts, and CLP not classified	
		A Lists	CLP, industry	Screening		Category 1	Category 2	"Not Classified"	
	Both	B Lists	EU H-statements	Authoritative			H336		
		B Lists	EU R-phrases	Authoritative			R67		
Skin Sensitization	Data	GHS Criteria & Guidance			GHS Category 1A (high frequency of occurrence)	GHS Category 1B (low to moderate frequency of occurrence)		Adequate data available, and negative studies, no structural alerts, and GHS not classified.	
	A Lists	CLP, industry	Screening		Category 1A	Category 1B		"Not Classified"	
		MAK	Authoritative		Sensitizing Substances Sh (Skin) or Sah (Respiratory and Skin)				
	B Lists	EU H-statements	Authoritative		H317				
		EU R-phrases	Authoritative		R43				

End-point	Information Type	Information Source	List Type	Very High (vH)	High (H)	Moderate (M)	Low (L)
Respiratory Sensitization (SnR*)	Data	GHS Criteria & Guidance			GHS Category 1A (high frequency of occurrence)	GHS Category 1B (low to moderate frequency of occurrence)	Adequate data available, and negative studies, no structural alerts, and GHS not classified.
	A Lists	CLP, industry	Screening		Category 1A	Category 1B	"Not Classified"
		MAK	Authoritative		Sensitizing Substances Sa (Respiratory) or Sah (Respiratory and Skin)		
	B Lists	AOEC	Authoritative		Asthmagen (G)		
					Asthmagen (Rr) and/ or (Rs) and/or (Rrs)		
		EU H-statements	Authoritative		H334		
		EU R-phrases	Authoritative		R42		
Skin Irritation (IrS)	Data	GHS Criteria & Guidance		GHS Category 1 (Corrosive)	GHS Category 2 (Irritant)	GHS Category 3 (Mild irritant)	Adequate data available, and negative studies, no structural alerts, and GHS not classified.
		EU H-statements	Authoritative	H314	H315		
		EU R-phrases	Authoritative	R34 or R35	R38		
		CLP, industry	Screening	Category 1	Category 2	Category 3	"Not Classified"
Eye Irritation (IrE)	Data	GHS Criteria & Guidance		GHS Category 1 (Irreversible)	GHS Category 2A (Irritating)	GHS Category 2B (Mildly irritating)	Adequate data available, and negative studies, no structural alerts, and GHS not classified.
	A Lists	EU H-statements	Authoritative	H318	H319	H320	
		EU R-phrases	Authoritative	R41			
		CLP, industry	Screening	Category 1	Category 2A	Category 2B	"Not Classified"
	B Lists	EU R-phrases	Authoritative		R36		

TABLE 47
MODIFIED GREENSCREEN® CRITERIA FOR ENVIRONMENTAL ENDPOINTS

End-point	Information Type	Information Source		List Type	Very High (VH)	High (H)	Moderate (M)	Low (L)	Very Low (VL)
Acute Aquatic Toxicity (AA)	Data	GHS Criteria & Guidance			GHS Category 1	GHS Category 2	GHS Category 3	Sufficient data available and not classified	
		<i>Guidance Values (see GHS for further information)</i>	LC50 or EC50 (mg/L)		≤1	>1 to 10	> 10 to 100	>100	
	A Lists	EU H-statements		Authoritative	H400	H401	H402		
		EU R-phrases		Authoritative	R50	R51	R52		
		CLP (Harmonised; EU)		Authoritative	Category 1	Category 2	Category 3	"Not Classified"	
	B Lists	CLP (Industry classifications)		Screening	Category 1	Category 2	Category 3	"Not Classified"	
	Chronic Aquatic Toxicity (CA)	Data	GHS Criteria & Guidance					GHS Category 4	
		Guidance Value (mg/L)			≤0.1	>0.1 to 1.0	> 1.0 to 10	>10	
A Lists		EU H-statements		Authoritative	H410	H411	H412 or H413		
		EU R-phrases		Authoritative	R50/53	R51/53	R52/53 or R53		
		CLP (Harmonised; EU)		Authoritative	Category 1	Category 2	Category 3	"Not Classified"	
B Lists		CLP (Industry classifications)		Screening	Category 1	Category 2	Category 3	"Not Classified"	
Persistence (P)		Data	Soil or Sediment			>180 or recalcitrant	>60 to 180	16 to 60	< 16 OR GHS “Rapid degradability”
	<i>(1/2 life in days OR Result)</i>								
	Water			> 60 or recalcitrant	> 40 to 60	16 to 40	< 16 OR GHS “Rapid degradability”	Meets 10-day window in “Ready Bio-degradation Test”	
	<i>(1/2 life in days OR Result)</i>								
	Air			> 5 or recalcitrant	>2 to 5	< 2			

End-point	Information Type	Information Source	List Type	Very High (VH)	High (H)	Moderate (M)	Low (L)	Very Low (VL)
Bioaccumulation Potential (B)		<i>(1/2 life in days OR Result)</i>						
		Long-Range Environmental Transport			Evidence	Suggestive Evidence		
	Data	BAF (Bioaccumulation Factor)		> 5000	> 2000 to 5000	> 500 to 2000	> 100 to 500	≤ 100
		BCF (Bioconcentration Factor)		> 5000	> 2000 to 5000	> 500 to 2000	> 100 to 500	≤ 100
		Log Kow (<i>Log octanol-water partition coefficient</i>)		> 5.0*	> 4.5 to 5.0	> 4.0 to 4.5	>3.0 to 4.0	≤ 3
		Monitoring Data (<i>Presence in humans or wildlife</i>)			Evidence	Suggestive Evidence		

Remark on bioaccumulation: It should be noted that at very high Log Kow's (i.e. higher than about 7-8) the correlation between Log Kow and BCF is not valid. Thus, in its guidance for PBT assessment ECHA (2012) considers it unlikely that the B-criterion should be fulfilled for substances with Log Kow higher than 10.

Appendix 3

GreenScreen™ for Safer Chemicals - Definitions and Specified Lists

List Type		Definition	Can you modify results?	Level of Confidence
1. Authoritative Lists		Authoritative lists are those developed by governmental bodies or government recognized expert bodies and include chemicals listed based on results from expert review of test data and scientific literature.		
	Authoritative A	Each category in the list translates directly to a single level of concern for a single Green Screen hazard endpoint, or a single benchmark. The assigned hazard level cannot be modified using additional data.	NO	High
	Authoritative B	Lists that meet one or more of the following: 1) Each category in the list incorporates a single Green Screen hazard endpoint and does not translate directly to a single level of concern or benchmark; AND/OR 2) Each category in the list refers to more than one Green Screen hazard endpoint. When the range of hazard levels or benchmark levels is narrow, an initial default level of concern may be assigned and may be modified with additional data. When the range is broad, the default hazard level or benchmark is assigned as "unspecified (U)".	YES	High
2. Screening Lists		Screening lists are either 1) lists developed by authoritative bodies to target chemicals for additional scrutiny and testing and are often generated by models or screening tests; or they are 2) lists developed by non governmental bodies or experts not sanctioned by government.		
	Screening A	Each category in the list translates directly to a single level of concern for a single Green Screen hazard endpoint, or a single benchmark. The reviewer may modify the level based on weight of evidence.	YES	Low
	Screening B	Lists that meet one or more of the following: 1) Each category in the list incorporates a single Green Screen hazard endpoint and does not translate directly to a single level of concern or benchmark; AND/OR 2) Each category in the list refers to more than one Green Screen hazard endpoint. When the range of hazard levels or benchmark levels is narrow, an initial default level of concern may be assigned and may be modified with additional data. When the range is broad, the default hazard level or benchmark is assigned as "unspecified (U)".	YES	Low

GreenScreen™ for Safer Chemicals

Specified Lists

Modified by COWI, 3 September 2015

ID	Abbreviation	CPA List Type	Listed in DfE	List Name	Associated Green Screen Hazard Endpoints	URL and/or Reference
1	AOEC	Authoritative	Yes	Association of Occupational and Environmental Clinics (AOEC) Exposure Code List	Sensitization (respiratory including asthma)	http://www.aocedata.org/ExpCodeLookup.aspx (accessed 9/14/11)
4	DOT	Authoritative	No	US Department of Transportation Hazardous Materials Regulations	Acute Mammalian Toxicity, Irritation/Corrosivity, Flammability, Reactivity	[Chemicals Listed with Classification-49CFR 172.101] http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=4011663bcc8928d7775c0b077a36470e&rgn=div8&view=text&node=49:2.1.1.3.8.2.25.1&idno=49 (accessed 9/19/11); [Classification Criteria-49CFR 173] http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=/ecfrbrowse/Title49/49cfr173_main_02.tpl (accessed 9/14/11); http://environmentalchemistry.com/yogi/hazmat/placards/ (accessed 9/19/11)
7	EPA - C	Authoritative	Yes	US Environmental Protection Agency (EPA), National Center for Environmental Assessment, Integrated Risk Information System (IRIS) Database	Carcinogenicity	[Search for Cancer Categorization] http://www.epa.gov/ncea/iris/search_human.htm (accessed 9/14/11); [IRIS Database] http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList (accessed 9/14/11)
8	EU CMR (1)	Authoritative	Yes	Regulation on the Classification, Labelling and Packaging of Substances and Mixtures (CLP), EC 1272/2008 and subsequent amendments. Originally published in ECB, Annex I of Directive 67-548-EEC and subsequent amendments/adaptations, known as the Dangerous Substances Directive (DSD) or Directive on Dangerous Substances (DDS).	Carcinogenicity, Mutagenicity/Genotoxicity, Reproductive Toxicity, Developmental Toxicity	[CLP] http://ec.europa.eu/enterprise/sectors/chemicals/classification/index_en.htm (accessed 9/14/11); [DSD] http://ec.europa.eu/environment/chemicals/dansub/home_en.htm (accessed 9/14/11)
9	EU CMR (2)	Authoritative	Yes	Regulation on the Classification, Labelling and Packaging of Substances and Mixtures (CLP), EC 1272/2008 and subsequent	Carcinogenicity, Mutagenicity/Genotoxicity, Reproductive Toxicity, Developmental Toxicity	[CLP] http://ec.europa.eu/enterprise/sectors/chemicals/classification/index_en.htm (accessed 9/14/11)

GreenScreen™ for Safer Chemicals

Specified Lists

Modified by COWI, 3 September 2015

ID	Abbreviation	CPA List Type	Listed in DfE	List Name	Associated Green Screen Hazard Endpoints	URL and/or Reference
				amendments. [Conversion of CMR list from 67-548- EEC(Categories 1-3) to GHS Categories (Category 1A, 1B, 2)]		
10	EU ED	Screening	No	European Union Priority List of suspected endocrine disruptors (prioritized for further testing). Chemicals prioritized by the European Union for testing for endocrine disruption. DHI. 2007. Study on Enhancing the Endocrine Disruptor Priority List with a Focus on Low Production Volume Chemicals.	Potential Endocrine Disruptor	[Website] http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#priority_list (accessed 9/14/11); [Report] http://ec.europa.eu/environment/endocrine/documents/final_report_2007.pdf (accessed 9/23/11)
11	EU H-Statements	Authoritative	Yes	European Union List of Chemicals and their assigned GHS Hazard Statement is included in the Regulation on the Classification, Labelling and Packaging of Substances and Mixtures (CLP), EC 1272/2008 and subsequent amendments.	Carcinogenicity, Mutagenicity/Genotoxicity, Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, Systemic Toxicity/Organ Effects, Neurotoxicity, Sensitization, Irritation/Corrosivity, Flammability, Reactivity, Acute Aquatic Toxicity, Chronic Aquatic Toxicity, Ecotoxicity	[CLP] http://ec.europa.eu/enterprise/sectors/chemicals/classification/index_en.htm (accessed 8/1/11) [ESIS Database-CLP/GHS] http://esis.jrc.ec.europa.eu/index.php?PGM=cla (accessed 10/4/11)
12	EU PBT	Authoritative	No	European Union, European Chemicals Bureau, European Chemical Substances Information System (ESIS) PBT list	PBT and vPvB: Persistence, Bioaccumulation and any of the following: ecotox and/or human tox	[ESIS Database-PBT] http://esis.jrc.ec.europa.eu/index.php?PGM=pbt (accessed 9/14/11)
13	EU R-Phrases	Authoritative	Yes	EU Risk-Phrases published in the Regulation on the Classification, Labelling and Packaging of Substances and Mixtures (CLP), EC 1272/2008 and subsequent amendments. Originally published in ECB, Annex	Carcinogenicity, Mutagenicity/Genotoxicity, Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, Systemic Toxicity/Organ Effects, Neurotoxicity, Sensitization, Irritation/Corrosivity, Flammability	[CLP] http://ec.europa.eu/enterprise/sectors/chemicals/classification/index_en.htm (accessed 9/14/11); [DSD] http://ec.europa.eu/environment/chemicals/dansub/home_en.htm (accessed 9/14/11)

GreenScreen™ for Safer Chemicals Specified Lists Modified by COWI, 3 September 2015						
ID	Abbreviation	CPA List Type	Listed in DfE	List Name	Associated Green Screen Hazard Endpoints	URL and/or Reference
				I of Directive 67-548-EEC and subsequent amendments/adaptations, known as the Dangerous Substances Directive (DSD) or Directive on Dangerous Substances (DDS).	bility, Reactivity, Acute Aquatic Toxicity, Chronic Aquatic Toxicity, Ecotoxicity	
14	EU SVHC	Authoritative	No	European Union Substances of Very High Concern Authorization List (Note: Inclusion of the Candidate List to be determined.)	Carcinogenicity; Mutagenicity/Genotoxicity; Reproductive Toxicity; Developmental Toxicity; PBT: Persistence, Bioaccumulation, and ecotoxicity and/or human toxicity; vPvB: very persistent and very bioaccumulative, other serious concerns (e.g. Endocrine Activity)	http://echa.europa.eu/consultations/authorisation/svhc/svhc_cons_en.asp (accessed 9/14/11)
16	IARC	Authoritative	Yes	International Agency for Research on Cancer (IARC), Agents Reviewed by the IARC Monographs	Carcinogenicity	[List of Classifications] http://monographs.iarc.fr/ENG/Classification/index.php (accessed 9/14/11); [Monographs] http://monographs.iarc.fr/ (accessed 9/14/11)
17	MAK	Authoritative	No	MAK Commission of Germany; Occupational Toxicants and MAK Values: Annual Thresholds and Classifications for the Workplace	Carcinogenicity, Reproductive and Developmental Toxicity including Developmental Neurotoxicity, Sensitization	[DFG Working Group Chairs] http://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/structure/working_groups/derivation_mak/index.html (accessed 10/4/11) 1) Professor Dr. Andrea Hartwig Karlsruher Institut für Technologie (KIT): (andrea.hartwig@kit.edu, phone: +49 721 608 47645) 2) Prof. Dr. med. Hans Drexler, Universität Erlangen-Nürnberg: (Hans.Drexler@ipasum.uni-erlangen.de, phone: +49 9131 85-22312); [Publication] List of MAK and BAT Values 2011: Maximum Concentrations and Biological Tolerance Values at the Workplace, Report 47 Deutsche Forschungsgemeinschaft (DFG) (Editor) ISBN: 978-3-527-33061-4 Paperback; 292 pages; December 2011 [Purchase from Wiley] http://www.wiley.com/WileyCDA/WileyTitle/productCd-

GreenScreen™ for Safer Chemicals Specified Lists Modified by COWI, 3 September 2015						
ID	Abbreviation	CPA List Type	Listed in DfE	List Name	Associated Green Screen Hazard Endpoints	URL and/or Reference
						3527330615.html (accessed 9/23/11)
18	NIOSH-C	Authoritative	Yes	National Institute of Occupational Safety and Health Carcinogen List	Carcinogenicity	http://www.cdc.gov/niosh/topics/cancer/npotocca.html (accessed 9/19/11)
26	Stockholm	Authoritative	No	United Nations Environment Programme (UNEP), Stockholm Convention Secretariat Stockholm Convention on Persistent Organic Pollutants (POPs)	Persistence, Bioaccumulation and any of the following: ecotox and/or human tox	http://chm.pops.int/Convention/ThePOPs/tabid/673/language/en-US/Default.aspx (accessed 9/19/11)
28	TRI PBT	Authoritative	No	US Environmental Protection Agency (EPA), Toxics Release Inventory (TRI) Program, "TRI PBT Chemical List"	Persistence, Bioaccumulation, Acute Aquatic Toxicity	http://www.epa.gov/tri/trichemicals/pbt%20chemicals/pbt_chem_list.htm (accessed 9/19/11)
35	SIN	Screening	No	International Chemical Secretariat (ChemSec) Substitute it Now (SIN) List; SIN List 2.0 Available 2011	Carcinogenicity; Mutagenicity/Genotoxicity; Reproductive Toxicity; Developmental Toxicity; PBT: Persistence, Bioaccumulation, and ecotoxicity and/or human toxicity; vPvB: very persistent and very bioaccumulative, other serious concerns (e.g. Endocrine Activity)	http://www.chemsec.org/list/sin-database (accessed 9/19/11)
36	VwVwS	Screening	No	German Federal Environment Agency, Administrative Regulation on the Classification of Substances hazardous to waters into Water Hazard Classes (Verwaltungsvorschrift wassergefährdende Stoffe - VwVwS)	Any combination of the following: Acute Toxicity, Systemic Toxicity/Organ Effects, Carcinogenicity, Reproductive Toxicity, Developmental Toxicity, Acute Aquatic Toxicity, Chronic Aquatic Toxicity, Persistence, Bioaccumulation. Any combination results in Classification of 0-3.	[Database of Chemicals and Classifications] http://webriqoletto.uba.de/rigoletto/public/searchRequest.do?sessionId=88A1AE1DEE0223CFE7DD76B71FE35F67?event=request (accessed 9/19/11); [Information] http://webriqoletto.uba.de/rigoletto/public/downloadShow.do?event=show&rubric=5 ; http://www.umweltbundesamt.de/wgs-e/wgs-down.htm#a1-2 (accessed 9/19/11);

1 Classification according to (DSD) Council Directive 67/548/EEC

* Note: The Green Screen List of Lists includes all publically accessible published lists of chemicals classified using the Globally Harmonized System of Classification and Labeling and published by an authoritative governmental organization of a country. Country-specific GHS lists may be published by specifying GHS Categories or GHS H- statements for a group of chemicals. As of July 2011, the countries with published lists include the European Union, Japan, Korea, and New Zealand.

Appendix 4

GreenScreen™ for List Translator – Benchmark 1 only + Possible Benchmark 1

GreenScreen™ List Translator Benchmark 1 Lists Only Modified by COWI, 3 September 2015								
GreenScreen® Supporting List Information			GreenScreen® List Translator					
ID	List	List Category	Green Screen Hazard	List Type	A or B	Hazard Range	Display in Hazard Box (See Notes)	Benchmark Score
20	EPA-C	(1986) Group A - Human Carcinogen	Carcinogenicity	Authoritative	A	H	H	1
21	EPA-C	(1986) Group B1 - Probably human carcinogen	Carcinogenicity	Authoritative	A	H	H	1
22	EPA-C	(1986) Group B2 - Probably human carcinogen	Carcinogenicity	Authoritative	A	H	H	1
23	EPA-C	(1996) Known/likely human carcinogen	Carcinogenicity	Authoritative	A	H	H	1
24	EPA-C	(1999, 2005) Carcinogenic to humans	Carcinogenicity	Authoritative	A	H	H	1
25	EPA-C	(1999, 2005) Likely to be carcinogenic to humans	Carcinogenicity	Authoritative	A	H	H	1
32	EU CMR (1)	Carcinogen Category 1: "known"	Carcinogenicity	Authoritative	A	H	H	1
33	EU CMR (1)	Carcinogen Category 2: "should be considered carcinogenic to humans"	Carcinogenicity	Authoritative	A	H	H	1
34	EU CMR (1)	Mutagen Category 1: "Substances known to be mutagenic to man"	Mutagenicity/Genotoxicity	Authoritative	A	H	H	1
35	EU CMR (1)	Mutagen Category 2: "Substances which should be regarded as if they are mutagenic to"	Mutagenicity/Genotoxicity	Authoritative	A	H	H	1

GreenScreen™ List Translator
Benchmark 1 Lists Only
Modified by COWI, 3 September 2015

GreenScreen® Supporting List Information			GreenScreen® List Translator					
ID	List	List Category	Green Screen Hazard	List Type	A or B	Hazard Range	Display in Hazard Box (See Notes)	Benchmark Score
		man"		tive				
38	EU CMR (2)	Carc 1A	Carcinogenicity	Authorita-tive	A	H	H	1
39	EU CMR (2)	Carc 1B	Carcinogenicity	Authorita-tive	A	H	H	1
40	EU CMR (2)	Muta 1A	Mutagenicity/Genotoxicity	Authorita-tive	A	H	H	1
41	EU CMR (2)	Muta 1B	Mutagenicity/Genotoxicity	Authorita-tive	A	H	H	1
48	EU H-statem	H360D "May damage the un-born child."	Developmental Toxicity	Authorita-tive	A	H	H	1
49	EU H-statem	H360FD "May damage fertility. May damage the unborn child."	Developmental Toxicity	Authorita-tive	A	H	H	1
50	EU H-statem	H360Df "May damage the unborn child. Suspected of damaging fertility."	Developmental Toxicity	Authorita-tive	A	H	H	1
54	EU H-statem	H350 "May cause cancer "	Carcinogenicity	Authorita-tive	A	H	H	1
55	EU H-statem	H350i "May cause cancer by inhalation"	Carcinogenicity	Authorita-tive	A	H	H	1
78	EU H-statem	H340 "May cause genetic de-fects "	Mutagenicity/Genotoxicity	Authorita-tive	A	H	H	1
88	EU H-statem	H362 "May cause harm to breast-fed children."	Developmental Toxicity	Authorita-tive	A	H	H	1
89	EU H-statem	H360F "May damage fertility."	Reproductive Toxicity	Authorita-tive	A	H	H	1
		H360FD "May damage fertility.						

GreenScreen™ List Translator Benchmark 1 Lists Only Modified by COWI, 3 September 2015								
GreenScreen® Supporting List Information			GreenScreen® List Translator					
ID	List	List Category	Green Screen Hazard	List Type	A or B	Hazard Range	Display in Hazard Box (See Notes)	Benchmark Score
90	EU H-statem	May damage the unborn child."	Reproductive Toxicity	Authoritative	A	H	H	1
91	EU H-statem	H360Fd "May damage fertility. Suspected of damaging the unborn child."	Reproductive Toxicity	Authoritative	A	H	H	1
96	EU R-phrases	R45 "May cause cancer"	Carcinogenicity	Authoritative	A	H	H	1
118	EU R-phrases	R49 "May cause cancer by inhalation"	Carcinogenicity	Authoritative	A	H	H	1
122	EU R-phrases	R46 "May cause heritable genetic damage"	Mutagenicity/Genotoxicity	Authoritative	A	H	H	1
137	EU R-phrases	R60 "May impair fertility"	Reproductive Toxicity	Authoritative	A	H	H	1
138	EU R-phrases	R61 "May cause harm to the unborn child"	Developmental Toxicity	Authoritative	A	H	H	1
142	EU R-phrases	R64 "May cause harm to breastfed babies"	Developmental Toxicity	Authoritative	A	H	H	1
148	EU SVHC	Reason for inclusion: Carcinogenic	Carcinogenicity	Authoritative	A	H	H	1
149	EU SVHC	Reason for inclusion: Mutagenic	Mutagenicity/Genotoxicity	Authoritative	A	H	H	1
150	EU SVHC	Reason for Inclusion: Other concern - Endocrine Activity	Endocrine Activity	Authoritative	A	H	H	1
153	IARC	Group 1: Agent is carcinogenic to humans	Carcinogenicity	Authoritative	A	H	H	1

GreenScreen™ List Translator Benchmark 1 Lists Only Modified by COWI, 3 September 2015								
GreenScreen® Supporting List Information			GreenScreen® List Translator					
ID	List	List Category	Green Screen Hazard	List Type	A or B	Hazard Range	Display in Hazard Box (See Notes)	Benchmark Score
154	IARC	Group 2A: Agent is probably carcinogenic to humans	Carcinogenicity	Authoritative	A	H	H	1
158	MAK	Carcinogenic Group 1	Carcinogenicity	Authoritative	A	H	H	1
159	MAK	Carcinogenic Group 2	Carcinogenicity	Authoritative	A	H	H	1
174	NIOSH-C	Occupational Cancer	Carcinogenicity	Authoritative	A	H	H	1
8	Stockholm	POP	PBT [Persistence, Bioaccumulation and any of the following: Ecotoxicity and/or Human Toxicity (Human Health Effects)]	Authoritative	A	U	Mult*	1
9	WA PBT	PBT	PBT [Persistence, Bioaccumulation and any of the following: Ecotoxicity and/or Human Toxicity (Human Health Effects)]	Screening	A	U	<i>Mult*</i>	1
10	EPA PBT	PBT	PBT [Persistence, Bioaccumulation and any of the following: Ecotoxicity, Carcinogenicity, Mutagenicity, Reproductive Toxicity, Developmental Toxicity, Neurotoxicity, Other chronic effects, or effects from site releases]	Authoritative	A	U	Mult*	1
11	EU PBT	PBT	PBT [Persistence, Bioaccumulation and any of the following: Ecotoxicity and/or Human Toxicity (Human Health Effects)]	Authoritative	A	U	Mult*	1
11.5	EU PBT	POP	Persistent Organic Pollutant [Persistence, Bioaccumulation and any of the following: Ecotoxicity and/or Human Toxicity (Human Health Effects)]	Authoritative	A	U	Mult*	1
12	TRI PBT	PBT	PBT [Persistence, Bioaccumulation, and Acute Aquatic Toxicity]	Authoritative	A	U	Mult*	1
13	OSPAR	PBT	PBT [Persistence, Bioaccumulation, and any of the following: Acute Aquatic Toxicity, Chronic Aquatic Toxicity, Carcinogenicity, Mutagenicity, Reproductive Toxicity, Developmental Toxicity, Systemic Toxicity/Organ Effects repeated exposure]	Authoritative	A	U	Mult*	1
			PBT [Persistence, Bioaccumulation, and any of the following:					

GreenScreen™ List Translator Benchmark 1 Lists Only Modified by COWI, 3 September 2015								
GreenScreen® Supporting List Information			GreenScreen® List Translator					
ID	List	List Category	Green Screen Hazard	List Type	A or B	Hazard Range	Display in Hazard Box (See Notes)	Benchmark Score
14	EU SVHC	Reason for Concern: PBT	Acute Aquatic Toxicity, Chronic Aquatic Toxicity, Carcinogenicity, Mutagenicity, Reproductive Toxicity, Developmental Toxicity]	Authoritative	A	U	Mult*	1
20	EU CMR (2)	Repr 1A	Reproductive and/or Developmental Toxicity	Authoritative	B	H (R and/or D)	<i>Mult*</i>	1
21	EU CMR (2)	Repr 1B	Reproductive and/or Developmental Toxicity	Authoritative	B	H (R and/or D)	<i>Mult*</i>	1
22	EU CMR (1)	Reproduction Category 1: "known" to impair fertility in humans or cause developmental toxicity in humans"	Reproductive and/or Developmental Toxicity	Authoritative	B	H (R and/or D)	<i>Mult*</i>	1
23	EU CMR (1)	Reproduction Category 2: "should be regarded as if" they impair fertility to humans or cause developmental toxicity to humans"	Reproductive and/or Developmental Toxicity	Authoritative	B	H (R and/or D)	<i>Mult*</i>	1
24	EU SVHC	Reason for inclusion: Toxic for reproduction	Reproductive and/or Developmental Toxicity	Authoritative	B	H (R and/or D)	<i>Mult*</i>	1
25	EU H-statement	H360 (with any combo of letters or no letters) "May damage fertility or the unborn child <state specific effect if known > <state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard"	Reproductive and/or Developmental Toxicity	Screening	B	H (R and/or D)	<i>Mult*</i>	1

GreenScreen™ List Translator Benchmark 1 Lists Only Modified by COWI, 3 September 2015								
GreenScreen® Supporting List Information			GreenScreen® List Translator					
ID	List	List Category	Green Screen Hazard	List Type	A or B	Hazard Range	Display in Hazard Box (See Notes)	Benchmark Score
38	EU PBT	vPvB	vPvB [Persistence, Bioaccumulation]	Authoritative	A	U	Mult*	1
39	EU SVHC	Reason for Concern: vPvB	vPvB [Persistence, Bioaccumulation]	Authoritative	A	U	Mult*	1
40	SIN	CMR	One or more of the following: Carcinogenicity, Mutagenicity, Reproductive Toxicity, Developmental Toxicity.	Screening	A	U	<i>Mult*</i>	1
41	SIN	PBT	PBT [Persistence, Bioaccumulation and any of the following: Ecotoxicity and/or Human Toxicity (Human Health Effects)]	Screening	A	U	<i>Mult*</i>	1
42	SIN	vPvB	Persistence and Bioaccumulation	Screening	A	U	<i>Mult*</i>	1

1 Classification according to (DSD) Council Directive 67/548/EEC

2 Classification according to (CLP) Regulation (EC) No 1272/2008

GreenScreen™ List Translator Possible Benchmark 1 (Benchmark 1 or 2 Lists Only) Modified by COWI, 3 September 2015								
GreenScreen® Supporting List Information			GreenScreen® List Translator					
ID	List	List Category	Green Screen Hazard	List Type	A or B	Hazard Range	Display in Hazard Box (See Notes)	Benchmark Score
45	EU ED	Category 1 (“at least one in-vivo study providing <i>clear evidence</i> for endocrine disruption in at least one species using intact animals”),	Endocrine Activity	Screening	B	H or M	<i>H or M (3)</i>	Possible BM 1
46	EU ED	Category 2 (“Potential for endocrine disruption. <i>In-vitro</i> data indicating potential for endocrine disruption in intact organisms. Also includes effects <i>in-vivo</i> that may, or may not, be ED- mediated.”)	Endocrine Activity	Screening	B	H or M	<i>H or M (3)</i>	Possible BM 1
161	MAK	Germ Cell Mutagen 2	Mutagenicity/Genotoxicity	Authoritative	B	H or M	<i>H or M (3)</i>	Possible BM 1
162	MAK	Germ Cell Mutagen 3a	Mutagenicity/Genotoxicity	Authoritative	B	H or M	<i>H or M (3)</i>	Possible BM 1
165	MAK	Pregnancy Risk Group A	Developmental Toxicity	Authoritative	B	H or M	<i>H or M (3)</i>	Possible BM 1
166	MAK	Pregnancy Risk Group B	Developmental Toxicity	Authoritative	B	H or M	<i>H or M (3)</i>	Possible BM 1
196	SIN	Reason for Inclusion: Endocrine Disruptor	Endocrine Activity	Screening	B	H or M	<i>H or M (3)</i>	Possible BM 1
197	TEDX	Listed on the TEDX List of Potential Endocrine Disruptors	Endocrine Activity	Screening	B	H or M	<i>H or M (3)</i>	Possible BM 1
31	EU R-phrases	R50/53 "Very Toxic to Aquatic Organisms, May cause long-term adverse effects in the aquatic environment"	T & P and/or B [Chronic Aquatic Toxicity and sometimes Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	Authoritative	B	U	<i>Mult*</i>	Possible BM 1
32	EU R-phrases	R51/53 Toxic to Aquatic Organisms, May cause long-term adverse effects in the aquatic environment	T & P and/or B [Chronic Aquatic Toxicity and sometimes Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	Authoritative	B	U	<i>Mult*</i>	Possible BM 1

GreenScreen™ List Translator Possible Benchmark 1 (Benchmark 1 or 2 Lists Only) Modified by COWI, 3 September 2015								
GreenScreen® Supporting List Information			GreenScreen® List Translator					
ID	List	List Category	Green Screen Hazard	List Type	A or B	Hazard Range	Display in Hazard Box (See Notes)	Benchmark Score
33	EU H-statement	H410 "Very toxic to aquatic life with long lasting effects."	T & P and/or B [(Chronic Aquatic Toxicity and sometimes Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	Screening	B	U	<i>Mult*</i>	Possible BM 1
34	EU H-statement	H411 "Toxic to aquatic life with long lasting effects."	T & P and/or B [(Chronic Aquatic Toxicity and sometimes Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	Screening	B	U	<i>Mult*</i>	Possible BM 1
44	VwVwS	Class 2-"hazard to waters"	Any combination of the following: Acute Mammalian Toxicity, Systemic Toxicity/Organ Effects, Carcinogenicity, Reproductive Toxicity, Developmental Toxicity, Acute Aquatic Toxicity, Chronic Aquatic Toxicity, Persistence, Bioaccumulation.	Screening	B	U	<i>Mult*</i>	Possible BM 1
45	VwVwS	Class 3-"severe hazard to waters"	Any combination of the following: Acute Mammalian Toxicity, Systemic Toxicity/Organ Effects, Carcinogenicity, Reproductive Toxicity, Developmental Toxicity, Acute Aquatic Toxicity, Chronic Aquatic Toxicity, Persistence, Bioaccumulation.	Screening	B	U	<i>Mult*</i>	Possible BM 1
160	MAK	Germ Cell Mutagen 1	Mutagenicity/Genotoxicity	Authoritative	B	H or M	<i>H or M (3)</i>	Possible BM 1

Appendix 5

Phenol, isobutyleneated, phosphate, CAS No. 68937-40-6

NOTE: Data from REACH registration dossiers are mostly on commercial substances such as Phosflex, Furquel etc.. According to REACH registration, phenol, isobutyleneated, phosphate is made up of four different constituents: p-t-butylphenyl diphenyl phosphate, bis(p-t-butylphenyl) phenyl phosphate, tris(p-tert-butylphenyl) phosphate and triphenyl phosphate.

Regarding the data from Brooke et al. 2009 it is stated that the assessment covers the commercial substances tertbutylphenyl diphenyl phosphate (CAS No. 56803-37-3/EC no. 260-391-0) and Phenol, isobutyleneated, phosphate (3:1) (Cas no. 68937-40-6/EC no. 273-065-8). It is furthermore stated in Brooke et al. (2009) that CAS No. 220352-35-2 (butylated triphenyl phosphate) is also used by European suppliers of this substance, although this is not listed on the European Inventory of Existing Commercial Chemical Substances (EINECS). Akzo Nobel data is for Butylated triphenyl phosphate (CAS No. 220352-35-2) and t-butylphenyl diphenyl phosphate is mentioned as a synonym.

A notified classification is available for Phenol, isobutyleneated, phosphate (3:1); Aquatic Chronic 1 (H410; 1 notifier) and Aquatic Chronic 3 (H412; 1 notifier).

Phenol, isobutyleneated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0			
Property/Endpoint	Data	Reference	Comments
Physical/chemical properties			
Melting Point (°C)	- 21 °C (for tertbutylphenyl diphenyl phosphate) (measured)	REACH registration data; Brooke et al. 2009.	Reported in a secondary source. Reliable, however, data is for tertbutylphenyl diphenyl phosphate (EC no. 260-391-0) Melting point is reported as pouring point.
Boiling Point (°C)	260-420 °C for commercial products of tertbutylphenyl diphenyl phosphate (measured)	Brooke et. al. 2009	Reported in a secondary source (review)
	> 400 °C for the commercial product Phosflex 61B (t-Butylated triphenyl phosphate ester) (measured)	REACH registration data	Reported in a secondary source. Experimental value, reliable (standardised guidelines)
Vapour Pressure (Pa)	3.24 x 10 ⁻⁴ Pa at 20 °C for the commercial product Phosflex 71B (t-Butylated diphenyl phosphate) (measured)	REACH registration data	Reported in a secondary source. Experimental value, reliable (standardised guidelines, GLP compliance)
	4.2 x 10 ⁻⁵ Pa at 25 °C (specific test compound not specified,	REACH registration data	Reported in a secondary source. Experi-

Phenol, isobutyleneated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0			
Property/Endpoint	Data	Reference	Comments
	i.e. commercial product name) (measured)		mental value, reliable (standardised guidelines)
	7.8 × 10 ⁻⁵ Pa at 20°C and 1.5×10 ⁻⁴ Pa at 25°C for tertbutylphenyl diphenyl phosphate (estimated)	Brooke et al. 2009	Reported in a secondary source (review). Estimated based on information on boiling points at reduced pressures and vapour pressure at elevated temperature from different data sources. Estimates are based on mathematical modelling.
	1.08 x 10 ⁻³ Pa at 20°C for the commercial product Phosflex 61B (t-Butylated triphenyl phosphate ester)	Akzo Nobel, 2004	Reported in a secondary source.
Water Solubility (mg/L)	3.2 mg/L at room temperature (test substance: tertbutylphenyl diphenyl phosphate along with triphenyl phosphate and bis(tertbutylphenyl) phenyl phosphate) (measured)	Brooke et al. 2009	Reported in a secondary source (review), test substance close to similar to phenol, isobutyleneated, phosphate
	0.04 mg/L (test substance tertbutylphenyl diphenyl phosphate) (measured)	Akzo Nobel, 2004	Reported in a secondary source, standardised guideline
	0.009 mg/L at 25°C (estimated, based on a log kow of 6.61)	Brooke et al. 2009	Reported in a secondary source (review). Data estimated using the Syracuse Research Corporation WSKOW version 1.30 software
Log Kow	5.12 (test substance: tertbutylphenyl diphenyl phosphate along with triphenyl phosphate and bis(tertbutylphenyl) phenyl phosphate) (measured)	Brooke et al. 2009	Reported in a secondary source (review). Test substance close to similar to phenol, isobutyleneated, phosphate
	6.61 (for tertbutylphenyl diphenyl phosphate (estimated on the basis of the compound structure)	Brooke et al. 2009	Data estimated using the Syracuse Research Corporation WSKOW version 1.30 software
	Weighted average log Kow (Pow) 4.86 for the commercial	REACH registration data	Reported in a secondary source. Weighted

Phenol, isobutyleneated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0			
Property/Endpoint	Data	Reference	Comments
	product Phosflex 71B t-Butylated diphenyl phosphate) (calculated based on measured data)		average is based on log Kow values for the two main mixture components (TTP and C4)
	4.85 for the commercial product Phosflex 61B (measured data)	Akzo Nobel, 2004	Reported in a secondary source.
pKa	The pKa of the leaving phenol group is around 10, and a similar value would be expected for the tertbutylphenyl leaving group (estimated)	Brooke et al. 2009	Reported in a secondary source (review).

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
Human health effects				
Toxicokinetics		No data		
Dermal absorption <i>in vitro</i>		No data available	Brooke et al. 2009	
Absorption, Distribution, Metabolism & Excretion	Oral, dermal or inhaled	No data available	Brooke et al. 2009	
	Other	No data available	Brooke et al. 2009	
Acute mammalian toxicity		LOW: Oral LD50 in rats and mice is >5,000 mg/kg and the dermal LD50 in rabbits is >2,000 mg/kg in tests with a commercial products containing 75-80 % w/w tertbutylphenyl diphenyl phosphate, 20-25 % w/w triphenyl phosphate CAS No. 115-86-6.		
Acute lethality	Oral	Rat, oral LD ₅₀ > 5000 mg/kg bw for commercial product Phosflex 51B ((75-80 % w/w tertbutylphenyl diphenyl phosphate, 20-25 % w/w triphenyl phosphate CAS No. 115-86-6)	Akzo Nobel, 2004	Reported in a secondary source. Guideline EPA OTS 798.1175 , no GLP compliance. Reliability 1 according to Akzo Nobel.
		Rat, oral LD ₅₀ > 5000 mg/kg bw for commercial product Fyrquel LT for male and female rats	REACH registration data	Reported in a secondary source. Non-GLP study according to methodology comparable to OECD guideline 401. Several minor deviations from guideline. Reliability 2
	Dermal	Rabbit, dermal LD ₅₀ > 2000 mg/kg bw for commercial product Phosflex 72B for male and female rabbits	REACH registration data	Reported in a secondary source. Non-GLP study according to methodology comparable to OECD guideline 402. Several minor deviations from guideline. Reliability 2
		Rabbit, dermal LD ₅₀ > 2000 mg/kg bw for commercial product Phosflex 51B (75-80 per cent w/w tertbutylphenyl diphenyl phosphate, 20-25 per cent w/w triphenyl phosphate CAS No. 115-86-6) for male and female rabbits	Akzo Nobel, 2004	Reported in a secondary source. Guideline EPA OTS 798.1100, no GLP compliance. Reliability 1 according to Akzo Nobel.
	Inhalation	Rat, inhalation LC ₅₀ > 3.1 mg/l (highest dose tested) for	Akzo Nobel, 2004, Brooke	Reported in a secondary source. Guide-

Phenol, isobutyleneated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
		commercial product Phosflex 51B (75-80 per cent w/w tertbutylphenyl diphenyl phosphate, 20-25 per cent w/w triphenyl phosphate CAS No. 115-86-6) for male and female rats	et al. 2009	line OPPTS 870.1300, no GLP compliance. Reliability 1 according to Akzo Nobel.
		Male rats, inhalation LC ₅₀ > 0.4 mg/l (only dose tested) of vaporized test material for, 6h for the commercial product Santicizer 154. No mortality occurred.	REACH registration data	Reported in a secondary source. Early GLP, but no guideline followed. Reliability 2
Carcinogenicity		No data		
	QSAR results from the literature (e.g. Danish QSAR database)	No data located		
	Carcinogenicity (Rat and Mouse)	No data available	Brooke et al. 2009	
	Combined Chronic Toxicity/Carcinogenicity	No data available	Brooke et al. 2009	
	Other	No data located		
Genotoxicity		LOW: A commercial product containing 75-80 % w/w tertbutylphenyl diphenyl phosphate, 20-25 % w/w triphenyl phosphate CAS No. 115-86-6 was not mutagenic in bacteria or mammalian cells in vitro and did not cause chromosomal aberrations or sister chromatide exchanges in vitro.		
	Gene Mutation <i>in vitro</i>	Commercial product Phosflex 51B: Negative, Ames Assay in <i>Salmonella typhimurium</i> strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100, with and without metabolic activation.	Akzo Nobel, 2004; Brooke et al.2009	Reported in a secondary source.
		Commercial product Phosflex 51B: Negative, forward mutation assay in mouse lymphoma L5178Y cells in the presence and absence of an induced rat live metabolic activating system	Akzo Nobel, 2004; Brooke et al.2009	Reported in a secondary source.
	Gene Mutation <i>in vivo</i>	No data available	Brooke et al. 2009	
	Chromosomal Aberrations <i>in vitro</i>	Commercial product Phosflex 51B: Did not induce chromo-	Akzo Nobel, 2004; Brooke	Reported in a secondary source.

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
		somal aberrations or sister chromatid exchanges in the mouse lymphoma cytogenetic assay, in the presence and absence of an induced rat liver metabolic activating system.	et al.2009	
	Chromosomal Aberrations <i>in vivo</i>	No data available	Brooke et al. 2009	
	DNA Damage and Repair	No data located		
	Other	No data located		
Reproductive effects		LOW: Based on a rat oral reproductive/developmental NOAEL = 1000 mg/kg-bw/day for reproductive effects (highest dose tested).		
	Reproduction/Developmental Toxicity Screen	Reproductive/developmental oral gavage study in rats (14 days pre-mating, 14 days during mating and through gestation and lactation (approx. 8 weeks in total), 12/sex/group, test dose: 0, 50, 250 or 1,000 mg/kg bw/day of the commercial product Phosflex 61B. Based on the lack of parental and foetal toxicity, the no observed adverse effects level (NOAEL) for this study was greater than 1,000 mg/kg bw/day.	Akzo Nobel, 2004; Brooke et al. 2009	Reported in a secondary source (review). The study was conducted to OECD 421 and EPA OPPTS 870.3550 test guidelines and to GLP
	Continuous breeding study	A modification of the National Toxicology Program's (NTP) Continuous Breeding Protocol was conducted in F344 rats exposed orally to 0, 600, 1000, or 1700 mg/kg butylated triphenyl phosphate-based hydraulic fluid for 135 days. LOAEL = 1000 mg/kg-bw/day (based on multiple effects in males and females) NOAEL = 600 mg/kg-bw/day	US EPA 2008	Reported in a secondary source.
	Combined Repeated Dose with Reproduction/Developmental Toxicity Screen	No data located		
	Reproduction and Fertility Effects	No data located		
	Other	No data located		
Developmental effects		LOW: Based on a rat oral reproductive/developmental NOAEL = 1000 mg/kg-bw/day for developmental effects (highest dose tested). There were no data located for the developmental neurotoxicity endpoint. Decreased cholinesterase activity in pregnant lab animals has		

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
		been shown to have a negative impact on foetal brain development. As a result, there is uncertain potential for developmental neurotoxicity for this substance.		
	Reproduction/Developmental Toxicity Screen	Reproductive/developmental oral gavage study (14 days pre-mating, 14 days during mating and through gestation and lactation (approx. 8 weeks in total), 12/sex/group, test dose: 0, 50, 250 or 1,000 mg/kg bw/day of the commercial product Phosflex 61B. No effect on litter size or the number of live pups on postnatal days 0 and 4.	Akzo Nobel, 2004; Brooke et al. 2009	Reported in a secondary source. The study was conducted to OECD 421 and EPA OPPTS 870.3550 test guidelines and to GLP
		21 day teratogenicity study: 30 pregnant rats/group received either 0, 100,400, or 1000 mg/kg/day of Phosflex 5 1 B by oral gavage from gestation day 6 through gestation day 20. A significant dose-related increase in absolute and relative liver weights was observed in all treatment groups, which was considered by the authors to be an adaptive response (enzyme induction) rather than due to toxicity of the compound, although no data were presented to support this conclusion. It was not possible to propose a NOAEL for maternal toxicity. The NOAEL for developmental toxicity is, however, considered to be greater than the highest dose tested, 1,000 mg/kg bw/day. A LOAEL for maternal toxicity is 100 mg/kg bw, based on the increased liver weights.	Brooke et al. 2009 (study presented in Akzo Nobel, 2004 as well).	Reported in a secondary source (review)
	Combined Repeated Dose with Reproduction/ Developmental Toxicity Screen	No data located		
	Prenatal Development	No data located		
	Postnatal Development	No data located		
	Prenatal and Postnatal Development	No data located		

Phenol, isobutyleneated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
	Developmental Neurotoxicity	No data located		
	Other	No data located		
Neurotoxicity (single dose and repeated)		MODERATE: Based on significant inhibition (56%) of plasma cholinesterase activity, but no inhibition of NTE activity after repeated dosing. Phosflex 5 1B caused cholinesterase inhibition at a single very high dose of 10 ml/kg (11.7 g/kg), but no evidence of cholinesterase inhibition at significantly lower doses. There is potential for neurotoxic effects based on a structural alert for organophosphates .		
	Acute and delayed neurotoxicity tests in hens	Test substance was the commercial product Phosflex 51B. 15 adult hens, exposed to 11.7 g/kg at the start of the study and again 21 days later, and all hens were terminated 21 days after the second dose. A negative and a positive control was included in the study as well. Phosflex 5 1B administered to hens at the very high dose of 11.7 g/kg did not cause neurotoxicity.	Akzo Nobel, 2004	Reported in a secondary source.
		Test substance was the commercial product Phosflex 51B. 4 adult hens/group, 3 groups in total received a single oral gavage dose of 10 ml/kg. A positive control (TOCP) was also included. The animals were terminated after 24 h, and plasma cholinesterase activity and brain neurotoxic esterase (NTE) activity were measured. Phosflex 5 1B produced significant inhibition (56%) of plasma cholinesterase activity, but did not inhibit NTE activity (0% inhibition). Although Phosflex 5 1B caused cholinesterase inhibition at the very high dose of 10 ml/kg (11.7 g/kg), there is no evidence that the substance causes cholinesterase inhibition at significantly lower doses, which would be more representative of levels of human exposure. The authors concluded that Phosflex 5 1B did not demonstrate neurotoxic activity.	Akzo Nobel, 2004	Reported in a secondary source. EPA OTS Guideline for Acute Neurotoxicity Testing, no GLP
		Test substance was the commercial product Durad 220B. 3 groups of adults hens (9 per group) received a single oral dose of either Durad (2 g/kg), tap water, or a positive control. Brain and spinal cord neurotoxic esterase (NTE) activity and brain acetylcholinesterase activity was measured in 3 hens per group 48 hours after dosing. The remaining hens were	Akzo Nobel, 2004	Reported in a secondary source. EPA OTS Guideline for Acute Neurotoxicity Testing, no GLP

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
		sacrificed after 21 days observational period. No inhibition of brain or spinal cord NTE activity or brain acetylcholinesterase activity was observed in Durad 220B treated hens, and Durad 220B did not express neurotoxic activity.		
		The neurotoxic potential of a jet engine lubricant containing synthetic turbo jet oil and 3 % butylated triphenyl phosphate (100% mixture of butyl and triphenyl phosphate mixtures). Groups of 17-hens were given the test substance by oral gavage at a limit dose of 1 g/kg, 5 days a week for 13 weeks. A positive and negative control was also included. NTE and AChE activities were assayed in 2brain and spinal cord from 4 hens in each group after 6 and 13 weeks of dosing. NTE and AChE activity was not significantly different from control after 6 weeks dosing, but NTE activity was inhibited 23-34% in brains of lubricant treated hens. AChE activity was not inhibited after either 6 or 13 weeks. There was no difference in the clinical assessments between the lubricant treated hens and the negative control group. There was no indication of organophosphorus-induced delayed neuropathy (OPIDN).	Daughtrey et al. 1996, Brooke et al. 2009	Primary source. Also reported in a secondary source.
	Other	There is potential for neurotoxic effects based on a structural alert for organophosphates (Estimated)	Expert judgement	Estimated based on a structural alert for organophosphates.
Repeated Dose Effects		MODERATE: Based on the liver and kidney weight effects observed at the highest orally administered dose in a 90-day study and a NOEL of 26.7 mg/kg bw/day, and a dermal NOAEL of 10 mg/kg bw/day based on evident dose response depression of terminal cholinesterase.		
	Sub-chronic oral repeated dose	90 days repeated dose oral exposure study in rats. Exposed to the commercial product Phosflex 51B blended in the diet at doses of 0, 100,400, or 1600 ppm. Parameters measured include body weight, food consumption, clinical observations, hematology, clinical chemistry, and cholinesterase activity. Based on the organ weight effects (liver and kidney) observed	Akzo Nobel, 2004; Brooke et al. 2009. Primary source: Freudenthal et al. 2001	Reported in a secondary source – consistent with data in the primary source.

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
		at the highest dose of Phosflex 51B, the NOEL for this study is 26.7 mg/kg bw/day in male rats or 30.0 mg/kg bw/day in female rats (equivalent to 400 ppm).		
		Phosflex 51B was administered to rats in concentrations of 0, 100, 400 and 1600 ppm by diet (= mg/kg food) was not regarded as a toxic and therefore not an adverse effect. Under the conditions of this study, the 90-day administration of Phosflex 51B by diet in rats showed to induce no adverse effects. Therefore, a NOAEL of 107.5 and 124.8 mg/kg bw/day (equivalent to 1600 ppm) was established for males and females, respectively.	REACH registration data	Reported in a secondary source. Same study as reported above, however different conclusion regarding the NOAEL value. Not consistent with the primary source (Freudenthal et al. 2001).
	Sub-chronic inhalation repeated dose	The toxicity of the commercial product Santicizer 154 was determined in a 90-day inhalation study in rats. Male and female animals were exposed for 6 hours a day, 5 days a week to 0, 10.1 or 101.1 mg/m ³ . Under the conditions of the study, no clear test article- or dose-related effects were observed in rats as a result of exposure to Santicizer 154. Therefore, a NOAEL of 101.1 mg/m ³ was established.	REACH registration data	Reported in a secondary source. Study was conducted according to a method comparable to OECD guideline 413, but not under GLP conditions. Reliability 2.
	Dermal repeated dose	The toxicity of the commercial product Santicizer 154 was determined in a 21-day repeated dose dermal toxicity study in rabbits. Santicizer-154, at dose levels of 10, 100 and 1000 mg/kg/day, was applied to the clipped dorsal surface of New Zealand White rabbits daily, 5 days per week for three weeks. Based on evident dose response depression of terminal cholinesterase in the Santicizer-154 treated males and females, which was significant in the mid and high dose, a NOAEL of 10 mg/kg bw/day was derived	REACH registration data	Reported in a secondary source. Study was not conducted under GLP, but was performed according to methods similar to OECD guideline 410. Reliability 2.
Skin Sensitization		LOW: Expert judgement based on human patch testing of 50 subjects with no sensitisation supported by human evidence from occupational use. No classification suggested.		
	Skin sensitization	The commercial product Phosflex 71B did not indicate a potential for dermal irritation or allergic contact sensitiza-	REACH registration data	Reported in a secondary source. Non-international guideline, GCP compliance.

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
		tion.		Reliability 1.
	Skin sensitization in humans	Based on 2 years of experience with the substance in various products on the production facility in Gallipolis Ferry, WV, US, there have been no incidences of sensitization of workers known to the management related to the use and production of the substance Phenol, isobutylated, phosphate (3:1) at the GF facility in the US. (data from workplace)	REACH registration data	Reported in a secondary source. Reliability 1.
Respiratory Sensitization		No data.		
	Respiratory Sensitization	No data located		
Eye Irritation		MODERATE: Fully reversible effects within 48 hours.		
	Eye Irritation	Mild redness of the conjunctiva was observed in two rabbits (one with a washed eye, the other with an unwashed eye) at the 24 hour observation. The two eyes cleared by 48 hours, but another eye (unwashed) showed mild redness of the conjunctiva at 48 hours. All eyes were clear of irritation at 72 hours and 96 hours, and remained so through the 7 day observation. The average irritation scores at 24 and 48 hours were 0.44 and 0.22, respectively, thus Phosflex 5 1 B is a very mild eye irritant.	Akzo Nobel, 2004, Brooke et al. 2009	Reported in a secondary source. Guideline EPA OTS 798.4500, no GLP compliance. Reliability 1 according to Akzo Nobel.
		The commercial product Phosflex 72B was a non-irritant in the eyes of albino rabbits. This formulation produced no eye irritation in rabbits whose eyes were left unwashed or in rabbits whose eyes were washed 20-30 seconds after treatment.	REACH registration data	Reported in a secondary source. Non-GLP study according to EPA Guideline, which is consistent with OECD Guideline 405, 1981. Reliability 2
Dermal Irritation		MODERATE: Fully reversible effects within 72 hours.		
	Dermal Irritation	Mild to moderate erythema was observed 24 hours after treatment; the number of rabbits with erythema was not reported. At 48 hours after treatment, mild erythema was	Akzo Nobel, 2004, Brooke et al. 2009	Reported in a secondary source. Guideline EPA OTS 798.4470, no GLP compliance. Reliability 1 according to Akzo Nobel.

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
		present in four of the individual animals, but at 72 hours no irritation was present. No observations of oedema were made. Primary irritation score was 0.5, indicating that the commercial product Phosflex 51B is a mild skin irritant.		
		The commercial product Phosflex 72B produced mild erythema (4 rabbits) and mild oedema (1 rabbit) in intact and abraded skin of albino rabbits following a 24 hour exposure. At the 72 hour observation, irritation decreased and included mild erythema in one of the six rabbits (no 14 days observation period done for reversibility). Primary irritant score was 0.46	REACH registration data	Reported in a secondary source. Non-GLP study according to EPA Guideline. Reliability 2
Endocrine Activity		No data		
	Endocrine activity	No data located		
Immunotoxicity		No data		
	Immune System Effects	No data located		

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0			
Property/Endpoint	Data	Reference	Comments
Ecotoxicity			
ECOSAR Class	Esters, esters (phosphate)		
Aquatic Acute Toxicity	VERY HIGH: Based on experimental EC ₅₀ 's for daphnia ranging from 0.2 – 0,289 mg/L. Also one fish LC ₅₀ is below 1 mg/L.		
Fish LC ₅₀ (Freshwater)	LC ₅₀ 96h: 0.8 mg/L (0.6 – 1.0 mg/l) (<i>Ictalurus punctatus</i>) (experimental) (test substance was the commercial product Fyrquel GT)	REACH registration data; Brooke et al. 2009	Reported in a secondary source.
	LC ₅₀ 96h : 13.7 mg/L (<i>Salmo gairdneri</i>) (experimental) (test substance was the commercial product Fyrquel GT)	Akzo Nobel, 2004	Reported in a secondary source, guideline study, but no GLP
Fish LC ₅₀ (Marine)	LC ₅₀ 96h: >1 mg/L (<i>Cyprinodon variegatus</i>) (experimental) (test substance tert-butylphenyl diphenyl phosphate)	Akzo Nobel, 2004	Reported in a secondary source, guideline study with GLP
Daphnid LC ₅₀ / EC ₅₀ (Freshwater)	EC ₅₀ 48h: 0.25 – 5 mg/L (<i>Daphnia magna</i>) (experimental, range from several studies) (test substance tert-butylphenyl diphenyl phosphate)	Brooke et al. 2009	Reported in a secondary source.
	EC ₅₀ 48h: 0.2-0.289 mg/L (<i>Daphnia magna</i>) (experimental) (test substance commercial product Santicizer 154)	REACH registration data	Reported in a secondary source
Daphnid LC ₅₀ / EC ₅₀ (Marine)	EC ₅₀ 96h: 0.39 mg/L (<i>Mysidopsis bahia</i>) (experimental) (test substance tert-butylphenyl diphenyl phosphate)	Akzo Nobel, 2004	Reported in a secondary source, guideline study with GLP
Green Algae IC ₅₀ / EC ₅₀	EC ₅₀ 96h: 2.6 ppm (2.6 mg/L). Endpoint: decrease in cell no. (<i>Selenastrum capricornutum</i>) (experimental) (test substance Santicizer 154)	Akzo Nobel, 2004	Reported in a secondary source, guideline study but no GLP. Also referred to in Brooke et al., 2009, where the study is assessed as not assignable.
Aquatic Chronic Toxicity	VERY HIGH: Based on experimental chronic (21d) NOEC's for daphnia ranging from 0.01 to 0,.04 mg/L		
Fish ChV NOEC (Freshwater)	NOEC 90 d: 0.194 mg/L (growth) 0.093 mg/L (mortality) (<i>Pimephales promelas</i>) (experimental) ((test substance was the commercial product Fyrquel	REACH registration data, Brooke et al. 2009	Reported in a secondary source.

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
		GT)		
Daphnid NOEC (Freshwater)		NOEC 21 d: 0.01-0.04 mg/L (<i>Daphnia magna</i>) (experimental) (test substance tertbutylphenyl diphenyl phosphate)	Brooke et al. 2009	Reported in a secondary source.
		NOEC 21d: 0.040 mg/l (<i>Daphnia magna</i>) (experimental) (test substance commercial product Santicizer 154)	Akzo Nobel, 2004	Reported in a secondary source.
Green Algae NOEC		NOEC 14d: 1.0 mg/L (<i>Selenastrum capricornutum</i>) (experimental)	Brooke et al. 2009	Reported in a secondary source. Assessed by authors as not valid study.
Transport		Results of Level III fugacity modelling indicate that at equilibrium the substance will be found almost exclusively in water (55%) and sediment (45%). The expected mobility in soil is moderate based on an estimated K_{OC} of about 4,800. The vapour pressure of the substance is low and the Henry's Law Constant indicates that the volatility from water surfaces will also be low (approx.. same rate as water) and in the atmosphere the substance is therefore expected to be present mainly associated with water aerosols and removal from air therefore primarily by wet deposition.		
	Henry's Law Constant (atm-m ³ /mole)	0.009 Pa m ³ /mole at 20°C (for tert-butylphenyl diphenyl phosphate) (estimated based on compound structure)	Brooke et al. 2009	Reported in a secondary source (review)
		8.9×10^{-7} atm-m ³ /mole (estimated)	US EPA 2008	Reported in a secondary source.
	Sediment/Soil Adsorption/Desorption – K_d/K_{OC}	$K_{OC} = 4,773$ L/kg (tert-butylphenyl diphenyl phosphate) (estimated based on compound log K_{OW})	Brooke et al. 2009	Reported in a secondary source (review)
	Level III Fugacity Model	Air 2.5×10^{-3} % Water 54.9 % Soil 7.5×10^{-3} % Sediment 45.1 % (estimated)	US EPA 2008	Reported in a secondary source.
		Air 0.27 % Water 10 % Soil 79.4 % Sediment 10.4% (estimated)	Brooke et al. 2009	Reported in a secondary source (review). Based on emission of 1000 kg/hour to soil, water and air, respectively.

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
Persistence		LOW: The substance was found to be readily biodegradable in an OECD screening test (measured). There is no data for the possible biodegradation in soil but in water/sediment system studies primary degradation was found to be rapid with half-lives from <0.5 days to 3 days. In one study 1.7% to 37% full mineralisation was found to take place within 8 weeks, depending on test substance concentration. Atmospheric half-life estimated to be 24 hours. Results of experimental studies of abiotic degradation by photolysis or hydrolysis indicate that these processes are likely to be of low importance in the environment.		
Water	Aerobic Biodegradation	Readily biodegradable: Degraded 61% after 28 days in closed bottle test (OECD 301D). Test parameter: O ₂ consumption. It is stated that the test validity criteria were met, but no mentioning of 10-day (or 14-day) window fulfilment (measured)	REACH registration data	Reported in a secondary source, (standardised test method)
	Volatilization Half-life for Model River	No data located		
	Volatilization Half-life for Model Lake	No data located		
Soil	Aerobic Biodegradation	No data located		
	Anaerobic Biodegradation	No data located		
	Soil Biodegradation with Product Identification	No data located		
	Sediment/Water Biodegradation	Half-life: < 0.5 for triphenyl phosphate 1 day for t-butylphenyldiphenyl phosphate 7 days for di(t-butylphenyl) phenyl phosphate (Test substance was the commercial product Santicizer(r) 154) (measured)	REACH registration data	Reported in a secondary source. Study carried out according to well described method and with GLP, but not according to international guideline

Phenol, isobutyleneated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
		Half-life for primary degradation: 1-3 days for a mixture of triphenyl phosphate and tribu- tylphenyl diphenyl phosphate in microcosm test with lake water and sediment. 2-3 days for a mixture of triphenyl phosphate and tribu- tylphenyl diphenyl phosphate in outdoor simulation test with well water and river sediment. (measured)	Brooke et al. 2009	Reported in a secondary source (review).
		"Experiments investigating degradation in sediments have generally shown reasonably rapid primary degradation (half- lives of 1 to 3 days in some experiments have been seen), but one series of experiments using sediment microcosms found that the rate of mineralisation depended on the actual con- centration of the test substance; mineralisation rates of 1.7 per cent up to 37 per cent over eight weeks were seen in these studies. The default mineralisation half-life of 90 days esti- mated above appears to be consistent with these data." (estimated based on identified data data)	Brooke et al. 2009	Expert judgement based on available data
Other	Biotic degradation.	28 fungi capable of metabolising tert-butylphenyl diphenyl phosphate have been identified. The main products formed were alkyl side chain-oxidised and aromatic ring- oxidised metabolites, with di- and monoaryl phosphates formed to a lesser extent.	Brooke et al. 2009	Reported in a secondary source (review).
Air	Atmospheric Half-life	24 h (for tert-butyl phenyl diphenyl phosphate) (estimated on basis of the compound structure)	Brooke et al. 2009	Reported in a secondary source (review).
Reactivity	Photolysis	Half-life > 14 days (test substance commercial product Santi- cizer(r) 154 (measured)	Akzo Nobel, 2004	Reported in a secondary source.
		Half-life infinite (tert-butylphenyl diphenyl phosphate) (es- timated based on measured data	Brooke et al. 2009	Reported in a secondary source (review). Estimate is based on collaboration of

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
				available information as well as expert judgement by the authors.
		Half-life >28 h (for the commercial product Santicizer(r) 154 (tert-butylphenyl diphenyl phosphate) (measured)	REACH registration data	Reported in a secondary source.
	Hydrolysis	Half-life at 25°C: 60 days at pH 4; 14 days at pH 7; 5.4 days at pH 9 At 15°C: >100 days at pH 4; 28 days at pH 7; 15 days at pH 9 (test substance butylated triphenyl phosphate) (measured)	Akzo Nobel, 2004	Reported in a secondary source.
		Half-life infinite (tert-butylphenyl diphenyl phosphate) (estimated based on measured data	Brooke et al. 2009	Reported in a secondary source (review). Estimate is based on collaboration of available information as well as expert judgement by the authors.

Phenol, isobutylenated, phosphate/CAS No. 68937-40-6/EC No. 273-065-8/700-990-0				
Property/Endpoint		Data	Reference	Comments
Environmental Half-life		No data located		
Bioaccumulation		MODERATE: Based on measured BCFs for fish in the range 778-1850 and an estimated BCF for earthworms of 1583. Log Kow values are in the range 4.8 to 6.6 thus indicating an even higher bioaccumulation potential. However, measured BCF values have preference over predictions based on Kow.		
	Fish BCF	778 L/kg (for ¹⁴ C-labelled tert-butylphenyl diphenyl Phosphate) (estimated based on identified BCF data)	Brooke et al. 2009	Reported in a secondary source (review). Estimate is based on collaboration of available information as well as expert judgement by the authors.
		1850 for t-butylphenyldiphenyl phosphate (Test substance was the commercial product Santicizer(r) 154) (calculated based on measured data)	REACH registration data	Reported in a secondary source.
	Other BCF	BCF for earthworms: 1,583 L/kg (estimated based on the log Kow)	Brooke et al. 2009	Reported in a secondary source (review). Authors report that the reliability of the estimate is unknown.
	BAF	No data located		
	Metabolism in Fish	No data located		
Environmental biomonitoring				
Ecological Biomonitoring		No data located		
Human Biomonitoring		No data located		

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Appendix 6

Phosphinic acid, aluminium salt (3:1), CAS No. 7784-22-7

No harmonized classification (CLP) is available for the substance. 356 of 364 industry notifications suggest a classification with Aquatic Chronic 3 (as of 11.10.2015). Apart from REACH registration data, no other data sources provide information on the substance. QSAR estimations are not appropriate because the substance is inorganic.

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8			
Property/Endpoint	Data	Reference	Comments
Physical/chemical properties			
Melting Point (°C)	≥ 310 °C Decomposition occurs before melting.	REACH registration data	Reliability 1 Study conducted according to internationally accepted testing guidelines and performed according to GLP.
Boiling Point (°C)	Data waiving	REACH registration data	
Vapour Pressure (Pa)	Data waiving	REACH registration data	
Water Solubility (mg/L)	ca. 24000 mg/L at 20 °C, pH ca. 3.2	REACH registration data	Reliability 1 GLP compliant with international guideline
Log Kow	Data waiving	REACH registration data	Inorganic substance
pKa	No data located.		

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8				
Property/Endpoint		Data	Reference	Comments
Human health effects				
Toxicokinetics				
Dermal absorption <i>in vitro</i>		No data located.		
Absorption, Distribution, Metabolism & Excretion	Oral and intravenous	Absorption and distribution of aluminium following and intravenous + oral administration of Sprague-Dawley rats at a dose equivalent to 8.1 mg/kg one per day, two days exposure. Main ADME results: <i>absorption</i> 27% from oral <i>distribution</i> plasma <i>metabolism</i> none <i>excretion</i> 27% urine, remaining faeces as not absorbed	REACH registration data	Reliability 2 Old study (1986) plus Reviews from authoritative source
Acute mammalian toxicity		LOW: Based on the oral LD50 in rats of >2,000 mg/kg and the dermal LD50 in rabbits of >2,000 mg/kg. The study on inhalation exposure was evaluated to be insufficient for consideration for the score.		
Acute lethality	Oral	Six Sprague-Dawley rats were exposed to 2000 mg/kg bw. LD50 > 2000 mg/kg bw	REACH registration data	Reliability 2 Study conducted according to OECD Guideline 423 and performed according to GLP. Nevertheless, many details were missing and no information about the test material is available.
	Dermal	5 female and 5 male Sprague-Dawley were exposed for 24 hr to 2000 mg/kg bw. LD50 > 2000 mg/kg bw	REACH registration data	Reliability 1 Study conducted according to OECD Guideline 402 and performed according to GLP.
	Inhalation	5 male and 5 female Wistar rats were exposed to 3.30 mg/l for 4 hours. Nose only the snouts and nostrils of the animals	REACH registration data	Reliability 1 Study conducted according to OECD

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8				
Property/Endpoint		Data	Reference	Comments
		were exposed to the aerosol. LC50 (4h) > 3.30 mg/l (only dose tested) Considering the fact that no mortality occurred, a classification category cannot be assigned.		Guideline 403 and performed according to GLP.
Carcinogenicity		DG		
	QSAR results from the literature (e.g. Danish QSAR database)	Not applicable.		
	Carcinogenicity (Rat and Mouse)	No data located.		
	Combined Chronic Toxicity/Carcinogenicity	No data located.		
Genotoxicity		LOW: Negative in <i>in vitro</i> Mammalian chromosome aberration test and <i>in vivo</i> micronucleus assay.		
	Gene Mutation <i>in vitro</i>	No data located.		
	Gene Mutation <i>in vivo</i>	No data located.		
	Chromosomal Aberrations <i>in vitro</i>	Mammalian chromosome aberration test Concentration range in the main test (with metabolic activation): 45, ..., 405 µg/ml Concentration range in the main test (without metabolic activation): 38, ..., 650 µg/ml Exposure period (with metabolic activation): 3 hours Exposure period (without metabolic activation): 21 hours. There was no evidence of induction of chromosome aberrations either in the presence or absence of metabolic activation,	REACH registration data	Reliability 1 OECD Guideline 473
	Chromosomal Aberrations <i>in vivo</i>	Micronucleus assay with mouse exposed via two oral gavages (two treatments at 24 hour intervals) to 0, 250, 500 and 1000 mg/kg bw. Aluminium hypophosphite was concluded to be negative in	REACH registration data	Reliability 1 GLP compliant with international (OECD Guideline 474) and Asian guideline

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8				
Property/Endpoint		Data	Reference	Comments
		the <i>in vivo</i> mouse micronucleus assay.		
	DNA Damage and Repair	No data located.		
Reproductive effects		LOW: NOAEL > 1000 ppm in a reproduction/developmental toxicity Screening study.		
	Reproduction/Developmental Toxicity Screen	Male and female Wistar rats were exposed to 0, 100, 300, 1000 ppm nominal in the diet for 2 consecutive weeks prior to pairing and thereafter during pairing, post coitum and post partum periods until Day 4. NOAEL (general toxicity and for fertility and reproduction parameters) male was considered to be the highest dose tested, i.e. 1000 ppm (corresponding to 77 mg/kg bw/day; actual dose received) NOAEL (general toxicity and for fertility and reproduction parameters) female was considered to be the highest dose tested, i.e. 1000 ppm (corresponding to 95 mg/kg bw/day (actual dose received)	REACH registration data	Reliability 1 Study conducted according to OECD Guideline 421 and 422 and performed according to GLP.
	Continuous breeding study	No data located.		
	Combined Repeated Dose with Reproduction/Developmental Toxicity Screen	No data located.		
	Reproduction and Fertility Effects	No data located.		
Developmental effects		LOW: NOAEL > 1000 ppm in a reproduction/developmental toxicity Screening study.		
	Reproduction/Developmental Toxicity Screen	Males were treated for 2 weeks prior to pairing and during pairing with females until the day before necropsy, for a total of 29 days. Females were treated for 2 weeks prior to pairing, during	REACH registration data	Reliability 1 Study conducted according to OECD Guideline 421 and performed according to GLP.

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8				
Property/Endpoint		Data	Reference	Comments
		pairing and throughout the gestation and lactation periods until Day 3 post partum. Pups: until Day 4 post partum. Doses of 0, 100, 300, 1000 ppm nominal in the diet. No treatment-related effects were observed for these parameters. Litter data and sex ratios were unaffected by treatment. Clinical signs of pups: There were no treatment-related effects. Necropsy findings in decedent pups and in pups sacrificed on Day 4 post partum did not reveal any treatment-related effect. NOAEL for general toxicity and for fertility and reproduction parameters was considered to be the highest dose tested, i.e. 1000 ppm for males and females (corresponding to 77 and 95 mg/kg bw, respectively).		
	Combined Repeated Dose with Reproduction/ Developmental Toxicity Screen	No data located.		
	Prenatal Development	No data located.		
	Postnatal Development	No data located.		
	Prenatal and Postnatal Development	No data located.		
	Developmental Neurotoxicity	No data located.		
Neurotoxicity				
	Acute and delayed neurotoxicity tests in hens	No data located.		

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8				
Property/Endpoint		Data	Reference	Comments
Repeated Dose Effects		Moderate: Based on the NOAEL of ca. 35.2 mg/kg bw/day. There is uncertainty about repeated dose effects, because no concentrations with significant toxic effects were reported and no 90-day exposure study is available. The score is based on a conservative approach.		
	Sub-chronic oral repeated dose	Phoslite IP-A was administered to Wistar rats (5 animals/sex/group) in the diet for 4 weeks at doses of 0, 100, 300, 1000 ppm, equal to compound intake of 0, 9.9, 27.8 and 86.9 mg/Kg/bw on males and 0, 11.4, 35.2 and 121.2 mg/Kg/bw on females. NOAEL female rats: ca. 35.2 mg/kg bw/day (nominal) NOAEL male rats: ca. > 86.9 mg/kg bw/day (nominal) Effects based on increased platelet count and mean corpuscular haemoglobin concentration and a decrease of haematocrit.	REACH registration data	Reliability 1 Full GLP study, OECD guideline 407
	Sub-chronic inhalation repeated dose	Data waiving	REACH registration data	
	Dermal repeated dose	Data waiving	REACH registration data	
Skin Sensitization		LOW: Negative		
	Skin sensitization	Female guinea pig, intradermal induction and challenge exposure to test item at 50% concentration in sterile water. Conclusion: not sensitising	REACH registration data	Reliability 1 OECD guideline 406
	Skin sensitization in humans	No data located.		
Respiratory Sensitization		DG		
	Respiratory Sensitization	No data located.		
Eye Irritation		MODERATE: Fully reversible effects within 7 days.		
	Eye Irritation	3 New Zealand White rabbits were exposed for 7 days to 100 mg of the test item.	REACH registration data	Reliability 1 OECD guideline 405

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8				
Property/Endpoint		Data	Reference	Comments
		Observation after 1, 24, 48, 72 hours and 7 days. 1-hour after application the following ocular reactions were observed: iritis grade 1 in 1/3 test eyes; redness grade 2 in 2/3 test eyes and grade 1 in 1/3 test eyes; chemosis grade 2 in 1/3 test eyes and grade 1 in 2/3 test eyes. Reversibility of any observed effect: Changes fully reversible within 7 days. Conclusion: not irritating		
Dermal Irritation		LOW: No irritation was observed.		
	Dermal Irritation	3 New Zealand White rabbits were exposed for 4 hr to 500 mg of the test item. No irritation was observed. Conclusion: not irritating	REACH registration data	Reliability 1 OECD guideline 404
Endocrine Activity		DG		
	Endocrine activity	No data located.		
Immunotoxicity		DG		
	Immune System Effects	No data located.		

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8			
Property/Endpoint	Data	Reference	Comments
Ecotoxicity			
ECOSAR Class	None (Inorganic compound)		
Aquatic Acute Toxicity	Moderate: Based on a EC50 (biomass) of ca. 29 mg/L in an algae growth inhibition test with <i>Pseudokirchneriella subcapitata</i>		
Fish LC ₅₀ (Freshwater)	Static test with <i>Danio rerio</i> exposed to a nominal concentration of 100 mg/L 96 h, LC50 > 100 mg/L	REACH registration data	Reliability 2 According to OECD Guideline 203. The concentration of the substance tested was not satisfactorily maintained throughout the test
Fish LC ₅₀ (Marine)	No data		
Daphnid LC ₅₀ / EC ₅₀ (Freshwater)	Static <i>Daphnia</i> sp. Acute Immobilisation Test, exposure to a nominal concentration of 100 mg/L. 48 h, EC50 (immobilisation) > 100 mg/L	REACH registration data	Reliability 2 Study conducted according to OECD Guideline 202 and performed according to GLP. The average analytical recovery of phosphorus (P) was 87.6 % during the exposure period, while the analytical recovery of aluminium (Al) was lower than the Limit Of Detection of the analytical method (LOD: 0.25 mg Al/l) already immediately after the test solution preparation. These results were likely due to the precipitation of aluminium in the test medium.
Daphnid LC ₅₀ / EC ₅₀ (Marine)	No data		

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8			
Property/Endpoint	Data	Reference	Comments
Green Algae IC ₅₀ / EC ₅₀	Growth Inhibition Test with <i>Pseudokirchneriella subcapitata</i> with nominal concentrations of 10.0 ,17.8 , 31.6, 56.2 and 100 mg/L. 72 h, EC50 (growth rate) > 100 mg/L 72 h, EC50 (biomass) ca. 29 mg/L	REACH registration data	Reliability 2 Study conducted according to OECD Guideline 201 and performed according to GLP.
Microorganisms IC ₅₀ / EC ₅₀	Static test with domestic, activated sludge at nominal concentrations of 1.0, 3.2, 31.6 and 100 mg/L, exposure duration 3 hr. 3 h, IC50 (respiration rate) > 100 mg/L 3 h, NOEC (respiration rate) 31.6 mg/L	REACH registration data	Reliability 1 Study conducted according to OECD Guideline 201 and performed according to GLP.
Aquatic Chronic Toxicity	Moderate: Based on notified classification, because experimental data are insufficient.		
Fish NOEC (Freshwater)	Semi-static test with <i>Danio rerio</i> exposed for 14 days to nominal concentrations of 4.48, 9.86, 21.7, 47.7 and 105 mg/L 14 d, NOEC (mortality) 105 mg/L The study is a prolonged toxicity test and thus not sufficient for assessing chronic toxicity.	REACH registration data	Reliability 2 Study conducted according to OECD Guideline 204 and performed according to GLP. The substance concentration has not been satisfactorily maintained throughout the test: the elemental analytical concentrations were in the range 90 - 103 % in the case of phosphorus, but they were in the range of 0.20 – 22.30 % in the case of the aluminium.
Daphnid NOEC (Freshwater)	No data		
Green Algae NOEC	No data		
	Aquatic Chronic 3, H412	C&L Inventory	Notified classification and labelling
Transport	The substance is an inorganic salt, which according to information from the registrant is fully soluble and fully dissociated in its ionic forms (at the concentrations tested in the adsorption study). Phosphorus was fully recovered (80–120 %), indicating that the phosphorus-containing component (phosphinic acid) does not adsorb in soil. The study does not provide any details on aluminium adsorption. In the		

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8				
Property/Endpoint		Data	Reference	Comments
		atmosphere, the substance is expected to be present only associated with water aerosols and removal from air is therefore by wet deposition. The substance will therefore be found almost exclusively in the water compartment.		
	Henry's Law Constant (atm-m ³ /mole)	No data		
	Sediment/Soil Adsorption/Desorption – K _d /K _{oc}	The analysis of Phoslite IP-A is conducted with HPLC for determination in soil and water. The method was developed to determine the total phosphorus in water and soil using the ammonium molybdate spectrophotometric method ($\lambda = 700$ nm with Agilent Vis-UV 8453), to calculate the Phoslite IP-A content through the determination of phosphorus in this environment. Adsorption of Phoslite IP-A was tested in triplicate on three different soils: Black, Brown and Red at concentrations of 48.0, 72.0 and 96.0 µg/ml. Results show the method is fit for determination of Phoslite IP-A in soil and that the recovery of Phoslite IP-A in chernozem, brown soil, red soil and cinnamon soil is range from 80~120 %. Conclusion of the study: Phoslite IP-A is an inorganic salt, which is fully soluble and fully dissociated in its ionic forms. As expected, there is no adsorption in soil.	REACH registration data	Reliability 2 Study conducted according to internationally accepted testing guidelines and performed according to GLP. Nevertheless, only non-official English translation is available.
	Level III Fugacity Model	Not applicable		
Persistence		Very high: Phosphinic acid is not expected to be degraded by hydrolysis and the metal ion is recalcitrant. Information about other environmental degradation pathways for phosphinic acid are lacking.		
Water	Aerobic Biodegradation	Data waiving		

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8				
Property/Endpoint		Data	Reference	Comments
	Volatilization Half-life for Model River	No data		
	Volatilization Half-life for Model Lake	No data		
Soil	Aerobic Biodegradation	Data waiving	REACH registration data	
	Anaerobic Biodegradation	No data		
	Soil Biodegradation with Product Identification	No data		
	Sediment/Water Biodegradation	No data		
Other	Biotic degradation.	No data		
Air	Atmospheric Half-life	No data		
Reactivity	Photolysis	No data		
	Hydrolysis	Read-across with sodium phosphinate (structural analogue or surrogate) In the test conditions, the tests at pH 4.0, pH 7.0 and pH 9.0 showed no significant degradation of sodium phosphinate (Solid) at 50 °C. The hydrolysis of sodium phosphinate (Solid) was less than 10% after 5 days. As no degradation was observed, sterility tests were not considered as needed. Therefore, the estimated half-life time is higher than one year under representative environmental conditions (25 °C). Therefore, sodium phosphinate (Solid) and phosphinic acid are considered to be hydrolytically stable.	Reach registration data for phosphonic acid (CAS nr. 6303-21-5)	Reliability 2 (reliable with restrictions), according to OECD Guideline 111 (Hydrolysis as a Function of pH)

Phosphinic acid, aluminium salt (3:1) /CAS No. 7784-22-7 /EC No. 479-150-8				
Property/Endpoint		Data	Reference	Comments
Environmental Half-life		No data		
Bioaccumulation		LOW: The substance is not expected to have potential for bioaccumulation based on professional judgement.		
	Fish BCF	No data		
	Other BCF	aquatic / sediment Data waiving	REACH registration data	
	BAF	No data		
	Metabolism in Fish	No data		
Environmental biomonitoring				
Ecological Biomonitoring		No data		
Human Biomonitoring		No data		

C&L Inventory: <http://echa.europa.eu/information-on-chemicals/cl-inventory-database> using CAS No. 7784-22-7 as search term.

REACH registration data: <http://echa.europa.eu/da/information-on-chemicals/registered-substances> using CAS No. 7784-22-7 as search term.

Appendix 7

Melamine phosphate (1,3,5-triazine-2,4,6-triamine phosphate), CAS No. 41583-09-9

This profile is for melamine phosphate (1,3,5-triazine-2,4,6-triamine phosphate, CAS No. 41583-09-9). Only few data are available. Most data in the REACH registration dossier are based on the substance melamine. The substance does not have a harmonised CLP classification. All notifiers, except one, suggest "no classification".

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7			
Property/Endpoint	Data	Reference	Comments
Physical/chemical properties			
Melting Point (°C)	The substance decomposes before melting. Decomposition temperature of 350°C, no sublimation	REACH registration data	Reliability 2 non GLP, non-standard method (Thermogravimetric analysis), no details on test item, but method well described.
Boiling Point (°C)	Data waiving	REACH registration data	
Vapour Pressure (Pa)	Data waiving	REACH registration data	
Water Solubility (mg/L)	3900 mg/L at 20°C	REACH registration data	Reliability 1 (standardised guidelines)
	max. 5 g/l (for the commercial product MPT11)	Metadynea, 2014	
	<3 g/l (for the commercial product Melapur® MP)	BASF, 2010	
Log Kow	- 3.0	REACH registration data	Reliability 2 (OECD 107 + GLP compliant, but water solubility not checked for the estimation method)
pKa	Read-across based on grouping of substances. The pKa values are 5.39, 3.05 and 0.48.		Reliability 2 Scientifically acceptable software
	Read-across based on grouping of substances. The pKa values are 2.21, 7.21 and 12.38.		Reliability 2 Authoritative handbook
	Read-across based on grouping of substances. The pKa is 5.		Reliability 2 Peer reviewed database
	Read-across based on grouping of substances.		Reliability 2

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7			
Property/Endpoint	Data	Reference	Comments
	The pKa values are 2.15, 7.09 and 12.32.		Authoritative handbook
Other relevant physical/chemical properties	The test substance is not considered highly flammable.		

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7				
Property/Endpoint		Data	Reference	Comments
Human health effects				
Toxicokinetics				
Dermal absorption <i>in vitro</i>		No data located		
Absorption, Distribution, Metabolism & Excretion	Oral	Metabolism, disposition and excretion of 14C-Melamine (CAS No. 108-78-1) in male Fischer 344 rats after administration of a single oral dose of 0 .025 mCi/rat (approximately 1 .3 mg/kg body weight). Distribution: Concentrations of [14C]melamine in the blood, plasma, bladder, liver, kidney and ureter of male Fischer 344 rats treated orally with a single dose were generally very low (0 – 12 pbb). Excretion: The percentages of radioactivity present as melamine in the urine, blood, plasma and faeces after 0.5, 1.0, 4.0, 8.0, 24.0, 48.0, 72.0, and 96.0 were generally high (ranging between 94.9 and 99.5% of total). Conclusion: No bioaccumulation potential based on study results	REACH registration data	Reliability 2 Comparable to guideline study with acceptable restrictions (only one dose level tested), read-across from supporting substance (structural analogue or surrogate)
	Oral	Clinical test in man. Melamine is a metabolite of hexamethylmelamine after demethylation steps. The experiments indicate that the s-triazine ring is very stable and that it does not undergo cleavage. This is suggested by the fact that there is no production of 14CO2 after administration of HMM-ring-14C to either man or rats. The identification of the major urinary metabolites as methylmelamines and melamine also confirms the stability of the s-triazine ring in mammalian systems. The results of our experiments show that any metabolites formed from the opening of the s-triazine ring of HMM	REACH registration data	Reliability 2 Not according to any guideline, sufficiently good description of the method.

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7				
Property/Endpoint		Data	Reference	Comments
		in man or rats would be present in small quantities only.		
	Other	No data located		
Acute mammalian toxicity		LOW: Based on an oral LD50 > 2000 mg/kg bw for male and female rats.		
Acute lethality	Oral	LD50 > 2000 mg/kg bw for male and female rats Interpretation: practically nontoxic	REACH registra- tion data	Reliability 1 GLP and guideline compliant study with well- characterized sample.
	Dermal	Data waiving	REACH registra- tion data	
	Inhalation	LC50 > 5190 mg/m ³ air (analytical), exposure duration 4 hours. No mortalities during exposure to the test item or during the observation period.	REACH registra- tion data	Reliability 2 GLP and OECD testing guideline compliant study. It is acceptable to use the data of melamine for melamine phosphate because phosphate is not relevant for acute systemic toxicity.
Carcinogenicity		MODERATE: Based on read-across with melamine.		
	QSAR results from the literature (e.g. Danish QSAR database)	No data located		
	Carcinogenicity (Rat and Mouse)	Read-across with melamine (CAS No. 108-78-1). Carcinogenesis Bioassay of Melamine in F344/N Rats and B6C3F1 Mice (Feed Study). Duration of treatment 103 weeks, doses of: male rats 2250; 4500 ppm (ca. 150; 300 mg/kg bw/day), female rats: 4500; 9000 ppm (ca. 300; 600 mg/kg bw/day) Incidences of urinary bladder and kidney lesions, as well as tumour incidences were observed in the urinary bladder, pancreatic islets, thyroid and uterus.	REACH registra- tion data	Reliability 2 Comparable to guideline study with acceptable re- strictions (only two dose levels tested), study with melamine

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7				
Property/Endpoint		Data	Reference	Comments
		NOAEL carcinogenicity 2250 ppm for male rats NOAEL carcinogenicity 4500 ppm for female rats		
	Combined Chronic Toxicity/Carcinogenicity	No data located		
	Other	Melamine is not classifiable as to its carcinogenicity to humans (Group 3).	IARC Monograph	
		MODERATE hazard designation for carcinogenicity: Estimated based on the dissolution product melamine. There is experimental evidence that oral melamine exposure causes carcinogenicity in animals; however, no data were located to support its carcinogenicity in humans. Tumour formation in animals appeared to happen in a mechanical nature under conditions in which it produced bladder calculi.	US EPA, 2014	Report using the GreenScreen® methodology for an alternatives assessment for the flame retardant decabromodiphenyl ether (decaBDE).
Genotoxicity		LOW: Based on negative results in bacterial reverse mutation assays and micronucleus assays		
	Gene Mutation in vitro	Bacterial Reverse Mutation Assay, Negative, in <i>Salmonella typhimurium</i> strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100, with and without metabolic activation. Bacterial Reverse Mutation Assay, Negative, in <i>E. coli WP2 uvr A</i> , with and without metabolic activation.	REACH registration data	Reliability 1 GLP and OECD guideline compliant study.
	Gene Mutation in vivo	No data located		
	Chromosomal Aberrations in vitro	No data located		
	Chromosomal Aberrations in vivo	Micronucleus assay on chromosome aberration in male mouse via intraperitoneal administration. Negative.	REACH registration data	Reliability 2 Comparable to guideline study with acceptable restrictions
	DNA Damage and Repair	No data located		

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7				
Property/Endpoint		Data	Reference	Comments
	Other			
Reproductive effects		LOW: Based on read-across with melamine.		
	Reproduction/Developmental Toxicity Screen	No data located		
	Combined Repeated Dose with Reproduction/ Developmental Toxicity Screen	No data located		
	Reproduction and Fertility Effects	Read across with melamine: Study details not provided. There was no evidence of adverse effects on reproductive organs - mammary glands, ovaries, prostate, seminal vesicles, testes and uterus (macroscopic and microscopic examination) - from 13-week or carcinogenicity studies with rats and mice.	REACH registration data for melamine	Reliability 2 NTP studies are of known high reliability.
	Other	Data for the melamine component support a low hazard designation.	US EPA, 2014	Report using the GreenScreen® methodology for an alternatives assessment for the flame retardant decabromodiphenyl ether (decaBDE).
Developmental effects		LOW: Based on read-across with melamine.		
	Reproduction/ Developmental Toxicity Screen	No data located		
	Combined Repeated Dose with Reproduction/ Developmental Toxicity Screen	No data located		
	Prenatal Development	Read across with melamine: Wistar rats were exposed continuously to ca. 136; 400; 1060 mg/kg bw/day during post coitum days 6 - 16 (= 11 days) NOAEL maternal toxicity ca. 400 mg/kg bw/day	REACH registration data	Reliability 2 Guideline Study (according to the former OECD 414 - exposure time from gd6-20) performed with melamine

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7				
Property/Endpoint		Data	Reference	Comments
		NOAEL teratogenicity >= 1060 mg/kg bw/day		
	Postnatal Development	No data located		
	Prenatal and Postnatal Development	No data located		
	Developmental Neurotoxicity	No data located		
	Other	For melamine, no adverse effects on gestational parameters, no signs of developmental toxicity have been reported.	US EPA, 2014	Report using the GreenScreen® methodology for an alternatives assessment for the flame retardant decabromodiphenyl ether (decaBDE).
Neurotoxicity		No data located		
	Neurotoxicity Screening Battery (Adult)	No data located		
	Other	No data located		
Repeated Dose Effects		MODERATE: Based on read-across with melamine, oral LOAEL for urinary bladder stones in male rats of 72 mg/kg bw/day.		
	Oral	Subchronic study with male and female Fischer 344 rats exposed for 13 weeks to: First study males 0, 560, 850, 1100, 100, 1700 mg/kg/day; females 0, 560, 880, 1200, 1400, 1600 mg/kg/day. Second study males 0, 72, 150, 300, 590, 1300 mg/kg/day; females 0, 84, 150, 300, 600, 1300 mg/kg/day NOAEL formation of urinary bladder stones and reduced body weights in female rats: 1400 mg/kg bw/day, LOAEL urinary bladder stones in male rats: 72 mg/kg bw/day	REACH registration data	Reliability 2 Read-across from supporting substance. Meets generally accepted scientific standards, well documented and acceptable for assessment, performed with melamine

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7				
Property/Endpoint		Data	Reference	Comments
	Oral	Male rats were exposed for 28 days at doses of 0; 2000; 4000; 7000; 10000; 13000; 16000; 19000 ppm (equivalent to ca. 200 - 1900 mg/kg bw/day). NOAEL urinary tract calculi 240 mg/kg bw/day	REACH registration data	Reliability 2 Read-across from supporting substance. Well-reported non-standard study, performed with melamine
	Oral	Subchronic study with male and female Fischer 344 rats exposed for 13 weeks to 0, 10000, 18000 ppm (plus 1% ammonium chloride in drinking water). LOAEL male/female (effect not specified) 1600 mg/kg bw/day	REACH registration data	Reliability 2 Read-across from supporting substance. Meets generally accepted scientific standards, well documented and acceptable for assessment, performed with melamine
Skin Sensitization		LOW: Based on negative results in Guinea pig maximisation test with melamine.		
	Skin Sensitization	Guinea pig maximisation test, intradermal and epicutaneous induction exposure with readings after 24 and 48 hours. No positive skin reaction in any animal at any reading time. Interpretation of results: not sensitising	REACH registration data	Reliability 2 GLP and OECD guideline compliant study with melamine.
Respiratory Sensitization		NO DATA LOCATED		
	Respiratory Sensitization	No data located		
Eye Irritation		NO DATA LOCATED		
	Eye Irritation	No data located		
Dermal Irritation		LOW: Based on negative results in an Acute Dermal Irritation / Corrosion study with melamine in rabbits.		
	Dermal Irritation	A skin irritation study with rabbits according to EU-, OECD- and EPA-methods was performed. Exposure to melamine resulted in no skin irritation in the treated skin-areas of the 6 rabbits. No signs of systemic intoxication were observed during the study period. Dermal application of melamine resulted in a primary irritation	REACH registration data for melamine	Reliability 1 Guideline study with GLP.

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7				
Property/Endpoint		Data	Reference	Comments
		index of 0 (non-irritating), when applied to the intact rabbit skin.		
Endocrine Activity		No data located		
		No data located		
Immunotoxicity		NO DATA LOCATED		
	Immune System Effects	No data located		

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7			
Property/Endpoint	Data	Reference	Comments
Ecotoxicity			
ECOSAR Class	Anilines (amino-meta), Melamines		
Aquatic Acute Toxicity	LOW: Two fish studies, including 5 species, with melamine are available, but no mortality occurred (mortality was not the primary effect tested) and LC50 values have therefore not been determined. Experimental data on algae exposed to melamine yield an EC50 > 325 mg/L. QSAR estimates on alga toxicity yield EC50 > 100 mg/L for the structural similar compound class of anilines. Based on the experimental data, a low hazard score is applied.		
Fish LC ₅₀	96 h, LC50 3.3 * 10 ⁵ mg/L (Estimated) ECOSAR: Anilines (amino-meta)	ECOSAR version 1.11	
	96 h, LC50 15254 mg/L (Estimated) ECOSAR: Melamines	ECOSAR version 1.11	
	Fish (and pig and cat) were fed melamine and/or cyanuric acid for 3 days, to investigate induced renal crystals. Test organisms: 75 fish (21 tilapia, 24 rainbow trout, 15 channel catfish, and 15 Atlantic salmon) were used. None of the control fish or fish to which only melamine was administered had any clinical signs of distress, nor were any gross lesions detected during necropsies. No crystals were detected in any fish kidneys from control fish or fish to which only melamine was administered.	REACH registration data for melamine	Reliability 2 Acceptable publication without GLP.
	The aim of the study was to examine the pathological effects of feeding melamine (or cyanuric acid, separately or in combination) to walking catfish (140 fish). Exposure: 2 weeks, nominal concentrations concerning melamine alone: 0 (group 1) - 0.5 (group 2) - 2 % (group 4) melamine in the feed. The catfish developed darkening of the skin as early as 3	REACH registration data for melamine	Reliability 2 Acceptable, not well-documented publication without GLP.

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7			
Property/Endpoint	Data	Reference	Comments
	days post feeding. None of the catfish died during the 2-week experiment. Melamine-related crystals were not detected in fish, fed melamine alone.		
Daphnid LC ₅₀	Static freshwater test with melamine in <i>Daphnia magna</i> exposed to nominal concentrations of 0 mg/L, 56 mg/L, 100mg/L, 180 mg/L, 320 mg/L, 560 mg/L, and 1000 mg/L 48 h, LC50 > 1000 mg/L (nominal) 24 h, LC50 > 1000 mg/L (nominal) 48 h, EC50 (mobility and behaviour) 200 mg/L (nominal) 24 h, EC50 (mobility and behaviour) 400 mg/L (nominal) 48 h, NOEC (mobility and behaviour) < 56 mg/L (nominal)	REACH registra- tion data	Reliability 1 Guideline study with GLP on melamine
Green Algae LC ₅₀	96 h, EC50 21.8 mg/L (Estimated) ECOSAR: Anilines (amino-meta)	ECOSAR version 1.11	
	96 h, EC50 15969 mg/L (Estimated) ECOSAR: Melamines	ECOSAR version 1.11	
	Static freshwater test with melamine in <i>Pseudokirchnerella subcapitata</i> Nominal Concentrations: Control, 1000 ppm, 320 ppm, 100 ppm, 32 ppm and 10 ppm. 96 h, EC50 (area under the growth curve) > 325 mg/L (nominal)	REACH registra- tion data for mel- amine	Reliability 2 A old study with GLP, but with poor description of the methods. No analytical determination of the concentrations used.
Aquatic Chronic Toxicity	LOW: Based on the lowest available NOEC for melamine, which is a NOEC in <i>Daphnia magna</i> of 18 mg/L.		
Fish NOEC	A semi-static test of the subacute effects of melamine to	REACH registra-	Reliability 2

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7			
Property/Endpoint	Data	Reference	Comments
	juvenile fish of Rainbow trout (<i>Oncorhynchus mykiss</i>) was conducted over a 28 day period at concentrations of 0, 750, 1500, and 3000 ppm. NOEC weight 1500 mg/L, nominal concentration NOEC mortality 1500 mg/L, nominal concentration LC50 mortality >3000 mg/L, nominal concentration	tion data	Well-documented study report, conducted with a method similar to present guidelines.
	260 mg/L, Fish ChV	PBTprofiler.net	QSAR estimation
Daphnid NOEC	Chronic toxicity and reproduction semi-static test to <i>Daphnia magna</i> exposed to melamine for 7 - 21 d at concentrations of 100, 180, 320, 560, 1000 and 1800 mg/L (first test), 10, 18, 32, 56 and 100 mg/L (second test), and 5.6, 10, 18, 32 and 56 mg/L (third test). 7 d, LC50 > 32 < 56 mg/L, nominal 21 d, LC50 > 32 < 56 mg/L, nominal 21 d, NOEC reproduction 18 mg/L, nominal 21 d, NOEC mortality 18 mg/L, nominal	REACH registration data	Reliability 2 Old study (1978) and short description in the report. Method similar to OECD guideline. No analytical determination of the test media concentrations.
Green Algae NOEC	Algal growth inhibition test with <i>Pseudokirchneriella subcapitata</i> exposed to 1000ppm, 320ppm, 100ppm, 32ppm and 10 ppm 96 h, EC50 area under the growth curve 325 mg/L nominal 96 h, NOEC (effect not specified) 98 mg/L nominal. Conclusion: The toxicity of melamine to algae, as measured by growth inhibition, is low.	REACH registration data	Reliability 2 A old study (1988) with GLP, but with poor description of the methods. No analytical determination of the concentrations used.
Transport	Results of Level III fugacity modelling indicate that at equilibrium the substance will be found exclusively in water (25%) and soil (75%). The expected mobility in soil is high, based on an estimated log Koc of 1.31 – 1.51. The Henry's Law Constant indicates that the substance will not		

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7				
Property/Endpoint		Data	Reference	Comments
		volatilise from the water surface.		
	Henry's Law Constant (atm m ³ /mol)	0 (QSAR)	REACH registration data	Reliability 2 QSAR-method used by US EPA on melamine.
	Sediment/Soil Adsorption/Desorption – K _d /K _{oc}	logK _{oc} = 1.13 (1) logK _{oc} = 1.51 (2)	REACH registration data	Reliability 2 Two QSAR estimations are performed on melamine. One is described in the EU Technical Guidance Document (1), the other is used by the UDS EPA (2).
	Level III Fugacity Model	Water 25% Soil 75% Sediment 0% Air 0%	PBTprofiler.net	QSAR estimation
Persistence		VH: Experimental data show that melamine is not readily biodegradable in neither water nor soil. QSAR-estimates support the experimental data. The estimated half-life of 340 days in sediment leads to the very high hazard designation.		
Water	Aerobic Biodegradation	Ready Biodegradability test on melamine. 0 % Degradation after 2 weeks (activated sludge). Melamine is not readily biodegradable.	REACH registration data	Reliability 2 Database source, only few details are provided, but database is created and used by the Japanese authorities, and is therefore considered to be sufficiently reliable.
	Volatilization Half-life for Model River	No data located		
	Volatilization Half-life for Model Lake	No data located		
	Half-Life Water	38 days	PBTprofiler.net	QSAR estimation
Soil	Aerobic Biodegradation	Degradation of melamine was measured in a silty clay loam (soil 1, pH 8.2, initial concentration 2000 and 230 mg/kg soil) for 28 weeks and in a sandy loam (soil 2, pH 5.2, initial concentration 230 mg/kg soil) for 24 weeks. Soil 1:	REACH registration data	Reliability 2 Publication, which meets basic scientific principles, but which is rather old (1964) and not well described.

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7																																					
Property/Endpoint		Data		Reference	Comments																																
		<table><tr><th>Weeks</th><th>% Degr.</th><th>Parameter</th></tr><tr><td>6</td><td>6.4</td><td>nitrification; solution</td></tr><tr><td>6</td><td>7.7</td><td>nitrification; powder</td></tr><tr><td>10</td><td>0.7</td><td>nitrification; % of organic N, found as NO3- N; granules.</td></tr><tr><td>12</td><td>9.1</td><td>nitrification; solution</td></tr><tr><td>12</td><td>9.1</td><td>nitrification; powder</td></tr><tr><td>18</td><td>10.5</td><td>nitrification; solution</td></tr><tr><td>18</td><td>15.4</td><td>nitrification; powder</td></tr><tr><td>24</td><td>13.7</td><td>nitrification; solution</td></tr><tr><td>24</td><td>17.9</td><td>nitrification; powder</td></tr><tr><td>28</td><td>0</td><td>nitrification; granules</td></tr></table>	Weeks	% Degr.	Parameter	6	6.4	nitrification; solution	6	7.7	nitrification; powder	10	0.7	nitrification; % of organic N, found as NO3- N; granules.	12	9.1	nitrification; solution	12	9.1	nitrification; powder	18	10.5	nitrification; solution	18	15.4	nitrification; powder	24	13.7	nitrification; solution	24	17.9	nitrification; powder	28	0	nitrification; granules		
		Weeks	% Degr.	Parameter																																	
		6	6.4	nitrification; solution																																	
		6	7.7	nitrification; powder																																	
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	Weeks	% Degr.	Parameter																																		
	6	0	nitrification; powder																																		
	12	0	nitrification; powder																																		
	18	3.9	nitrification; powder																																		
	24	8.9	nitrification; powder																																		
	Anaerobic Biodegradation		No data located																																		
Soil Biodegradation with Product Identification		No data located																																			
Sediment/Water Biodegradation		No data located																																			
Half-life soil		75 days	PBTprofiler.net	QSAR estimation																																	
Half-life sediment		340 days	PBTprofiler.net	QSAR estimation																																	
Air	Atmospheric Half-life	24 days	PBTprofiler.net	QSAR estimation																																	

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7				
Property/Endpoint		Data	Reference	Comments
Reactivity	Photolysis	No data located		
	Hydrolysis	No data located		

1,3,5-triazine-2,4,6-triamine phosphate/ CAS No. 41583-09-9/ EC no. 255-449-7				
Property/Endpoint		Data	Reference	Comments
Environmental Half-life		No data located		
Bioaccumulation		VL: Based on measured BCF values for melamine < 100.		
	Fish BCF	Flow-through test with melamine on <i>Cyprinus carpio</i> , 6 week exposure at 2 mg/L and 0.2 mg/L. BCF at 2 ppm < 0.38 BCF at 0.2 ppm < 3.8	REACH registration data	Reliability 2 Database source, only few details are provided, but database is created and used by the Japanese authorities, and is therefore considered to be sufficiently reliable.
	Fish BCF	Static test with melamine on <i>Pimephales promelas</i> , 96 and 72 h exposure. BCF at 0.082 mg/L < 0.48 (96 h, basis viscera) BCF at 0.082 mg/L < 0.26 (96 h, basis carcass)	REACH registration data	Reliability 2 Old (1984) but reasonably well described study. Similar to present guidelines.
	Fish BCF	Determination of BCF after static exposure of <i>Oncorhynchus mykiss</i> to melamine for 72 h. BCF at 0.089 mg/L < 0.11 (72 h, basis viscera) BCF at 0.089 mg/L < 0.26 (72 h, basis muscle) BCF at 0.091 mg/L < 0.11 (64 h, basis viscera) BCF at 0.091 mg/L < 0.03 (64 h, basis muscle)	REACH registration data	Reliability 2 Old (1984) but reasonably well described study. Similar to present guidelines.
	Other BCF	3.2	PBTprofiler.net	QSAR estimation
	BAF	No data located		
	Metabolism in Fish	No data located		
Environmental biomonitoring				
Ecological Biomonitoring		No data located		
Human Biomonitoring		Recoveries of melamine ranged between 90.3 +/- 7.8 and 102.1 +/- 5.6% at levels of 0.6 to 2.4 ppm in 4 kinds of beverages. The quantitation limit was 2.5 micrograms melamine in 50 mL beverage.	REACH registration data	Reliability 2 Documented analytical method. No GLP.

BASF, 2010: Technical data sheet for Melapur® MP.

ECOSAR/EPI (EPIWIN/EPISUITE) Estimations Programs Interface for Windows, Version 1.11. U.S. Environmental Protection Agency: Washington D.C. <http://www2.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model>

IARC Monograph: Melamine. Available at: monographs.iarc.fr/ENG/Monographs/vol73/mono73-17.pdf

Metadynea, 2014: Technical data sheet MPT11, 1,3,5-Triazine-2,4,6-triaminephosphate.

PBTprofiler.net: US EPA PBT Profiler, Model tool available at <http://www.pbtprofiler.net/>, search termes CAS No.: 41583-09-9, Name: 1,3,5-triazine-2,4,6-triamine phosphate, SMILES: n1c(N)nc(N)nc1N P(=O)(O)(O)O

REACH registration data: [http://echa.europa.eu/da/information-on-chemicals/registered-substances using](http://echa.europa.eu/da/information-on-chemicals/registered-substances-using) CAS No. 41583-09-9 as search term.

US EPA (2014). An alternatives assessment for the flame retardant decabromodiphenyl ether (decaBDE). US Environmental Protection Agency.

Appendix 8

Ethylenediamine phosphate, CAS No. 14852-17-6

Ethylenediamine phosphate consists of a mixture of ethylenediamine and phosphoric acid. Ethylenediamine (CAS No. 107-15-3) is therefore used as chemical surrogate in case of lack of data for ethylenediamine phosphate.

Ethylenediamine has a harmonised classification comprising the following health hazards: Acute Tox. 4 * (H302), Acute Tox. 4 * (H312), Skin Corr. 1B (H314), Skin Sens. 1 (H317), Resp. Sens. 1 (H334). Phosphoric acid (CAS No. 7664-38-2) also has a harmonised classification: Skin Corr. 1B (H314).

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9			
Property/Endpoint	Data	Reference	Comments
Physical/chemical properties			
Melting Point (°C)	325 °C There was no decomposition & sublimation observed of ethylenediamine, salt with phosphoric acid at the melting point.	REACH registration data	Reliability 1
	Decomposition starts at (°C) 230	Metadynea, 2014	No study details provided
Boiling Point (°C)	340 °C No decomposition of ethylenediamine, salt with phosphoric acid was observed at the boiling point.	REACH registration data	Reliability 1
Vapour Pressure (Pa)	0.000000034 Pa at 25 °C	REACH registration data	Reliability 2 estimated by calculation
Water Solubility (mg/L)	3000 mg/L	REACH registration data	Reliability 1
	50 g/L (for commercial product)	Metadynea, 2014	No study details provided
Log Kow	-2.522 at 28 °C and pH of 6.69	REACH registration data	Reliability 1
pKa	0.2760 x 10 ⁻¹²	REACH registration data	

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
Human health effects				
Toxicokinetics		Based on the available studies, the substance appears to have low bioaccumulation potential. Ethylenediamine (EDA) is readily absorbed after oral and respiratory administration in animal models. Absorption was rapid as the EDA concentration in plasma reached a maximum at about 1 hour after dosing in mice. EDA is distributed throughout the body, with the liver and kidney attaining the highest concentration among the major organs. Urine is the major route of excretion (ca. 45 – 55 %), smaller fractions (ca. 4 – 16% and 6 – 8%, respectively) are excreted via faeces and respiration, and excretion was quite rapid. The principle metabolite in the urine was N-acetylethylenediamine.		
Dermal absorption <i>in vitro</i>		No data located.		
Absorption, Distribution, Metabolism & Excretion	Oral, dermal or inhaled	Read- across with ethylenediammonium dichloride (CAS No. 333-18-6): Metabolism and pharmacokinetics of ethylenediamine in the rat following oral, endotracheal or intravenous administration. Doses: 5, 50 and 500 mg/kg bodyweight, 24 or 48 hours study of distribution following single dose. Results: Rapid absorption from gastrointestinal as well as from respiration tract. Distributed in body, but liver, kidneys, thyroid and bone marrow contained highest concentrations. Excretion via urine: 45-55%, faeces: 4-16%, CO ₂ : 6-8%. Interpretation of the results: low bioaccumulation potential based on study results	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 No data on GLP, study from 1982.
		Read- across with ethylenediammonium dichloride (CAS No. 333-18-6): Oral gavage, endotracheal or intracardial administration of EDA*2HCl in male mice. Doses: 5, 50 and 500 mg/kg bodyweight, 48 hours study of distribution following single dose. Results:	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 No data on GLP, study from 1982.

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
		Readily absorbed from the gut, bioavailability, 87% measured at 50 mg/kg. Rapid absorption, EDA concentration in plasma reached a maximum 1 h after dosing. Distributed throughout the body, with the liver and kidney attaining the highest concentration among the major organs. Excretion via urine was the major route of excretion >50 %. Faecal: 4-13 %, respiratory: 8%. Excretion was rapid > 70% eliminated within 24 h. Clearance and terminal half-life varies only slightly depending on route of administration. Interpretation of the results: low bioaccumulation potential based on study results		
	Other	Absorption through inhalation is not considered a relevant exposure pathway due to the low vapour pressure of the substance. Based upon the physico-chemical properties and BCF of ethylenediamine, salt with phosphoric acid, it has been deduced that the chemical has potentially low bio-accumulative property and hence shall be eliminated from the body system through urine or faeces.	REACH registration data	Reliability 2 Based on the weight of evidence of various physical- chemical and bioaccumulative parameters in the dossier
Acute mammalian toxicity		LOW: Based on the oral and dermal LD50 > 2000 mg/kg bw for female rats.		
Acute lethality	Oral	Oral exposure study with Wistar rats according to OECD Guideline 423. LD50 > 2000 mg/kg bw for female rats	REACH registration data	Reliability 1 according to OECD Guideline 423
	Dermal	Dermal exposure study with Wistar rats according to OECD Guideline 402 (Acute Dermal Toxicity). The test compound CAS No. 14852-17-6 when applied dermally at the dose level of 2000 mg/kg b.wt. on Wistar albino rats	REACH registration data	Reliability 1 according to OECD Guideline 402

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
		did not produce any mortality during the observation period of 14 days. LD50 > 2000 mg/kg bw for male/female rats		
	Inhalation	Data waiving due to exposure considerations	REACH registration data	
Carcinogenicity		LOW: Based on a carcinogenicity study with a chemical surrogate.		
	QSAR results from the literature (e.g. Danish QSAR database)	No data located.		
	Carcinogenicity (Rat and Mouse)	Read-across with ethylenediammonium dichloride (CAS No. 333-18-6). 2 Year oral exposure study with Fischer 344 rats, exposure every 2 nd week in dose groups of 20, 100, and 350 mg/kg bw. 10 rats/sex/dose and control group were scheduled for sacrifice at 6 and 12 month, 20 rats/sex/dose and control group were scheduled for sacrifice at 18 month. NOAEL carcinogenicity 159 mg/kg bw/day (actual dose received) There was no evidence of carcinogenic effects.	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 No GLP data
	Combined Chronic Toxicity/Carcinogenicity	No data located.		
Genotoxicity		LOW: Based on negative results in the bacterial reverse mutation assay and QSAR estimations for ethylenediamine phosphate and the conclusion on genotoxicity for ethylenediamine.		
	Gene Mutation <i>in vitro</i>	Bacterial reverse mutation assay: The Salmonella Mutagenicity Test is negative with and without metabolic activation.	REACH registration data	Reliability 2 Authoritative data base
		QSAR Toolbox 2.3.0.1132 prediction for "Gene Mutation" read across evaluation for 14852-17-6	REACH registration data	Reliability 2 Prediction report

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
		The prediction is done for ethylenediamine, salt with phosphoric acid for <i>S. typhimurium</i> TA 1535, TA 1537, TA 98 and TA 100 for genetic toxicity without metabolic activation. The substance is estimated to be negative.		
	Gene Mutation <i>in vivo</i>	No data located.		
	Chromosomal Aberrations <i>in vitro</i>	QSAR Toolbox 2.3.0.1132 prediction for "Chromosome Aberration" read across evaluation for 14852-17-6 The prediction is done for ethylenediamine, salt with phosphoric acid for Chinese Hamster Lungcell for genetic toxicity with metabolic activation is estimated to be negative.	REACH registration data	Reliability 2 Prediction report
	Chromosomal Aberrations <i>in vivo</i>	No data located.		
	DNA Damage and Repair	No data located.		
	Other	SIDS Initial Assessment Profile on ethylenediamine. Conclusion on review of eight genotoxicity studies: <i>The weight of evidence from both in vitro and in vivo tests indicates that ethylenediamine is unlikely to be genotoxic. It was also negative in chronic bioassays via two routes, oral and dermal.</i>	UNEP, 2001	
Reproductive effects		LOW: Based on read-across with ethylenediammonium dichloride, resulting in a NOAEL of 500 mg/kg/day (highest dose given) in rats.		
	Reproduction/Developmental Toxicity Screen	Read-across with ethylenediammonium dichloride (CAS No. 333-18-6): In a two-generation study, male and female Fischer 344 rats were fed diets containing 0, 50, 150 or 500 mg/kg/day. There was no indication of reproductive toxicity in Fischer 344 rats, following exposure to dietary EDA for two generations, leading to a NOAEL of 500 mg/kg/day (highest dose given) in rats.	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 pre-GLP (1984)

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
	Continuous breeding study	No data located.		
	Combined Repeated Dose with Reproduction/Developmental Toxicity Screen	QSAR Toolbox Two-generation study in which 25 male and female rats were studied at doses 5, 10 and 25 mg/kg/day. LOEL for the F2 Generation (male/female) 35.46 mg/kg bw/day (effect: Pituitary Pathology and Weight)	REACH registration data	Reliability 2 Prediction report
	Reproduction and Fertility Effects	No data located.		
	Other	No data located.		
Developmental effects		Moderate: Based on weight of evidence from available studies with ethylenediammonium and ethylenediammonium dichloride. A single study in rats noted reduction of body weight gain and diet consumption, decreased number of live foetuses/litter and increased number of resorptions/litter in dams receiving 1000 mg/kg/day, these effects are most likely due to maternal toxicity. None of the studies identified teratogenic effects. A NOAEL for maternal toxicity $\geq$ 80 mg/kg bw/day (highest dose tested) was identified in two rabbit studies. The score “moderate” is assigned based on a conservative approach due to maternal toxicity.		
	Reproduction/Developmental Toxicity Screen	QSAR Toolbox Developmental Study in which 25 female rats were studied at doses 5, 10 and 25 mg/kg/day LOEL fetotoxicity 106.44 mg/kg bw/day	REACH registration data	Reliability 2 Prediction Report
		Read-across with ethylenediammonium dichloride (CAS No. 333-18-6). In a gavage study ten Fischer 344 rats were fed ethylenediamine di-hydrochloride by gavage 1000 mg/kg/day on gestation day 6-15. The aim was to decide if this dose by gavage would reduce diet consumption, similar to results shown in a diet study. Reduction of body weight gain and diet consumption, decreased number of live foetuses/litter and increased number of resorptions/litter were noted.	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 pre-GLP (1987)
		Read-across with ethylenediammonium dichloride (CAS No. 333-18-6). Rats were administered a dietary dose of 1000 mg/kg/day on	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 pre-GLP (1984)

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
		gestation day 6- 15. The results of these studies indicate that ethylenediamine dihydrochloride was not teratogenic in the Fischer 344 rat.		
	Combined Repeated Dose with Reproduction/ Developmental Toxicity Screen	Oral exposure study with New Zealand White rabbits exposed to 0, 10, 40 or 80 mg/kg/day. The maternal and developmental NOAEL for EDA in the New Zealand White rabbit exposed during major organogenesis is greater than or equal to 80 mg/kg/day. Higher doses were not evaluated in this study due to the observation of greater than or equal to 20% maternal mortality at greater than or equal to 100 mg/kg/day in a preliminary investigation. There were no treatment-related maternal deaths in this study, and no characteristic clinical signs of toxicity in EDA-treated dose. Uterine examination on gd 30 revealed no adverse effects of EDA upon prenatal viability, litter size, fetal weight or fetal morphology. NOAEL maternal toxicity ≥ 80 mg/kg bw/day (highest dose tested)	REACH registration data	Reliability 2 Authoritative data base, NTP Study: TER92020, 2012, according to Guideline EPA OPPTS 870.3700
		Read-across with ethylenediammonium (EDA) dichloride (CAS No. 333-18-6). Rabbits were dosed during gestation days 6 - 19. On day 21 uterine contents are examined, and the foetuses are evaluated for externally visible anomalies and for soft tissue and skeletal changes. Maternal examinations were fetal growth, viability and morphological development. NOAEL maternal toxicity ≥ 80 mg/kg bw/day (highest dose tested) No characteristic clinical signs of toxicity were observed. No effect on maternal food intake, body weight or weight gain,	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 No guideline followed, no information on GLP.

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
		liver or kidney weight. No adverse effects on prenatal viability, litter size, fetal weight or fetal morphology was observed		
	Prenatal Development	No data located.		
	Postnatal Development	No data located.		
	Prenatal and Postnatal Development	No data located.		
	Developmental Neurotoxicity	No data located.		
	Other	No data located.		
Neurotoxicity		DG		
	Acute and delayed neurotoxicity tests in hens	No data located.		
	Other	No data located.		
Repeated Dose Effects		MODERATE: Based on a NOAEL of 22 mg/kg/day EDA and a NOEL of 20 mg/kg/day EDA in a 13-week and 2-year rat study, respectively.		
	Sub-chronic oral repeated dose	QSAR Toolbox Chronic Study with rats exposed at doses of 0.00, 7500.00, 15000.00 (unit not specified) for 540 days. LOEL (male/female) 966.34 mg/kg bw/day (body weight decreased)	REACH registration data	Reliability 2 Prediction Report
		Read-across with ethylenediammonium dichloride (CAS No. 333-18-6). In a three month dietary study, male and female rats were fed targeted doses of 0, 50, 250 or 1000 mg/kg/day EDA-2HCl. There were no deaths and no abnormal clinical signs noted during the study. Body weight gains were significantly decreased in the high dose group, which affected a number of absolute and relative organ weights in both males and females. Water consumption was comparable to control values at all	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 The study was performed pre-GLP. No guideline was available.

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
		dose levels in males but was decreased in a dose-response manner in female rats at all 3 dose levels. Slight reductions in serum glucose levels and an elevation of alkaline phosphatase, AST and ALT activities were observed in the high dose group. An elevation of ALT activity was also observed in the intermediate dose male rats. Urinary pH in the high dose group was decreased in both males and females. There were no dose-related gross lesions in any animal on the study. The most significant histopathologic lesion, hepatocellular pleomorphism, was observed primarily in the high dose female and, to a lesser extent, male rats. LOAEL 114 mg/kg/day EDA (250 mg/kg/day EDA-2HCl) NOAEL 22 mg/kg/day EDA (50 mg/kg/day EDA-2HCl)		
		Review of seven dietary/oral gavage studies: <i>Conclusions: In repeated dose studies, decreased body weight and water and feed consumption have been observed and are probably related to the irritating nature of EDA and it's high pH.</i> <i>Hepatocellular pleomorphism has been observed in several dietary studies of varying duration. The lowest LOAEL was 100 mg/kg/day with a NOEL of 20 mg/kg/day in the chronic dietary feeding study (two-year bioassay) .</i>	UNEP, 2001	
	Sub-chronic inhalation repeated dose	No data located.		
	Dermal repeated dose	No data located.		
Skin Sensitization		HIGH: Based on harmonised classification of ethylenediamine. Since sub-category (1A or 1B) is not specified, we precautionously assign the score "high" (corresponding to sub-category 1A).		
	Skin sensitization	QSAR predictions by Danish EPA model, Guinea pig maximisation test or human experience.	REACH registration data	Reliability 2 Prediction model

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
		Skin sensitisation potential of ethylenediamine, salt with phosphoric acid is estimated to be positive.		
		QSAR Toolbox Version 2.3 prediction for "Skin Sensitisation" read across evaluation for 14852-17-6	REACH registration data	Reliability 2 Prediction model
		Based on this prediction it can be concluded that ethylenediamine, salt with phosphoric acid is classified as skin sens.1 as per the criteria of CLP regulation.		
		Notified classification and labelling according to CLP criteria (8 notifiers) Skin Sens. 1	ECHA C&L inventory	
		Advisory health classification: SkinSens1	Danish Environmental Protection Agency	
		Skin Sens. 1 (H317 - May cause an allergic skin reaction). Sub-category (1A or 1B) is not specified, possibly due to insufficient data.	ECHA C&L inventory for ethylenediamine (CAS No. 107-15-3)	Harmonised classification
	Skin sensitization in humans	No data located.		
Respiratory Sensitization		HIGH: Based on harmonised classification of ethylenediamine. Since sub-category (1A or 1B) is not specified, we precautiously assign the score "high" (corresponding to sub-category 1A).		
	Respiratory Sensitization	Resp. Sens. 1 (H334)	ECHA C&L inventory for ethylenediamine (CAS No. 107-15-3)	
Eye Irritation		LOW: Based on guideline study.		
	Eye Irritation	Study on New Zealand White rabbits The eyes were examined at 1, 24, 48 and 72 hours after test substance application. The grades of ocular reaction (conjunctiva, cornea and iris) were recorded at each observation. To	REACH registration data	Reliability 1 OECD Guideline 405

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
		determine the reversibility of the effect the animal was observed normally for 21 days. Practically not irritating effects were fully reversible. Interpretation of results: not irritating		
Dermal Irritation		VH: Based on harmonised classification for ethylenediamine and phosphoric acid.		
	Dermal Irritation	Study on New Zealand White rabbits Skin reaction The test compound CAS No. – 14852-17-6 applied at the dose level of 0.5 gm on shaven back skin (approximately 6 cm ²) of rabbit did not produce any clinical signs of irritation to skin during period of observation. The duration of application of test compound was 24th hour and the observation period 14 days. Conclusion: not irritating	REACH registration data	Reliability 1 OECD Guideline 404
		Skin Corr. 1B (H314 - Causes severe skin burns and eye damage)	ECHA C&L inventory for ethylenediamine (CAS No. 107-15-3)	
		Skin Corr. 1B (H314 - Causes severe skin burns and eye damage)	ECHA C&L inventory for phosphoric acid (CAS No. 7664-38-2)	
Endocrine Activity		DG		
	Endocrine activity	No data located.		
Immunotoxicity		DG		
	Immune System Effects	No data located.		

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9			
Property/Endpoint	Data	Reference	Comments
Ecotoxicity			
ECOSAR Class	Aliphatic Amines		
Aquatic Acute Toxicity	MODERATE: Based on an EC50 of 16.7 mg/L for <i>Daphnia magna</i> .		
Fish LC ₅₀ (Freshwater)	Short term toxicity to fish by ECOSAR Version 1.10 96 h, LC50 24,0000 mg/L	REACH registration data	Reliability 2 Prediction model
	QSAR Toolbox 2.3.0.1132 prediction for LC50 read across evaluation on <i>Oncorhynchus mykiss</i> 96 h, LC50 203.3 mg/L	REACH registration data	Reliability 2 Prediction model
	Study on ethylenediammonium (EDA). Semi-static test with <i>Poecilia reticulata</i> exposed to 0, 180, 320, 560, 1000, and 1800 mg/l nominal concentrations. 96 h, LC50 640 mg/L	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 Study performed under GLP and according to guidelines (EU Method C.1). No analytical monitoring was performed.
Fish LC ₅₀ (Marine)	No data located.		
Daphnid LC ₅₀ / EC ₅₀ (Freshwater)	Short term toxicity to aquatic invertebrates by ECOSAR Version 1.10 on <i>Daphnia magna</i> 48 h, LC50 6266.7 mg/L	REACH registration data	Reliability 2 Prediction model
	QSAR Toolbox 2.3.0.1132 prediction for EC50 read across evaluation on <i>Daphnia magna</i> 48 h, EC50 191 mg/L	REACH registration data	Reliability 2 Prediction model
	Study on ethylenediammonium (EDA). <i>Daphnia magna</i> exposed to 0, 5.6, 10, 32, 56, and 100 mg/l nominal concentrations.	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 Study performed under GLP and according to guidelines (EU Method C.2). No

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9			
Property/Endpoint	Data	Reference	Comments
	48 h, EC50, 16.7 mg/L		analytical monitoring was performed.
Daphnid LC ₅₀ / EC ₅₀ (Marine)	No data located.		
Green Algae IC ₅₀ / EC ₅₀	Short term toxicity to aquatic algae by ECOSAR Version 1.10 on green algae	REACH registration data	Reliability 2 Prediction model
	96 h, EC50 321 mg/L (growth rate)		
	QSAR predictions by Danish EPA, Multicase model is used to estimate EC50 (growth) of algae <i>Pseudokirchneriella subcapitata</i>	REACH registration data	Reliability 2 Prediction model
	No details on exposure duration, EC50 386 mg/L (growth rate)		
	Study on ethylenediammonium (EDA). <i>Pseudokirchneriella subcapitata</i> exposed to 0, 3.2, 10.2, 32.8, 104.9, and 335.5 mg/l nominal concentrations. 72 h, EC50 (biomass) 71 mg/L 72 h, EC50 (growth rate) 645 mg/L	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 Study performed under GLP and according to according to EU Method C.3 (Algal Inhibition test) including updates published 1988. No analytical monitoring was performed.
Aquatic Chronic Toxicity	HIGH: Based on a 21 d NOEC of 0.16 mg/L for <i>Daphnia magna</i> .		
Fish NOEC (Freshwater)	Data waiving, study scientifically unjustified	REACH registration data	
	Study on ethylenediammonium (EDA). Semi-static test with <i>Gasterosteus aculeatus</i> on early-life stage: reproduction, (sub)lethal effects. A preliminary test was performed with the following concentrations: 0, 1, 10, 50, 100, 300 mg/l . 10 eggs were used per concentration. On the basis of these results a limit test was performed at 10 mg/l, using 60 eggs.	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 Study performed under GLP and according to OECD Guideline 210. No analytical monitoring was performed.

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
		28 d, NOEC > 10 mg/L		
Daphnid NOEC (Freshwater)		Data waiving, study scientifically unjustified	REACH registration data	
		Study on ethylenediammonium (EDA). Semi-static test with <i>Daphnia magna</i> exposed to 0.08 -5 mg/L.	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 Limited information on procedures, no GLP.
		21 d, NOEC (reproduction rate) 0.16 mg/L		
Green Algae NOEC		QSAR Toolbox 2.3.0.1132 prediction for NOEDC read across evaluation on <i>Pseudokirchneriella subcapitata</i>	REACH registration data	Reliability 2 Prediction model
		72 h, NOEC 3.06 mg/L (growth)		
		Study on ethylenediammonium (EDA). Static test with <i>Pseudokirchneriella subcapitata</i> exposed to 0, 3.2, 10.2, 32.8, 104.9, and 335.5 mg/l nominal concentrations. 72 h, NOEC 3.2 mg/L (growth rate)	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 Study performed under GLP and according to according to EU Method C.3 (Algal Inhibition test) including updates published 1988. No analytical monitoring was performed.
Transport		The substance shows considerable water solubility. According to QSAR predictions, ethylenediamine-o-phosphate will be found primarily in the water compartment (78.1 %), with a smaller fraction in soil (21.8%) and very little in air (0.1%). In the atmosphere, the substance is expected to be present only associated with water aerosols and removal from air is therefore by wet deposition. Experimental data for EDA indicate relative immobility in soil ($K_{oc} = 4,786$), and phosphates are known to sorb strongly to i.e. clay particles in soil.		
	Henry's Law Constant (atm-m ³ /mole)	HENRYs LAW CONSTANT by EPI (Estimation Programs Interface) Suite 9.14 * 10 ⁻²² Pa m ³ /mol	REACH registration data	Reliability 2 Prediction model
	Sediment/Soil Adsorption/Desorption – K_d/K_{oc}	Adsorption by EPI Suite Estimated via MCI method $K_{oc}=6.27$; log $k_{oc}=0.797$	REACH registration data	Reliability 2 Prediction model
		Study on ethylenediammonium (EDA).	REACH registration data	Reliability 1

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
		Six different soils were used. Five were collected from the vadose zone: two sandy loams, a sandy clay loam, a silty loam, and a clay. The sixth soil was a sand collected from an aquifer. Conclusions: Batch equilibrium adsorption studies were conducted which showed a log K_{oc} of 3.68 (K_{oc} = 4,786), indicating relative immobility in soil.	for ethylenediamine (CAS No. 107-15-3)	equivalent or similar to OECD Guideline 106
	Level III Fugacity Model	Model for EDA: Using the default emissions of equal amount to soil, air and water (1000 kg/hour for each compartment), the percentage of ethylenediamine in bulk water, air and soil predicted by the Level III model are 78.1, 0.1 and 21.8% respectively. Regardless of the media to which EDA is released, most of the EDA at steady state is in the water phase. These results are consistent with the physical properties of EDA, namely the high water solubility and low air-water and octanol-water partition coefficients.	UNEP, 2001	
Persistence		VERY LOW: Based on biodegradation test with EDA (95 % degradation in 28 d) and QSAR estimations resulting in a half-life in water of 15 days and of 3.01 h due to biodegradation and hydrolysis, respectively.		
Water	Aerobic Biodegradation	Bio-degradation in water by Environmental Science Center's PBT profiler, ready biodegradability Half-life 15 days (readily biodegradable)	REACH registration data	Reliability 2 Prediction model
		Biodegradation in water by EPI (Estimation Programs Interface) Suite Half-life 15 days (readily biodegradable)	REACH registration data	Reliability 2 Prediction model
		Activated sludge, from an activated sludge plant, was used as inoculum. Ethylenediamine is degraded 95% in 28 days in the Closed Bottle Test and can be considered readily biodegradable.	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 1 according to EU Method C.4-E (Determination of the "Ready" Biodegradability - Closed Bottle Test)

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
	Volatilization Half-life for Model River	No data located.		
	Volatilization Half-life for Model Lake	No data located.		
Soil	Aerobic Biodegradation	Bio-degradation in soil by Environmental Science Center's PBT profiler, ready biodegradability Half-life 30 days (readily biodegradable)	REACH registration data	Reliability 2 Prediction model
	Anaerobic Biodegradation	No data located.		
	Soil Biodegradation with Product Identification	No data located.		
	Sediment/Water Biodegradation	No data located.		
Other	Biotic degradation.	No data located.		
Air	Atmospheric Half-life	No data located.		
Reactivity	Photolysis	Phototransformation in air by Environmental Science Center's PBT profiler 50 % Degr. in air: 0.38 days	REACH registration data	Reliability 2 Prediction model
		Phototransformation by EPI (Estimation Programs Interface) Suite Half-life 6.08 h	REACH registration data for ethylenediamine (CAS No. 107-15-3)	Reliability 2 Prediction model
	Hydrolysis	Hydrolysis by EPI (Estimation Programs Interface) Suite Half-life 3.01 h	REACH registration data	Reliability 2 Prediction model

Ethylenediamine-o-phosphate /CAS No. 14852-17-6 /EC No. 238-914-9				
Property/Endpoint		Data	Reference	Comments
Environmental Half-life		No data located.		
Bioaccumulation		VERY LOW: Based on QSAR estimates resulting in BCFs << 100 and a measured log Kow << 3.		
	Fish BCF	Bioaccumulation by Environmental Science Center's PBT profiler, fish BCF 3.2 (non bioaccumulative)	REACH registration data	Reliability 2 Prediction model
		Bioaccumulation by EPI (Estimation Programs Interface) Suite, whole body, test organism not specified BCF 3.16 (non bioaccumulative)	REACH registration data	Reliability 2 Prediction model
	Other BCF	No data located.		
	BAF	No data located.		
	Metabolism in Fish	No data located.		
Environmental biomonitoring				
Ecological Biomonitoring		No data located.		
Human Biomonitoring		No data located.		

Danish Environmental Protection Agency, Database with QSAR predictions for classification: <http://mst.dk/virksomhed-myndighed/kemikalier/stoflister-og-databaser/vejledende-liste-til-selvklassificering-af-farlige-stoffer/clp/> using CAS No. 14852-17-6 as search term.

ECHA C&L inventory: <http://echa.europa.eu/information-on-chemicals/cl-inventory-database> using CAS No. 14852-17-6 as search term.

Metadynea, 2014: EP11, Technical Data Sheet. November 2014.

REACH registration data: <http://echa.europa.eu/da/information-on-chemicals/registered-substances> using CAS No. 14852-17-6 as search term unless specified otherwise.

Appendix 9

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide, CAS No. 848820-98-4

A notified classification is available for 6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide: Skin Irrit. 2 (H315; 29 notifiers), Aquatic Chronic 3 (H412; 28 notifiers), Acute Tox. 4 (H302, 1 notifier). The latter hazard statement is erroneous (there is no Category 4 for Acute Aquatic toxicity and H302 is a health hazard code) and is therefore disregarded.

Data for this substance were basically only available from the REACH registration data. QSAR estimates (from ECOSAR and PBT profiler) are therefore used to support available data and fill some of the data gaps.

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide/CAS No. 848820-98-4/EC No. 805-659-5			
Property/Endpoint	Data	Reference	Comments
Physical/chemical properties			
Boiling Point (°C)	Two experiments were conducted with the Siwoloboff method. No boiling point could be determined because of starting decomposition of the test item taking place at approx. 362 °C (635 K). Decomposition was indicated by a change of the colour of the test item, which became darker and finally red / brown during the tests.	REACH registration data	Reliability 1 OECD Guideline 103
	Decomposition starts at 250 °C	Metadynea, 2014	No further details
Vapour Pressure (Pa)	at 20 °C: $9.48 \cdot 10^{-8}$ Pa at 25 °C: $1.97 \cdot 10^{-7}$ Pa	REACH registration data	Reliability 1 OECD Guideline 104
Water Solubility (mg/L)	Mean water solubility at the plateau is 176.1 ± 5.9 mg/L.	REACH registration data	Reliability 1 OECD Guideline 105
Log Kow	3.32	REACH registration data	Reliability 1 OECD Guideline 117
	EPISuite WSKowwin v1.43 Estimate 3.390	ECOSAR v1.11	QSAR estimate
pKa	No data located.		

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide/CAS No. 848820-98-4/EC No. 805-659-5				
Property/Endpoint		Data	Reference	Comments
Human health effects				
Toxicokinetics				
Dermal absorption <i>in vitro</i>		No data located.		
Absorption, Distribution, Metabolism & Excretion	Oral, dermal or inhaled	No data located.		
	Other	No data located.		
Acute mammalian toxicity		LOW: Based on a single oral dose of 2000 mg/kg, yielding no lethality, clinical symptoms, or changes in general state and behaviour.		
Acute lethality	Oral	No lethality was noted at single oral dose of 2000 mg/kg bw. No clinical symptoms were observed on the day of the treatment and during the 14-day observation period, the general state and behaviour of experimental animals were normal. The body weight development was undisturbed in all animals.	REACH registration data	Reliability 1 OECD Guideline 423
	Dermal	No data located.		
	Inhalation	No data located.		
Carcinogenicity		DG		
	QSAR results from the literature (e.g. Danish QSAR database)	No data located.		
	Carcinogenicity (Rat and Mouse)	No data located.		
	Combined Chronic Toxicity/Carcinogenicity	No data located.		
	Other	No data located.		
Genotoxicity		DG		
	Gene Mutation <i>in vitro</i>	Test results:	REACH registration data	Reliability 1

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide/CAS No. 848820-98-4/EC No. 805-659-5				
Property/Endpoint		Data	Reference	Comments
		Species/strain <i>Salmonella typhimurium</i> (TA 97a, TA 98, TA 100, TA 102 and TA 1535), with and without metabolic activation, Genotoxicity: negative Mutagenicity: No significant increase of the number of revertant colonies in the treatments with and without metabolic activation was observed. No concentration-related increase over the tested range was found. Therefore the test item is stated as not mutagenic under the test conditions.		OECD Guideline 471
	Gene Mutation <i>in vivo</i>	No data located.		
	Chromosomal Aberrations <i>in vitro</i>	No data located.		
	Chromosomal Aberrations <i>in vivo</i>	No data located.		
	DNA Damage and Repair	No data located.		
	Other	No data located.		
Reproductive effects		DG		
	Reproduction/Developmental Toxicity Screen	No data located.		
	Continuous breeding study	No data located.		
	Combined Repeated Dose with Reproduction/Developmental Toxicity Screen	No data located.		
	Reproduction and Fertility Effects	No data located.		
	Other	No data located.		
Developmental effects		DG		
	Reproduction/Developmental Toxicity Screen	No data located.		

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide/CAS No. 848820-98-4/EC No. 805-659-5				
Property/Endpoint		Data	Reference	Comments
	Combined Repeated Dose with Reproduction/ Developmental Toxicity Screen	No data located.		
	Prenatal Development	No data located.		
	Postnatal Development	No data located.		
	Prenatal and Postnatal Development	No data located.		
	Developmental Neurotoxicity	No data located.		
	Other	No data located.		
Neurotoxicity		DG		
	Acute and delayed neurotoxicity tests in hens	No data located.		
	Other	No data located.		
Repeated Dose Effects		DG		
	Sub-chronic oral repeated dose	No data located.		
	Sub-chronic inhalation repeated dose	No data located.		
	Dermal repeated dose	No data located.		
Skin Sensitization		LOW: Based on results of a guideline study.		
	Skin sensitization	Mouse local lymphnode assay (LLNA): The test item KCCS DOB11 was not a skin sensitiser under the test conditions of this study.	REACH registration data	Reliability 1 OECD Guideline 429
	Skin sensitization in humans	No data located.		

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide/CAS No. 848820-98-4/EC No. 805-659-5				
Property/Endpoint		Data	Reference	Comments
Respiratory Sensitization		DG		
	Respiratory Sensitization	No data located.		
Eye Irritation		DG		
	Eye Irritation	KCCS DOB11 induces effects on the cornea with an in vitro irritation score (IVIS) >3 and ≤ 55. Therefore it cannot be classified in a UN GHS Category for eye damage. Because of the negative test result, a sequential testing strategy is necessary.	REACH registration data	Reliability 1 OECD Guideline 437
		No data located.		
Dermal Irritation		HIGH: Based on notified classification as Skin Irrit. 2 (H315) an irritation study with the human skin model EpiDermTM.		
	Dermal Irritation	Two tissues of the human skin model EpiDermTM were treated with KCCS DOB11 for three minutes and one hour, respectively. KCCS DOB11 is considered as not corrosive in the Human Skin Model Test.	REACH registration data	Reliability 1 OECD Guideline 431
		Three tissues of the human skin model EpiDermTM were treated with KCCS DOB11 for 60 minutes. KCCS DOB11 is considered as “irritant in the Human Skin Model Test”. In the UN GHS System for skin irritating substances, KCCS DOB11 should be classified in UN GHS category 2. KCCS DOB11 is considered as “irritant in the Human Skin Model Test”.	REACH registration data	Reliability 1 OECD Guideline 439
		Skin Irrit. 2 (H315: Causes skin irritation)	C&L inventory	Notified classification
Endocrine Activity		DG		
	Endocrine activity	No data located.		
Immunotoxicity		DG		

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide/CAS No. 848820-98-4/EC No. 805-659-5				
Property/Endpoint		Data	Reference	Comments
	Immune System Effects	No data located.		

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide/CAS No. 848820-98-4/EC No. 805-659-5			
Property/Endpoint	Data	Reference	Comments
Ecotoxicity			
ECOSAR Class	Esters (Phosphinates)		
Aquatic Acute Toxicity	MODERATE: A comparison of QSAR estimates for fish and crustaceans indicates that fish, for which experimental data are lacking, are less susceptible than crustaceans. At the same time, experimental data on daphnids and algae indicate that daphnids are less susceptible than algae. Furthermore, there is a large difference between the experimental and the estimated endpoint values for daphnids, the experimental study resulting in a much higher EC50 than the QSAR estimate. The acute aquatic toxicity score is therefore based on experimental data for algae with an EC50 (growth rate) of 13 mg/L.		
Fish LC ₅₀ (Freshwater)	Estimate for the ECOSAR class: Esters (Phosphinates) 96 h, LC50 1.96 mg/L	ECOSAR v1.11	QSAR estimate
Fish LC ₅₀ (Marine)	Estimate for the ECOSAR class: Esters (Phosphinates) 96 h, LC50 2.24 mg/L	ECOSAR v1.11	QSAR estimate
Daphnid LC ₅₀ / EC ₅₀ (Freshwater)	Semi-static test with <i>Daphnia magna</i> 24 h, EC50 (mobility) > 69 mg/L (nominal concentration) 48 h, EC50 (mobility) > 66 mg/L (nominal concentration)	REACH registration data	Reliability 1 OECD Guideline 202
	Estimate for the ECOSAR class: Esters (Phosphinates) 48 h, LC50 1.32 mg/L	ECOSAR v1.11	QSAR estimate
Mysid LC ₅₀ / EC ₅₀ (Marine)	Estimate for the ECOSAR class: Esters (Phosphinates) 96 h, LC50 0.255 mg/L	ECOSAR v1.11	QSAR estimate
Green Algae IC ₅₀ / EC ₅₀	Test with <i>Desmodesmus subspicatus</i> 72 h, EC50 (growth rate) 13 mg/L (nominal concentration)	REACH registration data	Reliability 1 OECD Guideline 201
Aquatic Chronic Toxicity	MODERATE: Based on experimental data for algae with an EC10 (growth rate) of 4.2 mg/L considering that, based on the available information, algae appear to be more susceptible than fish and crusteans.		
Fish NOEC (Freshwater)	No data located.		
	Estimate for the ECOSAR class: Esters (Phosphinates) ChV 0.054* mg/L	ECOSAR v1.11	QSAR estimate *The toxicity values was estimated through the application of acute-to-chronic ratios

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide/CAS No. 848820-98-4/EC No. 805-659-5													
Property/Endpoint		Data		Reference	Comments								
		Fish ChV 0.027 mg/L		PBT profiler	QSAR estimate								
Daphnid NOEC (Freshwater)		No data located.											
		Estimate for the ECOSAR class: Esters (Phosphinates) ChV 0.051* mg/L		ECOSAR v1.11	QSAR estimate *The toxicity values was estimated through the application of acute-to-chronic ratios								
Green Algae NOEC		Test with <i>Desmodesmus subspicatus</i> 72 h, EC10 (growth rate) 4.2 mg/L (nominal concentration)		REACH registration data	Reliability 1 OECD Guideline 201								
		Aquatic Chronic 3 (H412: Harmful to aquatic life with long-lasting effects)		C&L inventory	Notified classification								
Transport		Results of Level III fugacity modelling indicate that at equilibrium the substance will be found almost exclusively in soil (83%) and water (16%), while a small fraction will be in sediment. In the atmosphere, the substance is expected to be present only associated with water aerosols and removal from air is therefore by wet deposition.											
	Henry's Law Constant (atm-m ³ /mole)	No data located.											
	Sediment/Soil Adsorption/Desorption – K _d /K _{oc}	No data located.											
	Level III Fugacity Model	<table><tr><th>Media</th><th>Percent in each medium</th></tr><tr><td>Water</td><td>16%</td></tr><tr><td>Soil</td><td>83%</td></tr><tr><td>Sediment</td><td>1%</td></tr><tr><td>Air</td><td>0%</td></tr></table>	Media	Percent in each medium	Water	16%	Soil	83%	Sediment	1%	Air	0%	PBT profiler
Media	Percent in each medium												
Water	16%												
Soil	83%												
Sediment	1%												
Air	0%												
Persistence		High: A half-life was not determined in the OECD ready biodegradability screening test. At the end of the test (28d), only 19% of the test substance was degraded. Persistence is scored as "High" based on an estimated half-life of 140 days in sediment.											

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide/CAS No. 848820-98-4/EC No. 805-659-5				
Property/Endpoint		Data	Reference	Comments
Water	Aerobic Biodegradation	Activated sludge from a biologic sewage treatment plant was used inoculum (concentration in the test 25.0 mg dry matter/L). The test was left running for 28 days. The following data were determined for the test item KCCS DOB11: 10-day-window: day 11 – 21 degradation at the end of 10-day-window: 16 % degradation at the end of the test: 19 % pass level following guideline: 60% at the end of 10-day-window. Therefore, regardless of the 10-day-window, KCCS DOB11 is not biodegradable following OECD 301B/EU C.4-C.	REACH registration data	Reliability 1 OECD Guideline 301 B
	Volatilization Half-life for Model River	No data located.		
	Volatilization Half-life for Model Lake	No data located.		
Soil	Aerobic Biodegradation	No data located.		
	Anaerobic Biodegradation	No data located.		
	Soil Biodegradation with Product Identification	No data located.		
	Sediment/Water Biodegradation	No data located.		
		No data located.		

6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide/CAS No. 848820-98-4/EC No. 805-659-5					
Property/Endpoint		Data		Reference	Comments
Other	Biotic degradation.	No data located.			
Air	Atmospheric Half-life	No data located.			
Reactivity	Photolysis	No data located.			
	Hydrolysis	No data located.			
Environmental Half-life		Media Water Soil Sediment Air	Half-life (d) 15 30 140 1.3	PBT profiler	
Bioaccumulation		LOW: Based on measured log Kow of 3.32.			
	Fish BCF	No data located.			
	Other BCF	80		PBT profiler	QSAR estimate
	BAF	No data located.			
	Metabolism in Fish	No data located.			
Environmental biomonitoring					
Ecological Biomonitoring		No data located.			
Human Biomonitoring		No data located.			

ECOSAR/EPI (EPIWIN/EPISUITE) Estimations Programs Interface for Windows, Version 1.11. U.S. Environmental Protection Agency: Washington D.C. <http://www2.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model>, Input values: CAS No.: 848820-98-4; Name: 6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide; SMILES: O=C(OCCCC)CCP2(=O)Oc3ccccc3c1ccccc12; Water solubility: 176.1; Log Kow: 3.323.

Metadynea, 2014: DOB11, Technical Data Sheet. November 2014.

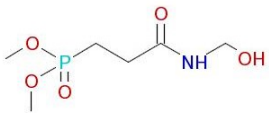
PBTprofiler.net: US EPA PBT Profiler, Model tool available at <http://www.pbtprofiler.net/>, Input values: CAS No.: 848820-98-4, Name: 6H-Dibenz[c,e][1,2]oxaphosphorin-6-propanoic acid, butyl ester, 6-oxide, SMILES: O=C(OCCCC)CCP2(=O)Oc3ccccc3c1cccc12.

REACH registration data: <http://echa.europa.eu/da/information-on-chemicals/registered-substances> using CAS No. 848820-98-4 as search term.

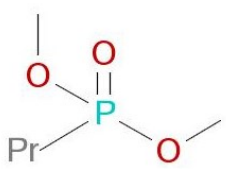
Appendix 10 Technical description of other phosphorous flame retardants

A10.1. Organophosphorous compounds

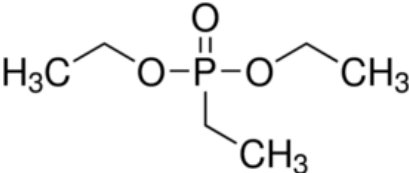
Dimethyl {3-[(hydroxymethyl)amino]-3-oxopropyl}phosphonate, CAS No. 20120-33-6

CAS No	20120-33-6
EC No	243-528-9
Chemical name	Dimethyl {3-[(hydroxymethyl)amino]-3-oxopropyl}phosphonate
Structural formula	 Registration
General formula	C ₆ H ₁₄ NO ₅ P
Phosphorous content	12% (min) (Everfos CP)
Abbreviation, synonyms	N-Hydroxymethyl-3-dimethylphosphonopropionamide
FR products and manufacturers	Everfors CP (Everkem)
Registered tonnage, t/year	100 – 1,000
Pinfa Product Selector	Not identified in PPS
Other information on substrate	Cotton textile
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	Alternative to decaBDE for natural cellulose fibres such as cotton, wool, rayon, and linen (Illinois EPA, 2007).
Halogen-containing flame retardants for the same application (examples)	

Dimethyl propyl phosphonate, CAS No. 18755-43-6

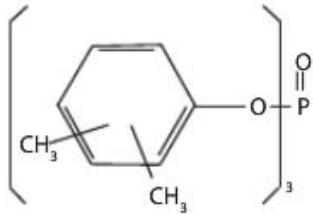
CAS No	18755-43-6		
EC No	242-555-3		
Chemical name	Dimethyl propyl phosphonate		
Structural formula	 Registration		
General formula	C5H13O3P		
Phosphorous content	20.3 % (Levagard DMPP)		
Abbreviation, synonyms	DMPP		
FR products and manufacturers	Levagard DMPP (Lanxess)		
Registered tonnage, t/year	100 – 1,00		
Pinfa Product Selector	Group: Foams Textile/Paint/Adhesives Thermosets	Substrate: PUR rigid foams Paints Unsaturated polyesters Epoxy resins	Applicability: Applicable Applicable Applicable Applicable
Other information on substrate	-		
End applications	-		
Reactive/additive	-		
Health env. profiles	-		
Availability	-		
Flame retardancy	-		
Halogen-containing flame retardants for the same application (examples)	Mainly marketed as alternative to dimethyl methylphosphonate not as alternative to halogenated flame retardants		

Diethyl ethylphosphonate, CAS No. 78-38-6

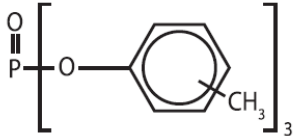
CAS No	78-38-6
EC No	201-111-9
Chemical name	Diethyl ethylphosphonate
Structural formula	 Sigma Aldrich Homepage
General formula	C ₆ H ₁₅ O ₃ P
Phosphorous content	19 % (Aflammit® PLF 822)
Abbreviation, synonyms	
FR products and manu- facturers	Aflammit® PLF 822 (THOR)
Registered tonnage, t/year	Preregistered
Pinfa Product Selector	Group: Foams Substrate: PUR rigid foam Applicability: applicable
Other information on substrate	"Low viscosity FR for use in rigid PUR and PIR foams. Good compatibility and FR performance at low dosage in epoxy and unsaturated polyesters" (THOR)
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (ex- amples)	

A10.2. Organophosphates (phosphate esters) – Aryl phosphates

Trixylyl phosphate, CAS No. 25155-23-1

CAS No	25155-23-1
EC No	246-677-8
Chemical name	Trixylyl phosphate
Structural formula	 Everkem product brochure
General formula	C ₂₄ H ₂₇ O ₄ P
Phosphorous content	7.8% (EVERFOS TXP)
Abbreviation, synonyms	TXP
FR products and manufacturers	EVERFOS TXP (Everkem)
Registered tonnage, t/year	100-1,000
Pinfa Product Selector	Not identified in PPS
Other information on substrate	EPDM, PVC, PC/ABS (alloys), rigid and flexible polyurethane, phenolics resin, Coating (paint), textile (back coating), adhesive
End applications	
Reactive/additive	
Health env. profiles	Has a harmonised classification according to the CLP regulation as reprotoxic (Repr. 1B) and has consequently not been selected for screening.
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

Tricresyl phosphate and trixylenyl phosphate mixture, CAS No. 1330-78-5, 78-32-0, 78-30-8 and 25155-23-1

CAS No	1330-78-5, 78-32-0, 78-30-8 and 25155-23-1
EC No	215-548-8
Chemical name	Tri(m,p-cresyl) phosphate mixture
Structural formula	 Lindol SDS from ICL-IP Europe
General formula	N.a.
Phosphorous content	8.4 (Lindol & Lindol XP Plus)
Abbreviation, synonyms	Tri(m,p-cresyl) phosphate mixture
FR products and manufacturers	Lindol & Lindol XP Plus (ICL-IP Europe)
Registered tonnage, t/year	CAS No. 1330-78-5: 1,000-10,000 CAS No. 25155-23-1: 100-1,000 CAS No. 78-32-0 and 78-30-8: preregistered
Pinfa Product Selector	Product not identified in PPS
Other information on substrate	PVC flexible, Cellulosic Plastic Composite
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

Proprietary aromatic phosphate

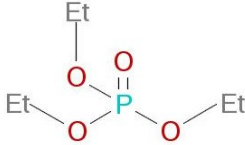
CAS No	Proprietary
EC No	-
Chemical name	Proprietary, aromatic phosphate, solid powder
Structural formula	N.a.
General formula	N.a.
Phosphorous content	10.5% (Fyrolflex Sol-DP)
Abbreviation, synonyms	
FR products and manufacturers	Fyrolflex DP (ICL-IP Europe)
Registered tonnage, t/year	
Pinfa Product Selector	Not identified in PSS
Other information on substrate	HIPS/PPO, PC/PC ABS
End applications	
Reactive/additive	Reactive
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

Proprietary halogen-free phosphorous ester

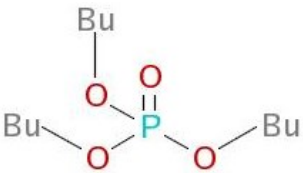
CAS No	Proprietary
EC No	-
Chemical name	Proprietary halogen-free phosphorus ester
Structural formula	N.a.
General formula	N.a.
Phosphorous content	8.5% (Fyrol A710)
Abbreviation, synonyms	
FR products and manufacturers	Fyrol A710 (ICL-IP Europe)
Registered tonnage, t/year	
Pinfa Product Selector	Not identified in PSS
Other information on substrate	Flexible Polyurethane foams
End applications	"recommended for use in the Automotive MVSS302 and furniture California Technical Bulletin 117 flammability tests" (ICL-IP Europe)
Reactive/additive	Additive
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

A10.3. Organophosphates (phosphate esters) – Alkyl phosphates

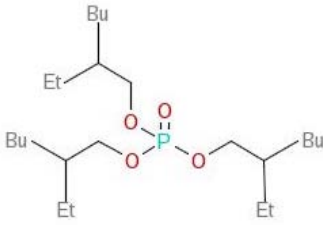
Triethyl phosphate, CAS No. 78-40-0

CAS No	78-40-0		
EC No	201-114-5		
Chemical name	Triethyl phosphate		
Structural formula	 Registration		
General formula	C6H15O4P		
Phosphorous content	17% (Levagard TEP-Z)		
Abbreviation, synonyms	TEP		
FR products and manufacturers	Levagard TEP-Z (Lanxess)		
Registered tonnage, t/year	1,000 – 10,000		
Pinfa Product Selector	Group: Foams Thermosets	Substrate: PUR rigid foam Unsaturated polyesters	Applicability: Applicable Applicable
Other information on substrate	PIR / PUR rigid foams and thermosets		
End applications			
Reactive/additive			
Health env. profiles	Not developed		
Availability			
Flame retardancy			
Halogen-containing flame retardants for the same application (examples)			

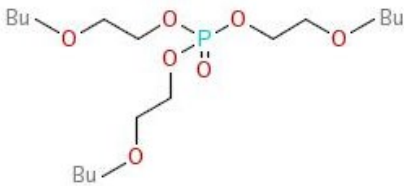
Tributyl phosphate, CAS No. 126-73-8

CAS No	126-73-8
EC No	204-800-2
Chemical name	Tributyl phosphate
Structural formula	 Registration
General formula	C ₁₂ H ₂₇ O ₄ P
Phosphorous content	11.7% (Phosflex 4)
Abbreviation, synonyms	TNBO, Tris(butyl) phosphate, Tri-n-butyl phosphate
FR products and manufacturers	Phosflex 4 (ICL-IP Europe)
Registered tonnage, t/year	1,000 – 10,000
Pinfa Product Selector	Not identified in PPS
Other information on substrate	PVC flexible, latex/adhesives, cellulosic plastic composite
End applications	
Reactive/additive	Additive
Health env. profiles	Has a harmonised classification according to the CLP Regulations as carcinogenic (Carc. 2) and has consequently not been selected for screening.
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

Tris-(2-ethylhexyl) phosphate, CAS No. 78-42-2

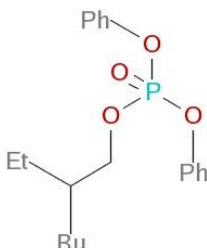
CAS No	78-42-2
EC No	201-116-6
Chemical name	Tris-(2-ethylhexyl) phosphate
Structural formula	 Registration
General formula	C ₂₄ H ₅₁ O ₄ P
Phosphorous content	
Abbreviation, synonyms	TEHP
FR products and manufacturers	Disflamoll TOF (Lanxess)
Registered tonnage, t/year	1,000 – 10,000
Pinfa Product Selector	Not included in the Product Selector
Other information on substrate	Many types of polymers including PVC flexible, PUR, NBR, SBR and EPDM.
End applications	
Reactive/additive	Additive
Health env. profiles	Profile not developed
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

Tris(2-butoxyethyl)phosphate, CAS No. 78-51-3

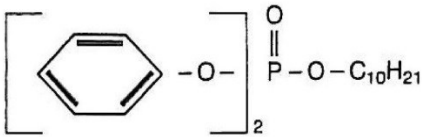
CAS No	78-51-3
EC No	201-114-5
Chemical name	Tris(2-butoxyethyl) phosphate
Structural formula	 Registration
General formula	C18H39O7P
Phosphorous content	7.8% (Phosflex T-BEP)
Abbreviation, synonyms	TBOEP; Ethanol, 2-butoxy-, 1,1',1''-phosphate; Ethanol,2-butoxy-, phosphate (3:1)
FR products and manufacturers	Phosflex T-BEP (ICL-IP Europe)
Registered tonnage, t/year	1,000 – 10,000
Pinfa Product Selector	Not identified in PPS
Other information on substrate	Rubbers/elastomers, latex/adhesives
End applications	
Reactive/additive	
Health env. profiles	Profile not developed
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

A10.4. Organophosphates (phosphate esters) – Aryl alkyl phosphates

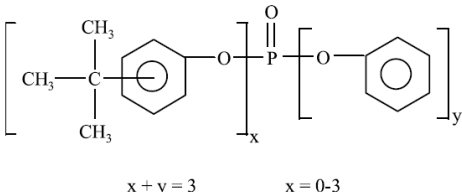
Diphenyl (2-ethylhexyl)phosphate, CAS No. 1241-94-7

CAS No	1241-94-7		
EC No	214-987-2		
Chemical name	Diphenyl (2-ethylhexyl) phosphate		
Structural formula	 Registration		
General formula	C20H27O4P		
Phosphorous content	8.5% (Phosflex 362) 8.6% (Disflamoll DPO)		
Abbreviation, synonyms	DPO		
FR products and manufacturers	Disflamoll DPO (Lanxess) Phosflex 362 (ICL-IP Europe)		
Registered tonnage, t/year	1,000 – 10,000		
Pinfa Product Selector	Group: Foams	Substrate: Rubbers/elastomers PVC/nitrile foam Paints PVC flexible	Applicability: Applicable Applicable Applicable Applicable
Other information on substrate	PVC, thermoplastic polyurethane, nitrile butadiene rubber, cellulose nitrate, cellulose acetate		
End applications			
Reactive/additive			
Health env. profiles	Profile not developed		
Availability			
Flame retardancy			
Halogen-containing flame retardants for the same application (examples)	Non-halogen flame retardants are the main FRs for PVC		

Isodecyl diphenyl phosphate, CAS No. 29761-21-5

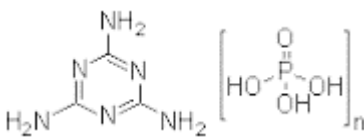
CAS No	29761-21-5
EC No	249-828-6
Chemical name	Isodecyl diphenyl phosphate
Structural formula	 Registration
General formula	C ₂₂ H ₃₁ O ₄ P
Phosphorous content	7.9% (Phosflex 390)
Abbreviation, synonyms	8-methylnonyl diphenyl phosphate
FR products and manufacturers	Phosflex 390 (ICL-IP Europe)
Registered tonnage, t/year	1,000 – 10,000
Pinfa Product Selector	Not identified in PPS
Other information on substrate	PVC flexible
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	Non-halogenated FRs are the main FRs for flexible PVC

t-butylated triphenyl phosphate mixture, CAS No. 56803-37-3, 65652-41-7, 78-33-1 and 115-86-6

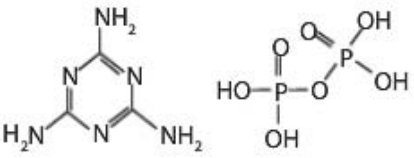
CAS No	56803-37-3, 65652-41-7, 78-33-1 and 115-86-6
EC No	260-391-0, 265-859-8, 201-106-1, and 204-112-2
Chemical name	t-butylated triphenyl phosphate mixture
Structural formula	 $x + y = 3$ $x = 0-3$ Phosflex 71B datasheet
General formula	
Phosphorous content	8.5% (Phosflex 71B)
Abbreviation, synonyms	
FR products and manufacturers	Phosflex 71B (ICL-IP Europe)
Registered tonnage, t/year	Substances are preregistered individually, except 115-86-6: 1,000 – 10,000
Pinfa Product Selector	Not identified in PPS
Other information on substrate	HIPS/PPO, PC/PC ABS, flexible PVC
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

A10.5. Melamine-derived and other organic phosphates (not being esters)

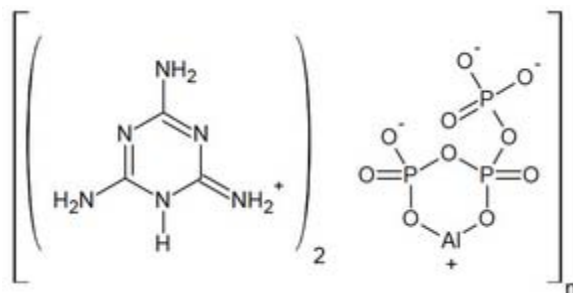
Melamine polyphosphate, CAS No. 218768-84-4

CAS No	218768-84-4		
EC No	*606-855-1		
Chemical name	Melamine polyphosphate		
Structural formula	 Lassen et al., 2006		
General formula	Not available		
Phosphorous content	Not available		
Abbreviation, synonyms	Melapur M 200, Melapur 200, MPP		
FR products and manufacturers	Melapur® 200 range (BASF) BUDIT 3141 (Budenheim) AFLAMMIT® PMN 200 (THOR)		
Registered tonnage, t/year	Pre-registered		
Pinfa Product Selector	Group:	Substrate:	Applicability:
	Solid Thermoplastics	PET	Applicable
		PBT	Applicable
		Polyamide (PA)	Applicable
		Polypropylene (PP)	Applicable
		HIPS/PPO	Applicable
	Textiles/Paints/Adhesives	Intumescent Coatings	Applicable
	Thermosets	Epoxy Resins	Applicable
		Phenolic Resins	Applicable
		Unsaturated polyesters	Applicable
		Acrylic resins	Applicable
Other information on substrate	-		
End applications	Construction EEE		
Reactive/additive	Additive		
Health env. profiles	Modified profile of the substance with nearly similar structure, CAS No. 15541-60-3, is presented above.		
Availability			
Flame retardancy	Vo-grade glass reinforced PA66 can be obtained with 26% melamine polyphosphate (Lassen et al., 2006) Melamine polyphosphate is mostly used in combination with other flame retardants, such as metal phosphinates, metal hydroxides and phosphates (Rakotamala et al., 2010)		
Halogen-containing flame retardants for the same application (examples)			

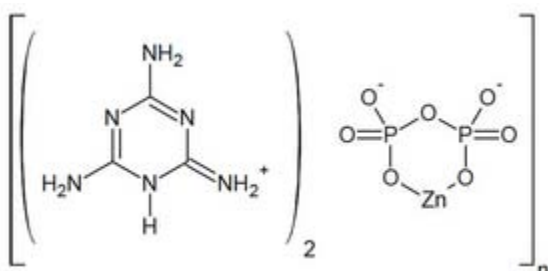
Melamine polyphosphate, CAS No. 20208-95-1

CAS No	20208-95-1
EC No	243-601-5
Chemical name	Melamine polyphosphate (Everkem)
Structural formula	 Everkem product catalogue
General formula	C ₃ H ₆ N ₆ (H ₃ PO ₄) _n (Everkem)
Phosphorous content	>31%
Abbreviation, synonyms	1,3,5-triazine-2,4,6-triamine monophosphate (pre-registration)
FR products and manufacturers	EVERFLAM MPP-1 (Everkem)
Registered tonnage, t/year	Pre-registered
Pinfa Product Selector	Not identified in PPS
Other information on substrate	Polyester, PA
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

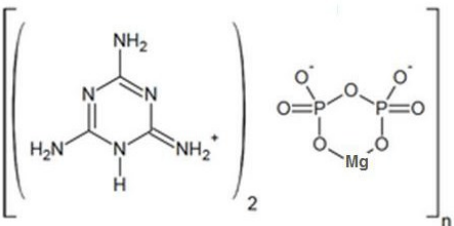
Melamine-poly(aluminium phosphate), CAS No. 1271168-40-1

CAS No	1271168-40-1		
EC No	Not available		
Chemical name	Melamine-poly(aluminium phosphate)		
Structural formula	 Safire presentation		
General formula	Not available		
Phosphorous content	17% (Safire® 200)		
Abbreviation, synonyms			
FR products and manufacturers	Safire® 200 (Floridienne Chimie s.a. (patent belongs to Catena additives))		
Registered tonnage, t/year	Neither registered nor Pre-registered		
Pinfa Product Selector	Group:	Substrate:	Applicability:
	Solid Thermoplastics	PET	Applicable
		PBT	Applicable
		Polyamide (PA)	Applicable
		Polypropylene (PP)	Applicable
		HIPS/PPO	Applicable
		Textiles/Paints/Adhesives	Intumescent Coatings
	Thermosets	Epoxy Resins	Applicable
		Phenolic Resins	Applicable
		Unsaturated polyesters	Applicable
		Acrylic resins	Applicable
Other information on substrate	PA, Nylon, PBT, PE, PP, PS, HIPS, PPE		
End applications	Automotive/ Transportation, Electrical component, Cables, Glass fibers		
Reactive/additive			
Health env. profiles			
Availability			
Flame retardancy			
Halogen-containing flame retardants for the same application (examples)			

Melamine-poly(zinc phosphate), CAS No. 1271172-98-5

CAS No	1271172-98-5		
EC No	Not available		
Chemical name	Melamine-poly(zinc phosphate)		
Structural formula	 Safire presentation		
General formula	Not available		
Phosphorous content	14% (Safire® 400)		
Abbreviation, synonyms			
FR products and manufacturers	Safire ®400 (Floridienne Chimie s.a. (patent belongs to Catena additives))		
Registered tonnage, t/year	Neither registered nor Pre-registered		
Pinfa Product Selector	Group: Solid Thermoplastics Textiles/Paints/Adhesives Thermosets	Substrate: PET PBT Polyamide (PA) Polypropylene (PP) HIPS/PPO Intumescent Coatings Epoxy Resins Phenolic Resins Unsaturated polyesters Acrylic resins	Applicability: Applicable Applicable Applicable Applicable Applicable Applicable Applicable Applicable Applicable
Other information on substrate	EVA, PA, Nylon, PBT, PE, PUR, PVC flexible, TPE and TPV		
End applications	Automotive/ Transportation, Buildings & construction, Electrical components, Cables, Glass fibers, Compoundings.		
Reactive/additive			
Health env. profiles			
Availability			
Flame retardancy			
Halogen-containing flame retardants for the same application (examples)			

Melamine-poly(magnesium phosphate), CAS No. Not identified

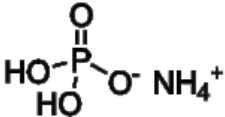
CAS No	Not identified
EC No	Not identified
Chemical name	Melamine-poly(magnesium phosphate)
Structural formula	 Safire presentation
General formula	Not available
Phosphorous content	17.6% (Safire® 600)
Abbreviation, synonyms	
FR products and manufacturers	Safire® 600 (Floridienne Chimie s.a. (patent belongs to Catena additives)
Registered tonnage, t/year	Neither registered nor Pre-registered
Pinfa Product Selector	Not identified in PPS
Other information on substrate	PBT PA, Nylon
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

1,3,5-Triazine-2,4,6-triaminephosphate, CAS No. 94031-26-2

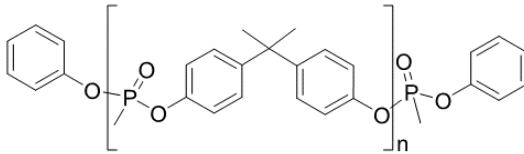
CAS No	94031-26-2
EC No	Not available
Chemical name	1,3,5-Triazine-2,4,6-triaminephosphate
Structural formula	Not available
General formula	Not available
Phosphorous content	16 – 18% (PPP111)
Abbreviation, synonyms	Flame retardant P
FR products and manufacturers	PPP111 (Metadynea Austria GmbH)
Registered tonnage, t/year	Neither registered nor Pre-registered
Pinfa Product Selector	Not identified in PPS
Other information on substrate	Intumescent flame retardant systems
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

A10.6. Inorganic phosphorous compounds

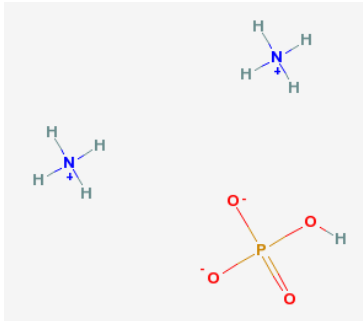
Monoammonium phosphate, CAS No. 7722-76-1

CAS No	7722-76-1
EC No	231-764-5
Chemical name	Monoammonium phosphate
Structural formula	 Registration
General formula	H3N.H3O4P
Phosphorous content	75-85% (PHOS-CHEK® MVP-F (also contains diammonium phosphate)) 8-12% (PHOS-CHEK® MVP-Fx (also contains diammonium phosphate))
Abbreviation, synonyms	Ammonium dihydrogenorthophosphate, ammonium phosphate
FR products and manufacturers	PHOS-CHEK® MVP-F (also contains diammonium phosphate), PHOS-CHEK® MVP-Fx (also contains diammonium phosphate) (BK Giulini&K Giulini GmbH)
Registered tonnage, t/year	1,000,000 - 10,000,000
Pinfa Product Selector	Not identified in PPS
Other information on substrate	-
End applications	Wildfire control
Reactive/additive	-
Health env. profiles	No profile developed
Availability	Widely available for flame retardancy and other applications
Flame retardancy	-
Halogen-containing flame retardants for the same application (examples)	Wildfire control is not a significant

Polyphosphonate, CAS No. 68664-06-2

CAS No	68664-06-2																				
EC No	Not available																				
Chemical name	Polyphosphonate (Mn >10,000)																				
Structural formula	 US EPA, 2014a																				
General formula	C15H16O2(C16H17O3P)n																				
Phosphorous content	10.8 wt. %																				
Abbreviation, synonyms	FRX 100 (polyphosphonate), Phosphonic acid																				
FR products and manufacturers	Nofia HM1100 (FRX Polymers)																				
Registered tonnage, t/year	Not reg/pre-reg																				
Pinfa Product Selector	<table><tr><td rowspan="3">Solid Thermoplastics</td><td>Thermoplastic elastomers</td><td>applicable</td></tr><tr><td>PBT</td><td>applicable</td></tr><tr><td>PET</td><td>applicable</td></tr><tr><td rowspan="2">Textiles/Paints/Adhesives</td><td>Other textile fibres</td><td>applicable</td></tr><tr><td>Polyester fibres</td><td>applicable</td></tr><tr><td>Wire and cables</td><td>TPU</td><td>applicable</td></tr><tr><td>Solid Thermoplastics</td><td>Thermoplastic elastomers</td><td>applicable</td></tr></table>			Solid Thermoplastics	Thermoplastic elastomers	applicable	PBT	applicable	PET	applicable	Textiles/Paints/Adhesives	Other textile fibres	applicable	Polyester fibres	applicable	Wire and cables	TPU	applicable	Solid Thermoplastics	Thermoplastic elastomers	applicable
Solid Thermoplastics	Thermoplastic elastomers	applicable																			
	PBT	applicable																			
	PET	applicable																			
Textiles/Paints/Adhesives	Other textile fibres	applicable																			
	Polyester fibres	applicable																			
Wire and cables	TPU	applicable																			
Solid Thermoplastics	Thermoplastic elastomers	applicable																			
Other information on substrate																					
End applications	Fibers: Carpets; Textiles Electronic Equipment and Consumer Electronics: Connectors; Wire & Cable Building and Construction: Transparent sheet products; Transparent blown film Transportation																				
Reactive/additive	Additive																				
Health env. profiles	Alternatives for the flame retardant decaBDE (US EPA, 2014a)																				
Availability	Readily available																				
Flame retardancy	Carpets and Textiles: Low Flame Spread; Radiant panel ASTM E-648, NFPA 701, MVSS 302; Connectors: UL94 V0 / 0.8mm Wire and Cable: VW1 (UL1581) Transparent sheet and blown films: E162 - Class A rating; E84 - Class A rating																				
Halogen-containing flame retardants for the same application (examples)	DecaBDE																				

Diammonium phosphate, CAS No. 7783-28-0

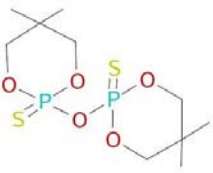
CAS No	7783-28-0
EC No	231-987-8
Chemical name	Diammonium phosphate
Structural formula	 Registration
General formula	H ₃ N.1/2H ₃ O ₄ P
Phosphorous content	8-12% (PHOS-CHEK® MVP-F (also contains monoammonium phosphate)) 75-85% (PHOS-CHEK® MVP-Fx (also contains monoammonium phosphate)) >90% PHOS-CHEK 259-F
Abbreviation, synonyms	Diammonium hydrogenorthophosphate, diammonium hydrogen phosphate
FR products and manufacturers	PHOS-CHEK® MVP-F (also contains monoammonium phosphate), PHOS-CHEK® MVP-Fx (also contains monoammonium phosphate), PHOS-CHEK 259-F, (BK Giuliniibk-giulini GmbH)
Registered tonnage, t/year	1,000,000 - 10,000,000
Pinfa Product Selector	Not identified in PPS
Other information on substrate	Wildfire control
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

Aluminium phosphates, CAS No. Not identified

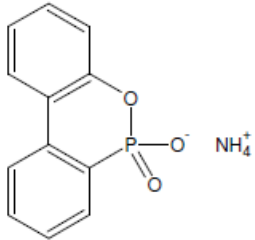
CAS No	Not identified
EC No	Not identified
Chemical name	Aluminium phosphates
Structural formula	Not available
General formula	Not available
Phosphorous content	Not available
Abbreviation, synonyms	
FR products and manufacturers	FR CROS 134 P, FR CROS 134 T (Budenheim)
Registered tonnage, t/year	
Pinfa Product Selector	Not identified in PPS
Other information on substrate	
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

A10.7. Other phosphorous and non-categorised substances

2,2'-oxybis[5,5-dimethyl-1,3,2-dioxaphosphorinane] 2,2'-disulphide, CAS No. 4090-51-1

CAS No	4090-51-1
EC No	223-829-1
Chemical name	2,2'-oxybis[5,5-dimethyl-1,3,2-dioxaphosphorinane] 2,2'-disulphide
Structural formula	 Registration
General formula	C ₁₀ H ₂₀ O ₅ P ₂ S ₂
Phosphorous content	Not available
Abbreviation, synonyms	
FR products and manufacturers	Exolit® 5060 PK (Clariant) Mileflame FR 5060 (MPI Chemie)
Registered tonnage, t/year	100 – 1,000
Pinfa Product Selector	Group: Textiles/Paints/Adhesives Substrate: Viscose Applicability: Applicable
Other information on substrate	Viscose fibres
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	Viscose fibres is not a significant application of halogenated flame retardants

**Ammonium 6H-dibenzo[c,e][1,2]oxaphosphinin-6-olate 6-oxide,
CAS No. 1402947-09-4**

CAS No	1402947-09-4
EC No	Not available
Chemical name	Ammonium 6H-dibenzo[c,e][1,2]oxaphosphinin-6-olate 6-oxide
Structural formula	 Technical Data Sheet for DXA 12
General formula	
Phosphorous content	12.0 – 12.5 % (DXA 12)
Abbreviation, synonyms	
FR products and manufacturers	DXA 12 (Metadynea Austria GmbH)
Registered tonnage, t/year	Neither registered nor Pre-registered.
Pinfa Product Selector	Not identified in PPS
Other information on substrate	
End applications	
Reactive/additive	
Health env. profiles	
Availability	
Flame retardancy	
Halogen-containing flame retardants for the same application (examples)	

Environmental and health screening profiles of phosphorous flame retardants

This is a survey that identifies phosphorous flame retardants and develops screening level substance hazard profiles, to be used for substitution consideration in a European REACH context by companies using flame retardants. The screening hazard profiles have been prepared based on a modified version of a method for hazard assessment of chemicals known as GreenScreen®. The GreenScreen® method was developed in the USA for the US EPA "Design for the Environment" (DfE) programme and consists of a hazard profiling part and a "benchmarking" part aimed to assess the relevance of a substance for consideration in a substitution context. For the purpose of the current project, the method has been reviewed and adapted as appropriate for use in a European regulatory context.



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Re-evaluation of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) as food additives

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS),
Maged Younes, Peter Aggett, Fernando Aguilar, Riccardo Crebelli, Birgit Dusemund,
Metka Filipič, Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy,
Gunter Georg Kuhnle, Claude Lambré, Jean-Charles Leblanc, Inger Therese Lillegaard,
Peter Moldeus, Alicja Mortensen, Agneta Oskarsson, Ivan Stankovic, Ine Waalkens-Berendsen,
Matthew Wright, Alessandro Di Domenico, Henk van Loveren, Alessandra Giarola,
Zsuzsanna Horvath, Federica Lodi, Alexandra Tard and Rudolf Antonius Woutersen

Abstract

The Panel on Food Additives and Nutrient Sources added to Food (ANS) provided a scientific opinion re-evaluating the safety of aluminium sulphates (E 520–523) and sodium aluminium phosphate, acidic (E 541) as food additives. The Panel considered that adequate exposure and toxicity data were available. Aluminium sulphates (E 520–523) and sodium aluminium phosphate, acidic (E 541) are permitted as food additives in only a few specific products and the exposure is probably near zero. Aluminium compounds have low bioavailability and low acute toxicity. There is no concern with respect to genotoxicity and carcinogenicity. The no observed adverse effect level (NOAEL) for aluminium compounds in subchronic studies was 52 mg Al/kg body weight (bw) per day in rats and 90 mg Al/kg bw per day in dogs and the lowest NOAEL for neurotoxicity in rats was 30 mg Al/kg bw per day and for developing nervous system was 10–42 mg Al/kg bw per day in studies in mice and rats. The Panel concluded that aluminium sulphates (E 520–523) and sodium aluminium phosphate, acidic (E 541) are of no safety concern in the current authorised uses and use levels.

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Keywords: aluminium, E 520, E 521, E 522, E 523, E 541, sulphates

Requestor: European Commission

Question number: EFSA-Q-2013-00697

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Panel members: Peter Aggett, Fernando Aguilar, Riccardo Crebelli, Birgit Dusemund, Metka Filipič, Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy, Gunter Georg Kuhnle, Claude Lambré, Jean-Charles Leblanc, Inger Therese Lillegaard, Peter Moldeus, Alicja Mortensen, Agneta Oskarsson, Ivan Stankovic, Ine Waalkens-Berendsen, Rudolf Antonius Woutersen, Matthew Wright and Maged Younes.

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Summary

The present opinion deals with the re-evaluation of the safety of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) as food additives.

Aluminium sulphates (E 520–523) and sodium aluminium phosphate, acidic (E 541) are authorised as food additives in the European Union (EU) in accordance with Annex II to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012.

Sodium aluminium phosphate (E 541) has been evaluated by the Scientific Committee for Food (SCF) in 1990 who agreed with the provisional tolerable weekly intake (PTWI) for Al of 7 mg/kg bw established by Joint FAO/WHO Expert Committee on Food Additives (JECFA).

The safety of aluminium from dietary intake was evaluated in 2008 by the EFSA Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (EFSA, 2008). Based on the range of available no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL), and applying a weight of evidence approach, the Panel established a tolerable weekly intake (TWI) of 1 mg Al/kg body weight (bw). This weekly health-based reference value took into account the potential accumulation of dietary aluminium in the body, and applied to all aluminium compounds in food, including additives.

Aluminium containing-food additives were also evaluated by JECFA several times, the latest in 2011. The Committee established a PTWI, which applied to all aluminium compounds in food. The PTWI was set at 2 mg Al/kg bw based on a NOAEL of 30 mg/kg bw per day from a neurodevelopmental study in rats (Poirier et al., 2011), with the application of a safety factor of 100. JECFA noted the complication of the identification of the LOAEL and NOAEL due to decreasing fluid consumption.

In 2017, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) published an opinion on tolerable intake of aluminium with regard to adapting the migration limits for aluminium in toys. The SCHEER used the same study of Poirier et al. (2011) and established a tolerable daily intake (TDI) of 0.3 mg/kg bw per day.

Aluminium compounds have low bioavailability and low acute toxicity. There is no concern with respect to genotoxicity and carcinogenicity.

The NOAEL for aluminium compounds in subchronic studies was 52 mg Al/kg bw per day in rats and 90 mg Al/kg bw per day in dogs.

Studies on reproductive, developmental and neurotoxicity were available; the lowest NOAEL for neurotoxicity in rats was 30 mg Al/kg bw per day and for developing nervous system was 10–42 mg Al/kg bw per day in studies in rats and mice.

Aluminium sulphates (E 520–523) are permitted as food additives in two food categories with further restriction in use and sodium aluminium phosphate, acidic (E 541) is only permitted as a food additive in one food category with further restriction in use.

The Mintel's Global New Products Database (GNPD) indicated that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) were used in a decreasing number of products over time, following the change in legislation coming into force in February 2014.

To assess the dietary exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) from their use as food additives, the exposure was only calculated based on the MPLs as set out in the EU legislation (defined as the *regulatory maximum level exposure assessment scenario*), because no use levels or analytical results were made available to EFSA.

The mean exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) from their use as food additives at the regulatory maximum level exposure assessment scenario (MPL) ranged from 0.0 mg/kg bw per day in all population groups to 0.21 mg/kg bw per day in children. The 95th percentile of exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) ranged from 0.0 mg/kg bw per day in all population groups to 0.88 mg/kg bw per day in toddlers and children.

The exposure estimates in this highly conservative scenario exceeded the TWI of 1 mg Al/kg bw (equivalent to ~ 0.14 mg Al/kg bw per day) for all population groups at the 95th percentile, and for toddlers and children at the mean (Table 9). However, considering that these additives are only authorised in niche products of which the consumption is not captured in the dietary surveys of the EFSA Comprehensive Database, the Panel considered that these estimates are highly uncertain and the real exposure is most probably near the lower end of the calculated exposure (approximately 0). Due to these uncertainties a comparison of the calculated exposure with TWI is of little or no value.

Considering that:

- bioavailability of aluminium compounds is low (approximately 0.1% from food and beverages);
- inorganic aluminium salts are of low acute toxicity;
- the NOAEL identified for aluminium compounds in subchronic studies was 52 mg Al/kg bw per day in rats and 90 mg Al/kg bw per day in dogs;
- the use of aluminium sulphates and sodium aluminium phosphate as food additives does not raise concern for genotoxicity and these compounds are unlikely to be human carcinogens;
- studies on reproductive, (neuro)developmental and neurotoxicity were available; the lowest NOAEL for neurotoxicity was 30 mg Al/kg bw per day and for developing nervous system was 10–42 mg Al/kg bw per day;
- aluminium sulphates (E 520–523) are permitted as food additives in two food categories with further restriction in use;
- sodium aluminium phosphate (E 541) is only permitted as a food additive in one food category with further restriction in use;
- the Mintel's GNPD indicated that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) were used in a decreasing number of products over time, following the change in legislation coming into force in February 2014, which is in line with the fact that EFSA did not receive any use levels of these additives from industry;
- these additives are only authorised in specific products which consumption is not captured in the dietary surveys of the EFSA Comprehensive Database the estimated exposure is most probably near the lower end of the calculated exposure (approximately 0).

The Panel concluded that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) are of no safety concern in the current authorised uses and use levels.

The Panel recommend that:

- the combined exposure to aluminium from all the aluminium-containing food additives should be assessed.

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1. Introduction

The present opinion document deals with the re-evaluation of aluminium sulphates (E 520–523) and sodium aluminium phosphate (SALP, E 541) when used as food additives.

1.1. Background and Terms of Reference as provided by the European Commission

1.1.1. Background

Regulation (EC) No 1333/2008¹ of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union. In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under the Regulation (EU) No 257/2010². This Regulation also foresees that food additives are re-evaluated whenever necessary in the light of changing conditions of use and new scientific information. For efficiency and practical purposes, the re-evaluation should, as far as possible, be conducted by group of food additives according to the main functional class to which they belong.

The order of priorities for the re-evaluation of the currently approved food additives should be set on the basis of the following criteria: the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive taking also into account the outcome of the Report from the Commission on Dietary Food Additive Intake in the EU³ of 2001. The report 'Food additives in Europe 2000'⁴ submitted by the Nordic Council of Ministers to the Commission, provides additional information for the prioritisation of additives for re-evaluation. As colours were among the first additives to be evaluated, these food additives should be re-evaluated with a highest priority.

In 2003, the Commission already requested EFSA to start a systematic re-evaluation of authorised food additives. However, as a result of adoption of Regulation (EU) 257/2010 the 2003 Terms of References are replaced by those below.

1.1.2. Terms of Reference

The Commission asks the European Food Safety Authority to re-evaluate the safety of food additives already permitted in the Union before 2009 and to issue scientific opinions on these additives, taking especially into account the priorities, procedures and deadlines that are enshrined in the Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with the Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives.

1.1.3. Interpretation of Terms of Reference

The Panel considered that aluminium sulphate (E 520), aluminium sodium sulphate (E 521), aluminium potassium sulphate (E 522), aluminium ammonium sulphate (E 523) and sodium aluminium phosphate acidic (E 541) are expected to dissociate in the gastrointestinal tract into their respective ions. The resulting sodium, potassium, ammonium and phosphate will enter normal physiological processes. Therefore, these ions are not discussed further in this opinion which deals only with the aluminium moiety released from these food additives, because the Panel considered aluminium the critical component at the level of use of these food additives. This opinion does not aim at revising the health-based guidance value for aluminium set by EFSA in 2008 (EFSA, 2008) even though new toxicological evidence has been reviewed.

¹ Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16–33.

² Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.

³ COM(2001) 542 final.

⁴ Food Additives in Europe 2000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers, TemaNord 2002, 560.

1.2. Information on existing authorisations and evaluations

Aluminium sulphates (E 520–523) and SALP (E 541) are authorised as food additives in the EU in accordance with Annex II to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012⁵.

In the EU, SALP (E 541) has been evaluated by the Scientific Committee for Food (SCF) in 1990 (SCF, 1991) who agreed with the provisional tolerable weekly intake (PTWI) for Al of 7 mg/kg bw established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

In 2008, the EFSA Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (EFSA AFC Panel, 2008) prepared a scientific opinion on safety of aluminium from dietary intake and in view of the cumulative nature of aluminium in the organism after dietary exposure, the Panel considered it more appropriate to establish a tolerable weekly intake (TWI) for aluminium rather than a tolerable daily intake (TDI). Based on the combined evidence from the above-mentioned studies, the Panel established a TWI of 1 mg aluminium/kg bw per week.

In 2011, a statement on the evaluation of a new study related to the bioavailability of aluminium in food was published by EFSA (2011a,b). EFSA concluded that the new study did not provide any additional information on the bioavailability of aluminium from aluminium-containing compounds that could modify the conclusions reached in 2008 by the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials. Therefore, EFSA concluded that this study did not give reason to reconsider the previous safety evaluation of aluminium-based food additives authorised in the EU performed by EFSA in 2008.

Aluminium salts (sodium and potassium sulphate) have been evaluated by JECFA in 1978 (JECFA, 1978) that concluded that the use of aluminium metal as a silvering decoration for certain items of confectionary was not considered to present a health hazard. SALP (E 541) was evaluated by JECFA in 1982, 1985, 1986, 1988, 2006 and 2011 (JECFA, 1982, 1986, 1987, 1989, 2007 and 2012). In its first evaluation in 1982, a temporary acceptable daily intake (ADI) of 0–6 mg/kg body weight (bw) was allocated due to insufficient data. This is equivalent to 0–0.6 mg/kg bw as aluminium. In 1985, in the light of new data, the Committee concluded that the previous temporary ADI should be applied to all aluminium salts added to food. In 1986, additional studies were reviewed and the temporary ADI of 0–0.6 mg/kg bw for aluminium was extended to be applied to all aluminium salts added to food. In 1989, the previous ADI for aluminium of 0.6 mg/kg bw was changed to a group PTWI of 7 mg/kg bw expressed as aluminium from all sources. The Committee concluded that there was no need to set a separate ADI for SALP, basic or acidic, since the PTWI included aluminium intake resulting from food additive sources. In 2006, the committee confirmed that the health-based guidance value should be expressed as a PTWI because of the potential of bioaccumulation. The Committee established a PTWI for Al of 1 mg/kg bw, which applies to all aluminium compounds in food, including additives. The previously established ADIs and PTWI for aluminium compounds were withdrawn. In 2011, JECFA established a PTWI of 2 mg/kg bw based on the no observed adverse effect level (NOAEL) of 30 mg/kg bw per day of a neurodevelopmental study (Poirier et al., 2011) and applying a safety factor of 100 (JECFA, 2012).

In 2017, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER, 2017) published an opinion on tolerable intake of aluminium with regards to adapting the migration limits for aluminium in toys. The SCHEER used the same study of Poirier et al. (2011) and established a TDI of 0.3 mg/kg bw per day.

SALP (E 541) has also been reviewed by the Nordic Council of Ministers (TemaNord, 2002), who concluded that 'The intake of food where this additive is used to the maximum level could lead to exceeding the PTWI. However, this salt is not soluble, so it should be investigated whether the aluminium is available to the same extent as from soluble aluminium salts'.

⁵ Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) no 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012, p. 1.

2. Data and methodologies

2.1. Data

The Panel on Food Additives and Nutrient Sources added to Food (ANS) was not provided with a newly submitted dossier. EFSA launched public calls for data⁶ and, if relevant, contacted other risk assessment bodies to collect relevant information from interested parties.

The Panel based its assessment on information submitted to EFSA following the public calls for data, information from previous evaluations and additional available literature up to last Working Group meeting before the adoption of the opinion.⁷ Attempts were made at retrieving relevant original study reports on which previous evaluations or reviews were based however these were not always available to the Panel.

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database⁸) was used to estimate the dietary exposure.

The Mintel's Global New Products Database (GNPD) is an online database which was used for checking the labelling of products containing aluminium sulphates (E 520–523) and SALP (E 541) within the EU's food products as the GNPD shows the compulsory ingredient information presented in the labelling of products.

2.2. Methodologies

This opinion was formulated following the principles described in the EFSA Guidance on transparency with regard to scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing guidance documents from the EFSA Scientific Committee.

The ANS Panel assessed the safety of aluminium sulphates (E 520–523) and SALP (E 541) as food additives in line with the principles laid down in Regulation (EU) 257/2010 and in the relevant guidance documents: Guidance on submission for food additive evaluations by the Scientific Committee on Food (SCF, 2001) and taking into consideration the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

When the test substance was administered in the feed or in the drinking water, but doses were not explicitly reported by the authors as mg/kg bw per day based on actual feed or water consumption, the daily intake was calculated by the Panel using the relevant default values as indicated in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012a,b,c) for studies in rodents or, in the case of other animal species, by JECFA (2000). In these cases, the daily intake is expressed as equivalent. When in human studies in adults (aged above 18 years), the dose of the test substance administered was reported in mg/person per day, the dose in mg/kg bw per day was calculated by the Panel using a body weight of 70 kg as default for the adult population as described in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012a).

Dietary exposure to aluminium sulphates (E 520–523) and SALP (E 541) from their use as food additives was estimated combining food consumption data available within the EFSA Comprehensive European Food Consumption Database with the maximum permissible levels (MPLs) according to Annex II to Regulation (EC) No 1333/2008⁹ and/or reported use levels submitted to EFSA following a call for data. Different scenarios were used to calculate exposure (see Section 3.4.1). Uncertainties on the exposure assessment were identified and discussed.

An extensive literature search (ELS) on aluminium sulphate (E 520), aluminium sodium sulphate (E 521), aluminium potassium sulphate (E 522), aluminium ammonium sulphate (E 523) and SALP, acidic, (E 541) has been performed, covering the period from January 1990 up to June 2018.

⁶ Call for technical and toxicological data on miscellaneous food additives to be re-evaluated under the Regulation (EU) No 257/2010 - Extended deadline: 31 January 2018: <https://www.efsa.europa.eu/en/data/call/170811>

⁷ 11–12/6/2018.

⁸ Available online: <http://www.efsa.europa.eu/en/food-consumption/comprehensive-database>

⁹ Commission Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16.

3. Assessment

3.1. Technical data

3.1.1. Identity of the substance(s)

Double salt compounds of the general formula $AlM(SO_4)_2$ – where M indicates a metal in its 1+ oxidation state – have traditionally been called alums (Darragh and Ertell, 2004); in particular, aluminium potassium sulphate ($AlK(SO_4)_2 \cdot nH_2O$) is the epitome of alums and is generally referred to as ordinary alum or potash alum.

Aluminium sulphate (E 520)

In Commission Regulation (EU) No 231/2012⁵, (anhydrous) aluminium sulphate (E 520) is identified by the same chemical name, has chemical formula $Al_2(SO_4)_3$, and molecular weight 342.13 g/mol; no EINECS (EC) or CAS Registry numbers are reported. In JECFA (2011),¹⁰ the chemical is defined as in the EU specifications and identified with CAS Registry No 10043-01-3.

In the EC inventory (online),¹¹ the EC number matching the aforesaid CAS is 233-135-0.

According to Commission Regulation No 231/2012 and JECFA (2011), aluminium sulphate is freely soluble in water and insoluble in ethanol; a 5% aqueous solution of the chemical shows an acidic reaction ($pH \geq 2.9$). Aluminium sulphate occurs as an odourless white powder, shining plates, or crystalline fragments.

Anhydrous aluminium sulphate melts at 700°C, with decomposition (WHO, 1997).

Based on Commission Regulation (EU) No 231/2012, JECFA (2011) and PubChem, aluminium sulphate is also known by several synonyms, a selection of which follows: alum; INS No 520; dialuminum sulphate; dialuminum trisulphate.

Aluminium sodium sulphate (E 521)

In Commission Regulation (EU) No 231/2012⁵, aluminium sodium sulphate (E 521) is identified by the same chemical name, has chemical formula $AlNa(SO_4)_2 \cdot nH_2O$ ($n = 0$ or 12), molecular weight 242.09 g/mol (anhydrous) and EINECS (EC) No 233-277-3 (anhydrous); no CAS Registry number is reported. According to WHO (2018),¹² the chemical – identified with CAS Registry No 10102-71-3 – was evaluated by JECFA in 1978 (WHO Technical Report Series 631, 1978); however, the evaluation was never consolidated into a subsequent final monograph and was later withdrawn (WHO, 2018).

According to Commission Regulation No 231/2012, aluminium sodium sulphate dodecahydrate is freely soluble in water; the anhydrous form is only slowly soluble in water. Both forms are insoluble in ethanol. The chemical occurs in the form of transparent crystals or white crystalline powder.

As reported by Darragh and Ertell (2004), aluminium sodium sulphate dodecahydrate (CAS Registry No. 7784-28-3) melts at 61°C and is the most water-soluble alum (75 g/100 mL of water at 20°C).

Based on Commission Regulation (EU) No 231/2012, WHO (2018) and PubChem, aluminium sodium sulphate is also known by several synonyms, a selection of which follows: soda alum; sodium alum; sodium aluminium sulphate; aluminium sodium disulphate.

Aluminium potassium sulphate (E 522)

In Commission Regulation (EU) No 231/2012⁵, aluminium potassium sulphate (E 522) is identified by the chemical name aluminium potassium sulphate dodecahydrate, has chemical formula $AlK(SO_4)_2 \cdot 12H_2O$, molecular weight 474.38 g/mol and EINECS (EC) No 233-141-3 (anhydrous); no CAS Registry number is reported. In JECFA (2011),¹³ two forms of the chemical are defined: aluminium potassium sulphate dodecahydrate and aluminium potassium sulphate anhydrous, respectively, identified with CAS Registry Nos 7784-24-9 and 10043-67-1,¹⁴ the chemical formula $AlK(SO_4)_2 \cdot nH_2O$ ($n = 12$ or 0), and respective molecular weights 474.38 and 258.21 g/mol.

¹⁰ Available online http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-017-m11.pdf

¹¹ Available online <https://echa.europa.eu/information-on-chemicals/ec-inventory>

¹² Available online <http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=844>

¹³ Available online http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-014-m11.pdf

¹⁴ Available online https://echa.europa.eu/it/information-on-chemicals/ec-inventory?p_p_id=disslists_WAR_disslistsportlet&p_p_lifecycle=1&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_pos=1&p_p_col_count=2&disslists_WAR_disslistsportlet_javax.portlet.action=searchDissLists

According to Commission Regulation No 231/2012 and JECFA (2011), aluminium potassium sulphate dodecahydrate is freely soluble in water and insoluble in ethanol; a 10% aqueous solution of the chemical shows an acidic reaction (pH 3.0–4.0). The chemical is odourless and occurs in the form of large, transparent crystals or crystalline fragments, or white crystalline powder.

Aluminium potassium sulphate dodecahydrate is reported to have a melting point of 92.5°C; it dehydrates at about 200°C yielding desiccated potassium aluminium sulphate $[\text{AlK}(\text{SO}_4)_2]$ (Darragh and Ertell, 2004).

Based on Commission Regulation (EU) No 231/2012, JECFA (2011) and PubChem, aluminium potassium sulphate is also known by several synonyms, a selection of which follows: potassium alum; potash alum; Burnt alum (anhydrous); INS No 522; aluminium potassium disulphate.

Aluminium ammonium sulphate (E 523)

In Commission Regulation (EU) No 231/2012⁵, aluminium ammonium sulphate (E 523) is identified by the same chemical name, has chemical formula $\text{AlNH}_4(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$, molecular weight 453.32 g/mol and EINECS (EC) No 232-055-3 (anhydrous); no CAS Registry number is reported. In JECFA (2011),¹⁵ the chemical is defined as in the EU specifications and identified with CAS Registry No 7784-25-0 for the anhydrous form.

The CAS Registry for aluminium ammonium sulphate dodecahydrate is 7784-26-1.

According to Commission Regulation No 231/2012 and JECFA (2011), aluminium ammonium sulphate dodecahydrate is freely soluble in water and soluble in ethanol. The chemical, odourless, occurs in the form of large, colourless crystals, white granules or white powder.

Aluminium ammonium sulphate dodecahydrate has a melting point of 94.5°C; it dehydrates at about 250°C to turn into the dry aluminium ammonium sulphate, $\text{AlNH}_4(\text{SO}_4)_2$ (Darragh and Ertell, 2004); the anhydrous form starts to decompose at 280°C. γ -Alumina ($\gamma\text{-Al}_2\text{O}_3$) is formed between 1,000°C and 1,250°C.

Based on Commission Regulation (EU) No 231/2012, JECFA (2011) and PubChem, aluminium ammonium sulphate dodecahydrate is also known by several synonyms, a selection of which follows: ammonium alum; INS No 523; ammonium aluminium sulphate hydrate; aluminium(III) ion ammonium dodecahydrate disulphate.

Sodium aluminium phosphate, acidic (E 541)

In Commission Regulation (EU) No 231/2012⁵, the food additive known as sodium aluminium phosphate, acidic (SALP, E 541) comprises two chemicals: (A) sodium trialuminium tetradecahydrogen octaphosphate tetrahydrate and (B) trisodium dialuminium pentadecahydrogen octaphosphate, and their respective chemical formulas and molecular weights are (A) $\text{NaAl}_3\text{H}_{14}(\text{PO}_4)_8 \cdot 4\text{H}_2\text{O}$, 949.88 g/mol, and (B) $\text{Na}_3\text{Al}_2\text{H}_{15}(\text{PO}_4)_8$, 897.82 g/mol. The EINECS (EC) No is 232-090-4 and no CAS Registry number is reported for either one. In JECFA (2011),¹⁶ the food additive is defined as in the EU specifications; no CAS Registry No is reported.

With reference to EC Inventory, the aforesaid EINECS (EC) number pairs with CAS Registry No 7785-88-8. For $\text{NaAl}_3\text{H}_{14}(\text{PO}_4)_8 \cdot 4\text{H}_2\text{O}$, Gard (2006) reports CAS Registry No 10305-76-7.

According to Commission Regulation No 231/2012 and JECFA (2011), SALP, acidic is a white odourless powder insoluble in water but soluble in hydrochloric acid. Loss on ignition at 750–800°C for 2 h is 19.5–21.0% for (A) and 15–16% for (B).

Based on Commission Regulation (EU) No 231/2012, JECFA (2011) and PubChem, SALP, acidic, is also known by several synonyms, a selection of which follows: SALP; INS No 541(i); phosphoric acid aluminium sodium salt; aluminium sodium salt; aluminium sodium phosphate; sodium aluminium phosphate.

3.1.2. Specifications

The specifications for aluminium sulphate (E 520), aluminium sodium sulphate (E 521), aluminium potassium sulphate (E 522), aluminium ammonium sulphate (E 523) and SALP, acidic (E 541) as defined in Commission Regulation (EU) No 231/2012 and by JECFA (2011) (with the exception of E 521) are listed in Tables 1, 2, 3, 4, and 5, respectively.

¹⁵ Available online http://www.fao.org/fyleadmin/user_upload/jecfa_additives/docs/monograph11/additive-012-m11.pdf

¹⁶ Available online at http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-012-m11.pdf

Table 1: Specifications for aluminium sulphate E 520 according to Commission Regulation (EU) No 231/2012 and JECFA (2011)^(b)

	Commission Regulation (EU) No 231/2012	JECFA (2011)
Definition	EINECS (EC) No: –	CAS No: 10043-01-3
	Chemical name: aluminium sulphate	Chemical name: aluminium sulphate
	Chemical formula: $\text{Al}_2(\text{SO}_4)_3$	Chemical formula: $\text{Al}_2(\text{SO}_4)_3$
	Molecular weight (g/mol): 342.13	Formula weight (g/mol): 342.13
	Assay: content not less than 99.5% on the ignited basis	Assay: not less than 99.5% on the ignited base
Description	White powder, shining plates or crystalline fragments	White powder, shining plates or crystalline fragments; odourless
Identification	Test for aluminium: passes test	Test for aluminium: passes test
	Test for sulphate: passes test	Test for sulphate: passes test
	pH: 2.9 or above (5% solution)	pH: 2.9 or above (5% solution)
	Solubility: freely soluble in water, insoluble in ethanol	Solubility: freely soluble in water, insoluble in ethanol
Purity	Loss on ignition: not more than 5% (500°C, 3 h)	Loss on ignition: not more than 5% (about 500°C, 3 h)
	Alkalies and alkaline earths: not more than 0.4%	Alkalis and alkaline earths: not more than 4 mg (about 0.4%) of residue remains from treating a 2 g sample ^(a)
	Selenium: not more than 30 mg/kg	Selenium: not more than 30 mg/kg
	Fluoride: not more than 30 mg/kg	Fluoride: not more than 30 mg/kg ^(a)
	Arsenic: not more than 3 mg/kg	–
	Lead: not more than 5 mg/kg	Lead: not more than 5 mg/kg
	Mercury: not more than 1 mg/kg	–

(a): In JECFA (2011) a specific test is directly available from the data sheet.

(b): Available online at http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-017-m11.pdf**Table 2:** Specifications for aluminium sodium sulphate E 521 according to Commission Regulation (EU) No 231/2012^(a)

	Commission Regulation (EU) No 231/2012
Definition	EINECS (EC) No: 233-277-3
	Chemical name: aluminium sodium sulphate
	Chemical formula: $\text{AlNa}(\text{SO}_4)_2 \cdot n\text{H}_2\text{O}$ ($n = 0$ or 12)
	Molecular weight (g/mol): 242.09 (anhydrous)
	Assay: content on the anhydrous basis not less than 96.5% (anhydrous) and 99.5% (dodecahydrate)
Description	Transparent crystals or white crystalline powder
Identification	Test for aluminium: passes test
	Test for sodium: passes test
	Test for sulphate: passes test
	Solubility: dodecahydrate is freely soluble in water; the anhydrous form is slowly soluble in water; both forms are insoluble in ethanol
Purity	Loss on drying: anhydrous form: not more than 10.0% (220°C, 16 h) dodecahydrate: not more than 47.2% (50–55°C, 1 h, then 200°C, 16 h)
	Ammonium salts: no odour of ammonia detectable after heating
	Selenium: not more than 30 mg/kg
	Fluoride: not more than 30 mg/kg
	Arsenic: not more than 3 mg/kg
	Lead: not more than 5 mg/kg
	Mercury: not more than 1 mg/kg

(a): The chemical was evaluated by JECFA in 1978 (WHO Technical Report Series 631, 1978); however, the evaluation was later withdrawn (WHO, 2018)^(b).(b): Available online <http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=844>

Table 3: Specifications for aluminium potassium sulphate E 522 according to Commission Regulation (EU) No 231/2012 and JECFA (2011)^(b)

	Commission Regulation (EU) No 231/2012	JECFA (2011)
Definition	EINECS (EC) No: 233-141-3	CAS No: 7784-24-9 (dodecahydrate) 10043-67-1 (anhydrous)
	Chemical name: aluminium potassium sulphate dodecahydrate	Chemical names: aluminium potassium sulphate dodecahydrate aluminium potassium sulphate anhydrous
	Chemical formula: $\text{AlK}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$	Chemical formula: $\text{AlK}(\text{SO}_4)_2 \cdot n\text{H}_2\text{O}$ (n = 0 or 12)
	Molecular weight (g/mol): 474.38	Formula weight: 474.38 (dodecahydrate) 258.21 (anhydrous)
	Assay: content not less than 99.5%	Assay: dodecahydrate: not less than 99.5% anhydrous form: not less than 96.5%
Description	Large, transparent crystals or white crystalline powder	Large, transparent crystals or crystalline fragments, or white crystalline powder; odourless
Identification	Test for aluminium: passes test	Test for aluminium: passes test
	Test for potassium: passes test	Test for potassium: passes test
	Test for sulphate: passes test	Test for sulphate: passes test
	pH: between 3.0 and 4.0 (10% solution)	pH: 3.0–4.0 (10% solution)
	Solubility: freely soluble in water, insoluble in ethanol	Solubility: freely soluble in water, insoluble in ethanol
Purity	Ammonium salts: no odour of ammonia detectable after heating	Ammonium salts: no odour of ammonia detectable after heating ^(a)
	Selenium: not more than 30 mg/kg	Selenium: not more than 30 mg/kg
	Fluoride: not more than 30 mg/kg	Fluoride: not more than 30 mg/kg ^(a)
	Arsenic: not more than 3 mg/kg	–
	Lead: not more than 5 mg/kg	Lead: not more than 5 mg/kg
	Mercury: not more than 1 mg/kg	–

(a): In JECFA (2011) a specific test is directly available from the data sheet.

(b): Available online at http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-014-m11.pdf**Table 4:** Specifications for aluminium ammonium sulphate E 523 according to Commission Regulation (EU) No 231/2012 and JECFA (2011)^(b)

	Commission Regulation (EU) No 231/2012	JECFA (2011)
Definition	EINECS (EC) No: 232-055-3	CAS No: 7784-25-0
	Chemical name: Aluminium ammonium sulphate	Chemical name: aluminium ammonium sulphate
	Chemical formula: $\text{AlNH}_4(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$	Chemical formula: $\text{AlNH}_4(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$
	Molecular weight (g/mol): 453.32	Formula weight (g/mol): 453.32
	Assay: content not less than 99.5%	Assay: not less than 99.5% of $\text{AlNH}_4(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$
Description	Large, colourless crystals or white powder	Large, colourless crystals, white granules or a powder; odourless
Identification	Test for aluminium: passes test	Test for aluminium: passes test
	Test for ammonium: passes test	Test for ammonium: passes test
	Test for sulphate: passes test	Test for sulphate: passes test
	Solubility: freely soluble in water, soluble in ethanol	Solubility: freely soluble in water, insoluble in ethanol

	Commission Regulation (EU) No 231/2012	JECFA (2011)
Purity	Alkali metals and alkaline earths: not more than 0.5%	Alkalis and alkaline earths: the weight of residue does not exceed 5 mg from treating a 1 g sample ^(a)
	Selenium: not more than 30 mg/kg	Selenium: not more than 30 mg/kg
	Fluoride: not more than 30 mg/kg	Fluoride: not more than 30 mg/kg ^(a)
	Arsenic: not more than 3 mg/kg	–
	Lead: not more than 3 mg/kg	Lead: not more than 3 mg/kg
	Mercury: not more than 1 mg/kg	–

(a): In JECFA (2011) a specific test is directly available from the data sheet.

(b): Available online at http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-014-m11.pdf

Table 5: Specifications for sodium aluminium phosphate, acidic E 541 according to Commission Regulation (EU) No 231/2012 and JECFA (2011)^(b)

	Commission Regulation (EU) No 231/2012	JECFA (2011) ^(a)
Definition	EINECS (EC) No: 232-090-4	–
	Chemical name: (A) sodium trialuminium tetradecahydrogen octaphosphate tetrahydrate (B) trisodium dialuminium pentadecahydrogen octaphosphate	Chemical name: (A) sodium trialuminium tetradecahydrogen octaphosphate tetrahydrate (B) trisodium dialuminium pentadecahydrogen octaphosphate
	Chemical formula: (A) $\text{NaAl}_3\text{H}_{14}(\text{PO}_4)_8 \cdot 4\text{H}_2\text{O}$ (B) $\text{Na}_3\text{Al}_2\text{H}_{15}(\text{PO}_4)_8$	Chemical formula: (A) $\text{NaAl}_3\text{H}_{14}(\text{PO}_4)_8 \cdot 4\text{H}_2\text{O}$ (B) $\text{Na}_3\text{Al}_2\text{H}_{15}(\text{PO}_4)_8$
	Molecular weight (g/mol): (A) 949.88 (B) 897.82	Formula weight (g/mol): (A) 949.88 (B) 897.82
	Assay: Content not less than 95.0% (both forms)	Assay: not less than 95% of (A) or not less than 95% of (B)
	White odourless powder	White, odourless powder
Description	White odourless powder	White, odourless powder
Functional uses	–	Raising agent
Identification	Test for sodium: passes test	Test for sodium: passes test
	Test for aluminium: passes test	Test for aluminium: passes test
	Test for phosphate: passes test	Test for phosphate: passes test
	pH: acid to litmus	pH: acid to litmus
	Solubility: insoluble in water; soluble in hydrochloric acid	Solubility: insoluble in water; soluble in hydrochloric acid
Purity	Loss on ignition: (A) 19.5–21.0% (750–800°C, 2 h) (B) 15–16% (750–800°C, 2 h)	Loss on ignition: (A) 19.5–21.0% (750–800°C, 2 h) (B) 15–16% (750–800°C, 2 h)
	Fluoride: not more than 25 mg/kg	Fluoride: not more than 25 mg/kg
	Arsenic: not more than 3 mg/kg	Arsenic: not more than 3 mg/kg
	Lead: not more than 4 mg/kg	Lead: not more than 2 mg/kg
	Cadmium: not more than 1 mg/kg	–
	Mercury: not more than 1 mg/kg	–

(a): In JECFA (2011), sodium aluminium phosphate, acidic and sodium aluminium phosphate, basic are identified with INS No 541(i) and INS No 541(ii), respectively.

(b): Available online http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-389-m11.pdf (INS No 541(i)) http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph11/additive-390-m11.pdf (INS No 541(ii))

The Panel noted that there was a difference in the claimed solubility in ethanol of aluminium ammonium sulphate dodecahydrate (E 523) (Table 4, Commission Regulation (EU) No 231/2012) between the EU and JECFA specifications.

The Panel further noted that in the case of aluminium sulphate (E 520), an upper limit of the pH was not given.

3.1.3. Manufacturing process

Aluminium sulphate ($\text{Al}_2(\text{SO}_4)_3 \cdot n\text{H}_2\text{O}$; $n = 0\text{--}27$) is usually produced by allowing bauxite – a mineral with a relatively high content of aluminium (oxy)hydroxides – or clay to react with sulfuric acid (Darragh and Ertell, 2004). Clay (e.g. kaolin) is roasted to remove organic substances, break down the crystal structure, and make it more reactive. The purity of the starting bauxite or clay, especially the iron and potassium contents, has a bearing on the purity of the final product; the conditions for roasting the clay and the strength of the sulfuric acid to be used depend on the particular raw material. Ground bauxite or roasted clay is digested with sulfuric acid near the boiling point of the solution: the relative concentrations of bauxite/clay and acid are adjusted to produce either acidic or basic alum; solids are removed by sedimentation. The iron-free grade ($< 0.005\%$ Fe_2O_3) of aluminium sulphate hydrate is manufactured from pure alumina trihydrate ($\text{Al}_2\text{O}_3 \cdot 3\text{H}_2\text{O}$) rather than from bauxite or clay. According to Park et al. (2004), high purity aluminium sulphate ($> 99.9\%$) was produced by the reaction of aluminium ammonium sulphate ($\text{AlNH}_4(\text{SO}_4)_2$) leach liquor derived from coal fly ash and 28% ammonia in water at a controlled pH, followed by successive crystallisation.

Aluminium sodium sulphate ($\text{AlNa}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$) occurs in nature as a rare mineral. However, the commercial product is obtained by adding a solution of sodium sulphate to a solution of aluminium sulphate. After adjusting the ratio of aluminium sulphate and sodium sulphate, water is evaporated to give a hard cake; this is further heated in roasters and ground to a powder of the desired particle size (Darragh and Ertell, 2004).

Aluminium potassium sulphate ($\text{AlK}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$) occurs naturally as a mineral. Commercial aluminium potassium sulphate is manufactured by treating bauxite with sulfuric acid followed by potassium sulphate (Darragh and Ertell, 2004). Alternatively, potassium sulphate is added to a concentrated solution of aluminium sulphate, or the mineral alunite ($\text{K}_2\text{Al}_6(\text{SO}_4)_4(\text{OH})_{12}$) is calcined and leached with sulfuric acid.

Aluminium ammonium sulphate ($\text{AlNH}_4(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$) is obtained by crystallisation from an aqueous mixture of ammonium and aluminium sulphates, or by treatment of aluminium sulphate and sulfuric acid with ammonia gas (Darragh and Ertell, 2004).

The general scheme to manufacture phosphate salts can be summarised as follows (Gard, 2006): orthophosphoric acid (H_3PO_4) is allowed to react with the appropriate bases (e.g. sodium hydroxide, aluminium hydroxide, ammonia) until neutralisation is reached, to yield a solution or slurry with an acid/base ratio according to the orthophosphate product desired. The orthophosphate salt(s) may be recovered by crystallisation from solution; alternatively, the entire solution or slurry may be evaporated to dryness. Dewatering is also a method that may be used if allowed by the solubility properties of the product and by some desired physical properties (e.g. crystal size and shape, bulk density, surface area). Acid orthophosphate salts may be converted to condensed phosphates by calcination. Phosphate salts containing sodium and aluminium – such as acidic $\text{NaAl}_3\text{H}_{14}(\text{PO}_4)_8 \cdot 4\text{H}_2\text{O}$ and $\text{Na}_3\text{Al}_2\text{H}_{15}(\text{PO}_4)_8$ – are manufactured by crystallisation from a concentrated solution containing the appropriate $\text{Na}_2\text{O}/\text{Al}_2\text{O}_3/\text{P}_2\text{O}_5$ ratio.

3.1.4. Methods of analysis in food

The review by Wood et al. (2004) provides a compilation of published analytical methods suitable for the determination of aluminium in foods. The specific method to be used is function of the matrix to be analysed, the detection limit required, and the instrumentation available in the laboratory; methods may need to be adapted. In general, methods require a preliminary digestion stage to decompose the food sample; aluminium measurement is subsequently carried out by different techniques, as per the following examples (LOD, limit of detection for aluminium):

- *duplicate diets, milk powders*: inductively coupled plasma (ICP) and atomic absorption spectrometry (AAS); LOD, 0.02–10 mg/kg;
- *infant formula, evaporated milk*: graphite furnace atomic absorption spectrometry (GF-AAS); LOD (rounded off), 0.01 µg/g;

- *wine*: graphite furnace atomic absorption spectrometry (GF-AAS); linear calibration, 0–100 µg/L;
- *fish*: graphite furnace atomic absorption spectrometry (GF-AAS); LOD, 1–30 ng/g on a dry weight basis;
- *coffee, tea, Port wine*: electrothermal atomic absorption spectrometry (ET-AAS); LOD (rounded off), 1–2 µg/L;
- *baby foods*: electrothermal atomic absorption spectrometry (ET-AAS); LOD, 50 pg (25 ng/g for a 10% (w/v) suspension);
- *foods*: spectrophotometric oxine (8-hydroxyquinoline) method (SO) and flame atomic absorption spectroscopy (F-AAS); LOD (SO), 0.5 µg/mL; LOD (F-AAS), 6 µg/mL;
- *seafood, meat*: inductively coupled plasma atomic emission spectrometry (ICP-AES); LOD, as required.

Some specific examples of determinations of aluminium in a variety of foods are described below.

Müller et al. (1998) investigated the aluminium content of a comprehensive food assortment typical of German nutritional habits (market basket studies); sampling was carried out in 1988 and 1991. All foodstuffs were prepared ready for cooking, but raw; in general, fruit and vegetables were peeled and/or washed, the inedible parts being removed from the samples; canned products were analysed without liquid. Samples were then dried at 105°C, dry-ashed in a muffle furnace at 450°C, and dissolved in diluted hydrochloric acid. Aluminium determination was carried out by GF-AAS, having adequate sensitivity for all assessments. Aluminium content of the food samples analysed was low and comparable with literature data: most foodstuffs contained less than 5 µg/g fresh matter. Highest concentrations were determined in cocoa/cocoa products (33 µg/g), spices (145 µg/g), and black tea leaves (899 µg/g). In general, aluminium content increased in the following order: beverages, food of animal origin, food of plant origin.

According to WHO (1998), referring to International Organization for Standardization (ISO) guidelines, aluminium can be reacted with pyrocatechol violet, thereby obtaining a coloured complex that is measured by an absorption spectrophotometric method: the method – applicable to the analysis of potable waters, ground waters, and lightly polluted surface and sea waters – is restricted to the determination of the aquated cations and other forms of aluminium readily converted to that cationic form by acidification (LOD, 2 µg/L). The LOD for the determination of aluminium to assess water quality by ICP-AES ranges from 40 to 100 µg/L. F-AAS and GF-AAS methods are applicable for the determination of aluminium in water at concentrations of 5–100 mg/L and 0.01–0.1 mg/L, respectively.

In order to investigate the changes in aluminium concentration along with those of aroma constituents in beer during storage at different temperatures, GF-AAS and gas chromatography with static headspace sampler (GC-HSS) were used by Ivušić et al. (2006). Analyses were conducted periodically throughout 7 months of storage on three different brands of beer. Samples were taken before and after filling in aluminium cans. One part of samples was stored in a refrigerator (4°C) and the other in a thermostatic chamber (22°C). The effects of beer brand and storage conditions on aluminium concentration and level of aroma constituents were measured. To prove the effect of aluminium concentration on the changes of aroma compounds, aluminium sulphate was added to bottled beer samples stored at 28°C. Samples that were stored in the refrigerator were protected from aluminium migration from the can to the beer and showed increased aroma stability. The level of aroma constituents in the beer brands was significantly different. Elevated aluminium concentration did not have any noticeable effect on the level of aroma compounds in beer samples stored at 28°C.

Hua et al. (2016) investigated the applicability of wavelength dispersive X-ray fluorescence spectrometry (WDXRF) for analysis of aluminium levels in youtiao, a typical Chinese fried food. Youtiao samples with known amounts of aluminium were used for calibration; linearity, accuracy, precision and detection and quantification limits (approximately, 10 and 30 mg/kg, respectively). Test youtiao samples were analysed by both WDXRF and inductively coupled plasma optical emission spectrometry (ICP-OES). Comparison of the two methods showed that measurement performance was not significantly different. The authors concluded that WDXRF can allow a suitable methodology for measuring the aluminium content of youtiao, and that it is a good candidate for replacing ICP-OES.

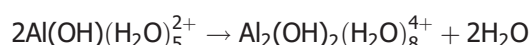
3.1.5. Stability of the substance, and reaction and fate in food

In aqueous media, water molecules form relatively strong bonds with the aluminium(III) ion. The coordinated water molecules exhibit an octahedral geometry: the species $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$ behaves as a weak acid due to ion dipole forces between Al^{3+} and the oxygen atoms of the coordinated water

molecules. However, because of its amphoteric character, Al^{3+} reacts with mineral acids and strong alkalis (EFSA, 2008, EFSA 2011a,b; WHO, 1997).

The solubility of Al^{3+} in equilibrium with solid phase $\text{Al}(\text{OH})_3$ is strongly pH-dependent. The ion $\text{Al}(\text{H}_2\text{O})_6^{3+}$ predominates at low pH values ($\text{pH} < 4$), but as the pH of the solution increases (e.g., pH 4–6) and/or the temperature rises, the positive charge of Al^{3+} forces hydrolysis of a water ligand producing the $\text{Al}(\text{OH})(\text{H}_2\text{O})_5^{2+}$ ion. The degree of hydrolysis increases as pH increases, resulting in a series of aluminium(III) hydroxide complexes – such as $\text{Al}(\text{OH})^{2+}$, $\text{Al}(\text{OH})_2^+$, $\text{Al}(\text{OH})_3$, and $\text{Al}(\text{OH})_4^-$ – accompanied by a corresponding decrease in the number of coordinating water molecules. Neutral solutions give an $\text{Al}(\text{OH})_3$ precipitate that redissolves owing to the formation of the aluminate anion $\text{Al}(\text{OH})_4^-$, with a tetrahedral geometry; a mixture of these species occurs at pH 5–7, but at $\text{pH} > 6.2$ $\text{Al}(\text{OH})_4^-$ is the predominant soluble aqueous species (Martin, 1986, 1992).

Aluminium begins to polymerise when the pH of an acidic solution increases distinctly above pH 4.5. Polymerisation implies that in the first step, two hydroxyls are shared by two aluminium atoms, e.g.:



Polymerisation gradually proceeds to larger structures, eventually leading to the formation of the ' Al_{13} ' polycation (Hem and Roberson, 1967; Parker and Bertsch, 1992a,b). As polymers coalesce, their molecular mass increases, eventually becoming large enough for aluminium hydroxide to precipitate from solution. Tipping et al. (1988) found that, if precipitation occurs at pH 4–6, it involves the formation of aluminium (oxy)hydroxide, a compound whose solubility is highly temperature dependent.

When present, fluoride ions (F^-) can readily replace the hydroxyl ions in aluminium(III) hydroxide complexes. At $\text{pH} > 7$, the latter predominate in waters that are low in dissolved organic matter and silicate. Under acidic conditions, sulphate ions (SO_4^{2-}) also form complexes with Al^{3+} . Even though sulphate concentrations are typically higher than those of fluoride in surface waters, aluminium(III) sulphate complexes are significant only at high sulphate concentrations and low pH values (WHO, 1997; EFSA, 2008, 2011a,b).

3.2. Authorised uses and use levels

Maximum levels of aluminium sulphates (E 520–523) and SALP (E 541) have been defined in Annex II to Regulation (EC) No 1333/2008¹⁷ on food additives, as amended. In this document, these levels are named maximum permitted levels (MPLs).

Currently, aluminium sulphates (E 520–523) are authorised food additives in the EU with MPLs in two food categories, whereas SALP (E 541) is authorised in one food category with MPL.

Tables 6 and 7 summarise the food categories (FCs) that are permitted to contain aluminium sulphates (E 520–523) and SALP (E 541), respectively, with the corresponding MPLs as set by Annex II to Regulation (EC) No 1333/2008.

Table 6: MPLs of aluminium sulphates (E 520–523) in foods according to Annex II to Regulation (EC) No 1333/2008

Food category number	Food categories	E-number	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
05.2	Other confectionery including breath freshening microsweets	E 520–523 ^(b)	Only candied cherries ^(a)	200 ^(c)
10.2	Processed eggs and egg products	E 520	Liquid egg white for egg foams only ^(d)	25 ^(c)

MPL: maximum permitted level.

(a): Period of application: from 1 February 2014. Until 31 January 2014: only candied, crystallised or glacé fruit and vegetables
MPL: 200 mg/kg.

(b): The additives may be added individually or in combination.

(c): Expressed as aluminium.

(d): Period of application: from 1 February 2014. Until 31 January 2014: E 520–E 523, only egg white, MPL: 30 mg/kg.

¹⁷ Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16.

Table 7: MPL of sodium aluminium phosphate (E 541) in foods according to Annex II to Regulation (EC) No 1333/2008

Food category number	Food categories	E-number	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
07.2	Fine bakery wares	E 541	Only sponge cakes produced from contrasting coloured segments held together by jam or spreading jelly and encased by a flavoured sugar paste (the maximum limit applies only to the sponge part of the cake) ^(a)	400 ^(b)

MPL: maximum permitted level.

(a): Period of application: from 1 February 2014.

Until 31 January 2014: only scones and sponge wares, MPL: 1,000 mg/kg.

(b): Expressed as aluminium.

Aluminium sulphates (E 520–523) and SALP (E 541) are not authorised according to Annex III of Regulation (EC) No 1333/2008.

3.3. Exposure data

3.3.1. Reported use levels or data on analytical levels of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541)

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, information on actual use levels is required for performing a more realistic exposure assessment.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives, EFSA issued public calls^{18,19} for occurrence data (usage level and/or concentration data) on aluminium sulphates (E 520–523) and SALP (E 541).

In response to these calls, no use level or concentration data on aluminium sulphates (E 520–523) and SALP (E 541) were submitted to EFSA by industry or Member States.

3.3.2. Summarised data extracted from the Mintel's Global New Products Database

The Mintel's GNPDP is an online database which monitors new introductions of packaged goods in the market worldwide. It contains information of over 2.5 million food and beverage products of which more than 900,000 are or have been available on the European food market. Mintel started covering EU's food markets in 1996, currently having 20 out of its 28 member countries and Norway presented in the Mintel GNPDP.

For the purpose of this Scientific Opinion, the Mintel's GNPDP was used for checking the labelling of food and beverages products and food supplements for aluminium sulphates (E 520–523) and SALP (E 541) within the EU's food market as the database contains the compulsory ingredient information on the label.

According to the Mintel's GNPDP, aluminium sulphates (E 520–523) were labelled on only 19 food products between January 2013 and February 2018 of which six belonged to food subcategory 'Cakes, Pastries & Sweet Goods' of the Mintel's GNPDP food classification. Overall percentage of labelled products per subcategories was less than 0.1%. Note that the food products listed to contain aluminium sulphates (E 520–523) in the Mintel's GNPDP were not in line with present authorisation (Tables 6 and 7).

SALP (E 541) was labelled in 117 products belonging to 14 food subcategories. Subcategories with the highest number of food products were 'Cakes, Pastries & Sweet Goods' (n = 53), 'Baking Ingredients & Mixes' (n = 37) and 'Bread & Bread Products' (n = 6). The percentages of labelled foods belonging to these subcategories were, again, less than 0.1%.

The Panel noted that a decrease of products labelled with aluminium sulphates (E 520–523) and SALP (E 541) observed during last 5 years period is in line with the fact that no use levels were reported by

¹⁸ <http://www.efsa.europa.eu/en/consultations/call/100608>

¹⁹ <https://www.efsa.europa.eu/en/data/call/170223>

industry during the call in 2017 (Table 8). The observed decrease in the uses in the first year (2013–2014) was most likely due to this change in the legislation which was coming into force in February 2014.

Table 8: Number of products labelled with aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) during last 5 years period^(a)

Ingredient	2013	2014	2015	2016	2017	Total products
Sodium aluminium phosphates	53	26	16	16	5	116
Sodium aluminium sulphate	1	4	2	1	1	9
Aluminium sulphate	1	0	2	3	0	6
Ammonium aluminium sulphate	0	0	2	0	0	2
Aluminium potassium sulphate	0	0	2	0	0	2

(a): The number of products for 2018 is not included in the table as the data reported were not for the whole year.

Non-authorised use of the additives aluminium sulphates (E 520–523) and SALP (E 541) from February 2014 onwards was investigated in the Mintel's GNPD as the change in their authorisation was coming into force that time (see Section 3.2).

The Panel noted that none of the 17 products (belonging to subcategories 'Baking Ingredients & Mixes', 'Cakes, Pastries & Sweet Goods', 'Hors d'oeuvres/Canapes', 'Seasonal Chocolate', 'Sweet Biscuits/Cookies', 'Poultry Products', 'Meat Products', 'Cooking Sauces', 'Corn-Based Snacks', 'Fish Products') in which aluminium sulphates (E 520–523) were listed as ingredient was in line with the current authorisation.

In addition, SALP (E 541) was also listed as ingredient in 17 food products belonging to the following Mintel's GNPD sub-categories, where its use is not authorised: 'Bread & Bread Products', 'Hors d'oeuvres/Canapes', 'Chilled Desserts', 'Sweet Biscuits/Cookies', 'Meal Kits', 'Poultry Products', 'Potato Products', 'Wheat & Other Grain-Based Snacks', 'Salads' and 'Pizzas'.

Appendix A lists the percentage of the food products labelled with aluminium sulphates (E 520–523) and SALP (E 541) out of the total number of food products per food subcategories according to the Mintel's GNPD food classification.

3.3.3. Food consumption data used for exposure assessment

EFSA Comprehensive European Food Consumption Database

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a). Consumption surveys added in the Comprehensive database in 2015 were also taken into account in this assessment.

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons should be interpreted with caution. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' underreporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database includes the currently best available food consumption data across Europe.

Food consumption data from the following population groups were used for the exposure assessment: infants, toddlers, children, adolescents, adults and the elderly. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 9).

Table 9: Population groups considered for the exposure estimates of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541)

Population	Age range	Countries with food consumption surveys covering more than 1 day
Infants	From more than 12 weeks up to and including 11 months of age	Bulgaria, Denmark, Finland, Germany, Italy, UK
Toddlers ^(a)	From 12 months up to and including 35 months of age	Belgium, Bulgaria, Denmark, Finland, Germany, Italy, Netherlands, Spain, UK
Children ^(b)	From 36 months up to and including 9 years of age	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Romania, Spain, Sweden, UK
The elderly ^(b)	From 65 years of age and older	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Romania, Netherlands, Sweden, UK

(a): The term 'toddlers' in the EFSA Comprehensive Database corresponds to 'young children' in Regulations (EC) No 1333/2008 and (EU) No 609/2013.

(b): The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a).

Consumption records were codified according to the FoodEx classification system (EFSA, 2011b). Nomenclature from the FoodEx classification system has been linked to the food categorisation system (FCS) as presented in Annex II of Regulation (EC) No 1333/2008, part D, to perform exposure estimates. In practice, the FoodEx food codes were matched to the FCS food categories.

Food categories considered for the exposure assessment of aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541)

The food categories in which the use of aluminium sulphates (E 520–523) and SALP (E 541) is authorised were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx classification system), at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b).

Some food categories or their restrictions/exceptions are not referenced in the EFSA Comprehensive Database and could therefore not be taken into account in the present estimate resulting potentially in an underestimation of the exposure. FC 10.2 'Processed eggs and egg products', (E 520), 'liquid egg for egg foams only' was considered very specific which cannot be specified in the FoodEx system, and represented only a very small part of the food category. Considering the whole food category would thus have resulted in an unduly large overestimation of the exposure.

A refinement of the exposure was elaborated for FC 07.2 'Fine bakery wares'. Taking into account the restriction 'only sponge cakes produced from contrasting coloured segments held together by jam or spreading jelly and encased by a flavoured sugar paste', all sponge cakes in the EFSA Comprehensive Database were considered instead of the full category. More specific FoodEx code was not available for specifying this type of sponge cake.

For FC 05.2 'Other confectionery including breath freshening microsweets' 'only candied cherries', the refinement was applied by selecting entries with the FoodEx code of 'candied cherry' from the Comprehensive Database (Appendix B).

3.4. Exposure estimate

3.4.1. Exposure to aluminium sulphates (E 520–523) and sodium aluminium phosphate acidic (E 541) from their use as food additives

The Panel estimated a combined chronic dietary exposure to aluminium from aluminium sulphates (E 520–523) and SALP, acidic (E 541) for the following population groups: infants; toddlers, children, adolescents, adults and the elderly. Dietary exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) was calculated by multiplying MPLs of aluminium sulphates (E 520–523)

and SALP (E 541) per food category (Appendix B) with their respective consumption amount per kilogram body weight for each individual in the Comprehensive Database. The exposure per food category was subsequently added to derive an individual total exposure per day. These exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. Dietary surveys with only 1 day per subject were excluded as they are considered not adequate to assess repeated exposure.

This was carried out for all individuals per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 9). On the basis of these distributions, the mean and 95th percentile of exposure were calculated per survey and per population group. The 95th percentile of exposure was only calculated for those population groups with a sufficiently large sample size (EFSA, 2011a). Therefore, in the present assessment, the 95th percentile of exposure for infants from Italy and for toddlers from Belgium, Italy and Spain were not estimated.

Exposure assessment to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) was carried out by the ANS Panel based on MPLs (expressed as aluminium) as set down in the EU legislation, defined as the *regulatory maximum level exposure assessment scenario*.

As no use levels or concentration data were available for aluminium sulphates (E 520–523) and SALP (E 541), refined exposure scenarios could not be carried out.

Regulatory maximum level exposure assessment scenario

The regulatory maximum level exposure assessment scenario is based on the MPLs as set in Annex II to Regulation (EC) No 1333/2008. For aluminium sulphates (E 520–523) and SALP (E 541), the MPLs (expressed as aluminium) used in the assessment are listed in Table 1.

The Panel considers the exposure estimates derived following this scenario as the most conservative since it is assumed that the population will be exposed to the food additive present in food at the MPL over a longer period of time.

Dietary exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541)

Table 10 summarises the estimated exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) from their use as food additives in six population groups (Table 9). Detailed results per population group and survey are presented in Appendix C.

Table 10: Summary of dietary exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) from their use as food additives in the maximum level exposure assessment scenario in six population groups (minimum–maximum across the dietary surveys in mg Al/kg bw per day)

	Infants		Toddlers		Children		Adolescents		Adults		The elderly	
	(12 weeks–11 months)		(12–35 months)		(3–9 years)		(10–17 years)		(18–64 years)		(≥ 65 years)	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Mean	0	0.03	0	0.15	0	0.21	0	0.08	0	0.05	0	0.04
95th percentile	0	0	0	0.88	0	0.88	0	0.48	0	0.38	0	0.43

The mean exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) from their use as food additives at the MPL ranged from 0.0 mg/kg bw per day in all population groups to 0.21 mg/kg bw per day in children. The 95th percentile of exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) ranged from 0.0 mg/kg bw per day in all population groups to 0.88 mg/kg bw per day in toddlers and children.

The vast majority (99–100%) of the exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) in all population groups comes from sodium aluminium phosphate (E 541). The intake of SALP (E 541) comes from the assumptions that all sponge cakes contain SALP (E 541), and that all sponge cakes are produced from contrasting coloured segments held together by jam or spreading jelly and encased by a flavoured sugar paste.

Uncertainty analysis

Uncertainties in the exposure assessment of aluminium from aluminium sulphates (E 520–523) and SALP (E 541) have been discussed above. In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the following sources of uncertainties have been considered and summarised in Table 11.

Table 11: Qualitative evaluation of influence of uncertainties on the dietary exposure estimate

Sources of uncertainties	Direction ^(a)
Consumption data: different methodologies/representativeness/underreporting/misreporting/no portion size standard	+/-
Use of data from food consumption surveys covering only a few days to estimate high percentiles (95th) long-term (chronic) exposure	+
Consumption of sponge cakes taken into account to represent consumption of specific cakes that can be assumed to be consumed rarely by a small percent of the population (occasional eating)	+
Assumption that all sponge cakes contain the additives while regulation indicates that only very specific cakes should contain the additive and the Mintel GNPD indicates that only a few sponge cakes were labelled with the additives	+
Food categories selected for the exposure assessment: exclusion of FC 10.2 processed eggs and egg products due to missing FoodEx linkage	-
Regulatory maximum level exposure assessment scenario: exposure calculations based on the MPL according to Annex II to Regulation (EC) No 1333/2008	+

(a): +, uncertainty with potential to cause overestimation of exposure; -, uncertainty with potential to cause underestimation of exposure.

The Panel noted that information from the Mintel's GNPD (Appendix A) indicated that aluminium sulphates (E 520–523) were only used in a limited number of products ($n = 19$). This is in line with the fact that EFSA did not receive any use levels of these additives from industry. The Panel also noted that the food products labelled with aluminium sulphates (E 520–523) in the Mintel's GNPD were not in line with the present authorisation, which only allows the use of these additives in candied cherry in confectionary and liquid egg white for egg foam only.

For SALP (E 541), the foods labelled according to the Mintel's GNPD belonged mainly to the food subcategories 'Cakes, Pastries & Sweet Goods' and 'Baking Ingredients & Mixes'. This was in line with the authorised use of this additive. However, also for this additive the percentage of foods labelled to contain the additive was very low. The assumption in the exposure assessment that all foods belonging to the two included food categories contained the additives was very likely conservative.

In addition, the restriction in legislation for the use of SALP (E 541) in FC 07.2 Fine bakery wares (Table 7) was very specific. This restriction could only be approximated and has very likely contributed to an overestimation of the exposure.

Given these observations, as well as those listed in Table 11, the Panel considered overall that the uncertainties identified result in an overestimation of the exposure to aluminium from aluminium sulphates (E 520–523) and SALP (E 541) from their use as food additives according to Annex II in the assessment.

3.4.2. Exposure via the regular diet

Aluminium is the most abundant metallic element in the earth's crust and diet is the most important source of exposure, both due to the natural occurrence in, e.g. fruit, vegetables, cereals, seeds and meat, and due to the use of aluminium and aluminium compounds as food additives, in food processing, packaging and storage (EFSA, 2008). In addition to the aluminium compounds evaluated in the present opinion other forms of aluminium are authorised as food additives: elemental aluminium (E 173), aluminium silicates (E 554 and E 555) and in the form of aluminium lakes of food colours. EFSA (2008) compiled data on dietary exposure to aluminium and reported that the mean exposure ranged from 1.6 to 13 mg aluminium per day, corresponding to an exposure of approximately 0.2–1.5 mg/kg bw/week from water and food in a 60 kg adult. Children generally have a higher food intake than adults when expressed on a body weight basis, and therefore represent the group with the highest potential exposure

to aluminium per kg body weight. In children and young people the estimated exposure at the 97.5th percentile in the UK and France ranged from 0.7 to 2.3 mg aluminium/kg bw/week'. It was not possible to distinguish between the specific sources of aluminium, such as the contribution of aluminium-containing food additives to the total dietary exposure of aluminium. Aluminium in drinking water was reported to represent a minor source of exposure.

More recent studies of dietary exposure to aluminium from EU countries have reported daily intake in adults at the lower end of the range reported by EFSA in 2008: 1.6 mg per day in Sweden (NFA, 2010); 0.04 mg/kg bw per day (equivalent to 2.8 mg per day at 70-kg bw) in France (ANSES, 2011); 3.7–6.4 mg per day in Greece (Bratakos et al., 2012); 0.03 mg/kg bw per day (equivalent to 2.1 mg per day at 70-kg bw) in Belgium (Fekete et al., 2013) and 0.04 mg/kg bw per day (equivalent to 2.8 mg per day at 70-kg bw) in Norway (VKM, 2013).

3.4.3. Exposure via other sources

The Panel is aware that exposure to aluminium can come from other sources for example from use in cosmetic and vaccines. The exposure assessment of aluminium by VKM (2013) showed that cosmetic products and in particular antiperspirants, contribute considerably more than diet to the total systemic aluminium exposure in persons using such products.

3.5. Biological and Toxicological data

The safety of dietary intake of aluminium from any sources (food, food additives, food contact materials and drinking water) was previously evaluated by the EFSA AFC Panel (2008). In addition, a new study related to the bioavailability of aluminium in food was evaluated in a Statement by EFSA (2011a,b).

The present section summarises the major findings from the previous EFSA evaluations (2008; 2011), and any additional data retrieved from the subsequent literature search.

3.5.1. Absorption, distribution, metabolism and excretion

The oral bioavailability of aluminium compounds depends on the chemical form, the pH in the gastrointestinal tract and the presence of complexing ligands. In the acidic stomach environment, most of ingested aluminium compounds exist mainly as $\text{Al}(\text{H}_2\text{O})_6^{3+}$. As a result of the increase in pH from the stomach to the intestines insoluble aluminium hydroxide is formed at the neutral pH in the intestines with subsequent faecal excretion, leaving only a minor fraction available for absorption.

Oral bioavailability in rats of aluminium from 12 radioactively labelled aluminium (^{26}Al) compounds was investigated in a study provided by the industry and evaluated by EFSA (2011a,b). The compounds included four soluble aluminium salts: citrate, chloride, nitrate and sulphate; and eight aluminium compounds administered in suspension: hydroxide, oxide, metallic, powdered pot electrolyte, FD&C red 40 aluminium lake, SALP acidic, SALP basic, and sodium aluminium silicate. The ratio was determined between the radioactivity left in the carcass seven days after oral administration of the aluminium compounds and the radioactivity left in carcass seven days after intravenous administration of radioactively labelled citrate. The oral bioavailability varied between 0.03% (aluminium hydroxide) and 0.21% (aluminium sulphate). Three compounds had carcass levels below detection limit: aluminium metal, and the two SALPs. The Panel noted that less than 10% of the bioavailable dose remained in the carcass after 7 days. In another rat study, the bioavailability of aluminium from SALP, acidic, when incorporated in a biscuit, was about 0.1% (as cited in EFSA, 2011a,b).

Blood and tissue levels of aluminium were analysed in rats ($n = 5$) gavaged with water (controls) or six different salts of aluminium: citrate, sulphate, nitrate, chloride and hydroxide with a daily dose of 30 mg Al/kg bw per day for 7 or 14 days (Poirier et al., 2011). There were no statistically significant differences in blood or brain concentrations between the groups, while kidney and bone levels of aluminium were statistically significantly increased in the group administered aluminium citrate compared to controls or the other aluminium salts.

Human data on toxicokinetics of aluminium compounds are very limited (Weisser et al., 2017). No data are available in children and adolescents (< 18 years of age) and data on kinetics in persons with renal dysfunction are available only from two patients (Steinhausen et al., 2004). Available studies indicate that the oral bioavailability of aluminium in humans and experimental animals from drinking water is in the range of 0.3%, whereas the bioavailability of aluminium from food and beverages generally is considered to be lower, about 0.1%. Bioavailability of sodium aluminium phosphate acidic

was demonstrated in a crossover study in 18 subjects consuming four pancakes per day for one week, containing 860 mg Al/kg (allowed concentration before 2014) (Glynn et al. unpublished; Document provided to EFSA n.3)). Creatinine-adjusted urinary excretion of Al (median 67 $\mu\text{mol Al/mol creatinine}$, range 23–230; corresponds to 16 $\mu\text{g Al/g creatinine}$) was increased approximately twofold (paired T-test, $p \leq 0.05$), compared to excretion after consumption of four pancakes per day without aluminium phosphate ($< 0.5 \text{ mg Al/kg}$) (32 $\mu\text{mol Al/mol creatinine}$, 4.5–103; corresponds to 7.6 $\mu\text{g Al/g creatinine}$).

Toxicokinetic data from subjects receiving an oral dose of AlCl_3 were used to predict plasma levels after exposure to the EFSA TWI of 1 mg/kg bw. The predicted steady state plasma levels were 1–4 $\mu\text{g/L}$ (Weisser et al., 2017). This is in accordance with reported normal levels of aluminium in serum of approximately 1–3 $\mu\text{g/L}$. Normal median (upper range) levels of aluminium in plasma are 3.2 (6) $\mu\text{g/L}$. After absorption, aluminium binds to transferrin and distributes to tissues, accumulating in the bone where it can persist for a very long time. Total body burden in healthy human subjects has been reported to be approximately 30–50 mg/kg bw, half of which or more is in the skeleton. Higher body burden and tissue levels of aluminium have been reported in dialysis encephalopathy patients. In persons with renal failure the ability to excrete aluminium is reduced and aluminium exposure may increase, due to aluminium-containing dialysis water or consumption of aluminium-containing phosphate binders. Mean concentrations of aluminium in the brain were higher in 7 patients dying in dialysis encephalopathy, 15.9 $\mu\text{g Al/g dry weight}$, than in 11 dialysed controls, 4.4 $\mu\text{g Al/g dry weight}$ and in two non-dialysed uraemic patients, 2.7 $\mu\text{g Al/g dry weight}$ (McDermott et al., 1978).

Following ingestion in humans, absorbed aluminium from the blood is eliminated primarily by the kidneys, presumably as the citrate, and excreted in the urine. Two patients with chronic renal dysfunction, administered a single oral dose of AlCl_3 (100 $\mu\text{g Al}$), had similar levels of aluminium in the plasma but lower levels in urine, compared to healthy persons, indicating that more aluminium is stored in the body (Steinhausen et al., 2004). Unabsorbed aluminium is excreted in the faeces. Excretion via the bile constitutes a secondary, but minor route.

Overall, oral bioavailability of aluminium from aluminium compounds is low as a result of formation of insoluble aluminium hydroxide at the neutral pH in the intestines. Data from humans and experimental animals indicate that the bioavailability is approximately 0.3% of aluminium compounds in drinking water and 0.1% in food and beverages. Predicted plasma levels at the EFSA TWI of 1 mg Al/kg bw were within the reported normal levels of aluminium in serum, 1–3 $\mu\text{g/L}$. Absorbed aluminium accumulates in the bone. Kidney is the main route of excretion. Increased brain levels of aluminium have been reported in dialysis encephalopathy patients.

3.5.2. Acute oral toxicity

The acute oral toxicity of a number of inorganic aluminium salts has been evaluated in rats and mice, and shows a wide range of LD_{50} values from 162 to 750 mg aluminium/kg bw in rats and from 164 to 980 mg aluminium/kg bw in the mouse for different compounds (EFSA, 2008).

3.5.3. Short-term and subchronic toxicity

In EFSA (2008), it was reported that aluminium nitrate in drinking water for 28 days caused mild histopathological changes in spleen and liver or decreased body weights in rats; the NOAEL for these effects was 52 mg Al/kg bw per day. In contrast, dietary exposure to SALP for 28 days had no adverse effects in the highest doses tested corresponding to 140–300 mg Al/kg bw per day. Similarly, no effects were reported in dogs exposed in the diet to acidic SALP providing daily doses of 90 mg Al/kg bw per day for 26 weeks.

The following oral toxicity study with aluminium compounds, published after the adoption of the previous opinion, was also considered in the current opinion.

In a short-term toxicity study of fluoride or aluminium, Swiss albino male mice (10/group, mean body weight of $30 \pm 0.5 \text{ g}$, age 75–80 days) received by oral gavage either distilled water (vehicle control) or sodium fluoride (NaF , 190 mg/kg bw per day), aluminium sulphate ($\text{Al}_2(\text{SO}_4)_3 \cdot 16\text{H}_2\text{O}$, 78.4 mg Al/kg bw per day) or aluminium fluoride (AlF_3 , 103 mg/kg bw per day) in a volume of 0.5 mL/animal for seven days (Sharma et al., 2010). In both aluminium-treated groups, blackening of nails and the tails, increase in abdominal circumference, dullness and a tendency to disperse, statistically significantly decreased feed and water intake and body weight, 20% mortality during clinical phase and ballooning of lungs and gastrointestinal tract due to presence of odorous gas at necropsy of surviving animals were reported. The changes to the vehicle control values in haematology parameters in both aluminium groups were a

statistically significant decrease in haemoglobin concentration and mean corpuscular haemoglobin concentration, and increased poikilocytosis. In the aluminium sulphate group, there were statistically significant increases of alanine aminotransferase, serum urea, globulin, cholesterol and total lipid, and statistically significant decreases in alkaline phosphatase activity, and bilirubin. The only statistically significant difference in organ weights as compared to the vehicle control group was a decreased absolute kidney weight. Histological examination was not performed on any of the tissues. The Panel considered that this study cannot be used for the risk assessment.

3.5.4. Genotoxicity

Published genotoxicity studies with aluminium compounds (aluminium sulphate, chloride, hydroxide and nitrate) were reviewed and evaluated by the EFSA AFC Panel in a previous opinion on the safety of aluminium from dietary intake (EFSA, 2008). The conclusions concerning genotoxicity were as follows: 'Aluminium compounds were non-mutagenic in bacterial and mammalian cell systems, but some produced DNA damage and effects on chromosome integrity and segregation *in vitro*. Clastogenic effects were also observed *in vivo* when aluminium sulphate was administered at high doses by gavage or by the intraperitoneal route. Several indirect mechanisms have been proposed to explain the variety of genotoxic effects elicited by aluminium salts in experimental systems. Cross-linking of DNA with chromosomal proteins, interaction with microtubule assembly and mitotic spindle functioning, induction of oxidative damage, damage of lysosomal membranes with liberation of DNAase, have been suggested to explain the induction of structural chromosomal aberrations, sister chromatid exchanges, chromosome loss and formation of oxidised bases in experimental systems. The Panel noted that these indirect mechanisms of genotoxicity, occurring at relatively high levels of exposure, are unlikely to be of relevance for humans exposed to aluminium via the diet'. The Panel noted that the conclusions on genotoxicity of aluminium in the Scientific Committee on Consumer Safety (SCCS 2014) and the European Commission and its Scientific Committee on Health, Environmental and Emerging Risks opinion (SCHEER, 2017) are in agreement with the EFSA (2008) evaluation.

The following genotoxicity studies of aluminium compounds, published after the adoption of the previous opinion, were also considered in the current opinion.

In vitro

Turkez and Geyikoglu (2011) reported that $\text{Al}_2(\text{SO}_4)_3$ induced increase in the frequencies of sister chromatid exchange (SCE) and chromosomal aberrations (CA) in isolated human white blood cells at 20 $\mu\text{g/mL}$, together with the decrease in the activities of antioxidant enzymes reduced glutathione (GSH), superoxide dismutase (SOD), glucose-6-phosphate dehydrogenase (G-6-PDH) and catalase (CAT). At the lower tested concentration 10 $\mu\text{g/mL}$, neither induction of SCE and CA nor inhibition of the activities of antioxidant enzymes was observed.

In an *in vitro* toxicity and genotoxicity test with zebrafish embryonic cells ZF4 (Pereira et al., 2013), AlCl_3 tested at concentrations 5–100 μM induced dose dependent cytotoxicity. Significant increase in DNA single-stranded binding (ssb), determined by comet assay, was observed only at 50 μM , an increase in DNA double-strand break (dsb) determined as γH2AX foci was observed at concentrations up to 30 μM with a decline at higher concentrations, whereas induction of micronuclei formation was dose dependent at all tested concentrations.

In vivo

In an *in vivo* study, 8 weeks aged rats were orally administrated 34 mg AlCl_3/kg bw for 30 days. AlCl_3 caused a significant increase the serum levels of alkaline phosphatase (ALP), transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) and lactate dehydrogenase (LDH). In liver, a significant increase in micronucleated hepatocytes was observed along with histopathological changes including sinusoidal dilatation, congestion of central vein, lipid accumulation and lymphocyte infiltration in liver. The toxic and genotoxic effects of aluminium administration were suppressed by the concurrent administration of propolis (50 mg/kg bw), suggesting the involvement of an oxidative stress mediated mechanism in Al genotoxicity, counteracted by the antioxidant properties of propolis (Turkez et al., 2010). The Panel noted that the test method used in this study, i.e. the analysis of micronuclei in rat liver after repeated administration, has not yet received sufficient validation. In particular, according to the IWGT (International Workshop on Genotoxicity Testing) recommendations, more data on non-genotoxic but toxic chemicals are considered necessary to

evaluate the test specificity and its suitability for risk assessment (Martus et al., 2015). The Panel also note the high level of toxicity elicited by $AlCl_3$ in this study, not consistent with findings from other studies. Overall, the Panel considered that this study should not be used for risk assessment.

CA in bone marrow and spermatocyte and sperm abnormalities were determined in an *in vivo* study with male white Swiss mice that were treated intraperitoneal (i.p.) with $Al_2(SO_4)_3$ (98%) daily for 3 weeks at doses of 47, 94 and 188 mg/kg bw representing 1/16, 1/8 and 1/4 of $Al_2(SO_4)_3$ LD₅₀. The results demonstrated significant increase in the percentage of bone marrow CA and spermatocyte and sperm abnormalities that were dose and time of exposure dependent. The genotoxic effects of Al administration were largely reduced (up to 83%) by the co-administration of a soybean supplemented diet or soybean extracts rich in antioxidants and antimutagens (isoflavons, saponins) (Al-Ashaal et al., 2012).

Swiss albino mice received single doses of 50, 100 and 150 mg aluminium acetate (basic) ($C_6H_9AlO_6$)/kg bw, or daily doses of 50 mg/kg bw for seven consecutive days, via i.p. administration. Evaluated genotoxicity endpoints were CA and micronuclei (MN) in bone marrow, MN in fetal liver and sperm abnormalities. CA and MN in bone marrow were analysed after 24, 48 and 72 h post-single treatment, and 24 h after repeated administration; MN in fetal liver were examined following treatment of pregnant females on day 14 of gestation and 24 h transplacental exposure of fetus; abnormalities in sperm were examined 5 weeks of treatment. In bone marrow time- and dose-dependent induction of CA was observed after single and repeated administration of aluminium acetate whereas MN induction was observed only after the repeated administration. The induction of CA and MN was associated with significant reduction of the mitotic index and of the polychromatic/normochromatic erythrocytes ratio, indicating a mitodepressive effect on bone marrow. The increase in MN frequency in fetal liver erythrocytes after single dose exposure indicated transplacental exposure to aluminium acetate. At all doses after the single exposure, a dose-dependent increase in different types of sperm abnormalities as well as reduced sperm count were observed (D'Souza et al. 2014).

The subchronic exposure of 8-week-old Sprague–Dawley rats to $AlCl_3$ administered i.p. for 10 weeks at dose of 5 mg/kg bw demonstrated increase in serum enzyme activities of ALP, AST, ALT and LDH, and the levels of creatinine, urea (U) and uric acid (UA) levels as indicators of hepatotoxicity and nephrotoxicity (Geyikoglu et al. 2012). The indicators of haematotoxicity red blood cells (RBCs), haemoglobin (Hb) concentration, haematocrit (Ht), platelets (PLTs) and white blood cells (WBCs) were compared to the control groups significantly decreased. In hepatocytes of $AlCl_3$ -treated animals, a significant increase in MN was observed. In addition in the samples of liver as well as in kidney of the exposed animals, severe pathological damages were observed.

Overall, the available studies indicate that aluminium compounds are genotoxic *in vitro*, inducing primary DNA damage and clastogenicity, and *in vivo* following i.p. administration, which however is not relevant for oral risk assessment. Only few of the available genotoxicity studies on aluminium compounds were performed with aluminium sulphates and phosphate. However, in view of the common activity profile of aluminium compounds, the Panel considered appropriate read-across among different aluminium salts, and all the available results relevant for genotoxicity assessment of E 521–523 and E 541. The Panel also noted that the genotoxic activity elicited by aluminium compounds is ascribed to indirect and thresholded mechanisms (EFSA, 2008), which are unlikely to be relevant at low dietary exposure levels, and considered that the use of aluminium sulphates and sodium aluminium phosphate acidic as food additives does not raise concern for genotoxicity.

3.5.5. Chronic toxicity and carcinogenicity

Cancer risk related to in aluminium production was evaluated by the International Agency for Research on Cancer (IARC, 1984). IARC concluded that the available epidemiological studies provided limited evidence that certain exposures in the aluminium production industry were carcinogenic to humans; however, IARC noted that aluminium exposure was confounded by exposure to other agents, and that there was no evidence of increased cancer risk in non-occupationally exposed persons. Overall, IARC did not implicate aluminium itself as a human carcinogen (IARC, 1984).

In its previous evaluation (EFSA, 2008), the AFC Panel noted that the database on carcinogenicity of aluminium compounds was limited, with the majority of available studies old, containing little experimental detail and with inadequate low dose levels. Overall, the AFC Panel concluded that it was not possible to reach a conclusion on the carcinogenicity of aluminium from these studies. The AFC Panel noted that in a poorly reported oral drinking water study in rats exposed to aluminium potassium sulphate, a significantly increased incidence of gross tumours was reported in males (Schroeder & Mitchner, 1975). The types of tumours were not further specified. The same authors reported that this

aluminium compound produced a significantly increased incidence of gross tumours and 'lymphoma leukaemia' in treated female mice. However, the more recent and robust study of Oneda and co-workers in the B6C3F1 mouse did not indicate any carcinogenic potential of aluminium potassium sulphate at levels of up to 850 mg Al/kg bw per day in the diet (Oneda et al., 1994). The AFC Panel also noted the absence of epidemiological evidence for carcinogenicity of aluminium compounds used therapeutically, the conclusion of IARC evaluation and concluded that aluminium is unlikely to be a human carcinogen at exposures relevant to dietary intake (EFSA, 2008). The Panel agreed with this overall conclusion.

3.5.6. Reproductive and developmental toxicity

Published reproductive and developmental toxicity studies with aluminium compounds (aluminium sulphate, chloride, hydroxide and nitrate) were reviewed and evaluated by the EFSA AFC Panel in a previous opinion on the safety of aluminium from dietary intake (EFSA, 2008). The conclusions were as follows:

'Several studies have been performed on the reproductive and developmental toxicity of aluminium compounds. Two studies in male mice using either intraperitoneal or subcutaneous administration of aluminium nitrate or chloride clearly demonstrated the ability of aluminium to produce testicular toxicity, decreased sperm quality and reduced fertility in male mice. However, no effects on male fertility were observed in one rat study where aluminium nitrate was administered by gavage. Unfortunately no data were reported on histological examination of testes, as it is well known that male rats maintain fertility even after severe testicular lesions. This also means that they may be less sensitive to this effect than humans. Reduced testicular weight and impaired semen quality have also been observed in male rabbits after daily administration by gavage of 34 mg/kg bw of aluminium chloride (corresponding to 6.4 mg aluminium/kg bw/day), the only dose applied, for 16 weeks. In male beagle dogs, dietary administration for 26 weeks of basic sodium aluminium phosphate (SALP), at a level corresponding to 75 mg aluminium/kg bw/day produced a decrease of testicular weight and degeneration of germinal epithelium. The NOAEL was 27 mg aluminium/kg bw/day. Only two studies are available on reproductive toxicity in females. No effects on female fertility was seen in rats after exposure for two weeks before mating and during gestation to aluminium nitrate by gavage or dissolved in drinking water. None of the aluminium compounds authorised as food additives in the EU have been tested for reproductive toxicity. However, the Panel noted that when SALP, acidic, was tested in dogs using a protocol similar to that used for SALP, basic, no testicular effects were reported after doses up to 88 mg aluminium/kg bw/day for 26 weeks. The potential of aluminium to produce embryotoxicity and teratogenicity has been demonstrated in rats given intraperitoneal injections of 0, 75, 100, or 200 mg aluminium chloride/kg bw/day on days 9–13 or 14–18 of pregnancy, corresponding to 15, 20, or 40 mg Al/kg bw/day. However, after oral administration, only one study has reported congenital malformations (cleft palate) in mice after gavage exposure to 627 mg aluminium lactate/kg bw/day. In this study 166 mg aluminium hydroxide/kg bw per day had no effect. In general, high doses of aluminium nitrate, chloride or lactate given by gavage were able to induce some signs of embryotoxicity in mice and rats, in particular, reduced fetal body weight or pup weight at birth and delayed ossification. The lowest LOAEL was reported for aluminium nitrate at a daily dose corresponding to 13 mg aluminium/kg bw/day in the rat. After dietary exposure of rats to aluminium chloride and lactate the lowest NOAEL was 100 mg aluminium/kg bw/day, respectively. Gavage administration of aluminium hydroxide at doses providing up to 264 mg aluminium/kg bw/day was without embryotoxic effects in rats.'

The following reproductive toxicity studies of aluminium compounds, published after the adoption of the previous opinion, were also considered in the current opinion.

Reproductive studies

A two-generation reproductive toxicity study was performed in Sprague–Dawley rats (24/dose per group) with aluminium sulphate ($\text{Al}_2(\text{SO}_4)_3$; purity 98.5%) which was administered in the drinking water at concentrations of 0, 120, 600 or 3,000 mg $\text{Al}_2(\text{SO}_4)_3/\text{L}$ (equal 0, 8.6, 41 or 188 mg $\text{Al}_2(\text{SO}_4)_3/\text{kg}$ bw per day for F_0 -males or, total Al exposure, drinking water and food combined, of 1.62, 2.96, 8.06 or 31.2 mg Al/kg bw per day; the exposure of males of the F_1 -generation and the females of both generations were higher) (Hirata-Koizumi et al., 2011a). The test concentrations were chosen based on a preliminary study in which toxicity was observed at 3,000 and 10,000 mg $\text{Al}_2(\text{SO}_4)_3/\text{L}$. The study included developmental landmarks and behavioural tests (spontaneous locomotor activity, and a T-maze test for spatial learning

ability). The latter results will be described in Section 3.5.7. Water consumption was decreased in all test substance-treated groups. The authors assumed this was related to palatability (acidity). In the mid- and high-dose groups, decreased water consumption was associated with decreased food consumption and with decreased body weight gain of both sexes in the high-dose group of the F_0 -generation. At the end of both lactation periods, the food consumption of the females was also decreased in the mid- and high-dose groups. High-dose group pups of both generations showed a decreased weight on postnatal day (PND) 21 and slight delay in vaginal opening of the F_1 -females. Pup organ weights were changed in the high-dose group (relative weight: brain increased, decreases in liver spleen, and thymus). No effects on fertility, reproductive (including oestrus cyclicity, sperm parameters and histopathology of the reproductive organs) or developmental parameters were observed. The authors concluded that 600 mg $Al_2(SO_4)_3/L$ is the NOAEL for parental and reproductive and developmental toxicity and stated that the Al dose for this group was calculated to be 8.06 mg Al/kg bw per day (including the intake of Al via the standard rat diet of 25–29 mg/kg diet). The Panel agreed with this conclusion however, agreed with Willhite et al. (2012) that the NOAEL identified in this study 'may reflect more the acidic properties of the water than any intrinsic systemic hazard posed by ingested Al'.

A two-generation reproductive toxicity study was performed in Sprague–Dawley rats (24/dose per group) with aluminium ammonium sulphate ($AlNH_4(SO_4)_2$; AAS; purity 99.5%) which was administered in the drinking water at concentrations of 0, 50, 500 or 5,000 mg AAS/L (equal 0, 3.78, 33.5 or 305 mg AAS/kg bw per day for F_0 -males or, total Al exposure, drinking water and food combined, of 1.56, 1.98, 5.35 or 36.3 mg Al/kg bw per day; the exposure of males of the F_1 -generation and the females of both generations were higher) (Hirata-Koizumi et al., 2011b). The study was performed according to the OECD guideline 416 and in compliance to Good laboratory practice (GLP). The test concentrations were chosen based on a preliminary study in which toxicity was observed at 3,000 and 10,000 mg AAS/L. The study included developmental landmarks and behavioural tests (spontaneous locomotor activity, and a T-maze test for spatial learning ability). The latter results will be described in Section 3.5.7. No treatment-related clinical observations were observed. Water consumption was decreased in all test substance-treated groups. The authors assumed this was related to palatability due to the astringent taste. Food consumption was significantly lower during week 1 of dosing of the F_1 -males of the high-dose group and in F_0 -females of the mid- and high-dose groups. In the F_0 -generation body weight was decreased compared to controls in the highest dose group in both sexes in the first 2–3 weeks of dosing and on day 21 of lactation of the F_1 -generation. High-dose group pups of both generations (only statistically significant in the F_1) showed a decreased weight on postnatal day (PND) 21 and delay in vaginal opening in the F_1 animals approx. 2 days and no clear relation to body weight was observed). Pup organ weights were changed in the high-dose group (relative weight: increase in brain, kidney and adrenals, decrease in liver, spleen, and thymus). No effects on fertility, reproductive (including oestrus cyclicity, sperm parameters and histopathology of the reproductive organs) or developmental parameters were observed. The authors concluded that 500 mg AAS/L is the NOAEL for parental and reproductive and developmental toxicity and stated that the Al dose for this group was calculated to be 5.35 mg Al/kg bw per day (including the intake of Al via the standard rat diet of 25–29 mg/kg diet). The Panel agreed with this conclusion.

Male Wistar rats ($N = 7$ per group) were administered 0, 200, 400 or 1,000 ppb Al ($Al_2(SO_4)_3$) (equivalent to 0, 0.01, 0.02 or 0.05 mg Al/kg bw per day) in drinking water during 6 months (Muselin et al. 2016). Three F_0 males of each group were mated with unexposed females (one male to 2 females). Females were exposed during gestation and lactation to the same levels as males. The authors described that 'the F_1 generation males were divided as described and exposed the same AS [aluminium sulphate] levels. The protocol to obtain F_2 was similar to that described for F_1 '. The authors described effects on testosterone levels (dose-related decrease in all generation males), sperm counts (decrease mainly in the F_1 and F_2 males), sperm motility and abnormal sperm (dose-related decrease in all generation males) and on serum LH (increase in the F_0). Testis weight and histopathology were affected. The Panel noted that the study showed limitations such as low number of animals per group, not clear from which litters pups were selected. The amount of Al added to the drinking water was very low; it might have been a mistake in the publication. In addition the purity of the test substance was unknown and the Al level in the diet was not measured. Therefore, the Panel considered that the study cannot be used for risk assessment.

Developmental studies

No additional developmental studies were available, however neurodevelopmental studies were reported (see Section 3.5.5).

Other studies on reproductive organs

Male albino rats (*Rattus rattus*) (N = 7 per group) were given daily by gavage 0 or 50 mg aluminium sulphate/kg bw per day (8 mg Al/kg bw per day for 45 days (Rawi and Seif al Nassr, 2015)). The purity of the test substance was not given. In this study also, the effects of zinc sulphate) and vitamin E and the combination of both in addition to aluminium sulphate were studied. Daily administration of 50 mg aluminium sulphate/kg bw per day induced decreased body weight, testis weight and histological changes. Treatment with zinc sulphate and/or vitamin A reduced the toxic effects.

Overall, as reported by the EFSA AFC Panel (EFSA, 2008), effects on male reproductive organs and/or semen were observed after oral administration in rabbits (LOAEL 6.4 mg Al/kg bw per day) and dogs (NOAEL 27 mg Al/kg bw per day). No effects on male and female fertility were observed in the rat after oral dietary administration. Furthermore, four additional reproductive studies or studies on reproductive organs were identified. The study of Rawi and Seif al Nassr (2015) and Muselin et al. (2016) could not be used for risk assessment. In the two-generation reproduction toxicity study in rats (Hirata-Koizumi et al., 2011a) exposed via the drinking water to aluminium sulphate a NOAEL of 8.06 mg Al/kg bw per day (including the intake of Al via the standard rat diet of 25–29 mg/kg diet) for parental, reproductive and developmental toxicity was identified. In another two-generation reproductive toxicity study in rats (Hirata-Koizumi et al., 2011b) also exposed via the drinking water to aluminium ammonium sulphate, a NOAEL of 5.35 mg Al/kg bw per day (including the intake of Al via the standard rat diet of 25–29 mg/kg diet) Al/kg bw was identified. Willhite et al. (2012) assumed that the NOAEL identified in the study with aluminium sulphate 'may reflect more the acidic properties of the water than any intrinsic systemic hazard posed by ingested Al'. The Panel agreed with these considerations as the effects observed were effects on body weight which may be due to decreased intake of water because of palatability at higher concentrations of aluminium in the drinking water for both two-generation reproductive toxicity studies.

As reported by EFSA AFC Panel (EFSA, 2008), oral administration of 57 mg aluminium/kg bw per day (as aluminium lactate) by gavage from GD 6 to GD 15 induced cleft palate in mice fetuses. The lowest dose which produced an effect on rat was 13 mg Al/kg bw per day (as aluminium nitrate) when administered by gavage from GD 1 to GD 14. Gavage administration of aluminium hydroxide up to 264 mg Al/kg bw per day from GD 6 to GD 15 did not induce developmental effects in rats. After dietary administration of aluminium chloride and lactate during gestation (GD 1 or 8 to parturition in the rat, the lowest NOAEL for developmental toxicity was 18 mg Al/kg bw per day. No additional developmental toxicity studies were identified.

3.5.7. Neurotoxicity and developmental neurotoxicity

Published neurotoxicity and developmental neurotoxicity studies with aluminium compounds (aluminium sulphate, chloride, hydroxide and nitrate) were reviewed and evaluated by the EFSA AFC Panel in a previous opinion on the safety of aluminium from dietary intake (EFSA, 2008). The conclusions concerning neurotoxicity were as follows: 'In humans neurotoxicity was observed in patients undergoing dialysis due to the use of unpurified water containing high concentrations of aluminium. Furthermore, aluminium was associated with Alzheimer's disease. However, the Panel and also the German Federal Institute for Risk Assessment (BfR, 2007) and the French Food Safety Agency (AFSSA, 2003) concluded that there is no scientific prove and that in addition the aluminium content of the diets was not taken into account. Aluminium is considered as a neurotoxicant in experimental animals (mice, rats), however, most of the studies showed limitations. Behavioural impairment (passive and conditioned avoidance responses) has been observed in the absence of overt encephalopathy or neurohistopathology in rats and mice exposed to soluble aluminium salts (e.g. lactate, chloride) in the diet or drinking water generally at doses of 200 mg aluminium/kg bw per day or higher. Effects recorded in more than one study in immature animals included impaired performance of reflexes and simple behaviours. Reduced grip strength and startle responsiveness were found to persist up to 150 days of age. There was no effect on reactions to the light avoidance task in rats after gestational or postnatal exposure. In these studies, LOAELs were identified that ranged from maternal doses of 50 to 500 mg aluminium/kg bw per day. From the study in mice where the lowest LOAEL of 50 mg aluminium/kg bw per day, given as lactate, was reported for neurodevelopmental effects in the offspring, NOAELs of 10 mg aluminium/kg bw per day in the mother during pregnancy and 42 mg/kg bw per day during lactation could also be identified. However, it should be noted that, in another study performed by the same group of researchers, with administration of aluminium lactate from conception throughout the whole lifespan at 100 mg/kg bw/day no clear signs of neurotoxicity were observed in the same strain of mice'.

The following neurodevelopmental toxicity studies of Al compounds, published after the adoption of the previous opinion, were also considered in the current opinion.

In a two-generation reproductive toxicity study with $\text{Al}_2(\text{SO}_4)_3$ in the drinking water, no changes in reflex ontogeny of the F_1 and F_2 pups and on spontaneous motor activity at 4 weeks of age were observed (Hirata-Koizumi et al., 2011a; study description see Section 3.5.6). In the T-maze water test a transient effect was only seen in the mid-dose groups at 600 mg $\text{Al}_2(\text{SO}_4)_3/\text{L}$, and therefore, this effect was not considered as a neurodevelopmental effect. The highest dose (3,000 mg $\text{Al}_2(\text{SO}_4)_3/\text{L}$, equal 188 mg $\text{Al}_2(\text{SO}_4)_3/\text{kg}$ bw or total Al exposure of 31.2 mg Al/kg bw per day for F_0 males) was the NOAEL for neurodevelopmental effects.

In a two-generation reproductive toxicity study with aluminium ammonium sulphate (AAS) in the drinking water, no changes in reflex ontogeny of the F_1 and F_2 pups. In the spontaneous locomotor activity a transient effect was only seen in the 500 mg AAS/L group and therefore this effect was not considered as a neurodevelopmental effect no dose-related effect on spontaneous motor activity at 4 weeks of age were observed (Hirata-Koizumi et al., 2011b; study description see Section 3.5.6). In the T-maze water test for spatial learning, no treatment-related effects were observed. The highest dose (5,000 mg AAS/L, equal 305 mg AAS/kg bw or total Al exposure of 36.3 mg Al/kg bw per day for F_0 males) was the NOAEL for neurodevelopmental effects.

A neurodevelopmental study in which Sprague-Dawley rats were exposed *in utero* and up to 12 months of age was described by Poirier (Poirier et al., 2011). The supplementary data containing individual test results including for example pivotal information on Functional Observational Battery (FOB) tests and clinical chemistry data were not available. Therefore, the Panel was not able to assess these results. The study was performed in compliance with GLP and was sufficiently powered. The groups were blinded for the test facility staff. Pregnant female rats ($n = 20/\text{group}$) were administered aluminium citrate (intended doses of 0, 30, 100 or 300 mg Al/kg bw per day) in the drinking water during gestation and lactation and F_1 animals were exposed to the same dose up to 364 days. Endpoints observed were general observations in dams and their litters and in F_1 animals. Furthermore, developmental landmarks, T-maze, auditory startle, the FOB with domains targeting autonomic function, activity, neuromuscular function, sensimotor function, and physiological function), cognitive function (Morris swim maze), haematology, clinical chemistry, tissue/blood levels of aluminium, brain weight, and neuropathology. In the high-dose group, renal pathology and significant morbidity and mortality were observed mainly in the male pups. Male F_1 -animals of this group were therefore euthanised on PND 89. In the FOB, an increased excitability was observed in female animals but not in males. No effect on autonomic and sensimotor dysfunctions was observed in the treated animals. A reduced auditory startle was observed on PND 64 in males of the high-dose group and on PND 120 in females of the high-dose group. The latter effects were not observed at PND 364. Furthermore, no evidence of significant effects on learning and memory were observed even not in the females of the high-dose group. In male and female animals of the mid- and high-dose groups, neuromuscular functions (hind-limb grip strength and to a lesser extent foot splay) were impaired according to the authors but data were not available. The authors reported that 'The effect was more pronounced in young animals; presumably because animals got larger and stronger over time, they better compensate for the original impairment'. However, the Panel noted that the dose (mg Al/kg bw per day) at a younger age is much higher than later in life. No treatment-related histopathological brain lesions were observed. The authors considered the mid-dose group as the LOAEL based on clinical observations and clinical biochemistry and FOB parameters (neuromuscular function). The target concentration of 100 mg Al/kg bw per day (mid-dose group) and the real concentration of this group indicated by the authors was 40 mg Al/kg bw per day differed significantly. The authors considered the low-dose group as the NOAEL (target concentration of 30 mg Al/kg bw per day; the real dose coming down to 5 and 10 mg/kg bw per day in males and females, respectively). However, the Panel noted the low intake of drinking water in all dose groups of F_1 animals and in F_1 controls, expected to be 120 ml/kg bw per day but was reported to be down to 20 mL/kg bw per day. The Panel agreed with JECFA (2012) describing the difficulties with the target versus the achieved dose as follows: JECFA noted the following: 'Identification of the LOAEL and NOAEL in this study is complicated by the decreasing fluid consumption and uncertainty regarding the critical exposure period. In the low-dose group, the achieved dose was about 40 mg/kg bw per day in the 1st week post-weaning, decreasing to 30 mg/kg bw per day (target dose) by week 5, and was about 15-45% of the target dose from post weaning week 13 onwards'.

Overall, in humans, neurotoxicity was observed in patients undergoing dialysis due to the use of unpurified water containing high concentrations of aluminium (EFSA, 2008). In 2008, the Panel and

also the German Federal Institute for Risk Assessment (BfR, 2007) and the French Food Safety Agency (AFSSA, 2003) concluded that there was no scientific proof aluminium was associated with Alzheimer's disease. Aluminium was considered as a neurotoxicant in experimental animals (mice, rats), however, most of the studies showed limitations. NOAELs of 10 mg Al/kg bw per day for neurodevelopmental effects were observed (EFSA, 2008). From two-generation reproductive toxicity studies in rats with $\text{Al}_2(\text{SO}_4)_3$ (Hirata-Koizumi et al., 2011a) or AAS (Hirata-Koizumi et al., 2011b) in drinking water, no neurodevelopmental effects were recorded up to 31.2 mg Al/kg bw per day or 36.3 mg Al/kg bw, respectively. From a neurodevelopmental study in rats (Poirier et al., 2011), a NOAEL for developmental toxicity was identified at 30 mg/kg bw per day (target low-dose level of the study). The Panel noted that in accordance with JECFA, there were uncertainties concerning the real dose level. Furthermore, the Panel was not able to assess the study due to non-availability of crucial data.

3.5.8. Immunotoxicity

Aluminium is applied in many vaccines as adjuvant, boosting the efficacy of the vaccines. Inadvertent enhanced immune responses may be regarded as adverse; hence, effects of aluminium on the immune system may pose a hazard. Whereas the activity of aluminium as an adjuvant may be local, i.e. at the site of vaccination, and whereas the action as an adjuvant is thought to be primarily based on the slow release of the antigen from the vaccination site, optimising the immune response, it cannot be excluded that some aluminium may get systemic into the body and has effects elsewhere than at the vaccination site. Zhu et al. (2014) reviewed the literature and concluded that the results of several studies in the literature demonstrated that Al could adversely affect the immune system. The Panel noted that most immune parameters reported to be influenced were intermediate parameters and cannot easily be interpreted in terms of adversity. Zhu et al. (2011) showed that reductions of total immunoglobulin M (IgM) levels and increases of IgA and IgG levels occurred in male Wistar rats orally exposed to 0, 64.18, 128.36 and 256.72 mg AlCl_3 /kg bw per day for 120 days, equivalent to 0, 13, 26 and 52 mg Al/kg bw per day.

3.6. Discussion

The present opinion deals with the re-evaluation of the safety of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) when used as food additives.

Aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) are authorised as food additives in the EU according to Annex II of Regulation (EC) No 1333/2008. Specifications for aluminium sulphates and sodium aluminium phosphate have been defined in the EU in Commission Regulation (EU) No 231/2012 and also by JECFA in 2011. The Panel is aware that, in addition to the aluminium compounds evaluated in the present opinion, other forms of aluminium are authorised as food additives: elemental aluminium (E 173), starch aluminium octenyl succinate (E 1452), aluminium silicates (E 554 and E 555) and in the form of aluminium lakes of food colours. These food additives are not considered in the present opinion.

The safety of aluminium from dietary intake was evaluated in 2008 by the EFSA Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (EFSA, 2008). Based on the range of available NOAEL and LOAEL, and applying a weight of evidence approach, the Panel established a TWI of 1 mg aluminium/kg bw per week. This weekly health-based reference value took into account the potential accumulation of dietary aluminium in the body, and applied to all aluminium compounds in food, including additives.

Aluminium-containing food additives were also evaluated by JECFA several times, the latest in 2011. The Committee established a PTWI, which applied to all aluminium compounds in food. The PTWI was set at 2 mg Al/kg bw per week based on a NOAEL of 30 mg/kg bw per day from a neurodevelopmental study in rats (Poirier et al., 2011), with the application of a safety factor of 100. JECFA noted the complication of the identification of the LOAEL and NOAEL due to decreasing fluid consumption.

The present opinion considered major findings from the previous EFSA evaluation (EFSA, 2008), and additional relevant data published since then and retrieved in an ELS covering the period from 1990 up to June 2018 (Documentation provided to EFSA n.2).

Available studies indicate that oral bioavailability of aluminium compounds is low as a result of formation of insoluble aluminium hydroxide at the neutral pH in the intestines. Data from humans and experimental animals indicate that the bioavailability is approximately 0.3% of aluminium compounds in drinking water and 0.1% in food and beverages. Predicted plasma levels at the EFSA TWI of 1 mg Al/kg bw were within the reported normal levels of aluminium in serum, 1–3 µg/L. Absorbed aluminium

is accumulating in the bone. Kidney is the main route of excretion. Increased brain levels of aluminium have been reported in dialysis encephalopathy patients.

The acute oral toxicity of inorganic aluminium salts in rats and mice shows a wide range of LD₅₀ values (from 162 to 750 mg Al/kg bw in rats and from 164 to 980 mg Al/kg bw in the mouse). In EFSA (2008), it was reported that aluminium nitrate in drinking water for 28 days caused mild histopathological changes in spleen and liver or decreased body weights in rats; the NOAEL for these effects was 52 mg Al/kg bw per day. In contrast dietary exposure to SALP for 28 days had no adverse effects in the highest doses tested corresponding to 140–300 mg Al/kg bw per day. Similarly, no effects were reported in dogs exposed in the diet to acidic SALP providing a dose of 90 mg Al/kg bw per day for 26 weeks.

The available genotoxicity studies indicate that aluminium compounds are genotoxic *in vitro*, inducing primary DNA damage and clastogenicity, and *in vivo* following i.p. administration, which however is not relevant for oral risk assessment. Only few of the available genotoxicity studies on aluminium compounds were performed with aluminium sulphates and phosphate. However, in view of the common activity profile of aluminium compounds, the Panel considered appropriate read-across among different aluminium salts, and all the available results relevant for genotoxicity assessment of E 520–523 and E 541. The Panel also noted that the genotoxic activity elicited by aluminium compounds is ascribed to indirect and thresholded mechanisms (EFSA, 2008), which are unlikely to be relevant at low dietary exposure levels, and considered that the use of aluminium sulphates and sodium aluminium phosphate acidic as food additives does not raise concern for genotoxicity.

The database on carcinogenicity of aluminium compounds is limited. In its previous evaluation (EFSA, 2008), the AFC Panel noted that dose levels of aluminium were generally low and that it was not possible to reach a conclusion on the carcinogenicity of aluminium from these studies. However, a more robust study in the B6C3F1 mouse (Oneda et al., 1994) did not indicate any carcinogenic potential of aluminium potassium sulphate at levels of up to 850 mg Al/kg bw per day in the diet. The Panel also noted the absence of epidemiological evidence for carcinogenicity of aluminium compounds used therapeutically, and the conclusion of IARC that aluminium itself is unlikely to be a human carcinogen. Overall, the Panel considered that aluminium is unlikely to be a human carcinogen at exposures relevant to dietary intake.

The EFSA AFC Panel (EFSA, 2008) reported effects on male reproductive organs and/or semen after oral administration in rabbits (LOAEL 6.4 mg Al/kg bw per day) and dogs (NOAEL 27 mg Al/kg bw per day). No effects on male and female fertility were observed in the rat after oral dietary administration. In a two-generation reproduction toxicity study in rats (Hirata-Koizumi et al., 2011a) exposed via the drinking water to aluminium sulphate, a NOAEL of 8.06 mg Al/kg bw per day for parental, reproductive and developmental toxicity was identified. In another two-generation reproductive toxicity study in rats (Hirata-Koizumi et al., 2011b) also exposed via the drinking water to aluminium ammonium sulphate, a NOAEL of 5.35 mg Al/kg bw per day (including the intake of Al via the standard rat diet of 25–29 mg/kg diet) Al/kg bw was identified. Willhite et al. (2012) assumed that the NOAEL identified in the study with aluminium sulphate 'may reflect more the acidic properties of the water than any intrinsic systemic hazard posed by ingested Al'. The Panel agreed with these considerations as the effects observed were effects on body weight which may be due to decreased intake water because of palatability at higher concentrations of aluminium in the drinking water for both two-generation reproductive toxicity studies.

The EFSA AFC Panel (EFSA, 2008) reported that oral administration of 57 mg Al/kg bw per day (as aluminium lactate) by gavage from GD 6 to GD 15 induced cleft palate in mice fetuses. The lowest dose which produced an effect on rat was 13 mg Al/kg bw per day (as aluminium nitrate) when administered by gavage from GD 1 to GD 14. Gavage administration of aluminium hydroxide up to 264 mg Al/kg bw per day from GD 6 to GD 15 did not induce developmental effects in rats. After dietary administration of aluminium chloride and lactate during gestation (GD 1 or 8 to parturition in the rat), the lowest NOAEL for developmental toxicity was 18 mg Al/kg bw per day. No additional developmental toxicity studies were identified.

In humans, neurotoxicity was observed in patients undergoing dialysis due to the use of water containing high concentrations of aluminium (EFSA, 2008). In 2008, the Panel and also the German Federal Institute for Risk Assessment (BfR, 2007) and the French Food Safety Agency (AFSSA, 2003) concluded that there was no scientific proof aluminium was associated with Alzheimer's disease. Aluminium was considered as a neurotoxicant in experimental animals (mice, rats), however, most of the studies showed limitations. NOAELs of 10 mg Al/kg bw per day for neurodevelopmental effects were observed (EFSA, 2008). From two-generation reproductive toxicity studies in rats with Al₂(SO₄)₃ (Hirata-

Koizumi et al., 2011a) or AAS (Hirata-Koizumi et al., 2011b) in drinking water, no neurodevelopmental effects were recorded up to 31.2 mg Al/kg bw per day or 36.3 mg Al/kg bw, respectively. From a neurodevelopmental study in rats (Poirier et al., 2011), a NOAEL for developmental toxicity was identified by the authors at 30 mg Al/kg bw per day (target low-dose level of the study). The Panel noted that in accordance with JECFA, there were uncertainties, such as declining fluid consumption in all groups of pups and the real dose levels. Furthermore, despite several requests, the supplementary information containing crucial data linked to the main publication was not provided to the Panel, and thus the Panel was not able to assess the study.

To assess the dietary exposure to aluminium from aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) from their use as food additives, the exposure was only calculated based on the MPLs as set out in the EU legislation (defined as the *regulatory maximum level exposure assessment scenario*), because no use levels or analytical results were made available to EFSA. The Panel noted that the vast majority (99–100%) of the estimated exposure to aluminium was coming from sodium aluminium phosphate (E 541) only from the consumption of fine bakery wares linked with sponge cake products. The Panel also noted that the estimated long-term exposures based on this scenario are very conservative, due to among others, the use of the MPL. Furthermore, as listed in Table 10, also other assumptions have resulted in an extreme overestimation of the exposure. Considering that these additives are only used in niche products which consumption is not captured in the dietary surveys of the EFSA Comprehensive Database, the Panel considered that these estimates are highly uncertain and are most probably near the lower end of the calculated exposure (approximately 0).

The Panel noted that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) were listed as ingredient in the Mintel GNPD subcategories where the uses are not authorised (see Section 3.3.2). However, the overall percentage of labelled products per subcategories was less than 0.1%.

The exposure estimates in this highly conservative scenario exceeded the TWI of 1 mg Al/kg bw (equivalent to ~ 0.14 mg Al/kg bw per day) for all population groups at the 95th percentile, and for toddlers and children at the mean (Table 9). Due to these high uncertainties in this exposure assessment, a comparison of the calculated exposure with TWI is of little or no value.

The Panel also noted that the estimated dietary exposure to aluminium in the general population, assessed in several European countries, varied from 0.2 to 1.5 mg/kg bw per week at the mean and was up to 2.3 mg/kg bw per week in highly exposed consumers (EFSA, 2008). Thus, the TWI of 1 mg/kg bw per week is likely to be exceeded in a significant part of the European population. The Panel noted that a holistic exposure assessment to aluminium from all sources would be desirable but it is out of the remit of the Panel.

Cereals and cereal products, vegetables, beverages and certain infant formulae appear to be the main contributors to aluminium intake. Even though the design of the studies performed did not allow to distinguish the specific contribution of aluminium-based food additives, the Panel noted that the limited authorised uses of E 520–523 and E541 would only provide a minor contribution to aluminium intake compared to other food categories identified as main sources of dietary aluminium (Stahl et al., 2011; Hardisson et al., 2017).

4. Conclusions

Considering that:

- bioavailability of aluminium compounds is low (~ 0.1% from food and beverages);
- inorganic aluminium salts are of low acute toxicity;
- the NOAEL identified for aluminium compounds in subchronic studies was 52 mg Al/kg bw per day in rats and 90 mg Al/kg bw per day in dogs;
- the use of aluminium sulphates and sodium aluminium phosphate acidic as food additives does not raise concern for genotoxicity and these compounds are unlikely to be human carcinogens;
- studies on reproductive, developmental and neurotoxicity were available; the lowest NOAEL for neurotoxicity in rats was 30 mg Al/kg bw per day and for developing nervous system was 10–42 mg Al/kg bw per day in studies in rats and mice;
- aluminium sulphates (E 520–523) are permitted as food additives in two food categories with further restriction in use;
- sodium aluminium phosphate (E 541) is only permitted as a food additive in one food category with further restriction in use;

- the Mintel's GNPD indicated that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) were used in a decreasing number of products over time, following the change in legislation coming into force in February 2014, which is in line with the fact that EFSA did not receive any use levels of these additives from industry;
- these additives are only authorised in specific products which consumption is not captured in the dietary surveys of the EFSA Comprehensive Database and the estimated exposure is most probably near the lower end of the calculated exposure (approximately 0).

The Panel concluded that aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) are of no safety concern in the current authorised uses and use levels.

5. Recommendations

The Panel recommend that:

- the combined exposure to aluminium from all the aluminium-containing food additives should be assessed.

Documentation provided to EFSA

- 1) CEFIC-PAPA, 2017. Reply to EFSA call for data – EFSA-Q-2013-00697 – Sodium Aluminium Phosphate Acidic – E541 on biochemistry and toxicology, preparation and use in studies of oral aluminum bioavailability from foods utilizing ²⁶Al as an aluminum tracer and Aluminium in the food chain with special respect to the safety of acid sodium aluminium phosphate (SALP) E 541 as additive in bakery products. Submitted on 1 December 2017.
- 2) Extensive Literature search covering from January 1990 up to June 2018. Analytica LASER submitted in June 2018.
- 3) Glynn A, 2018. Personal communication, unpublished study.

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Abbreviations

ADI	acceptable daily intake
AES	atomic emission spectrometry
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANS	EFSA Scientific Panel on Food Additives and Nutrient Sources added to Food
AST	aspartate aminotransferase
Bfr	German Federal Institute for Risk Assessment
bw	body weight
CA	chromosomal aberrations
CAS	Chemical Abstracts Service
CAT	catalase
CONTAM	EFSA Panel on Contaminants in Food Chain
EINECS	European Inventory of Existing Chemical Substances
ELS	extensive literature search
ET-AAS	electrothermal atomic absorption spectrometry
F-AAS	flame atomic absorption spectroscopy
FAO	Food and Agriculture Organization of the United Nations
FCs	food categories
FCS	food categorisation system
FOB	Functional Observational Battery
G-6-PDH	glucose-6-phosphate dehydrogenase
GC-HSS	gas chromatography with static headspace sampler
GD	gestation day
GF-AAS	graphite furnace atomic absorption spectrometry
GLP	Good laboratory practice
GNPD	Global New Products Database
GSH	glutathione
Hb	haemoglobin
HPLC	high-performance liquid chromatography
Ht	haematocrit
i.p.	intraperitoneal
ICP	inductively coupled plasma
Ig	immunoglobulin
ISO	International Organization for Standardization
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LDH	lactate dehydrogenase
LOD	limit of detection

MCP	monocalcium phosphate
MN	micronuclei
MPL	maximum permitted level
MS	mass spectrometry
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
OES	optical emission spectrometry
PLT	platelet
PND	postnatal day
PTWI	Provisional Maximum Tolerable Weekly Intake
RBC	red blood cell
SALP	sodium aluminium phosphate
SAS	sodium aluminium sulphate
SCE	sister chromatid exchange
SCF	Scientific Committee on Food
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SOD	superoxide dismutase
SO	spectrophotometric oxine
TDI	tolerable daily intake
TemaNord	is a publishing series for results of the often research-based work that working groups or projects under Nordic Council of Ministers have put in motion
TLC	thin-layer chromatography
UA	uric acid
U	urea
WBC	white blood cell
WDXRF	wavelength dispersive X-ray fluorescence spectrometry
WHO	World Health Organization

Appendix A – Number and percentage of food products labelled with aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) out of the total number of food products present in Mintel GNPD per food subcategory between January 2013 and February 2018

Appendix A can be found in the online version of this output ('Supporting information' section).

Appendix B – Summary Levels of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) used in the exposure scenario (mg/kg or mL/kg as appropriate)

Appendix B can be found in the online version of this output ('Supporting information' section).

Appendix C – Summary of total estimated exposure of aluminium sulphates (E 520–523) and sodium aluminium phosphate (E 541) from their use as food additives for the maximum level exposure scenario per population group and survey: mean and 95th percentile (mg/kg bw per day)

Appendix C can be found in the online version of this output ('Supporting information' section).

Safety Assessment of Alumina and Aluminum Hydroxide as Used in Cosmetics

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Abstract

This is a safety assessment of alumina and aluminum hydroxide as used in cosmetics. Alumina functions as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent. Aluminum hydroxide functions as a buffering agent, corrosion inhibitor, and pH adjuster. The Food and Drug Administration (FDA) evaluated the safe use of alumina in several medical devices and aluminum hydroxide in over-the-counter drugs, which included a review of human and animal safety data. The Cosmetic Ingredient Review (CIR) Expert Panel considered the FDA evaluations as part of the basis for determining the safety of these ingredients as used in cosmetics. Alumina used in cosmetics is essentially the same as that used in medical devices. This safety assessment does not include metallic or elemental aluminum as a cosmetic ingredient. The CIR Expert Panel concluded that alumina and aluminum hydroxide are safe in the present practices of use and concentration described in this safety assessment.

Keywords

alumina, aluminum hydroxide, safety, cosmetics

Introduction

This report addresses the safety of alumina and aluminum hydroxide as used in cosmetics. According to the *International Cosmetic Ingredient Dictionary and Handbook*,¹ alumina is reported to function in cosmetics as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent; aluminum hydroxide is reported to function as a buffering agent, corrosion inhibitor, and pH adjuster (Table 1).

These ingredients have been approved by the US Food and Drug Administration (FDA) for use in medical devices and over-the-counter (OTC) drugs (21 CFR 247.10; 21 CFR 331.11; 21 CFR 347.50).²⁻⁴ The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) concluded that the cosmetic ingredient alumina is chemically equivalent to the alumina used as part of color additives in medical devices such as bone cements and sutures. Alumina is also a material used in the construction of dental and hip implants. The FDA found that the information submitted for the approval of medical devices containing alumina was adequate and determined that alumina is safe for use in devices that come in contact with soft tissue, bone, and internal organs.² Additionally, alumina is approved by the FDA as an indirect food additive.⁵ The Panel concluded that the FDA's evaluations of alumina in medical devices, coupled with the Panel's review of information on aluminum hydroxide, were sufficient to support the safety assessment of alumina.

The Panel also concluded that the aluminum hydroxide used in cosmetics is chemically equivalent to that used in OTC antacid products. The FDA found that the information submitted for the approval of those drugs was adequate to support safe use (21 CFR 247.10; 21 CFR 331.11; 21 CFR 347.50). The FDA also determined that aluminum hydroxide is generally regarded as safe (GRAS) as a direct food additive (21 CFR 176.210, 177.1200, 177.2600).⁶ The Panel concluded that FDA's evaluations of aluminum hydroxide as a food additive and OTC drug, coupled with the Panel's review of primary scientific toxicity data, were sufficient to support the safety assessment of this ingredient as used in cosmetics.

The CIR has reviewed several cosmetic ingredients that consist of molecules containing aluminum atoms (Table 2). The conclusions were safe as used or safe with qualifications for all of these ingredients.

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Table 1. Definitions and Functions of the Ingredients in This Safety Assessment.^a

Ingredient CAS No.	Definition	Function
Alumina 1333-84-2 (hydrate (<i>"hydrate"</i> in reference to alumina often means aluminum hydroxide or something between alumina and aluminum hydroxide; alternative CAS No. for 21645-51-2) 1344-28-1	Alumina is an inorganic compound that conforms to the formula— Al_2O_3 . <i>Aluminum oxide, also known as alumina, is a mineral found as corundum, emery, ruby, sapphire, and in hydrated form (ie, aluminum hydroxide) as bauxite or gibbsite</i>	Abrasive, absorbent, anticaking agent, bulking agent, opacifying agent
Aluminum hydroxide 1333-84-2 21645-51-2	Aluminum hydroxide is an inorganic compound that conforms to the formula— $\text{Al}(\text{OH})_3 \cdot x\text{H}_2\text{O}$. <i>Alumina hydrates are true hydroxides (meaning they do not contain water of hydration; they are often called hydrated alumina or aluminum hydroxide) and are naturally occurring as minerals including bauxite or gibbsite</i>	Opacifying agent, skin protectant

Abbreviation: CIR, cosmetic ingredient review.

^aThe italicized text represents additions made by CIR staff.

The cosmetic ingredients alumina (aluminum oxide) and aluminum hydroxide are stable, oxidized aluminum compounds that differ substantially from aluminum (elemental or metallic) in chemical and physical properties, functions, and potential for toxicity. There has been substantial speculation in the literature that exposure to elemental aluminum or aluminum compounds could play a role in the etiology of Alzheimer's disease, breast cancer, and other health problems. Overall, scientific research has failed to find cause and effect relationships.⁷⁻⁵⁶ Furthermore, systemic exposure to aluminum from the use of alumina and aluminum hydroxide in cosmetics is expected to be negligible because it is poorly absorbed.^{7,40,57-69} The Panel considered the toxicological literature on aluminum and was satisfied that much of the speculation about aluminum toxicity is not relevant to the assessment of the safety of alumina and alumina hydroxide as used in cosmetics. A brief overview of aluminum toxicity studies is attached (Appendix A) to provide supplementary information reflecting the Panel's consideration of these issues.

Chemistry

Overview

Definitions, CAS numbers, and functions are provided in Table 1. The structures of alumina and aluminum hydroxide are presented in Figure 1.

Alumina, also known as aluminum oxide (Al_2O_3), is dehydrated (or calcined) aluminum hydroxide.⁷⁰ Alumina is also the primary constituent of emerald, ruby, and sapphire (the colors of which come from small impurities of heavy metals). The most common naturally occurring form of alumina is corundum. Corundum is primarily composed of α -alumina, which is crystalline. This water-insoluble, inorganic solid can form a number of other crystalline phases, and an amorphous form as well. Each phase has a unique crystal structure and varies in chemical properties, such as its acid-base reaction rate. When synthetically dehydrated from aluminum hydroxide, a mixture of alumina phases typically forms, unless specific controls are applied. Figure 1 schematically depicts both amorphous and crystalline alumina.

Aluminum hydroxide, also known as hydrated alumina, is most commonly found as the polymorphic mineral gibbsite (a component of the aluminum ore known as bauxite).^{70,71} This inorganic, amphoteric solid can also form 3 other polymorphs. However, the chemical formula of $\text{Al}(\text{OH})_3$ is the same for all polymorphs, each of which differs from the others only by interlayer spacing and, consequently, by relative acid/base reaction rates.

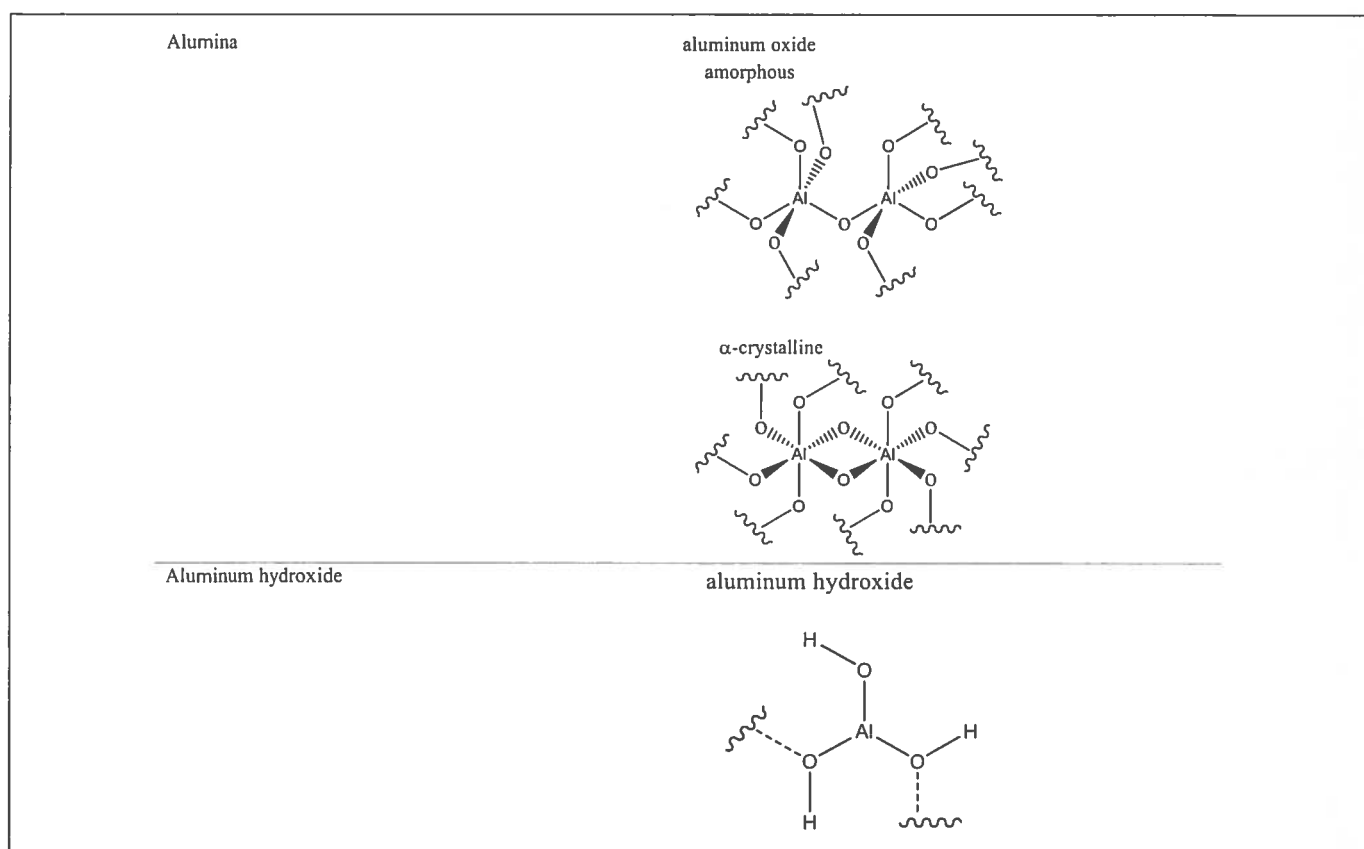
There are 4 known polymorphs of crystalline aluminum hydroxide: gibbsite, bayerite, nordstrandite, and doyleite, which can have different chemical/physical properties.⁷² The properties of the starting materials (pH, presence of anions or salt and mineral surfaces) influence the formation of particular polymorphs from aluminum interlayers and/or hydroxyl aluminum polymers. All the polymorphs of aluminum hydroxide consist of layers of aluminum octahedra with hydroxyl groups on either side, which hydrogen bond the layers together, and differences arising from variations in the stacking sequences of the layers. Of the possible configurations, gibbsite and bayerite represent the 2 ends of the spectrum of types of stacking sequences. Nordstrandite and doyleite have intermediate structures.

There is no universal standard nomenclature for aluminum oxides and hydroxides; thus, there may be inconsistencies in the use of these names among sources.⁷² Categorization is based on crystallographic structures found under environmental conditions and cited most often in the literature (Table 3). The α prefix is generally applied to hexagonal, close-packed, and related structures; these are aluminum minerals abundantly found in nature. The γ prefix is generally applied to designate polymorphism, structural alteration, or dehydration of these minerals (originally applied to all aluminum hydroxides and hydrolyzed aluminas other than the α -phase minerals). The γ -phase has cubic close-packed lattices or other related structures.

Table 2. Cosmetic Ingredients Containing Aluminum That Have Been Reviewed by CIR.

Ingredients	Conclusion	Maximum concentration (%)	Reference
Alumina magnesium metasilicate, aluminum calcium sodium silicate, aluminum iron silicate, sodium potassium aluminum silicate	Safe as used when formulated to be nonrespirable	44	108
Aluminum citrate	Safe as used	80	109
Aluminum dimyristate, aluminum isostearates/myristates, aluminum myristate, aluminum myristates/palmitates	Safe as used	82	110,111
Aluminum silicate, magnesium aluminum silicate	Safe as used	100	112
Aluminum starch octenylsuccinate	Safe as used with limitations on heavy metal content	30	113
Aluminum distearate, aluminum stearate, aluminum tristearate	Safe as used	25	114,115
Calcium aluminum borosilicate	Safe as used	97	116
Potassium aluminum polyacrylate	Safe as used when formulated to be nonirritating	25	117

Abbreviation: CIR, cosmetic ingredient review.

**Figure 1.** Formulas and idealized structures of the ingredients in this safety assessment.

Physical and Chemical Properties

Alumina and aluminum hydroxide are white, insoluble solids (Table 4). Alumina is the third hardest naturally occurring substance after diamond and carborundum (SiC).⁵⁵ The presence of trace amounts of chromium and cobalt creates ruby and sapphire, respectively.

Aluminum compounds cannot easily be oxidized, and thus, atmospheric oxidations generally are not expected to occur.⁷³ All forms of aluminum hydroxide are amphoteric (eg, they can

act as both acids and bases in solution).⁷⁴ Accordingly, aluminum hydroxides can serve as buffers to resist pH changes within the narrow pH range of 4 to 5.⁷⁵ Aqueous aluminum hydroxide gel has an effective pH of ~ 6 .⁷⁶

Method of Manufacture

Aluminum hydroxide is most commonly produced by aqueous alkaline extraction from bauxite ore, a method known as the

Table 3. Comparison of Nomenclature for Alumina and Aluminum Hydroxide.⁷²

Mineral name	Chemical composition	Common crystallographic designation	Past accepted crystallographic designation
Gibbsite (hydrargillite) ^{a,b}	Aluminum trihydroxide	α -Al(OH) ₃	γ -Al(OH) ₃
Bayerite	Aluminum trihydroxide	β -Al(OH) ₃	α -Al(OH) ₃
Nordstrandite	Aluminum trihydroxide	Al(OH) ₃	Al(OH) ₃
Doyleite	Aluminum trihydroxide	Al(OH) ₃	-
Boehmite	Aluminum oxyhydroxide	γ -AlOOH	γ -AlOOH
Diaspore	Aluminum oxyhydroxide	α -AlOOH	α -AlOOH
Corundum (α -alumina)	Aluminum oxide	α -Al ₂ O ₃	α -Al ₂ O ₃

^aHydrargillite is a mineral that was named after the Greek hydor (water) and argylles (clay). The name hydrargillite was mistakenly given to describe aluminum hydroxide but later was proven to be aluminum phosphate. However, both names are still used to describe aluminum hydroxide—gibbsite is preferred in the United States and hydrargillite is used more often in Europe.

^bThe terms in parentheses refer to possible forms.

Table 4. Chemical and Physical Properties of Alumina and Aluminum Hydroxide.

Property	Value	Reference
Alumina		
Physical form	Solid, crystalline powder	84,118
Color	White	84
Odor	None	118
Gram formula weight, g/mol	101.96	84
Density/specific gravity at 20°C	4.0	84
Viscosity (kg/[s·m]) at 20°C	Solid	118
Vapor pressure (mm Hg) at 20°C	Negligible	118
Melting point, °C	~2,000	84
Boiling point, °C	2,980	84
Water solubility	Insoluble	84
Aluminum hydroxide		
Physical form	Amorphous powder	84
Color	White	84
Gram formula weight, g/mol	78.00	84
Density/specific gravity	2.42	84
Melting point, °C	300	84
Water solubility	Practically insoluble	84

Bayer process.⁷⁰ Alumina is then produced from the resultant aluminum hydroxide simply by vigorous heating to drive off water.⁷⁷

Impurities

Alumina balls used in artificial hips must meet the following specifications: grain size <5 μ m and purity >99.7% aluminum

Table 5. Frequency of Use According to Duration and Exposure of Alumina and Aluminum Hydroxide.^{a,b,79-81}

Use type	Maximum concentration (%)		Maximum concentration (%)	
	Uses	Alumina	Uses	Aluminum hydroxide
Total/range	563	0.0004-60	578	0.0000008-10.1
Duration of use				
Leave on	523	0.0004-60	572	0.0000008-10.1
Rinse off	40	0.003-25	6	0.0022-8.8
Diluted for (bath) use	NR	NR	NR	NR
Exposure type				
Eye area	84	0.00075-30	80	0.009-10.1
Incidental ingestion	88	0.0004-6.7	155	0.0022-8.8
Incidental inhalation—sprays	7	6	6	NR ^c
Incidental inhalation—powders	41	0.0023-5	40	0.029-1.5
Dermal contact	441	0.0023-30	409	0.0000008-10.1
Deodorant (underarm)	NR	0.004-0.01	NR	NR
Hair—noncoloring	1	NR	NR	0.004-0.016
Hair—coloring	NR	1	NR	0.1
Nail	30	0.0048-60	7	0.016-1
Mucous membrane	107	0.0004-6.7	157	0.0022-8.8
Baby	NR	0.0023	NR	NR

Abbreviation: NR, not reported.

^aTotals = rinse-off + leave-on product uses.

^bBecause each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

^cThe Council reports that the skin care preparations and suntan preparations in their survey are not sprays.

oxide.⁷⁸ The maximum percentages for trace substances permitted are MgO, 0.2%; SiO₂, 0.01%; CaO, 0.03%; Na₂O, 0.02%; Fe₂O₃, 0.03%; and TiO₂, 0.01%.

When used in OTC drugs as a color additive, alumina should contain no more than 0.5% insoluble matter in dilute hydrochloric acid. The following are the limits of impurities: lead (as Pb) $\leq$ 10 ppm, arsenic (as As) $\leq$ 1 ppm, mercury (as Hg) $\leq$ 1 ppm, and aluminum oxide (Al₂O₃) $\geq$ 50% (21 CFR 73.1010).

Use

Cosmetic

Data on ingredient usage are provided to the FDA Voluntary Cosmetic Registration Program (Table 5).⁷⁹ A survey of the maximum use concentrations has been conducted by the Personal Care Products Council.^{80,81}

Alumina was reported to be used in 523 leave-on products at concentrations up to 60% (in nail products). It is reported to be used in 40 rinse-off products. Formulations include 84 products used around the eye at concentrations up to 30%, 87 lipsticks up to 6.7%, and 104 skin care preparations up to 25%.

Aluminum hydroxide was reported to be used in 572 leave-on products up to 10.1% and 6 rinse-off products up to 8.8%. Formulations include 80 products used around the eye at up to

10.1%, 154 lipsticks up to 7%, oral hygiene products up to 8.8%, and 6 suntan preparations up to 0.9%.

Noncosmetic

Aluminum salts are incorporated into some vaccine formulations as an adjuvant to enhance the immune response to vaccination.⁸² The aluminum compounds used in some US licensed vaccines are aluminum hydroxide, aluminum phosphate, alum (potassium aluminum sulfate), or mixed aluminum salts. Aluminum hydroxide may be used in vaccines up to 25 µg/L in large-volume parenteral drug products (21 CFR 201.323) and up to 1.25 µg in single-dose products (21 CFR 610.15), depending on the calculation method (Table 6).

The FDA evaluated the safety of aluminum hydroxide in OTC drugs (Table 6). The FDA stated that the oral maximum daily dose of an antacid containing aluminum hydroxide dried gel is 8 g (21 CFR 331.11). A chewable tablet of aluminum hydroxide:magnesium trisilicate (80:20 mg) was approved by the FDA.³ Two other chewable tablets were approved with aluminum hydroxide:magnesium trisilicate doses of 80:20 mg and 160:40 mg.⁴ Liquid suspensions of aluminum hydroxide are also used as antacids.⁸³

Aluminum hydroxide gel is approved for use in OTC skin protectant drug products as an active ingredient at 0.15% to 5%, with caution to consult a doctor for children younger than 6 months of age (Table 6; 21 CFR 247.10; 21 CFR 347.50).

The safety and effectiveness of aluminum hydroxide for use in OTC drugs has not been established for the treatment of diarrhea or the topical treatment of acne. Aluminum hydroxide has been approved for use in digestive aid drug products and preparations for treating diaper rash (21 CFR 346.14).

Alumina is used as an adsorbent, desiccant, and abrasive.⁸⁴ It is used as filler for paints and varnishes. It is also used in the manufacture of alloys, ceramic materials, electrical insulators and resistors, dental cements, glass, steel, and artificial gems. It is used in coatings for metals and other surfaces and as a catalyst or catalyst substrate for organic chemical reactions.

Alumina is approved as an indirect food additive by the FDA.⁵ Aluminum hydroxide is considered GRAS as a direct food ingredient by the FDA (21 CFR 176.210, 177.1200, 177.2600).⁶

There are many regulations and recommendations for aluminum compounds. Those that are informative for the purpose of this safety assessment are listed in Table 7.

Alumina in Medical Devices

Alumina has been approved by the FDA for use in medical devices. The alumina used in these devices must comply with ASTM F603-12, "Standard Specification for High-Purity Dense Aluminum Oxide for Medical Application."²

The FDA considered the safety of alumina when approving the following medical devices that contain this material:

- Color additives for polymethyl methacrylate (PMMA) bone cement and sutures.
- Endosseous dental implant abutments.
- Femoral bearing head of artificial hips.

Color Additives

Colors that contain alumina (eg, FD&C Blue #1 aluminum lake) are approved by the FDA to be used in color cosmetics, food, dietary supplements, drugs for internal and external use, and medical devices (ie, bone cement, surgical sutures).⁸⁵ The colors are created by applying the coloring material to an alumina substrate. Alumina has been approved as a color additive for OTC drugs (21 CFR 73.1010).

Ceramic Hip

The use of ceramic femoral heads (ie, CeramTec Alumina Heads, Alumina V40 Head) made of alumina/ceramic composites has been approved for use in hip joint replacements in humans. The materials conform to FDA's "Guidance Document for the Preparation of Premarket Notifications for Ceramic Ball Hip Systems."^{78,86,87} One of these hip replacement products was reported to consist of ~75% alumina, ~25% zirconia, and <1% chromium oxide.⁸⁸

Other Devices

Alumina has been approved for use in endosseous dental implant abutments (Table 6; 21 CFR 872.3630). Alumina/ceramic composite is used to make internal stents for treating tracheomalacia.⁸⁹ These stents are implanted inside the trachea.

Toxicokinetics

Overview

Aluminum hydroxide, as measured by aluminum content, is poorly absorbed through either oral or inhalation routes and is essentially not absorbed dermally in healthy humans.⁹⁰ Orally, the bioavailable forms of aluminum hydroxide are absorbed at only approximately 0.1%. Ingested aluminum hydroxide is excreted as aluminum in the feces. Studies on uptake and elimination rates of aluminum hydroxide indicate that a near steady state is maintained in most healthy adults, with aluminum body burdens varying slightly up and down over time with an overall small rate of increase over a lifespan. High-level, long-term use of antacids containing aluminum hydroxide will cause levels of aluminum to increase in the blood and other tissues. The levels return to normal upon cessation of high-level exposure. Under certain atypical conditions (eg, poor renal function with increased aluminum load), levels of aluminum in the body may rise high enough to cause toxicity in humans.

Blood and tissue (liver, spleen, kidney, brain, bone) levels of aluminum from the ingestion of aluminum hydroxide

Table 6. US Government Regulations for Medical Devices, Drugs, and Other Regulated Uses of Alumina and Aluminum Hydroxide.

Device/drug	Rule	Reference
Endosseous dental implant abutment	An endosseous dental implant abutment (made of alumina) is a premanufactured prosthetic component directly connected to the endosseous dental implant and is intended for use as an aid in prosthetic rehabilitation. Class II (special controls). The guidance document entitled "Class II Special Controls Guidance Document: Root-Form Endosseous Dental Implants and Endosseous Dental Implant Abutments" will serve as the special control.	21 CFR 872.3630
Hip joint metal/ceramic/polymer semi-constrained cemented or nonporous uncemented prosthesis	(a) A hip joint metal/ceramic/polymer semi-constrained cemented or nonporous uncemented prosthesis is a device intended to be implanted to replace a hip joint. This device limits translation and rotation in 1 or more planes via the geometry of its articulating surfaces. It has no linkage across the joint. The 2-part femoral component consists of a femoral stem made of alloys to be fixed in the intramedullary canal of the femur by impaction with or without the use of bone cement. The proximal end of the femoral stem is tapered with a surface that ensures positive locking with the spherical ceramic (aluminum oxide, Al_2O_3) head of the femoral component. The acetabular component is made of ultra-high-molecular-weight polyethylene or ultra-high-molecular-weight polyethylene reinforced with nonporous metal alloys and used with or without bone cement. (b) Classification: class II. (a) A hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis is a 2-part device intended to be implanted to replace the articulating surfaces of the hip while preserving the femoral head and neck. The device limits translation and rotation in 1 or more planes via the geometry of its articulating surfaces. It has no linkage across the joint. This generic type of device includes prostheses that consist of a femoral cap component made of a metal alloy, such as cobalt-chromium-molybdenum, or a ceramic material, that is placed over a surgically prepared femoral head and an acetabular resurfacing polymer component. Both components are intended for use with bone cement (888.3027). (b) Classification: class III. (c) <i>Date PMA or notice of completion of a PDP is required.</i> A PMA or a notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before January 3, 2005, for any hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis that was in commercial distribution before May 28, 1976, or that has, on or before January 3, 2005, been found to be substantially equivalent to a hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis that was in commercial distribution before May 28, 1976. Any other hip joint metal/polymer or ceramic/polymer semi-constrained resurfacing cemented prosthesis must have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.	21 CFR 888.3353 21 CFR 888.3410
OTC drugs	Section 350.50. Labeling of antiperspirant drug products. (c) <i>Warnings:</i> The labeling of the product contains the following statements under the heading "Warnings": (1) "Do not use on broken skin." (2) "Stop use if rash or irritation occurs." (3) "Ask a doctor before use if you have kidney disease." (4) <i>For products in an aerosolized dosage form.</i> (i) "When using this product, keep away from face and mouth to avoid breathing it." (a) Based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of aluminum hydroxide ingredients for the specified uses: (1) <i>Topical acne drug products.</i> (3) <i>Antidiarrheal drug products—(i) Approved as of May 7, 1991.</i> (8) <i>Digestive aid drug products—(i) Approved as of May 7, 1991.</i> (iii) <i>Diaper rash drug products.</i> (a) Aluminum-containing active ingredients: (1) Basic aluminum carbonate gel. (2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate co-dried gel, aluminum hydroxide-magnesium trisilicate co-dried gel, aluminum hydroxide sucrose powder hydrated). (3) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid. (4) Aluminum phosphate gel when used as part of an antacid combination product and contributing at least 25% of the total acid neutralizing capacity; maximum daily dosage limit is 8 g.	21 CFR 350.50 21 CFR 310.545 21 CFR 331.11

(continued)

Table 6. (continued)

Device/drug	Rule	Reference
	Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.	21 CFR 310.545
	(a) 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 (aluminum hydroxide) for the specified uses: topical acne drug products and antidiarrheal drugs.	
	The labeling of the product contains the following information for anorectal ingredients identified in 346.10, 346.12, 346.14, 346.16, 346.18, and 346.20 and for combinations of anorectal ingredients identified in 346.22 (up to 50%). Unless otherwise specified, the labeling in this subpart is applicable to anorectal drug products for both external and intrarectal use.	21 CFR 346.14
	(H) Temporarily relieves the symptoms of perianal skin irritation.	
	(iv) For products containing aluminum hydroxide gel identified in 346.14(a)(1) and for products containing kaolin identified in 346.14(a)(5). "For the temporary relief of itching associated with moist anorectal conditions."	
	For products containing aluminum hydroxide gel identified in 346.14(a)(1) and for products containing kaolin identified in 346.14(a)(5). "Remove petrolatum or greasy ointment before using this product because they interfere with the ability of this product to adhere properly to the skin area."	
	Listing of specific active ingredients	21 CFR 331.11
	(a) Aluminum-containing active ingredients:	
	(2) Aluminum hydroxide (or as aluminum hydroxide–hexitol stabilized polymer, aluminum hydroxide–magnesium carbonate co-dried gel, aluminum hydroxide–magnesium trisilicate co-dried gel, aluminum hydroxide–sucrose powder hydrated).	
	Permitted combinations of active ingredients.	21 CFR 347.10
	(a) <i>Combinations of skin protectant active ingredients.</i> (1) Any 2 or more of the ingredients identified in 347.10(a), (d), (e), (i), (k), (l), (m), and (r) may be combined, provided the combination is labeled according to 347.50(b)(1) and provided each ingredient in the combination is within the concentration specified in 347.10.	
	(2) Any 2 or more of the ingredients identified in 347.10(a), (d), (e), (g), (h), (i), (k), (l), (m), and (r) may be combined, provided the combination is labeled according to 347.50(b)(2) and provided each ingredient in the combination is within the concentration specified in 347.10.	
	(b) <i>Combination of ingredients to prepare an aluminum acetate solution.</i> Aluminum sulfate tetradecahydrate may be combined with calcium acetate monohydrate in powder or tablet form to provide a 0.13% to 0.5% aluminum acetate solution when the powder or tablet is dissolved in the volume of water specified in "Directions."	
Food packaging	Aluminum hydroxide is among the list of defoaming agents that may be safely used in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food.	21 CFR 176.210
	Aluminum hydroxide is among the list of substances that may be a component of cellophane as a food packaging substance.	21 CFR 177.1200
	Aluminum hydroxide is included in the list of fillers of rubber articles intended for repeated use may be safely used in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.	21 CFR 177.2600
Indirect food additive	Aluminum hydroxide is among the list of substances that may be safely used as colorants used in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, subject to the provisions and definitions set forth in this section.	21 CFR 178.3297
	(a) The term <i>colorant</i> means a dye, pigment, or other substance that is used to impart color to or to alter the color of a food-contact material but that does not migrate to food in amounts that will contribute to that food any color apparent to the naked eye.	
	(b) The colorant must be used in accordance with current good manufacturing practice, including use levels that are not in excess of those reasonably required to accomplish the intended coloring effect.	
	(c) Colorants in this section must conform to the description and specifications indicated.	
	(d) Color additives and their lakes listed for direct use in foods, under the provisions of the color additive regulations in parts 73, 74, 81, and 82 of this chapter, may also be used as colorants for food contact polymers.	

Abbreviations: PBP, pharmacy bulk packages; PDP, product development protocol.

Table 7. Organizational Findings and Government Regulations With Regard to Aluminum and Related Compounds.⁹⁰

Agency	Findings/regulation	Reference
International		
IARC	Group 1: Aluminum production carcinogenic to humans	119
WHO	Drinking water quality guidelines for aluminum	120
	≤0.1 mg/L in large water treatment facilities	
	≤0.2 mg/L in small water treatment facilities	
United States		
Air		
ACGIH	TLV (8-hour TWA) for aluminum and compounds (as Al)	121
	Metal dust—10 mg/m ³	
	Pyro powders—5 mg/m ³	
	Soluble salts—2 mg/m ³	
	Alkyls (NOS)—2 mg/m ³	
	TLV (8-hour TWA) for aluminum oxide ^a —10 mg/m ³	
NIOSH	REL (10-hour TWA)	122
	Aluminum	
	10 mg/m ³ (total dust)	
	5 mg/m ³ (respirable fraction)	
	Aluminum oxide	
	15 mg/m ³ (total dust)	
	5 mg/m ³ (respirable fraction)	
OSHA	PEL (8-hour TWA) for general industry for aluminum metal (as Al) and aluminum oxide	29 CFR 1910.10000
	15 mg/m ³ (total dust)	
	5 mg/m ³ (respirable fraction)	
Water		
EPA	Designated as hazardous substances in accordance with section 311(b)(2)(A) of the Clean Water Act for aluminum sulfate	40 CFR 116.4
	Drinking water standards and health advisories—0.05 to 0.2 mg/L	123
	National primary drinking water standards—no data	124
	National secondary drinking water standards for aluminum—0.05 to 0.2 mg/	40 CFR 143.3
	Reportable quantities of hazardous substances designated pursuant to section 311 of the Clean Water Act for aluminum sulfate—5,000 pounds	40 CFR 117.3
	Water quality criteria for human health for aluminum	125
	Freshwater CMC—750 µg/L	
	Freshwater CCC—87 µg/L	
Food		
FDA	Bottled drinking water for aluminum—0.2 mg/L	21 CFR 165.110
Other		
EPA	Pesticide exemptions from the requirement of a tolerance	40 CFR 180.910
	Aluminum hydroxide (for use as a diluent and carrier) ^b	
	Aluminum oxide (for use as a diluent)	

Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; Al, aluminum; CCC, criterion continuous concentration; CMC, criteria maximum concentration; EPA, Environmental Protection Agency; FDA, Food and Drug Administration; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health; NOS, not otherwise specified; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; TLV, threshold limit values; TWA, time-weighted average; WHO, World Health Organization.

^aTWA: The value is for particulate matter containing no asbestos and <1% crystalline silica.

^bPesticide exemptions from the requirement of a tolerance: residues of the following materials 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 growing crops or to raw agricultural commodities after harvest.

(100, 281, 1,500, 2,000 mg/kg/d) were increased by concurrent oral administration of citric, lactic, malic, oxalic, or tartaric acids in rats.⁹¹⁻⁹³

Dermal. Aluminum salts used in antiperspirants form hydroxide precipitates of denatured keratin in the cornified layer that surrounds and occludes the opening of sweat ducts.⁹⁴ This mechanism suggests that there is little or no dermal absorption of aluminum hydroxide or any other form of aluminum.

Oral—Nonhuman

Aluminum hydroxide. Bioavailability of orally administered [²⁶Al]aluminum hydroxide (in 2 mL water; pH 7) to male Wistar rats (n = 9) was 0.1%.⁹⁵ After administration, the rats were placed in metabolic cages and blood sampled at 20, 45, 60, 90, 150, and 300 minutes. The rats were then killed and necropsied.

The aluminum content returned to normal levels in the tissues of Sprague Dawley rats within 21 days after oral administration of aluminum hydroxide.⁹⁶ In the first study, the rats were fed a

control diet containing 26 µg Al/g ($n = 5$) or 989 µg Al/g ($n = 15$) for 16 days. All rats were then fed the control diet. Five rats were killed and necropsied at the end of the test period and 7 and 21 days thereafter. The treatment group had increased aluminum in the tibiae–fibulae, ulnae–radii, leg muscles, and kidneys. At day 21, all aluminum content measurements were similar to controls.

This experiment was repeated with 9 additional rats (control) and 1,070 µg Al/g in the diet, and the rats were killed and necropsied at 0, 3, and 7 days after treatment. The increase in aluminum content in the test group returned to control levels by day 7. Ingestion of aluminum hydroxide had no effect on the levels of phosphorus, calcium, magnesium, zinc, and iron in the tissues examined.

Only $0.45\% \pm 0.47\%$ of orally administered aluminum hydroxide (10,000 µmol/kg as concentrated aluminum hydroxide gel with 4 mL water by stomach tube) to renally intact rabbits ($n = 10$) was absorbed.⁹⁷ Renally impaired rabbits absorbed $0.36\% \pm 0.30\%$.

Oral—Human

Aluminum hydroxide. Orally administered aluminum hydroxide is poorly absorbed ($<0.01\%$) in humans.^{57,63} Using 26Al, the estimated aluminum absorption rates were 0.523%, 0.0104%, and 0.136% in 2 participants receiving a single dose of aluminum citrate, aluminum hydroxide, or aluminum hydroxide dissolved in an aqueous citrate solution, respectively.⁹⁸ The test materials were delivered to the stomach through a pediatric feeding tube. Blood was collected at 1, 4, and 14 hours. Feces and urine were collected for 6 days. The uptake of aluminum was greatest for the citrate form and least for aluminum hydroxide. The addition of citrate to aluminum hydroxide increased the 26Al uptake in both participants.

There was no appreciable increase in the amount of aluminum absorbed in participants ($n = 8, 10, 7$) administered with aluminum hydroxide (equal to 244, 976, or 1,952 mg Al in the form of antacid tablets; pH 9.2).⁹⁹ By measuring the amount of aluminum in the urine, the amount of aluminum absorbed was estimated to be 0.001%, 0.004%, and 0.007%, respectively. When the high dose was combined with orange juice (70 mL; pH 4.2) or citric acid (70 g in 1,000 mL distilled water; pH 2.4), absorption increased to 0.03% and 0.2%, respectively.

Intravenous

Aluminum hydroxide. The half-life of intravenously (IV) administered aluminum hydroxide (100 µmol/kg as concentrated aluminum hydroxide gel) in renally intact rabbits ($n = 10$) was 27 ± 13 hours.⁹⁷ In renally impaired rabbits, the half-life was 14 ± 5 hours. Blood was sampled at 24 hours and immediately prior to treatment and at approximately 5, 10, 20, 30, 45, and 60 minutes and 2, 4, 8, 12, 24, and 48 hours after treatment.

Toxicity

Repeated Dose

Oral—Animal

Aluminum hydroxide. When aluminum hydroxide (average 2,400 mg/kg/d in drinking water) was administered to Long

Evans male hooded rat weanlings ($n = 7$ or 8) for 60 days, there was no reduction in cognitive abilities.¹⁰⁰ At necropsy, the highest concentration of aluminum in the brain was in the hippocampus. The test group had decreased weight gain compared to controls, possibly reflecting reduced water intake at the beginning of the test period. The rats were assessed with an open-field activity test biweekly. At the end of the test period, the rats were tested for muricidal behavior by placing an albino mouse with each of the rats. Only 1 treated rat exhibited the behavior.

When aluminum hydroxide (300 mg/kg in carboxymethyl cellulose) and aluminum hydroxide (100 mg/kg) plus citric acid (30 mg/kg) were orally administered to Long Evans rats ($n = 10$ /sex), their learning ability was reduced as measured using a 4-T shaped labyrinth.¹⁰¹ Control rats learned the way to the goal in an average of 5.1 ± 2.88 times versus 16.0 ± 2.98 and 13.2 ± 5.39 times for the 2 treatment groups, respectively. The aluminum content of the brains of the control rats at necropsy was 6.6 ± 3.01 ppm compared to 18.0 ± 10.20 ppm and 11.0 ± 4.80 ppm in the 2 treatment groups, respectively. There was also increased acetylcholinesterase activity in the aluminum hydroxide plus citric acid group. There was no increase in choline acetyltransferase activity in the brains of either group. No other clinical signs or abnormalities were reported.

Intraperitoneal—Animal

Aluminum hydroxide. Male Wistar rats ($n = 12$) exhibited decreased weight gain and initial feed efficiency when administered intraperitoneal (IP) aluminum hydroxide (80 mg/kg) 3 times/week for 6 months.¹⁰² However, there were no differences in total feed intake. Aluminum hydroxide did not affect the peak growth rate or the time to reach maturity. The systemic calcium balance in the treated rats was altered, and there was an increase in the amount of calcium excreted in the feces. The rate of skeletal Ca^{++} accretion was decreased without changes in the bone calcium resorption.

Oral—Human

Aluminum hydroxide. There were no adverse effects observed when participants ($n = 9$ females, 4 males) were administered aluminum hydroxide (equal to 59 mg Al) 3 times daily for 6 weeks.¹⁰³ When compared to the control group ($n = 3$ females, 2 males), urinary Al was ~10- to 20-fold greater during treatment. The authors stated that this indicated that ingestion of an Al-containing antacid is associated with Al absorption above that originating from food and drinking water. There were no differences in the lymphocyte subpopulations, lymphocyte proliferation, and in vitro immunoglobulin and interleukin production. There were no differences between groups in the immune parameters examined, except for a slightly smaller $\text{CD8}^+\text{CD45RO}^+$ population (primed cytotoxic T cells) in the test group compared to the referents.

Reproductive and Developmental Toxicity

Aluminum Hydroxide

When aluminum hydroxide (0, 66.5, 133, or 266 mg/kg in distilled water) was administered by gavage on gestation days

6 to 15 to Swiss mice ($n = 20$), there were no effects attributed to the test substance.¹⁰⁴ There were no differences in maternal weights, feed consumption, appearance, or behavior. There were no differences in the number of total implants, resorptions, number of live or dead fetuses, fetal size parameters, or sex distribution observed at necropsy. There were no differences observed at gross external, soft tissue, and skeletal examinations.

When aluminum hydroxide (384 mg/kg/d; $n = 18$), aluminum citrate (1,064 mg/kg/d; $n = 15$), or aluminum hydroxide (384 mg/kg/d; $n = 19$) plus citric acid (62 mg/kg/d) was orally administered to Sprague Dawley rats (during gestation day 6 to 15), there were no differences among the groups in pre- or postimplantation loss, number of live fetuses per litter, or sex ratio.¹⁰⁵ Fetal body weight was reduced and skeletal variations (delayed ossification of occipital bone and sternbrae; absence of xiphoids) were increased in the aluminum hydroxide plus citric acid group. The absence of xiphoids was also observed in the aluminum citrate group. The dams exhibited decreased weight gain in the aluminum hydroxide plus citric acid group during treatment but recovered and caught up to the other groups post-treatment. There was increased aluminum in the livers, bones, and placentas of the dams in the aluminum citrate group; there were no differences in aluminum content in the kidneys and brains. Aluminum accumulation was not detected in whole fetuses of the treated mice compared with those in the control group ($n = 17$), which were administered water.

Irritation

Aluminum Hydroxide

Aluminum hydroxide (10% wt/vol in 0.2% Tween-80) was not irritating when applied to the shaved backs of female TF1 strain albino mice ($n = 5$; 0.5 mL), New Zealand white rabbits ($n = 3$; 0.5 mL), and large white strain pigs ($n = 2$; 1.0 mL) for 5 consecutive days.¹⁰⁶ The test substance was applied uncovered. The animals were restrained until the substance was dry.

Clinical Use

Clinical Trials

There are multiple clinical trials of artificial hips (with alumina-on-alumina ball and socket contact or alumina ceramic hips), alumina/ceramic composite stents, and dental implants. There were no adverse reactions reported. None of the failures reported were attributable to adverse health effects of the alumina but were related to mechanical or implantation technical issues (Table 8).

In a review of 4 case studies of alumina ceramic hip implant failures, it was determined that all problems were due to design issues, implementation issues, or surgical issues.¹⁰⁷ None of the failures were attributed to adverse reactions to the alumina.

Summary

Alumina functions in cosmetics as an abrasive, absorbent, anticaking agent, bulking agent, and opacifying agent; aluminum hydroxide functions as a buffering agent, corrosion inhibitor, and pH adjuster.

The alumina and aluminum hydroxide produced for cosmetics are chemically equivalent to the materials used in color surgical sutures and to the alumina in other medical devices, as well as to the alumina in OTC drugs. The safety information submitted for those medical devices and drugs was reviewed by the FDA, including the results of acute and long-term biocompatibility testing for cytotoxicity, irritation and intracutaneous reactivity, sensitization, systemic toxicity, implantation effects, and hematocompatibility studies. The FDA found the data to be adequate and determined that alumina was safe and effective for use in hip and dental implants, as well as for coloring PMMA bone cement and surgical sutures. Alumina is approved as an indirect food additive. Aluminum hydroxide is GRAS as a direct food additive and safe for use in OTC drugs.

Alumina was reported to be used in 523 leave-on products at concentrations up to 60% (in nail products). It is reported to be used in 40 rinse-off products at concentrations up to 25%. Aluminum hydroxide was reported to be used in 572 leave-on products up to 10.1% (in eye products) and in 6 rinse-off products up to 8.8% (in oral hygiene products).

Alumina is used in color additives for sutures and is a material used in the construction of endosseous dental implant abutments and femoral bearing heads of artificial hips. In clinical trials of artificial hips, dental implants, and esophageal stents, all adverse effects were from mechanical or installation problems, not attributable to exposure to alumina.

Orally administered aluminum in aluminum hydroxide has low bioavailability and is excreted primarily in the feces; the systemically absorbed aluminum in aluminum hydroxide is excreted primarily in the urine.

Aluminum hydroxide orally administered to rats at 2,400 mg/kg had no effect on cognitive abilities, but 100 mg/kg administered with citric acid reduced the rat's learning ability. Rats exhibited decreased weight gain and decreased initial feed efficiency when administered with aluminum hydroxide IP at 80 mg/kg 3 times/week for 6 months.

There were no effects on immunological parameters in humans when orally administered with aluminum hydroxide (equal to 59 mg Al) 3 times daily for 6 weeks. There were no reproductive effects in mice when orally administered with 266 mg/kg aluminum hydroxide during gestation days 6 to 15. There were also no reproductive effects in rats at 384 mg/kg aluminum hydroxide orally administered during gestation days 6 to 15. However, when administered to rats with citric acid, there was reduced weight gain in the dams and increased skeletal abnormalities in the pups. Aluminum hydroxide at 10% was not dermally irritating to mice, rabbits, or pigs ($n = 2$; 1.0 mL).

Table 8. Clinical Trials of Medical Devices Containing Alumina.

Study	Results	Reference
Artificial hips		
Alumina-on-alumina (n = 88 participants; 107 hips) and alumina ceramic bearing (n = 65; 71 hips) followed for an average of 6.84 ± 1.49 years and 7.73 ± 1.60 years.	No adverse effects from exposure to alumina.	126
Two alumina hips compared with and without alumina grit-blasted finish (n = 14, 18) followed for 12 months and compared for complications.	Alumina particles on the surface of prostheses had a histologically observable impact on surrounding tissues and leads to surface wear in vivo. This was considered mechanical and not a reaction to alumina.	127
Alumina-on-alumina (n = 849; 930 hips) followed for an average of 5.9 years for adverse events, 10 years for survivorship.	All adverse event/complications were of mechanical origin, not from exposure to alumina. Survival ^a of the hips at 10 years was 96.8%.	128
Fine-grained alumina ceramic hips, with and without zirconium oxide added (n = 29 women, 35 men and 21 women, 24 men) followed for an average of 73 (26-108) and 72 (31-98) months.	Survivorship was 95% and 93% at 6 years, respectively. There were no cases of osteolysis in the first group and 1 case in the second. No adverse effects attributed to alumina were reported.	88
Alumina-on-alumina hips (n = 77, 82 hips) were retroactively followed for 8 years.	Eight-year survival was 90.7% with no revisions, 94.4% with revisions. All issues were attributed to mechanical issues and not from exposure to alumina.	129
Alumina ceramic hips (n = 301) were followed for at least 10 years.	Survival was 98% (confidence interval 94.2%-99.6%) at 10 years. All adverse effects were due to mechanical issues.	130
Two alumina ceramic hips (n = 27, 23) comparing an alumina and a polyethylene liner followed for 2 years.	No adverse effects from either form of hip.	131
Dental implants		
Alumina ceramic attachment (> 95% alumina) to hold dentures (n = 20) were followed for 1 year.	No adverse effects from exposure to alumina.	132
Single crystal alumina endosteal dental implants (n = 29) followed for 5 years.	5 implants removed from study due to mechanical issues, infection, or patient discomfort. No adverse effects from exposure to alumina.	133
Single crystal alumina endosteal dental implants (n = 23; 15 participants) followed for 10 years. Six weeks after implantation, the implants served as abutments for fixed prostheses.	After 10 years, 21 baseline implants were still in place and 17 were fully functional (81% survival). All adverse events were mechanical and not due to exposure to alumina.	134
Glass infiltrated alumina crowns (n = 5 ³ ; 21 participants) followed for 5 years.	All adverse events were mechanical and not related to exposure to alumina.	135
Other devices		
Retrospective study (n = 12) of internal alumina/ceramic composite stents inserted for the treatment of tracheomalacia were followed.	None of the complications were due to the materials. In an assessment of biocompatibility, the authors concluded that there were no foreign body reactions, the inserts were stable, and were a long-term solution with proper suturing technique.	89

^aSurvival refers to how long the prosthesis is functional.

Discussion

The CIR Panel emphasized that this is a safety assessment of alumina and aluminum hydroxide and that these ingredients are not to be confused with elemental aluminum. The Panel noted that the scientific literature provides no plausible evidence linking Alzheimer disease or breast cancer to the use of these ingredients.

The Panel was not concerned with the potential for incidental ingestion of alumina when used in lipsticks or oral hygiene formulations. The amounts of aluminum ion that could be released in the digestive tract through the incidental ingestion of such cosmetic products are far below the levels of toxicological concern. There was no concern about dermal penetration or cosmetic application around the eye because

these ingredients are practically insoluble and are not irritating to the skin.

The Panel discussed the issue of incidental inhalation exposure to alumina and aluminum hydroxide in cosmetic powders and fragrance preparations. These ingredients are reportedly used at concentrations up to 6% in cosmetic products that may be sprayed and up to 5% in other products that may become airborne. The Panel noted that 95% to 99% of droplets/particles would not be respirable in any appreciable amounts. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for alumina and aluminum

hydroxide to cause dermal irritation and systemic toxicity in multiple clinical trials of medical devices consisting of alumina. Alumina and aluminum hydroxide are insoluble in water, thus not systemically available. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>.

Conclusion

The CIR Panel concluded that alumina and aluminum hydroxide are safe in the present practices of use and concentration described in this safety assessment.

Appendix A

Overview of Aluminum Toxicity Studies

Absorption. Aluminum in cosmetics and in antiperspirants is not systemically absorbed to any appreciable extent through the skin.^{56,136,137} Aluminum is poorly absorbed in both the respiratory tract and the gastrointestinal tract.⁷

Gastrointestinal absorption of dietary aluminum generally ranges from 0.01% to 0.6% in humans, although absorption of large bolus doses (up to 0.5 g) of aluminum hydroxide, ingested as antacids throughout the day, and other insoluble aluminum compounds is normally $\leq 0.01\%$.^{40,57,58,60-63,65-69} In contrast, the absorption of water-soluble aluminum compounds can range from 0.5% to 5%.⁷ Accordingly, dietary constituents can enhance or inhibit aluminum absorption in the digestive tract by forming absorbable, usually water-soluble, complexes (eg, citric, lactic, or other carboxylic acids) or by forming unabsorbable, generally insoluble compounds (eg, phosphate or dissolved silicate).^{7,59,64}

Osteomalacia. There are many case reports of osteomalacia in otherwise healthy children and adults after long-term ingestion of aluminum-containing antacids (eg, aluminum hydroxide given with buffered citrate) for gastrointestinal problems.^{7,18,22,24,138-140} Skeletal effects in these cases are attributable to impaired phosphate absorption through the formation of insoluble complexes between aluminum and dietary phosphorous in the gut, which leads to hypophosphatemia and phosphate depletion in the bone.

Dialysis encephalopathy. Most human studies on the toxicity of aluminum are reports of osteomalacia, microcytic anemia, and neurological effects in hemodialysis patients with chronic renal failure.^{7,13,14,16,19,36,40,46,49,52,55,56,64,139,141-148} Many of these patients developed signs of central nervous system toxicity, sometimes progressing to dialysis encephalopathy syndrome and even death. These effects are attributable to the accumulation of aluminum in the brain from long-term IV hemodialysis with aluminum-contaminated dialysis fluid and, often, concurrent high oral doses of aluminum hydroxide.^{7,33,40,139,149} However, these studies have limited usefulness for predicting toxicity in the general population because kidney failure,

coupled with very large aluminum exposures, causes atypical aluminum accumulation and risk of aluminum-induced effects in these patients.⁷

Alzheimer disease. The hypothesis that aluminum could be involved in the pathogenesis of Alzheimer disease stems from an early report that aluminum was detected in senile plaques and neurofibrillary tangles in brain tissue from patients with Alzheimer disease.²⁷ Since then, several authors reported increased aluminum concentrations in brain tissue from patients with Alzheimer disease compared to that from adults without Alzheimer disease.^{26,43,139,150-152} However, others found no increase in aluminum levels in brain tissues of patients with Alzheimer disease.^{23,139,143,153-155} Further, other researchers found patients with elevated brain aluminum levels but with no clinical signs of Alzheimer disease.^{12,17,139} In a study of brains taken at autopsy ($n = 50$), signs of dialysis encephalopathy were found in 10 hemodialysis patients with a history of high-dose aluminum ingestion (total doses up to 2,478 g), but no evidence of Alzheimer disease morphology was found in any of them.¹⁵⁶ In contrast, Alzheimer disease morphology was found in 6 patients who had ingested little or no aluminum-containing drugs. The authors concluded that there was no link between the total amount of ingested, bioavailable aluminum administered medically and the appearance of Alzheimer disease-associated aluminum inclusions in glial and neuronal cells.

Several epidemiological studies have examined the possible association between Alzheimer disease and exposure to aluminum in drinking water.^{7,34,37-39,41,53,54,157-166} These studies report conflicting results and have been criticized for flawed participant selection, small sample sizes, poor exposure assessment, inaccurate diagnosis of Alzheimer disease, weak statistical correlations, and failure to adjust for important confounding factors.^{7,32,40,42,56,65,139}

Other epidemiological studies have associated total dietary aluminum consumption with an increased risk of Alzheimer disease.^{139,167} However, no significant association was found between Alzheimer disease and the ingestion of aluminum from tea (typically 2 to 6 mg/L aluminum or 10 to 50 times higher than in drinking water).^{39,40,167,168} In addition, no significant association was found with the use of antacids (typically 300 to 600 mg aluminum hydroxide per tablet, capsule, or 5 mL liquid dose).^{7,15,21,25,39,44,51,56,139,169} Likewise, no significant association was found between Alzheimer disease and inhalation exposure to aluminum dusts and fumes in the workplace.^{7,45,47,139,170,171} Overall, the available studies have not substantiated a causal link between aluminum exposure and Alzheimer disease.^{7-9,35,40,48,65,139,172-174}

Breast cancer. A number of aluminum-containing compounds are used as active ingredients in underarm antiperspirant products (21 CFR 350.10).^{7,11,20,175,176} Compounds approved for this purpose do not include alumina or aluminum hydroxide. However, compounds such as aluminum zirconium octachlorohydrate and aluminum chlorohydrate can be used at

concentrations up to 20% and 25% by weight, respectively, in the United States and in Europe, and aluminum chloride has been used in antiperspirant products up to 15% in Europe (21 CFR 350.10).^{31,177}

Darbre and coworkers have suggested that long-term, regular underarm and breast-area application of products containing potential endocrine disruptors may promote the development of breast cancer.^{28-31,50,177-179} Furthermore, these authors have suggested that aluminum chloride and aluminum chlorohydrate have the potential to disrupt endocrine function in human breast cancer cells by interfering with the binding of estrogens to estrogen receptors and inducing estrogen-regulated gene expression, based on the results of in vitro experiments using the estrogen-sensitive MCF-7 breast cancer cell line.^{30,31,177}

High concentrations of aluminum salts perturbed estrogen receptor signaling in MCF-7 cells.^{31,177} The results of these experiments indicate that aluminum compounds, particularly water-soluble aluminum compounds at high concentrations, can perturb estrogen receptor-mediated activities in MCF-7 breast cancer cells. However, these observations cannot be considered relevant to the use of alumina and aluminum hydroxide in cosmetics, which are insoluble and are not absorbed through the skin to any significant extent.

Furthermore, there was no association between underarm antiperspirant or deodorant use and breast cancer in a population-based case-controlled epidemiological study conducted in the United States.¹⁸⁰ Briefly, patients with breast cancer ($n = 813$) were compared with control participants ($n = 793$) from the same population; the control participants were frequency matched to the patients with cancer by 5-year age-groups. Measures of antiperspirant or deodorant use included self-reported regular use (ever), exclusive use of antiperspirant versus deodorant (or vice versa), and regular use within 1 hour of underarm shaving. Odds ratios ranged from 0.9 to 1.2, and P values from 0.12 to 0.40. The assessment of both antiperspirant and deodorant use in this study helped address the possibility that some of the participants may have reported deodorant use when they actually used an antiperspirant (or vice versa) or may have used a combination of the 2. Overall, the scientific literature provides no plausible evidence linking breast cancer to the use of underarm antiperspirant or deodorant products.¹⁰

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, Washington, DC.

Author Contributions

Lillian C. Becker contributed to conception and design, contributed to acquisition, analysis, and interpretation, and drafted the manuscript. Ivan Boyer contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted the manuscript, and critically revised the manuscript. Lillian J. Gill, F. Alan Andersen, Wilma F. Bergfeld, Donald V. Belsito, Ronald A. Hill, Curtis D. Klaassen, Daniel C. Liebler, James G. Marks, Ronald C. Shank, Thomas J. Slaga, and Paul W. Snyder contributed to conception and design,

contributed to analysis and interpretation, and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Integrated Laboratory Systems

Aluminum Compounds

Review of Toxicological Literature Abridged Final Report

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EXECUTIVE SUMMARY

Aluminum Compounds was nominated by the Environmental Protection Agency (EPA) Office of Water for toxicity testing based on the limited data found for the potential neurotoxic effects of chronic exposure to the aluminum species existing in water. Aluminum has been extensively reviewed, and this report was prepared primarily from the most recent reviews available—the 1999 Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Aluminum*, the 1997 International Programme on Chemical Safety (IPCS) *Aluminum: Environmental Health Criteria 194*, and the current California EPA draft *Public Health Goal for Aluminum in Drinking Water*.

Aluminum, the most abundant metal in the earth's crust, occurs in only one oxidative state (Al^{3+}) and is found in combination with oxygen, silicon, fluorine, and other elements in soil, rocks, clays, and minerals. Elemental aluminum is clearly metallic, but its compounds are on the borderline between ionic and covalent. The trihalides (e.g., aluminum chloride) are covalent in character, except for the fluorides, which give ions of high charge density and are frequently ionic in character. These compounds can form a variety of complex compounds. For example, aluminum fluoride, having a great affinity for the fluoride ion, can form complexes of the types M_3AlF_6 and MAlF_4 , which are extremely stable. Upon acidification, the fluoride complexes yield a tetracoordinated fluoroaluminate complex, AlF_4^- , which acts as a structural analogue of PO_4^{3-} . Small amounts are also found in water in dissolved or ionic form. Soluble salts of weak acids (e.g., carbonates, acetates, sulfides, and cyanides) do not exist in aqueous solution or in water, since they undergo complete hydrolysis, resulting in the precipitation of aluminum hydroxide $[\text{Al}(\text{OH})_3]$. Many methods of analysis are available for aluminum, its metabolites, and other biomarkers of exposure and effect.

Aluminum-based products, particularly those for water treatment (e.g., aluminum sulfate [alum], polyaluminum chloride [PAC], and sodium aluminate), are commercially available. Aluminum sulfate was ranked 43rd among the top 50 chemicals during the years 1993 and 1994; annual production has been stable from 1984 to 1997. The production of PAC and aluminum chlorohydrate for use as water treatment chemicals has also been growing. Annual production capacity for aluminum oxide (alumina, calcined, reduction grade) has been fairly constant in the most recent years (1988-1995), while that for anhydrous aluminum chloride slightly increased during the period. The major uses of aluminum and its alloys are in packaging, building and construction, transportation, and electrical applications. Aluminum compounds, likewise, have a wide range of uses in industrial, domestic, consumer, and medicinal products.

Aluminum is ubiquitous. It is released to the environment by both natural processes and anthropogenic sources. The largest source of airborne aluminum-containing particulates is dust from soil, the weathering of rocks, volcanic activity, and human activities, such as mining and agriculture. Aluminum enters natural waters from the weathering of aluminum-containing rocks and minerals, human activity through industrial and municipal discharges, surface run-off, tributary inflow, groundwater seepage, and wet and dry atmospheric deposition. The concentration of aluminum in water, its bioavailability, and its toxicity is governed by chemical speciation. Aluminum is released to soil by the weathering of aluminum-containing rocks and minerals and as a constituent of many mining wastes and solid wastes from coal combustion,

aluminum reduction, and other metal processing operations. Aluminum also occurs naturally in many edible plants.

The ubiquitous nature of aluminum and its many uses make exposure to aluminum unavoidable. For the general population, exposure is mainly through oral intake, and the major sources are drinking water, residues in foods, cooking utensils, food and beverage packaging, and aluminum-containing medications (e.g., antacids and buffered aspirins). Children may additionally ingest aluminum from dirt from unwashed hands or when playing in contaminated soils, vitamin/mineral supplements, treatment for hyperphosphatemia, and from consumer products not normally ingested by adults (e.g., toothpaste). Exposure is also possible from parenteral sources (e.g., dialysis, vaccinations containing aluminum adjuvants, and parenteral solutions). Occupational exposure to aluminum occurs in the refining of the primary metal and in secondary industries that use aluminum products. Greater exposure to aluminum is possible for persons living in the vicinity of industrial emissions sources and hazardous waste sites, undergoing long-term hemodialysis treatment, drinking water from a residential well, and those consuming large quantities aluminum-containing medications. ATSDR has provided the concentrations of aluminum in a variety of products, including drinking water, infant and milk formulas, other beverages, food products, containers for food, as well as the atmosphere.

The aqueous chemistry of aluminum has been extensively reviewed. Concern over the use of aluminum compounds as coagulants in water treatment exists, since their addition usually results in an increase in the amount of aluminum in finished water. (Treatment can also reduce total aluminum content.) Generally, fractionation of aluminum in drinking water occurs by one of three methods. Drinking water production begins with coagulation, followed by flocculation, clarification, filtration, and lastly disinfection. Aluminum removal depends on the transformation of its ions into $\text{Al}(\text{OH})_3$ species. Additionally, fluorides are added to many water supplies for the prevention of dental carries, and systemic fluorosis can, therefore, be a problem. In the treated water, fluorides exist as less physiologically active fluoroaluminates.

The Occupational and Safety and Health Administration (OSHA), American Conference of Governmental Industrial Hygienists (ACGIH), and National Institute for Occupational Safety and Health (NIOSH) have established a permissible exposure limit (PEL) or guideline values for aluminum as the dust or metal. EPA regulates aluminum and certain aluminum compounds under the Clean Air Act (CAA), Clean Water Act (CWA), and the Safe Drinking Water Act (SDWA). Aluminum oxide, phosphide, fume, and dust are on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986." The reportable quantity limit for aluminum sulfate is 5,000 lb (2,270 kg) and 100 lb (45.5 kg) for aluminum phosphide. A tolerance limit of 0.1 ppm has been set for residues of aluminum phosphide in or on raw agricultural commodities. The Food and Drug Administration (FDA) has received several petitions for the use of aluminum compounds as food additives. Under the Federal Food, Drug, and Cosmetic Act, FDA has amended its regulations for aluminum content in large- and small-volume parenterals used in total parenteral nutrition (TPN), which become effective on January 26, 2001.

Human Toxicity

The effects of aluminum on humans have been extensively reviewed. Overall, there is little indication that aluminum is acutely toxic for the general population; few cases of acute aluminum toxicity during alum therapy (i.e., alum bladder irrigation) have been reported. Prolonged exposure to aluminum, however, can cause systemic toxicity, mainly affecting the gastrointestinal tract and causing neurological and skeletal effects. The production of aluminum-associated bone disease can be accelerated with the simultaneous ingestion of aluminum with citrate compounds. Chronic toxicity occurs almost exclusively in persons undergoing dialysis for renal failure, who are likely to develop osteomalacia or aplastic bone disease, while those undergoing long-term hemodialysis are also subject to dialysis encephalopathy; increased serum fluoride concentration and fluoride intoxication have been observed in the latter group. Respiratory diseases (e.g., pulmonary fibrosis, occupational or potroom asthma, and chronic bronchitis) have been observed primarily in workers in the aluminum industry. Neurological effects, including impairment of cognitive function and motor dysfunction, have also been associated with occupational exposure to aluminum in the workplace air. The accounts of excess lung, kidney, pancreas, and bladder cancer, however, have been linked to other potent carcinogenic chemicals found in the industrial processes. Epidemiological data on workers exposed solely to aluminum or its compounds are not available.

Aluminum is a potent neurotoxic agent in humans. The association between aluminum and characteristics of Alzheimer's disease have prompted numerous studies of all sources of intake of aluminum. Epidemiological and case control studies have examined the potential link between oral exposure to aluminum via drinking water and the disease. The causal role of aluminum, however, remains controversial. Some studies have found a significant relationship between the exposure to aluminum in water and an increased risk of Alzheimer's disease, while other studies have not. The causal role of aluminum is also questionable in amyotrophic lateral sclerosis (ALS), Parkinson's disease, and the dementia complex of Guam. There is, however, convincing evidence that aluminum is the causative agent in dialysis dementia, which is seen in patients undergoing long-term hemodialysis.

Developmental effects such as encephalopathy, bone disease, microcytic anemia, and rickets have occurred in premature infants with reduced or failed renal function receiving aluminum-containing treatment (e.g., dialysate or aluminum-based phosphate binders) and in nonuremic infants receiving parenteral nutrition with aluminum-containing fluids or high doses of aluminum antacids. There are no adequate studies of the long-term effects of aluminum exposure on brain development and skeletal maturation.

No immunotoxicity studies are available. Few cases, however, report of hypersensitivity to aluminum following dermal application or parenteral administration. There have also been no reports of genetic or reproductive effects in humans.

Absorption, Distribution, Metabolism, and Excretion

The human body burden originating from largely insoluble environmental sources of aluminum is very low (about 0.1%). Most aluminum compounds are poorly absorbed through the lungs, skin, and gastrointestinal tract. Uptake from the gastrointestinal tract may be regulated by water solubility of the aluminum species and by mucosally associated luminal metal-binding

ligands. Aluminum is also poorly distributed in most tissues except the lung. Aluminum transport in the blood is about 89% bound to iron transferrin and about 11% as aluminum citrate. Elimination of absorbed aluminum is mainly through the kidney. Chelation with compounds such as desferrioxamine (deferoxamine [DFO]) may increase urinary aluminum excretion.

Of particular concern is the possible enhancement of intestinal absorption in the presence of dietary constituents such as citrate and fluoride. Added or natural fluoride in drinking water may form strong, water-soluble aluminum complexes (one to five fluoride ions per aluminum atom). Slightly acidic pH favors formation of aluminum fluoride and citrate complexes.

The standard American diet contains about 4 g citrate per day. Citrate is known to increase intestinal absorption as well as tissue accumulation of aluminum. Aluminum concentrations in bone and gray matter of rats increased when aluminum was co-administered with citrate and when citrate was administered alone. The bone aluminum concentration in rats treated with aluminum hydroxide plus citrate was 41 times higher than in the bones of control rats treated with aluminum hydroxide alone. However, in one study with human volunteers administered aluminum and citrate in the drinking water, no difference was observed between the plasma concentrations of aluminum in subjects receiving citrate with the drinking water and those that did not. While increasing aluminum absorption, citrate may also enhance urinary excretion, resulting in no significant increase in aluminum plasma concentration in individuals with normal kidney function. The greatest risk of aluminum absorption and distribution after citrate exposure would be for those individuals with renal insufficiency or failure.

Aluminum may form complexes with other dietary acids, for example, malic, oxalic, tartaric, succinic, aspartic, and glutamic acids, which may increase its gastrointestinal absorption. Formation of aluminum maltolate from the dietary constituent maltol (a common food additive) may also occur. The aluminum maltolate complex is also associated with increased aluminum uptake.

Administration of fluoride with aluminum has resulted in decreased fluoride absorption from the intestinal tract, indicating that aluminum-fluoride complexes are not absorbed as readily as fluoride alone. It has been suggested, however, that administration of fluoride alone can cause the co-accumulation of aluminum in bone. Rabbits given only fluoride showed 7- to 11-fold dose-dependent increases in bone aluminum concentrations even when plasma aluminum concentrations showed no significant increase.

Animal Toxicity

Many unpublished studies of aluminum compounds (alone or in mixtures) have been submitted to the EPA.

Acute exposure: Oral and intraperitoneal (i.p.) LD₅₀ values for aluminum bromide, chloride, nitrate, and sulfate have been calculated for the mouse, rat, guinea pig, and rabbit. In Dobrá Voda mice, the oral LD₅₀ for aluminum chloride was 770 mg/kg bw (5.77 mmol/kg bw) and for aluminum sulfate was 980 mg/kg bw (5.73 mmol/kg bw), while in Swiss Webster mice, the values were 222 mg/kg bw (1.66 mmol/kg bw) and >730 mg/kg bw (4.27 mmol/kg bw), respectively. Additionally, oral LD₅₀s of 164 mg/kg bw (0.615 mmol/kg bw) for aluminum bromide and 286 mg/kg bw (1.34 mmol/kg bw) were found. Intraperitoneal LD₅₀ values for the

Swiss Webster mice were 108 mg/kg bw (0.405 mmol/kg bw) for aluminum bromide, 105 mg/kg bw (0.787 mmol/kg bw) for aluminum chloride, 133 mg/kg bw (0.624 mmol/kg bw) for aluminum nitrate, and 40 mg/kg bw (0.23 mmol/kg bw) for aluminum sulfate. In an unspecified strain, the oral LD₅₀ was 3850 mg/kg (28.87 mmol/kg) for aluminum chloride and 6200 mg/kg (36.24 mmol/kg) for aluminum sulfate, and the i.p. LD₅₀ was 320 mg/kg (1.50 mmol/kg) for aluminum nitrate and 140 mg/kg (0.818 mmol/kg) for aluminum sulfate.

In the Sprague-Dawley rat, the oral LD₅₀ values were 162 mg/kg bw (0.607 mmol/kg bw), 370 mg/kg bw (2.77 mmol/kg bw), 261 mg/kg bw (1.23 mmol/kg bw), and >730 mg/kg bw (4.27 mmol/kg bw) for the bromide, chloride, nitrate, and sulfate forms of aluminum. The i.p. LD₅₀ values were 82 mg/kg bw (0.31 mmol/kg bw), 81 mg/kg bw (0.61 mmol/kg bw), 65 mg/kg bw (0.31 mmol/kg bw), and 25 mg/kg bw (0.15 mmol/kg bw), respectively. In an unspecified strain, oral LD₅₀ values of 380 mg/kg (2.85 mmol/kg) and 760 mg/kg (5.70 mmol/kg) were obtained for aluminum chloride. For aluminum nitrate, oral LD₅₀s of 260 mg/kg (1.22 mmol/kg) and 4280 mg/kg (20.09 mmol/kg) were reported, and an i.p. LD₅₀ of 330 mg/kg (1.55 mmol/kg) was calculated.

In both guinea pigs and rabbits, an oral LD₅₀ of 400 mg/kg (3.00 mmol/kg) was calculated.

Topical application of aluminum (0.185-0.482 mmol) in the chloride and nitrate forms produced skin damage in mice, rabbits, and pigs. In rats, inhalation of aluminum (50-200 mg/m³; 45-181 ppm) caused changes in the cytological and enzymatic content of the lavage fluid, while oral intake of a diet (2665 mg Al/kg; 98.78 mmol/kg) containing aluminum resulted in a reduction of food intake and an increased fecal elimination of phosphorus. Intraperitoneal administration (1500 mg/kg; 5.099 mmol Al/kg) produced local toxic myopathy.

Inhalation studies (3-48 mg Al/m³; 3-43 ppm) in rabbits and hamsters caused decreases in body weight, significant increases in absolute lung weights, thickening of the alveolar walls, and the occurrence of small granulomatous foci at the bronchioalveolar junction. When rabbits were injected intracisternally with aluminum chloride (1000 µg; 7.500 µmol Al), microglia showed thinner, less complex branching patterns.

Short-term and subchronic exposure: In mice, oral administration of aluminum as aluminum ammonium sulfate decreased dopamine, dihydroxyphenylacetic acid, and homovanillic acid levels in the hypothalamus, and aluminum lactate increased the 2-thiobarbituric acid reactive substances (TBARS) in the brain but decreased brain stem weight.

In rats, oral administration of aluminum as the sulfate, nitrate, chloride, hydroxide, citrate, and lactate resulted in aluminum accumulation in bone, brain, spleen, liver, heart, gastrointestinal tract, and spleen. Significant decreases occurred in body weight, water consumption, urine volume, plasma glutamic-pyruvic transaminase, serum triglycerides, serum iron concentration, and alkaline phosphatase, ATP, ADP, and AMP, as well as in motor activity. Additional health effects include changes in the cytological and enzymatic content of the lavage fluid, inhibition of colony-forming units-erythroid (CFU-E), and neurobehavioral effects. When administered i.p., malondialdehyde was increased in all brain regions as were phospholipase C- δ 1 protein levels. Low molecular weight phosphotyrosine phosphatase (LMW-PTP) activity, however, was decreased compared to control rat brains. Subcutaneous (s.c.) injections of aluminum produced a significant decrease in iron levels in plasma and the striatum. Significant aluminum accumulation

was induced in the striatum, hippocampus, and cortex, and in the hippocampus, TBARS production was increased.

In guinea pigs and rabbits, oral administration of aluminum decreased alkaline phosphatase, ATP, ADP, and AMP. In hamsters, inhalation of aluminum as Alchlor produced an increase in the number of alveolar macrophages and heterophils, thickening of alveolar walls, and granulomatous nodules. Rabbits developed glomerular lesions and had tubulointerstitial nephrosis when aluminum was given intravenously (i.v.).

In an *in vitro* assay using cultures of cerebellar neurons from rats, glutamate-induced formation of cGMP and glutamate-induced activation of nitric oxide (NO) synthase were reduced; NO- and S-nitroso-*N*-acetylpenicillamine (SNAP)-induced formation of cGMP were also inhibited.

Chronic exposure: Chronic exposure studies in mice, rats, guinea pigs, and rabbits, via the inhalation and oral routes produced similar findings as in subchronic exposure studies. Additionally, in a series of rat experiments where aluminum hydroxide was administered i.p., significant decreases in the hematocrit index, hemoglobin levels, and serum iron concentration in the peripheral blood were observed. Although renal function was the same as in controls, the fractional excretion (FE%) of sodium, the FE% of phosphate, and the urinary excretion of phosphate in treated rats were decreased. In contrast, urinary excretion of calcium was significantly elevated. Furthermore, intracisternal injections produced dose-dependent motor degeneration in the rat.

In rabbits, the inoculums resulted in c-Jun positive staining in the cytoplasm of motor neurons and other smaller neurons. In the ventrolateral regions of the lumbar cord, basophilic inclusions were found in the cytoplasm of motor neurons, some exhibiting features of chromatolysis.

In dogs, oral administration of aluminum as sodium aluminum phosphate produced significant decreases in food consumption in both sexes. Aluminum concentration in the brain was also slightly increased. In males, body and testes weights were markedly reduced.

Synergism/Antagonism: Aluminum competes with cations such as iron and calcium and binds with anions such as fluoride. Certain counter ions increase the bioavailability of aluminum. Citrate enhances the absorption of aluminum in the gastrointestinal tract. Silicic acid, on the other hand, has been observed to decrease the bioavailability of aluminum. In turn, aluminum compounds can decrease the intestinal absorption of iron, fluoride, phosphorus, and calcium. Although fluoride has been seen to exert a protective effect against the biotoxic effect of aluminum, it also has a synergistic effect on the toxicity of aluminum. Aluminum has potentiated fluoride action on osteoblasts and bone. However, it can also exert antagonistic effects; for example, it has inhibited fluoride toxicity in rats, hens, turkey, and sheep. Aluminum fluoride complexes have been found to specifically and persistently activate G protein in several cell systems, as well as exert physiological and biochemical actions in tissues such as the brain, and kidneys. In rats, the toxicity of high dietary aluminum was found to be influenced by magnesium, boron, and manganese. In addition, the dietary level of aluminum has produced age-related effects on levels of copper, iron, zinc, calcium, magnesium, and manganese. Aluminum

may also potentiate the adverse effects of disease states and other biological activities, such as diabetes and iron-induced oxidative stress. In drinking water, the relationship between cognitive impairment and aluminum depends on pH and silica level. At low silica concentrations, high aluminum concentrations had an adverse effect; at high silica and pH levels, however, there was a protective effect.

Reproductive and Teratological Effects: Reproductive toxicity and teratogenicity from aluminum compounds has been reported in a number of papers. Reproductive effects observed in male mice, rats, or dogs given aluminum compounds orally or s.c. included repressed sexual behavior, decreased spermatogenesis, or other effects on the testes, sperm duct, and/or epididymis. Reproductive effects from oral administration to female rats included irregularity of the estrus cycle of female offspring or effects on the ovaries or fallopian tubes in treated adults. Maternal toxicity was observed in several studies in which pregnant mice, rats, or rabbits were administered aluminum compounds orally, i.p., or s.c. during gestation. Developmental toxicity from oral, i.p., or s.c. aluminum compound administration was also noted in some rat and mouse studies. Teratogenic effects induced by oral, i.p., or s.c. administration of aluminum compounds included skeletal or musculoskeletal variations, cleft palate or other craniofacial malformations, cardiovascular system abnormalities, and other unspecified physical effects. Injection of aluminum compounds into the yolk sac of fertilized chicken eggs induced similar developmental malformations. Neurotoxic effects were observed when aluminum compounds were given orally to mice, rats, or rabbits. A number of studies were also found that reported no reproductive, maternal, developmental toxicity or teratogenicity from oral, inhalation, i.p., or s.c. administration of aluminum compounds.

Carcinogenicity: The available carcinogenicity studies do not indicate that aluminum is carcinogenic. No initiation/promotion studies or anticarcinogenicity studies were available.

Genotoxicity: In one acellular assay, aluminum was found to bind to DNA through chelation. It was also found to reduce ^3H -thymidine incorporation in a transformed cell line, indicating that aluminum compounds may impede cell cycle progression. Aluminum compounds were not mutagenic in the preponderance of *Salmonella typhimurium* and *Escherichia coli* studies. Only one study reported a positive mutagenic response, in which aluminum acetylacetonate was tested on *S. typhimurium* strain TA104 in the absence of metabolic activation. Effects induced *in vitro* by aluminum compounds included crosslinking of chromosomal proteins in rat ascites hepatoma cells, anaphasic changes in BALB/c mouse 3T3 cells, and formation of DNA-protein crosslinks, micronuclei, sister chromatic exchanges (SCEs), and chromosomal aberrations in cultured human lymphocytes. Effects induced *in vivo* included SCEs in mice and sheep, delayed mitosis in mice and sheep, and formation of micronucleated polychromatic lymphocytes in mice, and chromosomal aberrations in rats and mice.

No cogenotoxicity studies were found. In one antigenotoxicity study, low concentrations of aluminum chloride inhibited the *in vitro* frequency of single- and double-stranded breaks induced by radiation in plasmid DNA.

Immunotoxicity: One *in vitro* immunotoxicity study using mouse macrophage cells found that the release of tumor necrosis factor (TNF)- α increased with increasing particle size and concentration of aluminum oxide, while interleukin (IL)-1 α or IL-1 β were not affected by treatment. Aluminum lactate, given subchronically in the diet of mice caused immunosuppression, while administration to mice during gestation and lactation induced a decrease in IL-2, interferon (IFN)- γ , and TNF- α in the spleen. Similarly, s.c. treatment of mice with alum at study initiation and two weeks later induced IL-4 production and T-helper cell type 2 (Th2) responses in the absence of IL-4 in mice deficient in either IL-4R α or Stat6. In rats, aluminum nitrate produced hyperemia in the red pulp of the spleen when given for a month, but an experiment using a higher concentration and a longer duration failed to duplicate this result. Bioceram[®], a bioinert ceramic material made from aluminum oxide induced low-grade tissue reactions when implanted s.c.

Neurotoxicity: Dementia in dialysis patients and encephalopathy in infants undergoing parenteral nutrition are well known examples of aluminum intoxication in humans. Numerous *in vitro* studies and epidemiological studies have examined the possible role of aluminum in Alzheimer's disease, other dementias, and cognitive dysfunction.

Numerous animal studies, particularly orally studies in mice and rats, show that aluminum compounds are neurotoxic, but species variation exist. The toxicity is characterized by progressive neurological impairment leading to death associated with repeated seizures. Morphologically, the progressive encephalopathy, associated with neurofibrillary pathology in neurons mostly in the spinal cord, brain stem, and the hippocampus and cingulate gyrus of the cortex, has been induced by aluminum in susceptible animals such as the rabbit, cat, guinea pig, and ferret when given as intrathecal, intracerebral, and subcutaneous injections. For example, in cats and rabbits intracerebral injections of soluble aluminum compounds resulted in impairment in learning and memory, and in rabbits repeated subcutaneous injections affected classical conditioning, while single or repeated intracisternal injection of metallic aluminum altered motor function. Oral administration of aluminum compounds, however, produced no encephalopathy or epilepsy but resulted in behavioral impairment.

Acute Exposure: In axotomized rabbits intracisternally inoculated with aluminum chloride, the number of microglia in the ventrolateral area ipsilateral to the axotomy at day 4 was significantly increased compared to that of the contralateral side and showed thinner, less complex branching patterns compared to controls. In cats, a single injection of aluminum chloride into the hippocampic space resulted in the development of a dementia similar to Alzheimer's disease. In an *in vitro* assay using synaptosomal fractions of rat brain, aluminum chloride caused an increase in mitochondrial acetyl-Coenzyme A (CoA) and a decrease in synaptoplasmic CoA simultaneously with inhibition of calcium-evoked acetylcholine (ACh) release.

Short-term and Subchronic Exposure: In mice, aluminum ammonium sulfate produced a decrease in dopamine, dihydroxyphenylacetic acid, and homovanillic acid levels in the hypothalamus. Aluminum as the lactate and chloride forms produced reduced motor activity,

decreased hind limb grip strength, decreased startle response, and increased aluminum tissue levels and 2-TBARS in the brain. In another mouse study with aluminum chloride, skilled motor coordination performance (roto-rod treadmill test) was impaired.

Oral studies with aluminum in rats produced accumulated aluminum levels in the brain as well as cognitive deficits and other changes, including decreased maze-learning ability, altered general motor activity, impaired motor coordination, impaired passive avoidance, and visual temporal acuity. Ingestion of aluminum compounds, specifically as the sulfate and the nitrate, was found to not only cause reduced retention of a learned passive avoidance task but also changes in brain chemistry (e.g., increased cyclic adenosine monophosphate levels, decreased concentrations of MAP-2 and other structural proteins, decreased dopamine and 5'-hydroxytryptamine, and increased norepinephrine). Furthermore, a study showed that basal extracellular cGMP was significantly reduced in rats fed aluminum but could be increased with the addition of NMDA or SNAP. NMDA-induced formation of nitric oxide (NO) was reduced, but the NO-induced activation of guanylate cyclase was increased in the brains of treated animals. Administration of aluminum (17 mg/kg/day as aluminum chloride) caused decreased alkaline phosphatase, ATP, ADP, and AMP not only in rats but also in guinea pigs and rabbits.

Intraperitoneal injection of aluminum lactate in rats significantly reduced brain weight and LMW-PTP activity and increased PLC- δ 1 protein levels in the cytosolic and particulate fractions, PLC activity in the cytosolic fraction, and lipid peroxidation in the hippocampus, cerebral cortex, and cerebellum. Subcutaneous injections of an aluminum *L*-glutamate suspension induced significant aluminum accumulation in the stratum, hippocampus, and cortex. Iron levels in the striatum were notably decreased and TBARS production increased in the hippocampus compared to controls.

In an *in vitro* assay using cultures of cerebellar neurons from rats, glutamate-induced formation of cGMP and glutamate-induced activation of NOS were reduced. NO- and SNAP-induced formation of cGMP were inhibited; however, no effect on the latter was seen in cultures from prenatally aluminum-exposed rats.

Chronic Exposure: In rats, aluminum chloride caused pathological changes in the brain, such as a scarcity of cells in the ganglionic layer, spongiform changes, and neurofibrillary degeneration, nuclear deformity, and vacuolization of the nuclei. In a separate study, the contents of aluminum and β -APP mRNA in the cortex and immunohistochemical positive index of GFAP in the hippocampus and cortex were significantly increased, suggesting that long-term exposure to aluminum results in proliferation of astrocytes and abnormality of β -APP gene expression. In other studies administering aluminum chloride orally in the diet or drinking water (93 μ mol-3.4 mmol/kg bw/day), decreased spontaneous locomotor activity, acquisition, retention of learned response, and extinction and relearning of an active avoidance task and impaired maze learning ability were observed. Additionally, lipid peroxidation in the brain was increased but Na⁺-, K⁺-, and Mg²⁺-ATPases were decreased. At the highest dose, extended cytoplasmic vacuolization in astrocytes, swelling of astrocytic processes, neuronal vacuolization, and nuclear inclusions were observed. Aluminum nitrate ($\leq$ 125 mg Al/kg/day) in the diet, however, resulted

in no effects on spontaneous motor activity (open-field) or passive avoidance operant training or performance.

In a series of studies using aluminum fluoride (0.5, 5.0, or 50 ppm) in deionized water for up to a year, increased aluminum levels and histological alterations in the brain, particularly increased numbers of abnormal and damaged neurons and reductions in cell density in areas of the hippocampus and neocortex, occurred. Behavioral tests indicated possible olfactory impairment, but no motor impairment or effects on spatial memory.

A single intracisternal injection of aluminum (1.8, 3.71, or 11.1 μmol) followed by the same dose three months later produced motor degeneration, consisting of slight to extreme chromatolysis, unusual localization of the nucleus, axonal and dendrital degeneration, swollen perikarya, ghost-cell appearance of neurons, and/or neurofibrillary tangle formation in the perikarya of severely damaged motor neurons, were seen.

In a series of rabbit studies where animals were intracisternally inoculated with aluminum chloride (0.750 mmol) at intervals of 28 days for a total of 267 days, basophilic inclusions were observed in the cytoplasm of motor neurons in the ventrolateral regions of the lumbar cord. Some motor neurons exhibited features of chromatolysis. The number of microglia in the region was significantly decreased. Microglia showed thinner, less complex branching patterns and were close to or attached to NFH positive structures in the spinal cord. After day 156, c-Jun positive staining in the cytoplasm of motor neurons and other smaller neurons was observed.

In dogs fed aluminum sodium phosphate, there was slight increase in aluminum concentration in the brain.

Other Data: In erythrocytes from New Zealand white rabbits treated with different aluminum compounds, morphological changes were produced in a metal-speciation dependent manner. Using male Wistar rat liver lysosomes, aluminum strongly inhibited the lysosomal proton activity, with aluminum sulfate showing the greatest inhibitory effect. This, however, did not occur in the absence of ATP and presence of nigericin. In *Nostoc linckia* and *Chlorella vulgaris*, a pH-dependent and non-competitive inhibition of Mg^{2+} - and Ca^{2+} -ATPase activities was observed when exposed to aluminum chloride, aluminum fluoride, sodium fluoride, and a combination of aluminum chloride and sodium fluoride.

In Wistar rat brain homogenate, aluminum has activated the enzymes α -ketoglutarate dehydrogenase and succinate dehydrogenase of the Krebs cycle and decreased the activity of aconitase in a dose-dependent manner. In addition, it inhibited glutamate dehydrogenase, an allosteric enzyme that catalyzes a reaction directly connected to the cycle.

A study using *S. typhimurium* TA98 found that aluminum was required for the intracellular transport of fluoride from the incubation medium. In the absence of the metal, the intracellular fluorine concentration was below the detection limit even when fluorine concentration was greater than 589 ppm. With the addition of aluminum, fluorine (>200 ppm) was detected in cells.

Structure-Activity Relationships

In regards to radii, aluminum (Al^{3+}) is similar in size to iron (Fe^{3+}) and magnesium (Mg^{2+}). In biological systems, Al^{3+} has been found to be competitive with Mg^{2+} as well as calcium (Ca^{2+}), although to a lesser extent; for example, it easily displaces both metals from citrate. In processes involving Mg^{2+} , interference by Al^{3+} is possible. It is 10^7 times more effective than Mg^{2+} in promoting polymerization of tubulin to microtubules. The slow ligand-exchange rate for Al^{3+} makes it useless in enzyme active site reactions. The 10^5 times faster rate for Mg^{2+} explains Al^{3+} inhibition of enzymes with Mg^{2+} cofactors. Processes involving rapid Ca^{2+} exchange would be stopped by substitution of Al^{3+} .

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1.0 BASIS FOR NOMINATION

The nomination of Aluminum Compounds by the Environmental Protection Agency (EPA) Office of Water for toxicity testing is based on the limited data found for the potential neurotoxic effects of chronic exposure to the aluminum species existing in drinking water. Studies focusing on the influence that various aluminum complexes, particularly aluminum citrate and aluminum fluoride complexes in the water, have on body burdens, on bone development and metabolic bone disease, and in offspring from exposure to aluminum during pregnancy and lactation were proposed.

2.0 INTRODUCTION AND CHEMICAL PROPERTIES

Aluminum has been extensively reviewed (e.g., IPCS, 1997; Rajwanshi et al., 1997; CAL-EPA, 2000). This report was prepared primarily from the most recent reviews available—the 1999 Agency for Toxic Substances and Disease Registry (ATSDR) *Toxicological Profile for Aluminum*, the 1997 IPCS *Aluminum: Environmental Health Criteria 194*, and the current California EPA draft *Public Health Goal for Aluminum in Drinking Water*. Additional current sources were used to supplement general and/or limited data.

Aluminum, the most abundant metal in the earth's crust, is found in combination with oxygen, silicon, fluorine, and other elements in soil, rocks, clays, and gems such as rubies, sapphires, and turquoise (ATSDR, 1999). Small amounts are also found in water in dissolved or ionic form, typically as complexes with hydroxy ions. Aluminum occurs in only one oxidative state (Al^{3+}). Aluminum compounds are used in a variety of industrial applications (e.g., alum in water treatment) and products (e.g., antacids, food additives, and cosmetics). Because of its ubiquitous state, exposure to aluminum is unavoidable.

2.1 Chemical Identification and Methods of Analysis

2.1.1 Chemical Identification

ATSDR (1999; Table 3-1, pp. 151-161) provides a table regarding the chemical identity of aluminum and several of its compounds, including synonym(s), registered trade name(s), and

several identifications numbers, such as Chemical Abstract Services (CAS) Registry, National Institute for Occupational Safety and Health Registry of Toxic Effects of Chemical Substances (NIOSH RTECS), and Hazardous Substance Data Bank (HSDB). In **Table 1** the Chemical Abstract Services Registry Number (CASRN), chemical formula(s), synonym(s), and trade name(s) are given for those compounds reported by the agency. Additional sources were used for compounds not mentioned in ATSDR (1999) but for which toxicity data were available. (*The Merck Index* provides data for many more aluminum compounds.)

Table 1. Chemical Identification of Aluminum and Its Compounds

Compound [CASRN]	Chemical Formula(s)	Synonyms	Registered Trade Name(s)
Alchlor [52231-93-3]	$\text{Al}_2(\text{OH})_5\text{Cl} \cdot n\text{H}_2\text{O} \cdot m\text{C}_2\text{H}_6\text{O}_2$; $\text{Al}_2(\text{OH})_5\text{Cl} \cdot n\text{H}_2\text{O} \cdot m\text{C}_3\text{H}_8\text{O}_2$; $\text{Al}_2(\text{OH})_4\text{Cl}_2 \cdot n\text{H}_2\text{O} \cdot m\text{C}_2\text{H}_6\text{O}_2$; $\text{Al}_2(\text{OH})_4\text{Cl}_2 \cdot n\text{H}_2\text{O} \cdot m\text{C}_3\text{H}_8\text{O}_2$	1,2-Propanediol, aluminum chloride hydroxide complex; 1,2-propanediol, basic aluminum chloride complex; aluminum chloride hydroxide, propylene glycol complex; aluminum chloride hydroxide [$\text{Al}_2\text{Cl}(\text{OH})_5$], propylene glycol complex	No data available
Aluminum [7429-90-5]	Al	Alumina fibre; metana; aluminum bronze; aluminum dehydrated; aluminum flake; aluminum powder; aluminium	Aluminum-27; Jisc 3108/3110; Metana; Noral Aluminum; Pap-1
Aluminum aceglutamide ^a [12607-92-0]	$\text{C}_{35}\text{H}_{59}\text{Al}_3\text{N}_{10}\text{O}_{24}$	No data available	No data available
Aluminum acetylacetonate ^{b,c} [not available]	$\text{Al}(\text{C}_5\text{H}_7\text{O}_2)_3$	Aluminum 2,4-pentanedionate	No data available
Aluminum calcium silicate ^d [1327-39-5]	Many different forms are known, the most common of which are $\text{CaAl}_2\text{Si}_2\text{O}_8$ and $\text{Ca}_2\text{Al}_2\text{SiO}_7$.	Calcium aluminosilicate. It occurs in nature as the following minerals: anorthite, bavenite, clinozoisite, didymolite, epistilbite, gehlenite, gismondite, grossularite, heulandite, hibsichte, laubanite, laumontite, lawsonite, levynite, margarite, meionite, plazolite, pumpellyite, scolecite, stellerite, vasuvianite, and zoisite	No data available
Aluminum carbonate [not available]	$\text{Al}_2\text{O}_3 \cdot \text{CO}_2$; normal aluminum carbonate $\text{Al}_2(\text{CO}_3)_3$ is not known as an individual compound	No data available	No data available

Table 1. Chemical Identification of Aluminum and Its Compounds (Continued)

Compound [CASRN]	Chemical Formula(s)	Synonyms	Registered Trade Name(s)
Aluminum chloride [7446-70-0]	AlCl_3	Aluminum trichloride; trichloroaluminum; aluminum chloride (1:3)	Pearsall
Aluminum chlorohydrate* [1327-41-9; 11097-68-0; 84861-98-3]	$\text{Al}_2\text{ClH}_5\text{O}_5$ or $\text{Al}_2(\text{OH})_5\text{Cl}\cdot 2\text{H}_2\text{O}$ or $[\text{Al}(\text{OH})_2\text{Cl}]_x$ or $\text{Al}_6(\text{OH})_{15}\text{Cl}_3$; $[\text{Al}_2(\text{OH})_5\text{Cl}]_x$	Aluminum chlorohydroxide; aluminum hydroxychloride; aluminum chloride, basic; aluminum chloride hydroxide, polyaluminum chloride	Astringen; Chlorhydrol; Locron
Aluminum citrate ^e [31142-56-0]	$\text{C}_6\text{H}_8\text{O}_7\cdot x\text{Al}$	Citric acid, aluminum salt (8CI); 1,2,3-propanetricarboxylic acid, 2-hydroxy-, aluminum salt (9CI)	Tiorco 677
Aluminum flufenamate [16449-54-0] ^a	$\text{C}_{42}\text{H}_{27}\text{AlF}_9\text{N}_3\text{O}_6$	Aluminum salt, flufenamic acid ^d	Alfenamin ^d ; Opyrin (Taisho) ^d
Aluminum fluoride [7784-18-1]	AlF_3	Aluminum trifluoride; aluminum fluoride monohydrate; Aluminum fluorure (French)	No data available
Aluminum hydroxide [21645-51-2]	AlH_3O_3 or $\text{Al}(\text{OH})_3$	α -Alumina trihydrate; alumina hydrate; alumina hydrated; aluminum oxide trihydrate; aluminum oxide hydrate; aluminum(III) hydroxide; hydrated alumina; hydrated aluminum oxide; aluminum hydrate; aluminum trihydrate; hydrated alumina	Alcoa 331/c 30BF/C 330/C 333; Alugel; Alumigel; BACO AF260; British Aluminum AF260; Calmogastrin; Higilite H 31S/ H 32/ H 42; Hychol 705; Hydrafil; Hydral 705/710; Martinal A/A-S/F-A; Reheis F 1000
Aluminum lactate [18917-91-4]	$\text{C}_9\text{H}_{15}\text{AlO}_9$; $(\text{HOCHCO}_2)_3\text{Al}$	Aluctyl; aluminum, tris(2-hydroxypropanoate- O^1, O^2); propanoic acid, 2-hydroxy-, aluminum complex; aluminum tris(α -hydroxypropionate)	No data available
Aluminum maltolate ^e [103616-17-7]	$\text{C}_{18}\text{H}_{15}\text{AlO}_9$	Aluminum maltol; Aluminum, tris[3-(hydroxy- κO)-2-methyl-4H-pyran-4-onato- κO^4]-, (OC-6-21)-(9CI); Aluminum, tris(3-hydroxy-2-methyl-4H-pyran-4-onato- O^3, O^4)-, (OC-6-21)-; maltolate; 4H-pyran-4-one, 3-hydroxy-2-methyl-, aluminum complex	No data available
Aluminum nitrate [13473-90-0]	AlN_3O_9	Aluminum trinitrate; aluminum(III) nitrate (1:3); nitric acid, aluminum salt; nitric acid, aluminum (3+) salt	No data available

Table 1. Chemical Identification of Aluminum and Its Compounds (Continued)

Compound [CASRN]	Chemical Formula(s)	Synonyms	Registered Trade Name(s)
Aluminum oxide [1344-28-1]	Al ₂ O ₃	Activated aluminum oxide; α-aluminum, α aluminum oxide; alumina; aluminum sesquioxide; aluminum trioxide; β-aluminum oxide; γ-alumina; γ-aluminum oxide	Almite; Alon; Aloxit; Alumite; Alundum; Campalox; Dispol Alumina; Exolon XW 60; Faserton; Hypalox II; Ludox CL; Martoxin; Microgrit WCA; Poraminar
Aluminum palmitate ^d [555-35-1]	C ₄₈ H ₉₃ AlO ₆ ; [CH ₃ (CH ₂) ₁₄ COO] ₃ Al	Hexadecanoic acid aluminum salt; palmitic acid aluminum salt	No data available
Aluminum phosphate [7784-30-7]	AlPO ₄	Aluminum orthophosphate; phosphoric acid; aluminum salt (1:1); aluminum phosphate tribasic	Alaphos (ingredient); Ukocid (ingredient); Phosphaljel (ingredient); Phosphalugel (ingredient); Phosphalutab (ingredient)
Aluminum phosphide [20859-73-8]	AlP	Aluminum monophosphide; Quick-Phos; Quick-Fume; AlP; Celphos; Detia; Phostoxin	Celphos; Delicia; Delicia Gastoxin; Detia GAS EX-B/EX-T; Phostoxin; Detia phosphine pellets
Aluminum potassium sulfate [10043-67-1]	AlK ₂ O ₈ S ₂	Sulfuric acid, aluminum potassium salt (2:1:1)	No data available
Aluminum sulfate [10043-01-3]	Al ₂ (SO ₄) ₃	Alum; peral alum; pickle alum; cake alum; filter alum; papermakers' alum; patent alum; aluminum sulfate (2:3); aluminum trisulfate; dialuminum sulfate; dialuminum trisulfate; sulfuric acid, aluminum salt (3:2)	cake alum; patent alum
Dihydroxyaluminum sodium carbonate ^d [539-68-4]	CH ₂ AlNaO ₅	[Carbonato(1-)-O] dihydroxyaluminum monosodium salt; aluminum sodium carbonate hydroxide	Kompensan (Roerig); Minicid

* Aluminum chlorohydrate is the common name for several different compounds, all containing aluminum, chloride, and hydroxyl ions; therefore, there are several chemical formulas and CAS numbers. Note: No data were found for aluminum calcium silicate, aluminum sodium silicate, and aluminum nitriloacetate complex.

Sources: ATSDR (1999); ^aLewis (1991); ^bAldrich (1994-1995); ^cLide (1991); ^dBudavari (1996); ^eRegistry (2000)

2.1.2 Methods of Analysis

ATSDR (1999, pp. 241-250 [also IPCS, 1997]) identifies well-established methods used as the standard methods of analysis for aluminum, its metabolites, and other biomarkers of exposure and effect. For the measurement of levels in biological materials, analytical methods,

which are often combined with front-end separation techniques such as chromatography, include accelerator mass spectroscopy (AMS), graphite furnace atomic absorption spectrometry (GFAAS), flame atomic absorption spectrometry (FAAS), neutron activation analysis (NAA), inductively coupled plasma-atomic emission spectrometry (ICP-AES), inductively coupled plasma-mass spectrometry (ICP-MS), laser ablation microprobe mass analysis (LAMMA), and electrothermal atomic absorption spectrometry (ETAAS). [AAS with electrothermal atomization (ETA-AAS) can be used to detect aluminum in foods; a detection limit of $\sim 0.02 \mu\text{g/g}$ is obtained in most foods (Delves et al., 1989).] Because of the ubiquitous nature of aluminum, contamination plays a major role in the analysis of aluminum by all techniques except AMS. AMS can accurately assess the concentration of radioactive ^{26}Al and stable ^{27}Al in a few milligrams of material; its detection limit is one atom in 10^{15} (1 part per quadrillion [ppq]).

GFAAS is the most commonly used method for determining low parts-per-billion ($\mu\text{g/L}$) levels of aluminum in serum, plasma, whole blood, urine, and biological tissues, primarily because it offers the best combination of sensitivity, simplicity, and cost (ATSDR, 1999). When employed as a detector for high-performance liquid chromatography (HPLC), it can analyze for species of complexed or bound aluminum. The limits of detection for GFAAS are $2.3 \mu\text{g/L}$ (2.3 ppb) for whole blood, and are in the low parts-per-billion levels for urine and biological tissues. NAA is another technique used to determine low levels of aluminum in biological tissues and urine. This technique has been shown to exhibit good sensitivity and to be relatively independent from matrix effects and interferences, although it is higher in cost and more difficult to perform. ICP-AES, a multi-elemental technique also relatively free of chemical interferences, is an excellent alternative to GFAAS; limits of detection are about 1 and 4 ppb of urine and blood, respectively. Although it is more costly, ICP-MS can measure the presence of more than 75 elements in a single scan, with detection limits down to parts per trillion (ppt) levels (two or three orders of magnitude lower than those obtained by ICP-AES). It can detect aluminum levels in urine and saliva as low as $0.02 \mu\text{g/mL}$ (20 ppb) and in blood serum as low as $0.001 \mu\text{g/mL}$ (1 ppb). Used as a detector for aluminum in tissue fractions separated by size-exclusion chromatography (SEC), detection limits of $0.05 \mu\text{g/g}$ (50 ppb) have been reported in femur, kidney, and brain. LAMMA

is used for the analysis of aluminum in brain tissue affected with Alzheimer's disease, with detection limits in the low parts-per-million range. It simultaneously images and analyzes features in unstained and untreated tissue sections, therefore avoiding contamination problems associated with tissue preparation.

Many analytical techniques are also available for the measurement of aluminum concentrations in environmental samples (ATSDR, 1999). These include GFAAS, FAAS, NAA, ICP-AES, ICP-MS, spectrophotometry using absorbance and fluorescence detection, phosphorimetry, and gas chromatography equipped with an electron capture detector (GC/ECD).

Many of the methods are those approved by federal agencies and organizations (ATSDR, 1999). NIOSH has recommended FAAS (Method 7013) and ICP-AES (Method 7300) for detecting aluminum and other elements in filter samples of workplace air particulates, with working ranges of 0.5-10 mg/m³ for a 100-L air sample and 0.005-2.0 mg/m³ for a 500-L air sample, respectively. EPA has recommended GFAAS (Method 202.1) and FAAS (Method 202.2) for measuring low levels of aluminum in water and wastewater. Detection limits of 3 µg of aluminum/L of sample and 100 µg of aluminum/L of sample were obtained, respectively.

Additionally, spectrophotometry and GC/ECD have been used to measure low parts-per-billion levels of aluminum in water; for the former technique, a sample detection limit of 4 ppb was reported (ATSDR, 1999). In the field and in the laboratory, flow-injection systems using absorbance and fluorescence detection have been used, with detection limits as low as 0.3 µg/L, while ion chromatography using spectrophotometric detection and on-line preconcentration had a detection limit less than 1 µg/L in aqueous samples. Ion-interaction reversed-phase liquid chromatography with fluorescence detection can detect aluminum as the 8-hydroxyquinoline-5-sulfonic acid complex in environmental water samples (Paull et al., 2000). For the measurement of low parts-per-billion aluminum levels in dialysis fluids, GFAAS is commonly used (ATSDR, 1999). It has also been used to measure levels in soil, and NAA has been used in fly ash. ICP-AES has been used to measure aluminum in rocks, soils, volcano magma, and print, and with pressurized digestion, ICP-AES detection has determined aluminum in air particulates and filters.

2.2 Physical-Chemical Properties

ATSDR (1999; Table 3-2, pp. 162-171) provides a table listing physical and chemical properties of aluminum and several of its compounds, including molecular weight, physical state, melting and boiling points, solubilities in water and organic solvents, and vapor pressure. **Table 2** reports some of these properties. Additional sources were used for compounds not mentioned in ATSDR (1999) but for which toxicity data were available. (*The Merck Index* provides data on many more aluminum compounds.) The **Appendix** presents the speciation of aluminum in biological systems.

Elemental aluminum is clearly metallic, but its compounds are on the borderline between ionic and covalent character (Cotton and Wilkinson, 1962). The trihalides of aluminum (e.g., aluminum chloride), except for the fluorides, are covalent in character; the fluorides of metals give ions of high charge density and are frequently ionic in character (Kleinberg et al., 1960). In aqueous solution, the trihalides are easily hydrated and their solutions exhibit a high electrical conductivity. The aluminum halides can also form complexes with alcohols, ethers, ketones, and aldehydes. The trihalides can form a variety of additional complex compounds. For example, aluminum fluoride, having a great affinity for fluoride ion, can form complexes of the types $M_3(AlF_6)$ (e.g., cryolite $Na_3[AlF_6]$) and $MAlF_4$. These fluoride complexes are extremely stable, and upon acidification yield a tetracoordinated fluoroaluminate complex, AlF_4^- , which acts as a structural analogue of PO_4^{3-} with a bond length equal to the P-O bond (Martin, 1986; Bigay et al., 1987; both cited by Husaini et al., 1996). With β -diketones, aluminum forms compounds that are also covalent in character, such as aluminum acetylacetonate (Kleinberg et al., 1960).

The aluminum(III) cation is sufficiently large to prefer a coordination number of six toward the small fluorine atom, so it adopts structures which are infinitely extended arrays of aluminum and fluorine atoms, leading to a high melting point (Cotton and Wilkinson, 1962). With the other halides, aluminum prefers a coordination number of four, and thus dimeric structures are formed, which have low melting points and may be split by reaction with donor molecules.

Table 2. Physical-Chemical Properties of Aluminum and Its Compounds

Compound	Molecular Weight	Physical State	Odor	Melting Point (°C)	Boiling Point (°C)	Density at 25 °C	Solubility	
							Water at 25 °C	Organic Solvents
Aluminum	26.98	tin-white with bluish tint malleable, ductile metal; crystalline solid	metallic odor when dust is inhaled	660	2327, 2450, 2467	2.70	insoluble; rapidly oxidized at 180 °C	soluble in alkalis and acids
Aluminum aceglutamide ^a	1084.98	no data available	no data available	no data available	no data available	no data available	no data available	no data available
Aluminum acetylacetonate ^{b,c}	324.31	colorless, monoclinic crystals	no data available	190-193	315	3.3	practically insoluble	very soluble in alcohol; soluble in ether and benzene
Aluminum carbonate	145.97	white lumps or powder	no data available	no data available	no data available	no data available	insoluble	dissolves in hot hydrochloric or sulfuric acid
Aluminum chloride	133.34	white (when pure), ordinarily gray, or yellow to greenish crystals	strong odor of hydrochloric acid	volatilizes without melting; 190 at 2.5 atm and 194 at 5.2 atm	182.7 at 752 mm Hg; sublimes readily at 178 or 181	2.44	reacts explosively, evolving hydrogen chloride gas	freely soluble in benzophenone, benzene, nitrobenzene, carbon tetrachloride, chloroform; soluble in alcohol and ether
Aluminum chlorohydrate	174.46	glassy solid	no data available	no data available	no data available	no data available	dissolves, forming slightly turbid colloidal solutions (up to 55% w/w)	no data available
Aluminum fluoride	83.98	white, colorless, or triclinic hexagonal crystals	no data available	1291; sublimes at 1272 (760 mm Hg)	1276 (sublimation point)	2.88	0.559 g/100 mL	sparingly soluble in acids and alkalis; insoluble in alcohol and acetone
Aluminum hydroxide	77.99	white bulky, amorphous powder	no data available	300	no data available	2.42	practically insoluble; forms gels on prolonged contact	soluble in alkaline aqueous solutions or in hydro-chloric and sulfuric acid
Aluminum lactate	294.18	colorless or white-yellowish powder	no data available	no data available	no data available	no data available	freely soluble	no data available
Aluminum maltolate ^d	402.18	no data available	no data available	no data available	no data available	no data available	no data available	no data available

Table 2. Physical-Chemical Properties of Aluminum and Its Compounds (Continued)

Compound	Molecular Weight	Physical State	Odor	Melting Point (°C)	Boiling Point (°C)	Density at 25 °C	Solubility	
							Water at 25 °C	Organic Solvents
Aluminum nitrate	213.00; 375.15 (hydrate)	white nonahydrate, deliquescent crystals	odorless	73	decomposes at 135	1.72 (hydrate)	very soluble (63.7 g/100 cc)	very slightly soluble in acetone; almost insoluble in ethyl acetate and pyridine
Aluminum oxide	101.94	white crystalline powder	no data available	~2000, 2030, or 2054	~3000	3.97	practically insoluble; soluble in cold water (0.000098 g/100 cc; 980 ppb)	slowly soluble in aqueous alkaline solutions; practically insoluble in nonpolar organic solvents
Aluminum palmitate ^e	793.24	white to yellowish mass or powder	no data available	no data available	no data available	no data available	practically insoluble	practically insoluble in alcohol; when fresh, dissolves in petroleum ether or oil turpentine
Aluminum phosphate	121.95	white infusible powder or crystals	no data available	>1460	no data available	2.56 at 23 °C	insoluble	very slightly soluble in concentrated hydrochloric or nitric acid
Aluminum phosphide	57.96	dark gray or dark yellow crystals	garlic odor	does not melt or decompose thermally at temperatures up to 1000	no data available	2.85 at 15 °C	decomposes	no data available
Aluminum potassium sulfate	258.21	white powder	no data available	no data available	no data available	no data available	50 g/L	insoluble in alcohol
Aluminum sulfate	342.14	white, lustrous crystals, pieces, granules, or powder	odorless	decomposes at 770 or 1040	no data available	2.71	soluble in 1 part water	soluble in dilute acids; practically insoluble in alcohol
Dihydroxyaluminum sodium carbonate ^e	144.00	amorphous powder or poorly formed crystals	no data available	no data available	no data available	2.144	no data available	no data available

Note: Alchlor is not included because no data were available. No data were also found for aluminum calcium silicate, aluminum sodium silicate, and aluminum nitriloacetate complex. Sources: ATSDR (1999); ^aLewis (1991); ^bAldrich (1994-1995); ^cLide (1991); ^dRegistry (2000); ^eBudavari (1996)

Soluble aluminum salts of weak acids, such as carbonates, acetates, sulfides, and cyanides, do not exist in aqueous solution or in water, since they undergo complete hydrolysis, resulting in the precipitation of aluminum hydroxide (Kleinberg et al., 1960; Cotton and Wilkinson, 1962). As an acid, salts containing the hydrated ions $[\text{Al}(\text{OH})_4]^-$ and $[\text{Al}(\text{OH})_6]^{3-}$ occur. Alkali metal aluminates, salts of a weak acid, are extensively hydrolyzed, and addition of carbon dioxide precipitates aluminum hydroxide from their solutions.

2.3 Commercial Availability

General Chemicals, with 34 alum plants and 45% of the market, is the largest U.S. producer of alum (aluminum sulfate) (Boswell, 1998). Additionally, its plant in East St. Louis, IL, manufactures polyaluminum chloride (PAC). Geo Specialty Chemicals is the second largest U.S. producer of alum. It has 11 plants in the Southeast, which is its primary market for the compound. PAC and aluminum chlorohydrate are also made in facilities located in Baltimore, MD, and Barksdale, LA. Other suppliers of PAC include Nalco and Imperial West, while Cytec manufactures alum (Chapman, 1995; Chem. Mark. Rep., 1996). Delta Chemical Corporation (2000), based in Baltimore, MD, manufactures a variety of PACs, which fall under the trade name DelPAC (e.g., DelPAC 2020 and DelPAC 2500) and are high performance coagulants, as well as sodium aluminate and alum.

United States Aluminate Company, an aluminum chemical manufacturer serving customers in the titanium dioxide, catalyst, zeolite, pulp and paper, construction, bioenzyme, and municipal and industrial water treatment industries, produces high-quality aluminum-based products, including alum and sodium aluminate (US Aluminate, 2000). It is headquartered in Baltimore, MD, and has plants in Ashtabula and Cincinnati, OH.

Aluminum chloride is marketed as the anhydrous and hydrous form (Heydorn et al., 1985). Available data indicate that in 1985, three U.S. companies were producing the anhydrous form, and six U.S. firms were producing the hydrous form. Also in that year, two companies were producing aluminum fluoride and 24 were producing aluminum sulfate. Sodium aluminate is

produced for captive consumption and for merchant use. As of 1985, 11 U.S. companies were producing the compound for the latter.

Many other aluminum compounds are available from Aldrich (1989-1999).

3.0 PRODUCTION PROCESSES

ATSDR (1999, pp. 173-175) provides the production processes for aluminum and several of its compounds. Aluminum is produced from raw materials including bauxite (which contains 40 to 60% aluminum oxide [Al_2O_3]), cryolite (Na_3AlF_6), aluminum fluoride, fluorspar (CaF_2), corundum ($\text{Al}_2\text{O}_3 \cdot x\text{H}_2\text{O}$), and kaolin materials. The basic method used in producing aluminum metal involves three major steps: refinement of bauxite by the Bayer process to produce alumina, electrolytic reaction of alumina by the Hall-Heroult process to produce aluminum, and then casting of aluminum into ingots.

Aluminum chloride is produced by the reaction of bauxite with coke and chlorine at a temperature of around 875 °C (ATSDR, 1999). The anhydrous form occurs from the chlorination of aluminum metal and is sold in technical (99.0% pure with an iron content less than 100 ppm) and reagent grade (iron content of less than 10 ppm) (Heydorn et al., 1985). Although it is the procedure used by most companies, some have employed a carbo-chlorination process, using clay as the starting material. Hydrous aluminum chloride can be produced from the anhydrous form by dissolving it in dilute hydrochloric acid. It is usually produced by dissolving hydrated alumina in concentrated hydrochloric acid, followed by the addition of gaseous HCl.

Aluminum fluoride can be produced by several processes (ATSDR, 1999). It is made by heating ammonium hexafluoroaluminate to red heat under nitrogen; by the action of fluorine or hydrogen fluoride gas on aluminum trihydrate at high temperatures, and then calcining the hydrate formed; by fusing cryolite or sodium fluoride with aluminum sulfate; or by the reaction of fluosilicic acid on aluminum hydrate.

Aluminum hydroxide is produced from bauxite (ATSDR, 1999). The ore is dissolved in a solution of sodium hydroxide, yielding aluminum hydroxide, which is precipitated from the solution by neutralization or by autprecipitation (Bayer process).

Aluminum nitrate is formed by dissolving aluminum or aluminum hydroxide in dilute nitric acid; the solution is then allowed to crystallize (ATSDR, 1999).

Aluminum oxide is produced during the recovery of bauxite, which is crushed, ground, and kiln dried (ATSDR, 1999). It is then leached with sodium hydroxide, yielding sodium aluminate, from which alumina trihydrate is precipitated and calcined (Bayer process).

Aluminum phosphide is made from red phosphorus and aluminum powder (ATSDR, 1999).

Aluminum sulfate is produced from the reaction of freshly precipitated pure aluminum hydroxide, bauxite, or kaolin, with sulfuric acid; the resulting solution is then evaporated and allowed to crystallize (ATSDR, 1999). This yields the commercial grade (iron content less than 0.75% Fe_2O_3 for dry and 0.35% Fe_2O_3 for liquid) (Heydorn et al., 1985). The iron-free grade (iron content less than 0.01% Fe_2O_3) is produced using the same process with the exception that alumina trihydrate is used instead of bauxite or kaolin.

Sodium aluminate, which exists in several forms depending on the manufacturing process used, is usually produced from the direct reaction of alumina trihydrate with sodium hydroxide (Heydorn et al., 1985).

4.0 PRODUCTION, IMPORT, AND EXPORT VOLUMES

ATSDR (1999, pp. 175-179) provides the production, import, and export volumes for aluminum, which are summarized in **Table 3**.

Although aluminum chloride is marketed as both the anhydrous and hydrous form, production of the latter has not been reported since 1980, when 5.2 thousand metric tons (12 million lb) were produced (Heydorn et al., 1985). Recent data for anhydrous aluminum chloride in thousand metric tons (million lb) were 34 (75), 37 (82), 46 (101), 51 (112), and 54 (119) in 1988, 1990, 1992, 1994, and 1995, respectively (ATSDR, 1999). During these same years, annual production capacity for aluminum oxide (alumina, calcined, reduction grade) remained fairly constant, averaging 4980 thousand metric tons (11.1 billion lb).

Table 3. Production, Import, and Export Volumes* for Aluminum

Year	Primary Production	Secondary Recovery	Import	Export
1991	4121 (9.1)	2290 (5.0)	1490 (3.3)	1760 (3.9)
1992	4042 (8.9)	2760 (6.1)	1730 (3.8)	1450 (3.2)
1993	3695 (8.1)	2940 (6.5)	2540 (5.6)	1210 (2.7)
1994	3299 (7.3)	3090 (6.8)	3380 (7.4)	1370 (3.0)
1995	3375 (7.4)	3190 (7.0)	2970 (6.5)	1610 (3.5)
1996	3577 (7.9)	3310 (7.3)	2810 (6.2)	1500 (3.3)
1997	3603 (7.9)	3690 (8.1)	3100 (6.8)	1600 (3.5)
1998	3700 (8.1)	-	-	-

* Data are given in thousand metric tons (billion lb).

Source: ATSDR (1999)

Annual U.S. production of aluminum sulfate (commercial, 17% Al_2O_3) has also been stable from 1984 to 1997, ranging from 1047 thousand metric tons (2.3 billion lb) in 1992 to a high 1268 thousand metric tons (2.8 billion lb) in 1985 (Chem. Eng. News, 1998; ATSDR, 1999). In 1993 and 1994, it was one of the top 50 chemicals produced in the United States, holding the rank at 43. Earlier production values as well as import and export volumes (for the years 1955 to 1984) are available from the *CEH (Chemical Economics Handbook) Product Review* for aluminum chemicals (Heydorn et al., 1985). [Other data provided: Production for aluminum fluoride has not been reported since 1982 when 76 thousand metric tons (170 million lb) were produced. Merchant production for sodium aluminate (62.2% Al_2O_3 basis) was last reported in 1984; the value was 45 thousand metric tons (99 million lb). Import volumes are also given for the period 1964-1985.]

With the global market for water treatment chemicals growing at a slow to moderate rate, organic coagulants and flocculants and PAC top the product list (Boswell, 1998; Ouellette, 1999). In 1997, North American consumption of all coagulants and flocculants (organic and inorganic) was \$1.3 billion, with alum and PAC along with other inorganics making up 30% of the market (an estimated 14% and 5% of consumption, respectively) (Boswell, 1998; PR Newswire, 1998). The growth of the U.S. alum market, estimated between 2 and 5%, is largely due to the Safe Drinking Water Act (SDWA), the Disinfectants/Disinfection By-Products (D/DBP) Rule

amendment to the SDWA, which limits the amount of total organic carbon allowed in water at the point of primary disinfection, as well as increases in the paper industry. Approximately 45% of the market for alum and related aluminum products is for the paper industry and another 45% for municipal water treatment. The annual growth of PAC is estimated between 15 and 20%. Although it is not as widely produced or used, the market for aluminum chlorohydrate is also growing.

5.0 USES

Among the numerous applications of aluminum and its alloys, the major uses are in packaging (25% consumption; e.g., drink cans and foil for pie plates and frozen foods), building and construction (15%; siding and roofing, doors, and windows), transportation (34%; bodies, trim, and mechanical parts of cars, boats, and planes), and electrical applications (8%; overhead transmission lines, cable sheathing, and wiring) (ATSDR, 1999).

Aluminum compounds, likewise, have a wide range of uses in industrial, domestic, consumer, and medicinal products. **Table 4** summarizes the uses of several of these compounds.

Because aluminum is more efficient at binding phosphorus than iron, resulting in the greater reduction of sludge, alum, aluminum chlorohydrate, and several high basicity PAC products were being considered over the iron salts as the preferred coagulants for wastewater (Boswell, 1998). PAC, which contains a larger amount of aluminum than alum, was taking over some market share from alum and the iron salts. However, with the passing of the D/DBP Rule amendment to the SDWA in 1998, the use of PAC and alum became limited (Jarvis, 2000). Furthermore, restriction has been placed on the levels of sulfate in potable water. Ferric chloride, therefore, is currently the preferred coagulant. Other commercially available polynuclear aluminum coagulants are polyaluminum silicate-sulfate (PASS) and acidified bauxite (PAX) (Milette and Basisio, 1989; Masschelein, 1992; both cited by LaZerte et al., 1997).

Besides water treatment, alum's other principal market is the pulp and paper industry; together they account for about 95% of consumption (Heydorn et al., 1985). The major use of alum in the pulp and paper industry is to precipitate rosin size on paper fibers. PAC, however,

Table 4. Uses of Aluminum Compounds

Compounds	Uses
alums*	as a hardening agent and setting accelerator for gypsum plaster; in tanning and dyeing; in styptic pencils (former use)
aluminas*	in water treatment; as an accelerator for concrete solidification (high alumina cements)
alkoxides*	in varnishes; for textile impregnation; in cosmetics; as an intermediate in pharmaceutical production
borate*	in the production of glass and ceramics
carbonate*	in antacids
chlorides	anhydrous form: as an acid catalyst (especially in Friedel-Crafts-type reactions); as a chemical intermediate for other aluminum compounds; in the cracking of petroleum; in the manufacture of rubbers and lubricants; as an antiperspirant hexahydrate form: in the preservation of wood; in the disinfection of stables and slaughterhouses; in deodorants and antiperspirants; in cosmetics as an astringent; in the refinement of crude oil; in dyeing fabrics; in manufacture of parchment paper
chlorohydrate	as the active ingredient in many antiperspirants and deodorants
hydroxide	in stomach antacids (including Maalox [®] , Mylanta [®] , and Delcid [®]); as a desiccant powder; in antiperspirants and dentifrices ^a ; in packaging materials; as a chemical intermediate; as a filler in plastics, rubber, cosmetics, and paper; as a soft abrasive for brass and plastics; as a glass additive to increase mechanical strength and resistance to thermal shock, weathering, and chemicals; in ceramics; to lower the plasma phosphorus levels of patients with renal failure
isopropoxide*	in the soap and paint industries; in waterproofing textiles
nitrate	in antiperspirants; for tanning leather; as a corrosion inhibitor; in the preparation of insulating papers; on transformer core laminates; in incandescent filaments; in cathode ray tube heating elements
oxide	in the production of aluminum; in the manufacture of abrasives, refractories, ceramics, electrical insulators, catalysts and catalyst supporters, paper, spark plugs, crucibles and laboratory works, adsorbent for gases and water vapors, chromatographic analysis, fluxes, light bulbs, artificial gems, heat resistant fibers, food additives (dispersing agent), and in hollow-fiber membrane units used in water desalination, industrial ultrafiltration, and hemodialysis; as a dosimeter for measuring personnel radiation exposure
phosphate	in over-the-counter stomach antacids
phosphide	as an insecticidal grain fumigant
silicate*	as a component of dental cement; in antacids and food additives
sulfate	as a flocculent for water purification systems and sewage treatment; in the paper and pulp industry; in fireproofing and waterproofing cloth; in clarifying oils and fats; in waterproofing concrete; in antiperspirants; in tanning leather; as a mordant in dyeing; in agricultural pesticides; as an intermediate in the manufacture of other chemicals; as a soil conditioner to increase acidity of plants; in cosmetics and soap; in the preparation of aluminum acetate ear drops Solutions containing 5-10% aluminum sulfate: as local applications to ulcers; to arrest foul discharges from mucous surfaces
trioxide*	as an absorbent, abrasive, and refractory material

Sources: ATSDR (1999); *IPCS (1997)

^a used as an abrasive in toothpaste; however, due to its costliness for the developing world, there is a drive towards using calcium carbonate (CaCO₃) (Williams, 2000)

is taking over alum's share since rosin-sized and unsized paper grades are being produced at high pH levels (PR Newswire, 1998). Given via intravesical irrigation, alum, furthermore, has also been used for decades to control severe hemorrhagic cystitis (Kravoussi et al., 1986; cited by Nakamura et al., 2000). It is also added as an adjuvant to allergenic extracts for hyposensitization or in the preparation of vaccines (May et al., 1986; cited by Klein, 1997).

Like alum, sodium aluminate markets include water treatment and papermaking industry (Heydorn et al., 1985). In the latter, it is a substitute for aluminum sulfate. In the former, it is used to treat potable water and industrial wastewater, serving as a water softener, as a flocculant to trap suspended solids, and to precipitate inorganic phosphates. Captive production of sodium aluminate is chiefly for the manufacture of sodium aluminosilicates and to coat titanium dioxide pigments to improve the pigment's resistance to ultraviolet light.

Additionally, water-soluble aluminum phthalocyanine-polymer conjugates are used as photosensitizers for photodynamic therapy of cancer (Brasseur et al., 1999). In a further application, a knee joint patellofemorotibial metal/polymer porous-coated uncemented prosthesis and its uni-compartmental model, intended for implantation to replace a knee joint or part of it, respectively, have a femoral component made of a surface-hardened titanium-aluminum-vanadium alloy, and tibial and patellar resurfacing components made of an ultra-high molecular weight polyethylene compound fixed to a metal base made of the alloy (FDA, 2000b).

6.0 ENVIRONMENTAL OCCURRENCE AND PERSISTENCE

ATSDR (1999, pp. 188-217) provides data on the releases and the fate of aluminum to the environment. Aluminum is released to the environment by both natural processes and anthropogenic sources, with the former the greater contributor. According to the Toxic Chemical Release Inventory (TRI) (note: only certain types of facilities are required to report; therefore, an exhaustive list is not available), in 1996, a reported 5,605,000 lb of aluminum was released to the environment (air, water, and soil) from 264 large processing facilities. Of this total, 1,683,000 lb were released to the air (accounting for about 30% of total environmental releases), 48,989 lb to water (0.9%), and 3,873,000 lb to soil (69%). An additional 12,754 lb of aluminum were released

indirectly to publicly owned treatment works (POTWs), some of which may have been ultimately released to surface waters.

Furthermore, 466,000 lb of aluminum oxide were released to the environment (air, water, and soil) from 41 large processing facilities in 1996 (ATSDR, 1999). Of this total, 107,000 lb were released to the air (accounting for 23% of total environmental releases), 505 lb to water (0.1%), and 358,000 lb to soil (77%). An additional 1,328 lb was released indirectly to POTWs.

Degradation does not occur since aluminum is an element (ATSDR, 1999).

6.1 Air

The largest source of airborne aluminum-containing particulates is dust from soil, the weathering of rocks, volcanic activity, and human activities, such as mining and agriculture (ATSDR, 1999). Aluminum is found as silicates, oxides, and hydroxides in the particles, which are deposited onto land and water by wet and dry deposition. Aluminosilicates from aluminum dust comprise up to 14% of the earth's surface (Casdorff and Walker, 1995).

Levels of aluminum vary in the atmosphere, depending on the location of the sampling site, meteorological conditions (e.g., summer versus winter), and the level of industrial activity or traffic in the area (ATSDR, 1999). They are expected to be low in areas near the ocean and high in areas with wind-blown soil. Background levels of aluminum in the atmosphere generally range from 0.005 to 0.18 ng/m³, but are significantly higher in U.S. cities and industrial areas, which range from about 0.4 to 10 ng/m³. In the late 1960s to mid-1970s, concentrations up to 8678 ng/m³ were measured (IPCS, 1997).

Anthropogenic releases are primarily to the atmosphere and account for about 13% of atmospheric aluminum (ATSDR, 1999). The major anthropogenic sources of aluminum-containing particulate matter include coal combustion, aluminum production, and other industrial activities processing crustal minerals. Aluminum levels ranging from 100 to 1000 ppm have been found in air particulate emissions from iron and steel foundries and brass and bronze refineries. High concentrations have also been observed in coal stack emissions from power plants in both the eastern and western United States. Additionally, motor vehicle emissions add 0.9 to 9% of

the observed elemental concentration of aluminum in the air. Aluminosilicates, which can be manmade, are found in products such as talcum powder, asbestos, cat-box litter, table salt, and cigarette smoke (Casdorff and Walker, 1995).

Because aluminum in compounds cannot be oxidized, atmospheric transformations are not expected to occur during transport (ATSDR, 1999). However, if aluminum metal particles are released during anthropogenic activities such as metal processing, they would be rapidly oxidized.

6.2 Water

Aluminum enters natural waters from the weathering of aluminum-containing rocks and minerals (ATSDR, 1999). Levels in surface waters are also affected directly or indirectly by human activity through industrial and municipal discharges (e.g., in the effluent from aluminum manufacturing facilities), surface run-off (e.g., from the weathering of sulfide ores in inactive mines and tailings dumps), tributary inflow, groundwater seepage, and wet and dry atmospheric deposition (e.g., acid precipitation).

The concentration of aluminum in water, as well as its bioavailability and toxicity, is controlled by the chemical speciation of aluminum (IPCS, 1997). (See Section 6.2.1 for further details.) Levels of dissolved aluminum in water vary with pH and the humic-derived acid content of the water (ATSDR, 1999). At pH<5, the concentration is high. Levels up to 269 mg/L were found in surface water samples contaminated with acidic mine drainage (pH 2.1-3.4) and collected at seven different locations in the vicinity of abandoned coal mines in west-central Indiana. Between pH 6 and 8, aluminum is only sparingly soluble. Since the pH of 95% of naturally occurring water is between 6 and 9, the aluminum concentration in most natural waters is extremely low (<0.1 mg/L [ppm]). Humic acid content also plays a role. At neutral pH levels, high dissolved aluminum levels were found in lakes with a high humic acid content.

In raw surface water samples dissolved aluminum concentrations have ranged from 0.001 to 2.76 mg/L in the United States and in finished drinking waters, from 0.003 to 2.67 mg/L (ATSDR, 1999). Aluminum salt coagulants, used in the treatment of potable drinking water, result in approximately 11% of unretained aluminum being transported through a water

distribution system. (See Section 6.2.3 for further details on water treatment.) Finished drinking water samples receiving no coagulation treatment had aluminum levels ranging from 0.016 to 1.167 mg/L (median of 0.043 mg/L), while water receiving alum coagulation treatment had levels ranging from 0.014 to 2.670 mg/L (median of 0.112 mg/L). In treated water at facilities using alum coagulation treatment of raw waters, levels ranged from about 0.01 to 1.3 mg/L (mean of about 0.157 mg/L). In a 1989 study, aluminum levels in drinking water collected from outlets in the western and central parts of the United States were found to be <0.1 ppm. Aluminum levels in household tap water ranged from 0 to 1.029 ppm. Areas with high aluminum concentrations in tap water included Peoria, IL (0.467 ppm), Coos Bay, OR (0.483 ppm), Watertown, SD (0.502 ppm), Waco, TX (0.520 ppm), Yellowstone National Park, WY (0.608 ppm), Philadelphia, PA (0.688 ppm), and Charleston, SC (1.029 ppm).

Compared to aluminum levels in freshwater lakes and streams, marine waters contain much lower aluminum concentrations (<0.001 mg/L; <1 ppb) (ATSDR, 1999). At neutral pH, groundwater wells generally contain aluminum levels less than 0.1 mg/L (<100 ppb); acid precipitation, however, can cause a greater than tenfold increase. In a 1984 study, levels (in finished water obtained from groundwater) ranged from 0.014 to 0.290 mg/L (median of 0.031 mg/L) and in surface water ranged from 0.016 to 1.167 mg/L (median 0.043 mg/L). Additionally, aluminum concentrations were greater than 0.05 mg/L in 55% of the raw surface water samples and in only 4% of the raw groundwater samples.

In atmospheric precipitation (i.e., rain and snow), aluminum concentrations up to 1.2 mg/L have been measured (ATSDR, 1999). The acid-leached concentrations of aluminum in rainwater samples collected in the North Atlantic for seven rainfall events ranged from 1.14 to 35.2 µg/L (ppb); total (dissolved plus particulate) aluminum concentrations ranged from 6.1 to 824 µg/L. During storms, higher concentrations of adsorbed aluminum occurred in the presence of high levels of suspended solids in stream surface water than in their absence.

6.2.1 Speciation of Aluminum in Water

The aqueous chemistry of aluminum has been extensively reviewed (e.g., Driscoll and Schecher, 1989). Three major categories define the various aluminum fractions in water (Srinivasan et al., 1999). These are the following: (1) total aluminum, which is the sum of suspended, colloidal, and monomeric forms of aluminum; (2) particulate aluminum, which is the sum of suspended and colloidal aluminum; and (3) monomeric aluminum, which is further divided into the two forms non-labile (aluminum associated with dissolved organic carbon) and labile (aquo, and hydroxide, fluoride, and sulfate complexes of aluminum). See **Figure 1**.

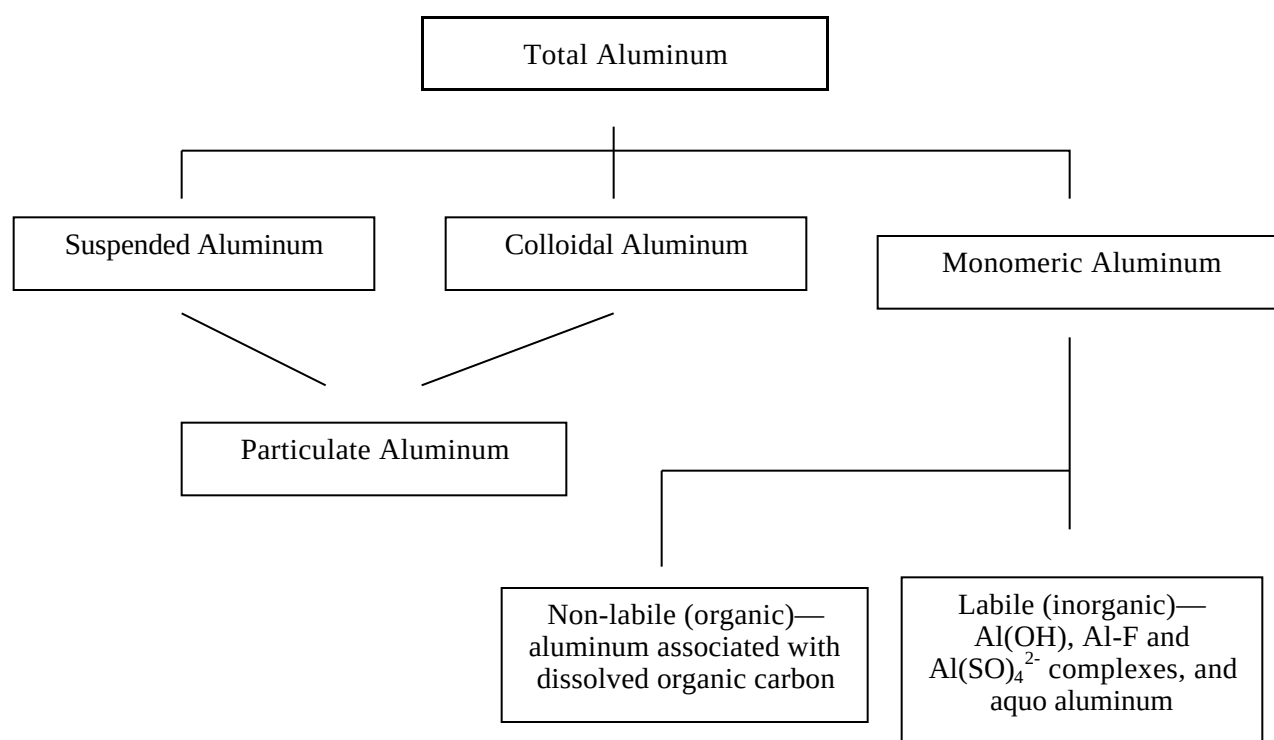


Figure 1. The Various Fractions of Aluminum in Water

Source: Srinivasan et al. (1999)

Raw Water: The solubility of aluminum in equilibrium with solid phase Al(OH)_3 depends on the surrounding pH (IPCS, 1997). The aquo complex $\text{Al(H}_2\text{O)}_6^{3+}$ predominates at $\text{pH} < 4$. As the pH (and/or temperature increases), the hydrated trivalent aluminum ion undergoes hydrolysis,

initially forming the $\text{Al}(\text{OH})(\text{H}_2\text{O})_5^{2+}$ ion and then hydroxyaluminum species such as $\text{Al}(\text{OH})_2^+$, $\text{Al}(\text{OH})_3$ (insoluble), $\text{Al}(\text{OH})_4^-$, $\text{Al}_2(\text{OH})_2^{4+}$, and $\text{Al}(\text{OH})_5^{2-}$, and eventually hydroxy polymers such as $\text{Al}_{13}(\text{OH})_{32}^{7+}$ (IPCS, 1997; ATSDR, 1999). [Fluoride ions can substitute in these complexes; however, in neutral and alkaline solutions, aluminum has greater affinity for the hydroxide ion (LaZerte et al., 1997).] Between pH 5 and 6, the predominant hydrolysis products are $\text{Al}(\text{OH})_2^+$ and $\text{Al}(\text{OH})_3$; between pH 5.2 and 8.8, the solid $\text{Al}(\text{OH})_3$ is most prevalent; and above pH 9, the soluble species $\text{Al}(\text{OH})_4^-$ is the predominant species and the only species present above pH 10. Throughout the pH gradient (pH 4.7 and 10.5), polymeric aluminum hydroxides can be found. As polymers come together, aluminum hydroxide becomes large enough to precipitate from solution. Additionally, at $\text{pH} > 7.0$ the aluminum hydroxide complexes dominate when the content of dissolved organic matter and silicate is low. At lower pH, aluminum sulfate complexes exist, as well as aluminum-humic acid and aluminum-fulvic acid complexes.

Coagulation of natural organic matter (NOM) in surface water (specifically, the Seine river near Paris, France) with aluminum produced flocs consisting mostly of polysaccharides (other biopolymers analyzed: aminosugars, polyhydroxy aromatics, and proteins), which decreased with increasing aluminum concentration, demonstrating the preferential binding between the metal and polysaccharides (Masion et al., 2000). Using a combination of solid state ^{27}Al NMR and Small Angle X-ray Scattering (SAXS), the presence of organically complexed aluminum and/or dimeric aluminum species, with aluminum in the flocs greater than 99% monomeric, was determined. The coagulation mechanism, therefore, is complexation for flocs formed with aluminum and NOM, where the structure of the aggregates is controlled by the NOM (i.e., structure is sensitive to pH variation, whereas speciation is not significantly affected).

Treated Water: The use of aluminum-based coagulants for the removal of particulate, colloidal, and dissolved substances in water usually results in an increase in the amount of aluminum in the finished water, with a portion of the coagulant remaining as residual aluminum, which consists of

dissolved and particulate species (Srinivasan et al., 1999). However, treatment can also decrease the total aluminum content. For example, use of PAC as the coagulant lowered the mean concentration of aluminum in raw waters from 960 µg/L to a mean value of 120 µg/L in finished water (Schintu et al., 2000). Generally, a concentration between 1 and 5 mg/L is desired with addition of an aluminum salt during water treatment (LaZerte et al., 1997).

The speciation of aluminum in the treated water depends on pH, temperature of the water during treatment, the type of organic and inorganic ligands in the raw water, and treatment conditions (e.g., the amount of coagulant employed) and therefore varies from one plant to another (Srinivasan et al., 1999). While much of the aluminum in raw water is bound with inorganic colloids or large organic molecules, treatment yields a greater amount of mononuclear species, specifically low-molecular-mass chemically reactive labile species.

In addition to aluminum-based coagulants, fluorides are added to many water supplies for the prevention of dental caries (Pitter, 1985). In natural water, the most likely soluble forms of fluorine are the free anion F^- , the undissociated hydrofluoric acid HF, and complexes with aluminum, iron, and boron; in treated water, fluorides exist as less physiologically active fluoroaluminates. In a theoretical study of the forms of fluorine in drinking water after coagulation with alum with artificial fluoridation (optimum free F^- concentration of 1.0 mg/L), fluoroaluminates were nearly all converted to hydroxoaluminates in neutral and alkaline solutions ($pH \geq 7$), and the concentration of the free F^- equaled that of the total fluoride concentration; the predominant part of fluorides is present probably in non-complexed form. At a pH of 6, only three complexes, AlF^{2+} , AlF_2^+ , and AlF_3 were thought to be significant. Given an alum dosage of 40 mg/L (0.12 mM Al), an operational pH from 5.5 to 7.5, and the presence of organics and fluoride at low concentrations (<1 mg/L), the amount of dissolved aluminum was observed to be a simple function of pH and primarily composed of $Al(OH)_2^+$ and $Al(OH)_4^-$ (Sung and Rezanian, 1985). At a pH range of 6.4 to 6.5, the minimum amount of soluble aluminum was about 30 µg/L, and the addition of fluoride at a level of 1 mg/L was found to increase the amount of soluble aluminum by a factor of 10.

Systemic fluorosis, therefore, can be a problem and is particularly so in developing countries, and a safe, efficient, and simple defluoridation process resulting in treated water free from residual aluminum is still underdevelopment (Agarwal et al., 1999). Fluoride removal has been conducted using activated alumina (e.g., Rubel and Woosley, 1979; Belle and Jersale, 1984; Rubel, 1984; Schoeman and Botha, 1985; Hao and Huang, 1986) and combinations with the compound (e.g., activated alumina with a carbon dioxide acidizing method [Xu, 1994] and fluidized activated alumina adsorption [Bishop and Sancoucy, 1978]) as well as activated aluminum oxide (Zhou, 1984). Polyaluminum species CF-1 and PC85-3 removed excess fluorides from water to an acceptable level for drinking use, but activated alumina and bone carbon were more effective filter (Qu and Et, 1994). Other materials employed for defluoridation include an electrocoagulation process using bipolar aluminum electrodes and aluminum sulfate and aluminum basic polychloride (Mameri et al., 1988; N'Dao et al., 1992). Recently, the possibility of removing fluoride and heavy metals from water using alum-treated flyash or PAC has been investigated (Malhotra et al., 1997; Mehrotra et al., 1999).

6.2.2 Fractionation of Aluminum in Drinking Water

Fractionation of aluminum in drinking water at ambient temperature generally occurs by one of three methods (Srinivasan et al., 1999). In the method of Driscoll and Letterman (1988; cited by Srinivasan et al., 1999), total reactive aluminum is separated out using acid digestion (HNO_3) at pH 1 for one hour; total monomeric aluminum is fractionated by extraction with 8-hydroxyquinoline; and the cation exchange-treated monomeric aluminum is passed through a strongly acidic cation-exchange resin. In the method by Van Benschoten and Edzwald (1990; cited by Srinivasan et al., 1999), total reactive aluminum is fractionated with acid digestion at pH 2 for one hour to obtain soluble aluminum; total dissolved aluminum is separated out by filtration of the acid-soluble aluminum through a 0.22 μm -pore size filter; dissolved monomeric aluminum is fractionated by rapid extraction with 8-hydroxyquinoline; dissolved organically bound aluminum is separated out by filtering the sample through a column with a strongly acidic cation exchange resin followed by acidification; and dissolved organic monomeric aluminum was

fractionated by passing the filtered sample again through resin and analyzed without acidification. In the method by Gardner and Gunn (1991; cited by Srinivasan et al., 1999), total aluminum is separated out by acid digestion; dissolved aluminum is separated out by passing the sample through a 0.45 μm -pore size filter; low-molecular weight aluminum is fractionated by dialysis; and the chemically labile aluminum is measured by its speed of reaction with an aluminum binding agent.

6.2.3 Water Treatment Processes

Drinking water production begins with coagulation, followed by flocculation, clarification, filtration, and finally disinfection (LaZerte et al., 1997). Aluminum removal depends on the transformation of the aluminum ions into $\text{Al}(\text{OH})_3$ species (Srinivasan et al., 1999). Treatment therefore involves chemical precipitation by pH adjustment (pH range 6.5-8.0). The addition of sulfate expands this range of coagulation (lowers the limit of pH to 6.0) while serving as a catalyst in the formation of solid $\text{Al}(\text{OH})_3$ particles.

Treatment by cation-exchange resin, reverse osmosis, and electrodialysis is the most effective process for the removal of aluminum in water (90-100% efficiency), whereas processes involving aeration and stripping, anion-exchange resin, and chemical oxidation/disinfection are poor (0-20% efficiency) (Srinivasan et al., 1999). Lime softening and coagulation coupled with sedimentation and filtration are moderately effective methods (0-70% efficiency).

The treatment of the water supply is not without problems (Srinivasan et al., 1998, 1999). The increased aluminum concentration in treated water can enhance turbidity through the post-precipitation of a hydrous aluminum precipitate in the distribution system, limit the disinfection process by enmeshing and protecting microorganisms, and reduce the carrying capacity of pipes with the accumulation of aluminum hydrolysis products on their walls. Reduction of residual aluminum, which consists primarily of particulate and dissolved forms of aluminum, as much as possible is, therefore, essential. Since particulate aluminum is mostly derived from turbidity-causing substances, the elimination of turbidity from raw water will reduce its presence in treated waters. Particulate aluminum can be readily removed by solid-

liquid separation facilities such as clarifiers (93-96% efficiency observed) and filters (75-87% efficiency observed using sand filtration). Preliminary data indicate that the soluble aluminum fraction can be removed by granular activated carbon (65% efficiency).

6.3 Soil and Sediment

Aluminum, found in soil complexed with electron-rich species such as fluoride, sulfate, and phosphate, is released to soil by the weathering of aluminum-containing rocks and minerals and as a constituent of many mining wastes and solid wastes from coal combustion, aluminum reduction, and other metal processing operations (ATSDR, 1999). Its concentration in soils varies widely, ranging from about 700 mg/kg to over 100,000 mg/kg. Varying concentrations can be found in different soil samples taken from the same area. For example, in different soils of Missouri, aluminum concentrations ranged from 4,800 to 58,000 mg/kg, while in Hawaii, aluminum contents were much higher with concentrations ranging from 79,000 to 317,000 mg/kg. In cultivated and uncultivated soil samples collected during a number of field studies, levels ranged from 7,000 mg/kg to over 100,000 mg/kg (mean of 33,000 mg/kg) for subsurface soils in the eastern United States, from 5,000 mg/kg to over 100,000 mg/kg (mean of 54,000 mg/kg) for subsurface soils in the western United States, and from 13,000 to 76,000 mg/kg (mean of 57,000 mg/kg) for surface horizon soils in Colorado. Aluminum levels in soil also vary with different vegetation types. For example, concentrations in the soils of coniferous forests are often higher than in soils of beech forests.

6.4 Other Environmental Media

Aluminum also occurs naturally in many edible plants (ATSDR, 1999). Acid rain ensures that more aluminum is available for plant uptake, which often occurs and is concentrated in root tissue. Concentrations vary. For example, aluminum content in tea (1% extract) has been measured from 0.378-2.445 mg/L (ppm), whereas in herbal tea, the levels were from 0.140-1.065 mg/L. In ash samples from cultivated plants such as lima beans, cabbage, and tomatoes, values

ranged from 50-30,000 mg/kg (ppm). (See Section 7.0 for more details of aluminum in plants and foods.)

7.0 HUMAN EXPOSURE

ATSDR (1999; pp. 183-130) provides a chapter dedicated to human exposure to aluminum. The large quantity of aluminum in nature and its many uses make exposure to aluminum unavoidable. Exposure for the generally population is mainly through oral intake, and the major sources are drinking water (from the use of aluminum in municipal water treatment), residues in foods, cooking utensils, food and beverage packaging, and aluminum-containing medications (e.g., antacids and buffered aspirins). Additionally, children may ingest aluminum from dirt from unwashed hands or when playing in contaminated soils, vitamin/mineral supplements, treatment for hyperphosphatemia, and from consumer products not normally ingested by adults (e.g., toothpaste) (ATSDR, 1999; Golub and Domingo, 1997). The daily ingestion of aluminum is 30 to 50 mg for almost every individual (Casdorff and Walker, 1995). Other sources for potential exposure to aluminum for children are vaccinations containing aluminum adjuvants, parenteral feeding of premature infants, and dialysis fluids. Other routes of potential exposure to aluminum are via inhalation of atmospheric dust and through the skin (e.g., via use of antiperspirants) (ATSDR, 1999; IPCS, 1997).

Occupational exposure to aluminum occurs in the refining of the primary metal and in secondary industries that use aluminum products, such as aircrafts, automotives, and metal products (ATSDR, 1999). Exposure estimates have been <1 mg per 8-hour shift, assuming that 10 m³ was inhaled per shift, for aluminum process and production workers (IPCS, 1997). Reported as total dust or particulate matter, other values were 1.67 mg/m³ for potroom workers, 10 mg/m³ for metal inert gas (MIG) welders, 1 mg/m³ for TIG welders, and 1.1 mg/m³ for those in aluminum soldering of aluminum cables. In workers at an aluminum fluoride plant, mean aluminum levels in urine were 0.011±0.007 mg/L for 15 plant workers, 0.032±0.023 mg/L for 7 foundry workers, and 0.054±0.063 mg/L for 12 potroom workers; the mean level was 0.005±0.003 mg/L for 230 unexposed controls (ATSDR, 1999). The most recent National

Occupational Exposure Study (NOES) conducted by NIOSH from 1981 to 1983 estimated that over 3.3 million workers were potentially exposed to aluminum and its compounds. ATSDR (1999; Table 5-8, p. 223) summarizes the results of this survey. The industries with the largest numbers included plumbing, heating and air conditioning; masonry and other stonework; electrical work; machinery except electrical; certified air transportation equipment; electrical components; fabricated wire products; general medical and surgical hospitals; industrial buildings and warehouses; and special dyes, tools, jigs, and fixtures.

Greater exposure to aluminum is possible for persons living in the vicinity of industrial emission sources and hazardous waste sites, undergoing long-term hemodialysis treatment, drinking water from a residential well, and those consuming large quantities of antacid formulations, anti-ulcerative medications, buffered analgesics, or kaolin-based antidiarrheal medications (ATSDR, 1999).

Below, the sources of potential aluminum exposure have been broken down into topics and discussed separately. (For easier reading, all units of mg/kg, µg/g, µg/L, and mg/L are presented in "ppm".)

Drinking water: Since large aluminum concentrations only occur at a pH <5 and about 95% of natural waters have a pH >6, human exposure to aluminum from water is not great (ATSDR, 1999). Because speciation of aluminum in drinking water is complicated with interactions of pH and various counter ions, measures other than total aluminum are currently not possible (CAL-EPA, 2000). Concentrations in finished waters have been measured from undetectable to 1.029 ppm throughout the United States. As discussed in Section 6.2, the median concentrations of aluminum in drinking water not receiving coagulation treatment and that receiving coagulation treatment were 0.043 ppm and 0.112 ppm, respectively. If an estimated 2 L is being consumed daily by adults, a corresponding 0.08 and 0.224 mg of aluminum is taken in per day (about 1% of the daily 7-9 mg from dietary sources). It is estimated that the daily consumption is 1 to 10 mg of aluminum by most adults from natural sources.

Tea: Tea is a major source of aluminum in the daily diet (Casdorff and Walker, 1995). Those made from Assam, Darjeeling, Ceylon, and some supermarket blends contain a greater amount of aluminum, and those brewed had levels in the range of 2 to 6 ppm, depending on the quality of the water. Using soft tap water, higher levels of aluminum were found (average of 1.6 ppm) compared to tea brewed in hard water. In addition, the substitution of milk for lemon in tea may be better since the absorption of aluminum from the gut is enhanced by citrate.

Beverages, food, and food products: Exposure to aluminum through food is low (ATSDR, 1999). In the Food and Drug Administration (FDA)'s 1991 Total Diet Study, reported daily dietary intakes were from 8 to 9 mg for adult males, ~7 mg for adult females, 11.5 mg for 14- to 16-year-old males, 6.8 mg for ten-year-olds, 6.5 mg for six-year-olds, 4.6 mg for two-year-olds, and 0.7 mg for infants. With low aluminum dietary intake (median of 24 mg/day for adults), there is no major concern regarding its toxicity.

The major contributors of aluminum are grain products (24-49%), dairy products (17-36%), desserts (9-26%), and beverages (5-10%) (ATSDR, 1999). ATSDR (1999; Table 5-4, pp. 207-210) provides a table giving the aluminum concentrations in a number of beverages, foods, and food products. The concentrations vary widely, depending upon the food product, the type of processing used, and the location from which they originate. For beverages (fruit juices, soft drinks, instant and whole coffee, etc.), the levels ranged 0.02-4.3 ppm; for animal products (cooked beef, cheese, milk, etc.), 0.06-14.10 ppm; for fruits (apples, peaches, dried raisins, etc.), 0.05-3.1 ppm; for grains (bread, cereal, rice, spaghetti, etc.), 0.040-400 ppm; vegetables and legumes (corn, peanut butter, potatoes, etc.), 0.1-25.2 ppm; and for dried herbs and spices (basil, cinnamon, thyme, etc.), 82-3,082 ppm. Other food products for which aluminum concentrations were reported were baking powder (2,300 ppm), Oreo cookies (12.7 ppm), and nondairy creamer (25.7-94.3 ppm). Unprocessed foods typically contain <5 ppm aluminum. Measured levels range from ~0.1 ppm in eggs, apples, raw cabbage, corn, and cucumbers to 7.16 ppm in lettuce.

Aluminum compounds are used as additives in many processed foods (e.g., processed cheeses, baked goods, grain products, and nondairy cream substitutes) (ATSDR, 1999).

Common food additives containing aluminum are acidic sodium aluminum phosphate (leavening agent in cake mixes, frozen dough, and self-rising flour [6.5% aluminum]), basic sodium aluminum phosphate (emulsifying agent in processed cheese [3.5%]), aluminum sulfates (acidifying agents [e.g., sodium aluminum sulfate is in baking powders {5.9%}; aluminum sulfate is part of food-starch modifiers {1.3%}; and aluminum ammonium sulfate and aluminum potassium sulfate are used as pickling salts {6.0 and 5.7%, respectively}]), bentonite (materials-handling aid), aluminum color additives (lakes) from various food dyes, and aluminum silicates (anti-caking agents [16.0%]) (ATSDR, 1999; Casdorph and Walker, 1995). Additionally, maltol is used as a food additive worldwide (Maitani et al., 1996).

The potential for accumulation of aluminum has been studied in several aquatic species including fish, amphibians, crustaceans, snails, aquatic insects, and aquatic plants (ATSDR, 1999). Because aluminum is not significantly bioaccumulated in most fish and shellfish (bioconcentration factor values are less than 300), consumption of contaminated fish does not appear to be a significant source of aluminum exposure in humans. Average concentrations (wet weight basis) of aluminum found in the four shellfish categories surveyed by the Food and Drug Administration (FDA) in the mid-1980s were 23 ± 23 ppm in hardshell clams, 115 ± 110 ppm in softshell clams, 33 ± 26 ppm in Eastern oyster, and 30 ± 28 ppm in Pacific oyster. An average of 1 and 0.4 ppm of aluminum were found in the muscle tissue of cod and bluefish tuna, respectively, from the Northwest Atlantic Ocean.

Exposure to aluminum is also possible from natural dietary supplements (ATSDR, 1999).

Milk or infant formulas: Potential exposure to aluminum also arises from the intake of infant milk formulas (ATSDR, 1999). Levels were reported to be lowest in human breast milk and cow's milk, bottled sterile water and glucose water, and most oral multivitamin preparations and highest in modified infant formulas, such as soy formulas, premature infant formulas, and products for specific metabolic disorders. The mean concentrations of aluminum in the latter group range from 0.14 to 3.74 ppm for liquid formulas and from 6.25 to 11.8 ppm for powdered formulas. Compared with a liter of breast milk (0.012-0.147 ppm), the aluminum content per

liter of reconstituted formula was up to 63 times greater. ATSDR (1999; Table 5-5, p. 213) gives aluminum levels in breast milk, humanized infant reconstituted formulas, and in special purpose infant reconstituted formulas. For breast milk, a mean concentration of 0.049 ppm was reported. For humanized infant formulas, the mean concentrations ranged from 0.072 ppm (Similac powder) to 1.463 ppm, while for special purpose infant formulas, the levels ranged from 0.062 ppm (special formulas, specifically Delact powder) to 1.711 ppm (soy formulas, specifically Posobee powder). Soy formulas had the largest concentrations of aluminum, means ranging from 1.192 ppm (Isomil powder) to 1.711 ppm (Prosobee powder). Based on human breast milk or cow's milk containing <0.05 ppm aluminum and ready-to-use milk-based and soy-based formulas containing 0.01-0.36 and 0.40-6.4 ppm aluminum, respectively, infants ingest 3 µg of aluminum a day when fed the former versus up to 2.1 mg aluminum a day when fed certain soy-based formulas, which is 700 times greater. Goat's milk, which usually contains no aluminum, has been recommended as an alternative (Casdorph and Walker, 1995).

Containers for food: Cooking foods in aluminum pots and pans or storing foods in aluminum foil or cans may result in increased aluminum concentrations in food (ATSDR, 1999). In precooked foods such as applesauce, green beans, beef, eggs, ham, pudding, rice, and tomato sauce, levels ranged from <0.1 to 21.6 ppm, while concentrations in the foods after cooking in conditioned aluminum pans ranged from 0.24 to 125 ppm compared to <0.1 to 3.4 ppm when cooked in stainless steel pans. The more acidic the food, the greater the migration of aluminum. The extent of exposure to aluminum from leaching from cookware, however, is uncertain (Rajwanshi et al., 1997). For example, studies have shown that the presence of fluoride results in aluminum leaching from cookware (Casdorph and Walker, 1995). When 1 ppm of fluoride in water, adjusted to a pH 3, was boiled in an aluminum container, almost 200 ppm of aluminum was released in 10 minutes and 600 ppm with prolonged boiling; without fluoride <0.2 ppm was measured. Rajwanshi et al. (1997) found levels ranging from 4.9 to 8.1 ppm under the same conditions during the first 10 minutes. Discrepancies were the result of several factors, including the composition and type of food cooked as well as the aluminum utensil used; previous use of

the utensil; duration of cooking; the presence of salt, sugar, and other ions; and the method of analysis.

Brewing coffee in a new aluminum pot can add 0.88 mg (immediately after brewing) to 1.18 mg aluminum (after a further 12-hour storage in the pot and reheating) to each cup (ATSDR, 1999). Percolators, however, only increase the aluminum content by 0.4 mg and 0.58 mg, respectively. Ground coffee beans contain 51.8 ppm of aluminum.

In canned drinks stored at 15-20 °C, aluminum levels ranged from <0.1 to 74 ppm (ATSDR, 1999). The study concluded that there appeared to be little basis for concern about the ingestion of aluminum when the internal protective coating of cans remains intact, the cans are stored properly, and the contents are consumed in a reasonable period of time. Aluminum, however, was observed to migrate from unlacquered aluminum cans, with beverage concentrations increasing with storage time. Aluminum levels ranged from 0.046-0.170 ppm in Coca-Cola® (pH 2.5, storage for 40-101 days) and from 0.014-0.250 ppm in diet Coca-Cola® (pH 3.0, storage for 44-173 days).

Medications: The intake of aluminum-containing medications such as antacids, buffered aspirins, kaolin-based antidiarrheal agents, and anti-ulcerative drugs at their recommended doses results in greater amounts of aluminum in the body versus that from the intake of food (ATSDR, 1999). It is estimated that from 126 to 5000 mg of aluminum are consumed, which is 6 to 250 times greater than that from food. Aluminum content per dose (single tablet or 5 mL liquid) ranges from 35-208 mg for antacids, 9-52 mg for buffered aspirins, 36-1,450 mg for antidiarrheal drugs, and is 207 mg for an anti-ulcerative drug. Casdorph and Walker (1995) provide the aluminum content of various antacids, buffered aspirin, and antidiarrheal drugs, as well as douches, sold over-the-counter.

Atmospheric dust: As discussed in Section 6.1, background levels of aluminum in the atmosphere generally range from 0.005 to a maximum of 0.18 ng/m³ in the United States (ATSDR, 1999). If the daily inhalation rate is taken to be 20 m³, then the maximum total amount of aluminum would

be 3.6 ng/day, which is negligible compared with the estimated dietary intake for adults. When taking into consideration the air in urban and industrial area, which ranges from 0.4-10 ng/m³, the total amount of aluminum inhaled would range from 8 to 200 ng/day, which is also negligible. Higher exposures are also possible from dusts arising from soil, particularly in industrial or agricultural areas, and from the metal surfaces of air conditioners.

Other products: Exposure may also occur through the use of aluminum-containing products, such as cosmetics and medical treatments (ATSDR, 1999). For example, higher than normal levels are found in patients undergoing long-term hemodialysis treatment. Another source of aluminum exposure is from the use of parenteral solutions (e.g., calcium gluconate, phosphate salts, multivitamin solutions, and human albumin solutions), since aluminum compounds are used in their manufacture or as a result of poor purification or contamination, such as from filters, filter aides, buffer solutions, anticoagulants, and the container itself (Klein, 1997; ATSDR, 1999). Significant contamination occurs in the small-volume parenterals versus the large-volume solutions (Klein, 1997). The main source of aluminum contamination was casein hydrolysate. Aluminum concentrations (μmol/L) ranged from 2-75 in sodium phosphate (3 mmol/L solution), 97-102 in potassium phosphate, 10-187 in calcium gluconate, 43-68 (25% solution; 18 for a 5% solution) in albumin, 3-51 for factor VIII, 8-21 for factor IX, 33-67 in multivitamin infusates, and was 9 in plasminase (50 g/L solution), 25 for heparin (1 mU/L solution), 5 in trace metal solutions, 135 in calcium glucoheptonate solutions, and 35 in magnesium sulfate solutions.

Measurement of aluminum levels in body tissues has been found to be method-dependent (ATSDR, 1999). Normal values range from 0.14-6.24 ppm in whole blood and from 0.13-0.16 ppm in plasma, while in serum levels are generally <0.01 ppm. Aluminum concentrations in urine typically range from 0.0027-0.0081 ppm. In bone, background levels are about 1-3 ppm (dry weight). In brain tissues (mostly gray matter), the background aluminum levels range from 1-3 ppm (dry weight) or <0.5 ppm (wet weight). Urinary and serum concentrations present good estimates of recent exposure, with the latter also providing an estimate of cumulative exposure (Kilburn, 1999).

8.0 REGULATORY STATUS

ATSDR (1999; Table 7-1, pp. 253-269) provides a table listing international, national, and state regulations and guidelines for aluminum and its compounds in air, water, and other media.

The Occupational Safety and Health Administration (OSHA) has established a permissible exposure limit (PEL) of 15 mg/m³ for total aluminum dust and 5 mg/m³ for respirable fractions as an 8-hour time-weighted average (TWA) (ATSDR, 1999). The American Conference of Governmental Industrial Hygienists (ACGIH) and the National Institute for Occupational Safety and Health (NIOSH) have set guideline values that range from 2 mg/m³ for soluble salts to 10 mg/m³ for aluminum metal.

The Environmental Protection Agency (EPA) regulates aluminum and certain aluminum compounds under the Clean Air Act (CAA) and has promulgated performance standards for primary and secondary aluminum plants (ATSDR, 1999). It also regulates aluminum under the Clean Water Act (CWA) and the Safe Drinking Water Act (SDWA). It has established a secondary maximum contaminant level for aluminum in drinking water at a concentration range of 0.05-0.2 mg/L. Furthermore, it regulates aluminum levels in effluents from several point-source categories, including electroplating, inorganic chemical manufacturing, iron and steel manufacturing, ore mining and dressing, coil coating, porcelain enameling, metal finishing, aluminum forming, nonferrous metals manufacturing, and metal molding and casting. EPA recommends that the highest concentrations of aluminum in fresh water that aquatic organisms can be exposed indefinitely and for a brief period, resulting in no unacceptable effect, are 87 and 750 µg/L, respectively. Regarding compounds, aluminum oxide and aluminum phosphide are on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" along with aluminum as fume or dust. EPA has established a reportable quantity (RQ) limit of 5,000 lb (2,270 kg) for aluminum sulfate and 100 lb (45.4 kg) for aluminum phosphide. A tolerance limit of 0.1 ppm has been set for residues of aluminum phosphide in or on raw agricultural commodities such as almonds, barley,

corn, dates, rice, sesame seeds, and wheat when it is used as a fumigant for post-harvest treatment.

The Association for the Advancement of Medical Instrumentation (AAMI) recommends that water used in the preparation of dialysate solution consist of <10 µg aluminum per liter (ATSDR, 1999). [The pH of the water of dialysate should be 7.4; a pH other than this increases the amount of dialyzable aluminum (Cornelius and Schutyser, 1984; Savory and Wills, 1984; both cited by Santos et al., 1986).]

In 1998, the Food and Drug Administration (FDA) amended Section 178.3130 of the food additive order to provide for the safe use of aluminum borate as an antistatic and/or antifogging agent for olefin polymers intended for use as food-packaging materials (Food Chem. News, 1999). As of December 31, 1998, three petitions regarding aluminum were still pending. As a direct additive, a petition was made by the International Association of Color Manufacturers to amend section 25.32(k) to provide for the safe use of D&C Red No. 28 and its aluminum lake to color food and dietary supplements. As an indirect additive, a petition was announced by Alcoa Separations Technology to amend Section 177.2910 to clear use of an ultra-filtration membrane consisting of a zirconium oxide membrane containing up to 5% yttrium oxide on a porous aluminum oxide support. Finally, a veterinary petition was made by Milwhite for the use of sodium calcium aluminosilicate, hydrated, as a binder for aflatoxin contamination in feeds. Recently, FDA amended the food additive regulations to provide for the safe use of hydroxybis[2,4,8,10-tetrakis(1,1-dimethylethyl)-6-hydroxy-12*H*-dibenzo[*d,g*][1,3,2]dioxaphosphocin 6-oxidato]aluminum as a clarifying agent for polypropylene and polypropylene copolymers intended for use in contact with food (FDA, 2000c).

Under the Federal Food, Drug, and Cosmetic Act, FDA (2000a) has amended its regulations adding certain labeling requirements for aluminum content in large- and small-volume parenterals as well as pharmacy bulk packages used in total parenteral nutrition (TPN). Furthermore, FDA has specified an upper limit of 25 µg Al/L for all large-volume parenterals used in TPN therapy and has required that applicants submit validated assay methods for the determination of aluminum content in parenteral drug products. The rule becomes effective on

January 26, 2001. FDA has also suggested 4-5 µg Al/kg/day as a possible safe upper limit for aluminum intake from TPN solutions in uremic patients (Klein et al., 1998; cited by CAL-EPA, 2000).

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APPENDIX: SPECIATION IN BIOLOGICAL SYSTEMS

The following discussion is largely based on the review by Martin (1997). Dissociation constants for aluminum complexes are provided in **Table 5**.

Only the Al^{3+} oxidation state needs to be considered in biological systems. Aluminum is comparable in size to atoms of iron and magnesium. This is important since ionic radii frequently have a greater effect on molecular activity than charge. Aluminum often appears to compete with magnesium for oxygen donor ligands and biological processes. Aluminum is most strongly bound by oxygen atoms in carboxylate, deprotonated hydroxy (as in catecholates and serine and threonine), phosphate groups, and other compounds that contain negatively charged oxygen atoms. Unlike heavy metals, which are bound by sulfhydryl and amine groups, aluminum is not bound to sulfhydryl groups and is only bound to amines as part of multidentate ligand systems (e.g., NTA or EDTA).

In water, the rate of ligand exchange of the aquo complex $\text{Al}(\text{H}_2\text{O})_6^{3+}$ (1.3 sec^{-1}) with water molecules outside the inner coordination sphere is much slower than that of several other aquo metal complexes, and other aluminum complexes have an even slower ligand exchange rate. This low exchange rate means that aluminum binding can inhibit the activity of enzymes that have metals of similar effective ionic radius as cofactors (e.g. Fe^{3+} , Mg^{2+}).

In aqueous solution, two species of aluminum predominate, the octahedral aluminum hexahydrate $[\text{Al}(\text{H}_2\text{O})_6^{3+}]$ at $\text{pH} < 5.5$ and the tetrahedral aluminate $[\text{Al}(\text{OH})_4^-]$ at $\text{pH} > 6.2$. In the narrow pH range 5.6-6.2, successive deprotonations give the species $\text{Al}(\text{OH})^{2+}$, $\text{Al}(\text{OH})_2^+$, and a soluble $\text{Al}(\text{OH})_3$. $\text{Al}(\text{OH})_3$ precipitates at neutral pH. At pH 7.5, the maximum concentration of total aluminum is about $8 \mu\text{M}$ (0.22 ppm), mostly as $\text{Al}(\text{OH})_4^-$, and the free aluminum concentration is only 3 pM. Polynuclear complexes in aqueous solution are unlikely to occur at less than $10 \mu\text{M}$ (0.27 ppm) total aluminum.

Ligands present, their stability constants with Al^{3+} , and the mole ratio of total Al(III) to total ligand also influence the amount of free Al^{3+} in aqueous solution. When Al^{3+} displaces a proton from an acidic ligand to form complexes, the amount of the free cation in neutral aqueous solution is pH-dependent.

Absorbed Al^{3+} readily forms low-molecular-weight complexes, physically bound macromolecular complexes, or covalently bound macromolecular complexes (Ganrot, 1986; cited by ATSDR, 1999). Aluminum may form low-molecular-weight complexes with carbohydrates, amino acids, phosphates, nucleotides, and other organic acids. These low-molecular-weight complexes may be very stable chelates and metabolically active. Much of the aluminum may form macromolecular complexes with biological compounds for which it has a high affinity, such as proteins, polynucleotides, and glycosaminoglycans. The macromolecular complexes are expected to be less metabolically active than the low-molecular-weight complexes and may be so stable that binding is considered to be irreversible.

The insoluble compounds formed with phosphate have variable compositions, with aluminum speciation ranging from an amorphous AlPO_4 at low pH to the formation of $\text{Al}(\text{OH})_3$ at high pH. Within the cell, ATP is the predominant small molecule aluminum binder, effectively competing for solid AlPO_4 . Because aluminum binds so strongly to phosphates, processes involving ATP or ADP may also transfer aluminum.

Probably the most important aluminum complex for intestinal absorption is that with citrate, and at concentrations of 0.1 mM in the blood plasma, citrate is the most important small molecule that binds Al^{3+} . Aluminum easily displaces alkaline earth metals from their citrate complexes. Citrate will solubilize Al^{3+} from the insoluble $\text{Al}(\text{OH})_3$ and AlPO_4 , resulting in greater bioavailability of Al^{3+} . At low pH values, such as might occur in the stomach, Al-citrate complexes are favored with some formation of Al^{3+} -oxalate around pH 2-3; however, most aluminum is absorbed in the small intestine where the pH may not be as low as in the stomach (Martin, 1986). Treatment of humans with citrate or citric acid along with aluminum compounds results in significant increases in tissue and urine aluminum concentrations, especially when high doses of aluminum are administered. At lower aluminum doses, it appears that the co-administration of citrate does not significantly raise the concentration of aluminum in tissue or plasma when compared to subjects dosed with low doses of aluminum alone (Greger, 1992).

Aluminum may also form relatively strong complexes with one to five fluoride ions (Martin, 1986). The fluoride- Al^{3+} complex is stronger than the fluoride- Fe^{3+} complex, which is different than with other ligands.

When there is an absence of phosphates, citrate, transferrin, and nucleotides, then catecholamine may be the major aluminum binding species. Neurotransmitters, such as DOPA and epinephrine are known to bind aluminum at picomolar concentrations at neutral pH. Aluminum may bind to the catechol moiety of norepinephrine and may disrupt neurochemical processes. It is interesting that in a recent study with rats it was found that aluminum had both a positive and negative effect, depending on the length of aluminum exposure, on the transport of methionine, which is a precursor for catecholamines and choline (Sedrowicz et al., 1998).

Table 5. Dissociation Constants for Complexes with Aluminum (Al^{3+})

Ligand	Complex	$-\log K_D$
Fluoride	AlF^{2+}	6.2
Hydroxide	$\text{Al}(\text{OH})^{2+}$	8.5
Malonate (Mal)	$\text{Al}(\text{Mal})$	7.6
Phosphate	$\text{Al}(\text{HPO}_4)^+$	9.7
Salicylate (Sal)	$\text{Al}(\text{Sal})^+$	14.1
Citrate (Cit)	$\text{Al}(\text{Cit})^0$	8.1
EDTA	$\text{Al}(\text{EDTA})^-$	24.1
Transferrin	AlTf^-	13.0

Source: Rowatt et al. (1997)



Scientific Committee on Consumer Safety

SCCS

OPINION

on the safety of aluminium in cosmetic products

- Submission III -



The SCCS adopted this document
by written procedure on 1 February 2023

- CORRIGENDUM adopted in plenary meeting on 21 March 2023 -

ACKNOWLEDGMENTS

Members of the Working Group are acknowledged for their valuable contribution to this Opinion. The members of the Working Group are:

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This Opinion has been subject to a commenting period of eight weeks after its initial publication (from 30 May to 25 July 2021). Comments received during this period were considered by the SCCS. For this Opinion, main changes occurred in the following sections: 3.1, 3.2.4.1 SCCS comment under Table 4A, 3.2.4.4 SCCS comment under Tables 10 and 10A, 3.2.4.5 SCCS comment under Figure 2, 3.2.4.6. SCCS comment under Table 15A, 3.2.4.7. SCCS comment under Table 17, 3.4 incl. Table 18, discussion, conclusion as well as the reference list.

A corrigendum has been adopted on 21 March 2023 adding a note explaining that “AP” means “antiperspirant” under Table 6 of the Applicant.

All Declarations of Working Group members are available on the following webpage:
[Register of Commission expert groups and other similar entities \(europa.eu\)](https://ec.europa.eu/europa.eu/working-groups/register)

1. ABSTRACT

The SCCS concludes the following:

1. In light of the new data provided, does the SCCS consider Aluminium compounds safe when used in cosmetic products other than deodorants, antiperspirants, lipsticks and toothpastes? In the event that the estimated exposure to Aluminium from cosmetic products is found to be of concern, SCCS is asked to recommend safe concentration limits for each category.

The SCCS considers that aluminium compounds are safe when used

- in non-sprayable product categories at the maximum levels indicated in Tables 4 and 6; and
- in sprayable products, at the maximum levels indicated in Table 4, provided that the percentage of particles/droplets with a diameter of less than 10 µm does not exceed 20% of the total aerosolised particles/droplets. Since the Applicant's data submission indicated that aluminium is not used in sunscreen aerosol sprays, this Opinion does not cover sunscreen aerosol sprays.

2. Does the SCCS have any further scientific concerns regarding the use of relevant Aluminium compounds in cosmetic products taking into account the newly submitted information on aggregate exposure to Aluminium from cosmetics, medicines (e.g. antacids) and food intake?

As aluminium does not belong to substances classified as CMR 1A or B, only exposure from cosmetic uses was considered in this safety assessment with the exposure assessment based on maximum use levels for cosmetic ingredients.

However, the submission also provided a scenario where realistic exposure from non-cosmetic sources of aluminium (food and pharmaceuticals) was aggregated along with exposure from cosmetics at use levels from the year 2016. From this scenario, it can be deduced that contribution to aluminium exposure from food may be at a similar order of magnitude to that from cosmetics used for the safety assessment. Considering the conservative nature of the estimates, the aggregate exposure to aluminium from cosmetic and non-cosmetic sources may exceed safe limits for consumers at the highest exposure ranges.

Keywords: SCCS, revision, scientific opinion, aluminium, submission III, Regulation 1223/2009

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About the Scientific Committees

Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

These Committees are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and they are made up of scientists appointed in their personal capacity.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide Opinions on questions concerning health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Aluminium (Al) and Al compounds are used in a variety of cosmetic products, predominantly in deodorants, antiperspirants, lipsticks and toothpastes. Several Al compounds are regulated in different entries of the Cosmetics Regulation (EC) No 1223/2009¹.

In 2013, a risk assessment issued by the Norwegian Scientific Committee for Food Safety reported that cosmetic products, and in particular antiperspirants, constitute a significantly larger contribution to the total systemic Al exposure compared to diet at least for the Norwegian population that was used in the study. As a result, SCCS was mandated to evaluate the possible risk for human health arising from the presence of Al in cosmetics. The assessment was based on products and aluminium compounds that contributed to the highest consumer's exposure, namely antiperspirants/deodorants, toothpastes and lipsticks. In its Opinion SCCS/1525/14, the SCCS concluded that, due to the lack of adequate data on dermal penetration, the requested risk assessment could not be performed². In 2016, industry submitted a new safety dossier to address the dermal penetration and the fate of Al (after skin application) based on a human exposure study. At its plenary meeting on 3 March 2020, the SCCS adopted its final Opinion SCCS/1613/19³ and in March 2021 an addendum to this Opinion was published⁴.

In the addendum, the SCCS concluded that the use of aluminium compounds is safe at the following equivalent aluminium concentrations up to:

- 6.25% in non-spray deodorants or non-spray antiperspirants
- 10.60% in spray deodorants or spray antiperspirants
- 2.65% in toothpaste, and
- 14% in lipstick

In addition, the SCCS stated *"...the systemic exposure to aluminium via daily applications of cosmetic products does not add significantly to the systemic body burden of aluminium from other sources. Exposure to aluminium may also occur from sources other than cosmetic products, and a major source of aluminium in the population is the diet. This assessment has not taken into account the daily dietary intake of aluminium"*.

Following the discussion at the Cosmetics Working Group held on 25 June 2020 and in light of the comments received on the use of Al compounds in a variety of products other than deodorants, antiperspirants, lipsticks and toothpastes, the Commission considered opportune to request from industry to submit additional information on the 'other product categories' and on the aggregate exposure not only from cosmetics.

In March 2021, industry submitted a dossier focusing on the aggregate exposure to aluminium concerning the European population when considering the use of cosmetics and personal care products, medicines (e.g. antacids) and dietary intake.

The current request is based on the dossier submission III by the Applicant in order to demonstrate the safe use of aluminium in product categories other than deodorants, antiperspirants, lipsticks and toothpastes, as well as concerning the aggregate exposure. The current submission includes in particular additional data and considerations on the MoS calculation and aggregate exposure from cosmetics, medicines and food intake.

¹ Annex III (entry 50 - Aluminium Zirconium Chloride Hydroxide, and entries 189, 190, 192 - hair dyes), in Annex IV (entries 117, 118, 119, 150 - colorants) and Annex VI (entry 27a - coating for UV-filter).

² "Aluminium is a known systemic toxicant at high doses. The SCCS is of the opinion that due to the lack of adequate data on dermal penetration to estimate the internal dose of aluminium following cosmetic uses, risk assessment cannot be performed. Therefore, internal exposure to aluminium after skin application should be determined using a human exposure study under use conditions" (Opinion SCCS/1525/14).

³ SCCS (Scientific Committee on Consumer Safety), Opinion on the safety of aluminium in cosmetic products, preliminary version of 30-31 October 2019, final version of 03-04 March 2020, SCCS/1613/19, [link](#).

⁴ https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_248.pdf

Terms of reference

1. *In light of the new data provided, does the SCCS consider Aluminium compounds safe when used in cosmetic products other than deodorants, antiperspirants, lipsticks and toothpastes? In the event that the estimated exposure to Aluminium from cosmetic products is found to be of concern, SCCS is asked to recommend safe concentration limits for each category.*
2. *Does the SCCS have any further scientific concerns regarding the use of relevant Aluminium compounds in cosmetic products taking into account the newly submitted information on aggregate exposure to Aluminium from cosmetics, medicines (e.g. antacids) and food intake?*

3. OPINION

During the commenting period, the Applicant has provided a new exposure calculation with adjusted factors for inhalation. The draft Opinion was updated with the submitted Tables which have received the same number as the original Table together with an A for transparency.

3.1 CHEMICAL AND PHYSICAL SPECIFICATIONS

Physicochemical properties of aluminium compounds that can generally be used as cosmetic ingredients have been summarised in Annex I of the previous SCCS Opinion (SCCS/1613/19). These encompass aluminium compounds in water-soluble and water-insoluble form. The water-soluble Al-containing compounds form are simple inorganic salts, simple organic salts, aluminium benzoate, and chlorohydrates, which can be used in skin care products. Water-insoluble aluminium containing ingredients can be minerals, glasses and clays, aluminium lakes, carbohydrates, fatty acid salts, which are typically added to cosmetic products as bulking agents, coloured pigments, and sometimes as mild abrasives.

The new submission presents an industry survey that indicates the substances actually in use along with their amounts. The INCI names and CAS numbers of these substances are given in Tables 2 and 3 of this Opinion. The respective physicochemical properties of the substances can be retrieved from Annex 1 of SCCS/1613/19.

On the basis of available information on solubility (Annex 1 of SCCS/1613/19), the SCCS agrees that aluminium citrate may exhibit the highest bioavailability amongst the Al salts assessed in this Opinion.

3.2 EXPOSURE ASSESSMENT & TOXICOKINETICS

3.2.1 Function and uses

Taken from the previous Opinion (SCCS/1613/19):

Antiperspirants

Aluminium salts in antiperspirants, such as aluminium chlorohydrate, form insoluble aluminium hydroxide polymer gel plugs within sweat ducts to temporarily prevent sweat reaching the surface of the skin. These substances are soluble at very low pH in the formulation; however, once applied on the skin they form chemically inert complexes with basic components of sweat and skin. The relatively high molecular weight of the compounds, low 'Log P' and positive charge limit the potential for skin penetration through the *stratum corneum*. Moreover, absorption across the skin is further minimised by the formation of protein complexes in the outermost layers of the *stratum corneum* (Hostynek, 2003). These chemical properties limit the systemic delivery of aluminium via the intake skin.

Lipsticks

Aluminium colloidal colorant 'lakes' are mainly used in lipsticks. Colloidal colourants are prepared under aqueous conditions by reaction between aluminium oxide and the organic pigments in order to make them insoluble. Aluminium oxide is usually freshly prepared by reaction of aluminium sulphate or aluminium chloride with sodium carbonate or sodium bicarbonate or aqueous ammonia. Due to the complex molecular structures and high molecular weights of organic lakes, the aluminium represents only a small part of the weight of the raw material of which the extractable (bioaccessible) part will represent only a fraction.

Toothpastes

Insoluble minerals are used in toothpastes mainly to act as mild abrasives and to provide shine/gloss benefit through the polishing of the enamel. They are also used to improve rheology in striped toothpastes. Toothpastes may also contain aluminium colloidal colourant "lakes" and pigments.

New submission:

In reply to a request of the European Commission regarding Al-content of 'other cosmetic products' than antiperspirants, lipsticks and toothpastes, the Applicant has submitted a report that includes the findings of a market survey on Al-containing products.

According to the Applicant, this company survey inquired in seven large multi-national companies for the total volume of products sold in Europe in 2016 (and toothpaste data from one company from 2020), whether or not the products included an aluminium containing ingredient, and the concentration values of aluminium and its compounds in the product formulations. The inclusion criteria were ingredients where aluminium comprised at least 0.01% of the material, and formulations where the aluminium containing ingredient was present in at least 0.01% in the formulation. Regarding the tonnage data, the criteria were products where at least 10 kg were placed on the market in 2016 within the EEC+5 region.

In total, around 5300 formulations were identified that contained Al-compounds as ingredients. A total of 51 different Al-compounds were identified. The reason why Al-compounds are used in these different product categories is because, like e.g. Aluminium Starch Octenylsuccinate, they may absorb oil, sweat or odour. Furthermore, they may function as pigments and thickening agents (<https://cosmeticsinfo.org/aluminum>). Table 1 lists the number of reported formulations for different product categories.

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Table 1: Number of unique formulations containing one or more Al-ingredients per product category

	Product as labelled in the model	Number of unique formulas
1	AfterShave	12
2	BarSoap	7
3	BodyLotion	102
4	BodySpray	3
5	DeoRollOn – Gel	37
6	DeoRollOn – RollOn	358
7	DeoRollOn – Stick	145
8	DeoRollOn – Wipes	0
9	DeoSpray – Anti-Perspirant	435
10	DeoSpray – Pump	27
11	EaudeParfum, EaudeToilette	3
12	EyeLiner	217
13	EyeShadow	728
14	FaceMoisturizer	378
15	HairSpray	6
16	HairStyling	45
17	HandCream	16
18	Lipstick	1346
19	LiquidHandSoap	0
20	LiquMakeupFoundation	979
21	MakeupRemover	33
22	Mascara	60
23	Mouthwash	0
24	RinseoffConditioner	93
25	Shampoo	181
26	Showergel	13
27	Toothpaste	68

Representativeness

According to the Applicant, the survey on occurrence and amount of Al-ingredients used in cosmetic products was conducted with the Al-consortium.

According to the Applicant, the Al consortium members represent approximately 40% of the EU market share based on retail value (source: Euromonitor 2016, data made available to the SCCS) and include some of the highest market shares. Of the total of the more than 389 companies represented, 370 (95%) have below 1% market share and 343 (88%) below 0.1% of the market share. The mean market share is below 0.2% for the non-consortium members. Therefore, the consortium believes that this Al Consortium data is representative of the EU marketplace. In addition, when comparing to subsequent years, the market share of the consortium members remains stable and within the same range as 2016.

SCCS comment

Based on the data presented, the SCCS considers the presented survey as largely representative for the aluminium-containing ingredients and aluminium-containing products on the European market.

3.2.2 Dermal / percutaneous absorption

The data related to dermal/percutaneous absorption were assessed and commented upon by the SCCS in the previous Opinion on Aluminum (SCCS/1613/19). Below is a brief summary.

Dermal absorption was calculated from an exposure study with 6 female volunteers after application of 0.75 g antiperspirant per axilla on 100 cm², respectively. The antiperspirant contained Aluminum-Chlorhydrate which had been doped with radioactive ²⁶Al and the volunteers were biomonitoring for ²⁶Al in 24h-urine (TNO, 2019). This yielded a skin absorption value of 0.00052%. Combined with the Al found in the feces in the same study (0.0014%), this yields an overall percentage of bioavailable Al of 0.00192%.

SCCS comment

The respective dermal absorption percentage of 0.00192% was used in the presented exposure calculation. This is considered a valid absorption value. Due to occlusion and formulation characteristics of antiperspirants, the dermal absorption for antiperspirants is considered to be a conservative value that is also valid for the other cosmetic products addressed in this opinion.

3.2.3 Other studies on toxicokinetics

Toxicokinetic studies were reviewed in SCCS/1613/19, and were summarised as follows:

Oral absorption: EFSA (2008) concluded that a value of 0.3% oral bioavailability was appropriate to use in human risk assessment for soluble aluminium in drinking water (*i.e.* without food) and 0.1% with food.

Lung absorption: Taken together, all available data suggest that absorption of aluminium from lung deposits in the blood is low. For the purposes of lung exposure modelling and risk assessment, a conservative value for aluminium uptake by the lung is 3% (Jones & Bennett, 1986; DeVoto & Yokel, 1994).

SCCS comment

The SCCS considers that oral bioavailability of 0.1% is an appropriate value for use in risk assessment for indirect ingestion after removal from the upper respiratory tract by the mucociliary elevator.

Regarding inhalation, as reported in the SCCS/1613/19, a conservative value for aluminium uptake by the lung of 3% is an appropriate value for use in risk assessment. From the upper respiratory tract, no data on bioavailability is available, but since mucociliary clearance will lead to expectorate or swallowing of the Al trapped in that part of the body, intestinal resorption values of 0.1 or 0.3% can be used (EFSA, 2008).

3.2.4 Calculation of SED/LED

The Applicant has submitted a comprehensive report on single product and aggregate exposure to Al via cosmetics, as well as an aggregate assessment of Al in cosmetics, medicines (antacids) and food. The assessment is based on a survey among the European industry that included 7 large producers.

3.2.4.1 Concentrations in cosmetics

According to the Applicant, the aluminium concentration data reported in this section were collected in the company survey. Six companies provided comprehensive data on Al use across a range of cosmetic products for the year 2016. An additional company provided comprehensive data on Al use in toothpastes for the year 2020. The seven companies

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participating in the project identified 51 different Al-ingredients that were present in cosmetic products sold in the European market.

The results of the survey showed that 21 Al-ingredients were uniquely reported by a single company, thus exhibiting a unique aluminium concentration data point, provided by that company. These single data points, listed in Table 2, were used as constants in the exposure model, meaning that these 21 Al-ingredients always had the same concentration of aluminium as reported by the company using it.

Table 2: Aluminium ingredients with constant aluminium concentration values

#	INCI NAME	CAS #	Aluminium Concentration in Ingredient
1	ALUMINA /SYNTHETIC RUBY POWDER	1344-28-1 / 1333-84-2	52.93%
2	ALUMINIUM HYDROXIDE SULPHATE	1332-73-6 / 21645-51-2 / 8011-94-7	19.26%
3	ALUMINIUM LACTATE	18917-91-4	9.17%
4	ALUMINIUM ZIRCONIUM PENTACHLOROHYDRATE	57158-29-9 / 173762-83-9	8.40%
5	ALUMINUM TRISTEARATE	637-12-7	3.08%
6	ALUMINUM BENZOATE	555-32-8	6.91%
7	ALUMINUM CALCIUM SODIUM SILICATE	1344-01-0	14.81%
8	ALUMINUM DIMYRISTATE	56639-51-1	5.41%
9	ALUMINUM DISTEARATE	300-92-5	4.42%
10	ALUMINUM POWDER	7429-90-5	100.00%
11	ALUMINUM SILICATE	1327-36-2	24.73%
12	CARMINE (COCHINEAL LAKE)	1390-65-4	21.50%
13	KAOLIN	1332-58-7	5.23%
14	Montmorillonite	10043-67-1	7.80%
15	RED 21 LAKE	15086-94-9 / 548-26-5 / 15876-39-8	6.20%
16	RED 22 LAKE	548-26-5	12.80%
17	RED 40 LAKE	68583-95-9 / 25956-17-6	24.70%
18	RED 7 LAKE	5281-04-9	22.60%
19	SAPPHIRE POWDER	1317-82-4	52.90%
20	SODIUM POTASSIUM ALUMINUM SILICATE	12736-96-8	11.75%
21	TOURMALINE	1317-93-7	20.70%

According to the Applicant, 30 additional Al-ingredients were reportedly used by more than one company and, as the individual companies use different raw materials, multiple concentration values were reported for these raw materials. Table 3 reports the summary statistics of the aluminium concentrations reported for these Al-ingredients. Concentration values were reported as a list of single values or as ranges. Ranges were treated by the exposure model as uniform distributions and the model randomly selected a single value from the distribution whenever it was required.

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Table 3: Summary statistics of aluminium concentrations in aluminium-ingredients with multiple values

#	INCI NAME	CAS #	Aluminium Concentration in Ingredient			
			Min	Max	Mean	# of reported concentrations
1	ALUMINA	1344-28-1	0.35%	0.69%	0.52%	2
2	ALUMINIUM, ZINC, MAGNESIUM AND CALCIUM STEARATES	7047-84-9	3.40%	3.70%	3.55%	2 (2 uniforms)
3	ALUMINUM CHLORIDE	7446-70-0 / 7784-13-6	10.00%	12.00%	11.09%	2 (1 uniform)
4	ALUMINUM CHLOROHYDRATE	1327-41-9	12.20%	30.90%	21.30%	14 (5 uniforms)
5	ALUMINUM HYDROXIDE	21645-51-2	1.19%	34.60%	11.57%	4
6	ALUMINUM SESQUICHLOROHYDRATE/ DIALUMINIUM CHLORIDE PENTAHYDROXIDE?	12042-91-0	11.50%	25.50%	18.48%	4 (2 uniforms)
7	ALUMINUM STARCH OCTENYLSUCCINATE	9087-61-0	0.16%	50.00%	27.85%	8 (1 uniform)
8	ALUMINUM STEARATE	7047-84-9	3.00%	7.83%	5.42%	2
9	ALUMINUM ZIRCONIUM OCTACHLOROHYDRATE	57158-29-9 / 98106-55-9	10.21%	10.21%	10.21%	2
10	ALUMINUM ZIRCONIUM TETRACHLORHYDRATE GLY	134910-86-4	14.50%	15.50%	15.33%	3 (1 uniform)
11	ALUMINIUM ZIRCONIUM TRICHLOROHYDREX GLY	134375-99-8	15.48%	17.80%	16.64%	2
12	BENTONITE	1302-78-9	9.00%	10.80%	9.90%	2
13	BLUE 1 LAKE/ ACID BLUE 9 ALUMINUM LAKE	68921-42-6	0.02%	31.50%	15.63%	4
14	CALCIUM ALUMINUM BOROSILICATE/ GLASS	65997-17-3	1.79%	13.20%	4.16%	5
15	MAGNESIUM ALUMINUM SILICATE	1327-43-1 / 12511-31-8	7.00%	18.82%	11.61%	3

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#	INCI NAME	CAS #	Aluminium Concentration in Ingredient			
			Min	Max	Mean	# of reported concentrations
16	MAGNESIUM ALUMINUM SILICATE (ARGILLA)	12199-37-0	1.40%	21.00%	8.40%	3 (2 uniforms)
17	MICA	12001-26-2	0.04%	21.20%	11.72%	59 (6 uniforms)
18	PERLITE	93763-70-3	7.40%	8.20%	7.80%	2
19	POTASSIUM ALUM	10043-67-1 / 7784-24-9	3.95%	6.25%	5.10%	2
20	POTASSIUM ALUMINIUM SULPHATE	10043-24-9 / 7784-24-9	5.68%	10.44%	8.06%	2
21	PUMICE	1332-09-8	6.60%	7.14%	6.78%	3
22	RED 28 LAKE	18472-87-2	24.70%	29.68%	27.53%	4
23	RED 30 LAKE	2379-74-0	20.76%	41.40%	27.99%	3
24	RED 33 LAKE	3567-66-6	30.10%	31.60%	30.85%	2
25	SILICA/KAOLIN	1332-58-7	19.30%	23.80%	21.33%	3
26	SYNTHETIC FLUORPHLOGOPITE	12003-38-2	4.62%	6.41%	5.52%	2
27	TITANIUM DIOXIDE COATED WITH ALUMINIUM OXIDE	1344-28-1	1.56%	26.50%	7.34%	5
28	ULTRAMARINES	101357-30-6	13.00%	16.70%	15.47%	3
29	YELLOW 5 LAKE	12225-21-7	23.00%	39.70%	30.10%	5
30	YELLOW 6 LAKE FD&C	12227-60-0 / 15790-07-5 / 2783-94-0 / 174514-58-0	0.47%	24.50%	12.49%	2

By combining % Al in the ingredient with % of Al-ingredient used in the product, the Applicant derived distributions for the concentration values for each product category included in the exposure assessment (see Table 4) and for the product categories not included in the exposure assessment (see Table 6).

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Table 4: Min, max and mean values of the reported concentrations of aluminium in each product type and category included in the exposure assessment.

	Product as labelled in the model	# of Al-ingredients identified across the product types	Aluminium concentrations (%) in products		
			Min	Max	Mean
1	AfterShave	1	0.00%	2.15%	0.59%
2	BarSoap	2	0.00%	0.07%	0.01%
3	BodyLotion	10	0.00%	3.81%	0.21%
4	BodySpray	1	1.10%	1.18%	1.12%
5	DeoRollOn – Gel	7	0.00%	6.18%	1.70%
6	DeoRollOn – RollOn	12	0.00%	5.63%	1.45%
7	DeoRollOn – Stick	9	0.00%	7.73%	1.05%
8	DeoRollOn – Wipes	0	0.00%	0.00%	0.00%
9	DeoSpray – Anti-Perspirant	8	0.00%	3.24%	0.32%
10	DeoSpray – Pump	5	0.00%	4.88%	1.17%
11	EaudeParfum, EaudeToilette	2	0.01%	0.05%	0.03%
12	EyeShadow	19	0.11%	43.31%	6.24%
13	EyeLiner	16	0.01%	15.76%	2.28%
14	FaceMoisturizer	19	0.00%	10.59%	0.69%
15	HairSpray	1	0.00%	0.00%	0.00%
16	HairStyling	7	0.00%	1.19%	0.10%
17	HandCream	2	0.00%	0.86%	0.30%
18	Lipstick	19	0.00%	14.62%	1.60%
19	LiquidHandSoap	0	0.00%	0.00%	0.00%
20	LiquMakeupFoundation	17	0.01%	6.59%	0.43%
21	MakeupRemover	14	0.00%	10.59%	0.62%
22	Mascara	11	0.00%	3.13%	0.53%
23	Mouthwash	0	0.00%	0.00%	0.00%
24	RinseoffConditioner	6	0.00%	7.14%	0.12%
25	Shampoo	7	0.00%	7.14%	0.45%
26	Showergel	7	0.00%	0.89%	0.13%
27	Toothpaste	6	0.00%	3.18%	0.07%

The product formulations reported in the company survey contain from 1 to 10 different Al-ingredients in combination. The products that contain the highest average number of Al-ingredients per product type are Lipstick with 3.6 Al-ingredients per formula; the formula with the absolute highest number of Al-ingredients (10) is also a lipstick. Lipsticks are followed by EyeShadow (2.55 Al-ingredients per formula) and LiquMakeupFoundation (1.88 Al-ingredients per formula). The averages of these and all other product types are presented in Table 5. The data collected in the company survey capture the co-occurrence of different Al-ingredients in the same product formulations; this information was incorporated in the exposure model.

Importantly, Table 4 represents those formulations reported to include aluminium containing ingredients, with the exception of Mouthwash, LiquidHandSoap, and Deo-wipes, which contain none. Although the minimum is rounded to 0.00% in the table, this reflects formulations containing low levels of aluminium (given the inclusion criteria discussed

above, the theoretical minimum for a formulation that includes 0.01% of an ingredient that contains 0.01% aluminium would be 0.000001%).

Table 5: Average number of Al-ingredients per formula per product type

	Product as labelled in the model	Average # Al-ingredients per formula
1	AfterShave	1
2	BarSoap	1
3	BodyLotion	1.12
4	BodySpray	1
5	DeoRollOn – Gel	1.27
6	DeoRollOn – RollOn	1.25
7	DeoRollOn – Stick	1.12
8	DeoRollOn – Wipes	0
9	DeoSpray – Anti-Perspirant	1.1
10	DeoSpray – Pump	1.26
11	EaudeParfum, EaudeToilette	1
12	Eyeliners	1.49
13	EyeShadow	2.55
14	FaceMoisturizer	1.28
15	HairSpray	1
16	HairStyling	1.11
17	HandCream	1
18	Lipstick	3.6
19	LiquidHandSoap	0
20	LiquMakeupFoundation	1.88
21	MakeupRemover	1.39
22	Mascara	1.42
23	Mouthwash	0
24	RinseoffConditioner	1.1
25	Shampoo	1.11
26	Showergel	1.23
27	Toothpaste	1.13

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Table 6: Min, max and mean values of the reported concentrations of aluminium in each product type and category that is **NOT** included in the exposure calculations.

Product Type	# of Al-ingredients included in the product type	Aluminium concentrations (%) in products		
		Min	Max	Mean
Other products with and without AP	3	0.00001%	2.794%	0.832%
Shaving products	1	0.09410%	0.094%	0.094%
Nail varnish	11	0.00223%	3.618%	0.166%
Eye contour products	7	0.00007%	1.290%	0.153%
Sun cream/lotion	10	0.00209%	8.403%	0.467%
Sun cream/lotion pump spray	2	0.33208%	0.332%	0.332%
Hair Color and Perms	2	0.00006%	0.002%	0.000%
Lip care products: Lip balm	3	0.00001%	0.606%	0.119%
Other products	17	0.01278%	15.887%	3.943%
Other products - Decoloration	2	0.00668%	4.760%	0.818%
Other products - oxidative coloration	2	0.01837%	0.120%	0.054%
Talc	1	0.01330%	0.013%	0.013%

According to the Applicant, the category “other products with and without AP” includes products for sweat control on hands and feet that are not considered daily use products frequently used by consumers. AP stands for “antiperspirant”.

Also, data on occurrence of Al in cosmetics was derived for product categories included in the assessment (see Table 7) and those not included in the exposure assessment (Table 8).

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Table 7: Product categories that can potentially contain Al and were included in the exposure assessment: Quantities sold in Europe in 2016 and relative occurrence of aluminium-containing products

	Product as labelled in the model	Quantity of all products sold (tonnes)	Quantity of products with aluminium sold (tonnes)	Occurrence
1	AfterShave	2,379.73	88.15	3.70%
2	BarSoap	42,259.45	983.45	2.33%
3	BodyLotion	75,047.33	21,872.97	29.15%
4	BodySpray	20,025.64	62.60	0.31%
5	DeoRollOn – Gel	975.33	959.83	98.41%
6	DeoRollOn – RollOn	16,980.30	15,751.75	92.76%
7	DeoRollOn – Stick	3,848.38	2,764.84	71.84%
8	DeoRollOn – Wipes	0.02	-	0.00%
9	DeoSpray – Anti-Perspirant	56,680.32	48,360.40	85.32%
10	DeoSpray – Pump	1,738.97	735.26	42.28%
11	EaudeParfum, EaudeToilette	3,927.52	0.31	0.01%
12	EyeLiner	69.79	41.82	59.92%
13	EyeShadow	116.49	116.28	99.82%
14	FaceMoisturizer	21,060.00	5,353.81	25.42%
15	HairSpray	40,048.88	19.79	0.05%
16	HairStyling	41,859.15	1,293.27	3.09%
17	HandCream	4,685.26	569.42	12.15%
18	Lipstick	298.02	261.30	87.68%
19	LiquidHandSoap	29,321.13	-	0.00%
20	LiquMakeupFoundation	2,516.76	2,284.24	90.76%
21	MakeupRemover	56,284.66	501.96	0.89%
22	Mascara	821.92	132.81	16.16%
23	Mouthwash	10,555.08	-	0.00%
24	RinseoffConditioner	148,701.36	8,470.45	5.70%
25	Shampoo	428,111.81	67,911.38	15.86%
26	Showergel	352,998.42	1,038.42	0.29%
27	Toothpaste*	76,634.45	19,632.27	25.62%

* One company shared Toothpaste data from 2020 and not 2016.

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Table 8: Product categories that can potentially contain Al and were **NOT** included in the exposure assessment: Quantities sold in Europe in 2016 and relative occurrence of aluminium-containing products

Product type	Quantity of all products sold (tons)	Quantity of products sold (tons) with aluminium	Occurrence
Other products with and without AP	207.29	143.63	69.29%
Body hair removal products	36.43	0	0.00%
Shaving products	35,184.80	0.57	0.00%
Eye liner & Eye pencil	69.79	41.82	59.92%
Nail varnish	613.27	190.09	31.00%
Eye contour products	242.23	99.33	41.01%
Sun cream/lotion	11,690.92	3398.42	29.07%
Sun cream/lotion aerosol spray	1,733.24	0	0.00%
Sun cream/lotion pump spray	5,454.00	55.12	1.01%
Hair Color and Perms	30,299.49	987.11	3.26%
Lip care products: Lip balm	493.72	124.44	25.20%
Other products	3,697.65	206.20	5.58%
Other products - Decoloration	8,763.56	850.52	9.71%
Other products - oxidative coloration	23,888.04	1661.23	6.95%
Talc	296.38	18.49	6.24%
Toners/astringents	1,970.74	0	0.00%

Additional information provided by the Applicant upon request (05.11.2021)

Upon request of the SCCS, the Applicant has stated that the beach products (*i.e.*, sunscreen lotion) and other product categories listed in Tables 6 and 8 were not part of the Creme model because they are only used periodically. Importantly, the additional exposure from the excluded cosmetic product categories listed in Tables 5 and 7 are a minor contribution to the aggregate and total daily exposure to aluminium. The Applicant has further provided a deterministic exposure assessment for sunscreens (Table 9):

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Table 9: Daily exposure estimate of aluminium. (Deterministic exposure calculations for sunscreen products combined with probabilistic assessment)

	Maximum / Day	Mean / Day
Aluminium in Product	8.40%	0.47%
Quantity of Product Per Day (g)	18	18
Dermal Absorption from SCCS Opinion	0.00192%	0.00192%
Systemic Exposure (µg/person)	29.04	1.61
Systemic Exposure (µg/kg bw/day)	0.484	0.03
MOS	375	6692
Proportion of PTWI	27%	1%
Probabilistic exposure All Sources P95 from Creme Report (µg/kg bw/day)	0.1631	0.1631
Total systemic body burden: Sunscreen + Probabilistic (µg/kg bw/day)	0.6471	0.1900
MOS (total systemic body burden)	278	947

Additional information provided by the Applicant after public consultation (22.09.2022)

A new scenario 1b has been calculated by the Applicant. According to the Applicant, scenario 1b is similar to Scenario 1 as it assumes 100% of cosmetic products contain Aluminium and concentrations are represented as single maximum values for each product. For a few products, the concentrations used in Scenario 1b are higher than the concentrations used in Scenario 1 and so it provides a more conservative estimate of exposure. The concentrations for Scenario 1b are shown in Table 4A.

Table 4A: Values of the concentrations of aluminium in each product type and category for Scenario 1b.

	Product as labelled in the model	Aluminium concentrations (%) in products in Scenario 1b
1	AfterShave	2.15%
2	BarSoap	4%
3	BodyLotion	3.81%
4	BodySpray	1.18%
5	DeoRollOn – Gel	6.18%
6	DeoRollOn – RollOn	5.63%
7	DeoRollOn – Stick	7.73%
8	DeoRollOn – Wipes	0%
9	DeoSpray – Anti-Perspirant	3.24%
10	DeoSpray – Pump	4.88%
11	EaudeParfum, EaudeToilette	0.05%
12	EyeShadow	43.31%
13	EyeLiner	15.76%
14	FaceMoisturizer	10.59%
15	HairSpray	0.15%
16	HairStyling	6.7%
17	HandCream	0.86%
18	Lipstick	14.62%
19	LiquidHandSoap	0.89%
20	LiquMakeupFoundation	23%
21	MakeupRemover	10.59%
22	Mascara	3.13%
23	Mouthwash	0%
24	RinseoffConditioner	7.14%
25	Shampoo	7.14%
26	Showergel	0.89%
27	Toothpaste	3.18%

SCCS comment

The SCCS considers the term “constant aluminium levels” in the header of Table 2 as confusing. The understanding of SCCS is that Table 2 lists Aluminium ingredients with one single concentration reported by one company that was subsequently used in the model as a point value. Likewise, the SCCS regards the title of Table 3 as confusing. The SCCS understands that Table 3 reports Al ingredients with a range of aluminium concentrations reported in industry survey (several companies).

The SCCS further understands that 'Al-concentrations' of Al-containing cosmetics ingredients mentioned in Tables 2 and 3 represent the Al-contents in terms of the stoichiometric ratios of Al in these ingredients.

It is unclear to the SCCS why a range of Al-contents ('Al-concentrations') in the Al-ingredient for some of the Al-ingredients may result from the defined stoichiometry of the chemical substance (e.g. for potassium aluminium sulphate in Table 3). However, the SCCS has calculated the Al-contents based on stoichiometry and found that the Al-content in the maximal value was not underestimated by using the ranges provided by the Applicant. Therefore, risk assessment based on exposure calculations with these maximum values is considered valid.

Some products had been excluded from the aggregate exposure assessment (see Tables 6, 8) without explanation in the submitted report. Upon request, the Applicant has submitted the explanation and an additional deterministic exposure assessment of sunscreens. The assessment using the maximum Al level possible (Table 9) is considered valid by the SCCS.

The SCCS considers that sunscreen products should be included in the assessment, because on a seasonal basis they are used regularly, even daily, and because the high amounts applied may represent a considerable source for exposure. Furthermore, the presence probability of aluminium in sunscreens (*i.e.* the fraction of products that contain the substance) is 30%, which cannot be considered negligible.

Some of the products that have not been considered may also be used on a regular basis (shaving products, eyeliner, eye contour products and lip care products). However, for these products the exposure potential is low and the tonnage of Al-containing products sold is also low. Therefore, their contribution to dermal exposure can be considered as negligible and therefore these products can be considered safe for use.

In scenario 1b the Applicant has used higher concentrations for the product categories BarSoap, HairStyling, LiquidHandSoap and LiquiMakeupFoundation. Since no reasoning for the new concentrations were given, the new values were not accepted by the SCCS. The SCCS will use the dermal and oral exposure values of the original report for its assessment.

Inhalation exposure was not calculated by the Applicant for sunscreens products. Therefore, this opinion considers only sunscreen lotions and creams, and not sunscreen products that may result in exposure of the lung.

3.2.4.2 Frequency of use and co-use

The frequency of application and co-use data for cosmetic products are available from Kantar Worldpanel, except for Mascara, Eye Shadow, Eye Liner and Makeup Remover. Kantar data on product usage frequency (at the resolution of one hour) were collected from consumer product consumption surveys from 2007 and 2008 for France, Germany, Spain, and the United Kingdom. In the case of Mascara, Eye Shadow, Eye Liner and Makeup Remover, frequency of use data is available from two studies (Bremmer, 2006a; Biesterbos, 2013). The Biesterbos study was based on 516 Dutch subjects (302 females, 210 males).

3.2.4.3 Amount per use

According to the Applicant, amount per use data comes from the Colipa studies (for Deo Roll-On (Gel, Roll-On, Stick), Deo Spray (Anti-Perspirant, Pump), cosmetics and toothpaste)) and additional data from the CTFA studies for certain cosmetics. The following is a set of abbreviations used here for the data sources mentioned above:

- COLIPA1: "European consumer exposure to cosmetic products, a framework for conducting population exposure assessments." (Hall *et al.*, 2007)
- COLIPA2: "European consumer exposure to cosmetic products, a framework for conducting population exposure assessments Part 2." (Hall *et al.*, 2010)
- CTFA1: "Exposure data for cosmetic products: lipstick, body lotion, and face cream." (Loretz L., *et al.*, 2005)
- CTFA2 "Exposure data for personal care products: hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. (Loretz *et al.*, 2006)
- CTFA3 "Exposure data for cosmetic products: facial cleanser, hair conditioner, and eye shadow." (Loretz *et al.*, 2008)

The amounts for Bar Soap products were taken from the publication of Comiskey *et al.* (2017), who report the amounts used for showering and washing hands. For conservative reasons, the exposure model was based upon the amounts of Bar Soap products used for showering as they are significantly higher than the amounts related to hand washing. The amounts for Liquid Hand Soap were derived from Ficheux *et al.* (2016), which is a study about the amount per use of cosmetic products consumed at home by the French adult, child and baby populations.

The amounts of Deo Spray products reported in COLIPA 1 only apply to pressurised (propellant-driven) sprays, since the amount used/day includes propellants. For Deo Spray-Pump products, lower values should be applied; in accordance with the consortium, it was decided to use the amounts of the DeoRollOn products as a proxy.

The amounts for Mascara, Eye liner and Make-up remover products come from Biesterbos *et al.* (2012).

3.2.4.4 Retention and bioavailability factors

According to the Applicant, users of cosmetic products may be exposed to aluminium via three different routes: the dermal route, which is applicable to all cosmetics, the inhalation route, which is applicable to spray products only, and the oral route, which is applicable to lipsticks and toothpastes only. These routes require three different sets of bioavailability and retention factors.

In the exposure report by the Applicant, dermal retention factors for personal care products vary depending on the product type with leave-on, non-spray products (e.g. body lotion) set at 100% and rinse-off products (e.g. Shampoo) conservatively set at 1% by default. The dermal retention factors for Toothpaste and Mouthwash are set at 1 to 5% and 10%, respectively; these are the values set by the SCCS guidelines (SCCS 2012-2018).

According to the Applicant, the dermal retention factor for DeoSpray products is based on findings from the literature, where it has been shown that, of the amount of spray that is directed to the skin, only 23.5% actually lands on the skin (Steiling *et al.*, 2012). The dermal retention factor for HairSpray is set at 10%, which means that 10% of sprayed

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product remains on the scalp (Api *et al.*, 2008, SCCS 2012-2018). According to Comiskey *et al.* (2017), 80% of EauDeToilette and EauDeParfum are retained on the skin.

A single aluminium percutaneous absorption factor of 0.00192% is assumed for all products applied to the skin. This is the dermal absorption percentage derived in the most recent SCCS opinion on aluminium (SCCS, 2020).

Bioavailability factors are the proportion of a substance which enters the circulation when it comes into contact with the body and are used to estimate the internal exposure from the external exposure. For toothpaste, mouthwash, and lipsticks, which may be partly or totally ingested, the model used an oral bioavailability value of aluminium of 0.1%, as per food and beverages. The amount of foods and antacids absorbed by the GI tract depends on the oral circulation through the GI tract. EFSA (2008) reports an oral bioavailability value of approximately 0.3% for Al in drinking water and less than 0.1% for Al in food and beverages.

Table 10 presents a summary of the used penetration, retention and bioavailability factors.

Table 10: Summary of assessment factors used in the exposure assessment

Product	Dermal retention factor	Dermal penetration factor	Adjusted Inhalation factor	Lung Bioavailability Factor (RF ^a)	Upper airways factor (NRF ^b)	Ingestion factor	Oral bioavailability factor
Food and beverages						100%	0.1%
Water						100%	0.3%
Antacids						100%	0.1%
AfterShave	100%	0.00192%					
BarSoap	1%	0.00192%					
BodyLotion	100%	0.00192%					
BodySpray	100%	0.00192%					
DeoRollOn – Stick	100%	0.00192%					
DeoRollOn – RollOn	100%	0.00192%					
DeoRollOn – Gel	100%	0.00192%					
DeoRollOn – Wipes	100%	0.00192%					
DeoSpray – Anti-Perspirant	23.5%	0.00192%	0.892%	3% (20%)	0.1% (80%)		
DeoSpray – Pump	23.5%	0.00192%	0.892%	3% (2%)	0.1% (98%)		
EauDeParfum EauDeToilette	80%	0.00192%	0.234%	3% (2%)	0.1% (98%)		
EyeShadow	100%	0.00192%					
Face Moisturizer	100%	0.00192%					
HairSpray	10%	0.00192%	1.047%	3% (20%)	0.1% (80%)		
HairStyling	10%	0.00192%					
HandCream	100%	0.00192%					
Lipstick	0%	0.00192%				100%	0.1%
LiquidHandSoap	1%	0.00192%					
LiquiMakeupFoundation	100%	0.00192%					
Mascara	100%	0.00192%					
Mouthwash	10%	0.00192%				10%	0.1%
RinseoffConditioner	1%	0.00192%					
Shampoo	1%	0.00192%					
Showergel	1%	0.00192%					
Toothpaste	5%	0.00192%				5%	0.1%
EyeLiner	100%	0.00192%					
MakeupRemover	1%	0.00192%					

^a Respirable Fraction

^b Non-Respirable Fraction

According to the Applicant, Table 10A shows a summary of the factors used in Scenario 1b with the Inhalation factor column derived from RIFM 2-box modelling using the more conservative inhalation parameters discussed in the preliminary SCCS opinion 2022 and outlined in Table 12A below (chapter 3.2.4.5). It should be noted that a substantial amount of formulation lands on skin, so assuming that 100% is available for inhalation is not realistic.

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Table 10A: Summary of Factors used in Scenario 1b

Product	Dermal retention factor	Dermal penetration factor	Inhalation factor	Lung Bioavailability Factor (RF ^a)	Upper airways factor (NRF ^b)	Ingestion factor	Oral bioavailability factor
Food and beverages						100%	0.1%
Water						100%	0.3%
Antacids						100%	0.1%
AfterShave	100%	0.00192%					
BarSoap	1%	0.00192%					
BodyLotion	100%	0.00192%					
BodySpray	100%	0.00192%					
DeoRollOn – Stick	100%	0.00192%					
DeoRollOn – RollOn	100%	0.00192%					
DeoRollOn – Gel	100%	0.00192%					
DeoRollOn – Wipes	100%	0.00192%					
DeoSpray – Anti-Perspirant	23.5%	0.00192%	1.208%	3% (20%)	0.1% (80%)		
DeoSpray – Pump	23.5%	0.00192%	1.208%	3% (2%)	0.1% (98%)		
EaudeParfum EaudeToilette	80%	0.00192%	1.213%	3% (2%)	0.1% (98%)		
EyeShadow	100%	0.00192%					
Face Moisturizer	100%	0.00192%					
HairSpray	10%	0.00192%	1.204%	3% (20%)	0.1% (80%)		
HairStyling	10%	0.00192%					
HandCream	100%	0.00192%					
Lipstick	0%	0.00192%				100%	0.1%
LiquidHandSoap	1%	0.00192%					
LiquMakeupFoundation	100%	0.00192%					
Mascara	100%	0.00192%					
Mouthwash	10%	0.00192%				10%	0.1%
RinseoffConditioner	1%	0.00192%					
Shampoo	1%	0.00192%					
Showergel	1%	0.00192%					
Toothpaste	5%	0.00192%				5%	0.1%
EyeLiner	100%	0.00192%					
MakeupRemover	1%	0.00192%					

^a Respirable Fraction

^b Non-Respirable Fraction

SCCS comment

In the original submission, the Applicant cites Steiling *et al.* 2012 to support a dermal retention of 23.5% to be used for reducing inhalation exposure. The cited value is the P90 for dermal load from an experimental study, which could be used as reasonable worst case for dermal exposure. However, subtracting an upper percentile value for dermal load from the total available amount will not result in a conservative value for inhalation and therefore cannot be used for deriving an adjustment factor for inhalation. Hence, the SCCS considered the “adjusted inhalation factors” for DeoSpray-antiperspirant and DeoSpray-pump in the original submission not valid.

In the new submission the Applicant has now provided an exposure assessment based on the upper bound of 100% for inhalation (see below). Therefore, the “adjusted inhalation factors” for DeoSpray-antiperspirant and DeoSpray-pump presented in Table 10A can now in principle be accepted. However, the transfer rate between Box 1 and Box 2 of the inhalation model is still very high (see chapter 3.2.4.5.)

Regarding Eau de Toilette, Eau de Parfum and HairSpray, Comiskey *et al.*, 2017 cite an internal report that is not available to the SCCS. Therefore, the 80% dermal retention factor

cannot be evaluated. Hence, the SCCS considered also the “adjusted inhalation factors” for Eau de Toilette, Eau de Parfum and HairSpray in the original assessment not valid.

In the new submission the Applicant has provided an exposure assessment based on the upper bound of 100% for inhalation (see below). Therefore, the “adjusted inhalation factors” for Eau de Toilette, Eau de Parfum and HairSpray presented in Table 10A can now be accepted.

3.2.4.5 Inhalation exposure

According to the Applicant, the exposure model developed by Creme Global, utilised in the exposure study, requires several inputs. Among them, there is the output obtained from a separate computational model, called the 2-box model, that returns the fraction of aluminium inhaled by the consumer of a spray product. Since higher tier experimental data on each individual spray product were not available, estimates of the contribution from lung exposure rely on conservative computational model predictions.

According to the Applicant, the inhalation route is applicable only to spray products: DeoSpray – Anti-Perspirant, DeoSpray-Pump, EAUdeParfum, EAUdeToilette, HairSpray. Cosmetic spray products (HairSpray, DeoSpray, EAUdeToilette and EAUdeParfum) are directed to the skin and may also be incidentally inhaled. After dermal exposure, a percentage of the product remains on the skin once applied (dermal retention factor). For inhalation exposure, a percentage of the amount of product that is released is available to be inhaled; this percentage is calculated as 100% minus the dermal retention factor. An ‘inhalation factor’ is proposed to calculate the percentage of chemical released into the atmosphere that is available for inhalation. The inhalation factor depends on the product and is based on calculations using the 2-box model. The dermal retention factors and the inhalation factors are shown in Table 11.

Table 11: Dermal retention and inhalation factors

Product	Dermal Retention Factor (DRF)	% Available for Inhalation (1-DRF)	Inhalation Factor (IF) ^d	Adjusted Inhalation Factor (IF x (1- DRF))
DeoSpray, Anti-Perspirant and Pump	23.5% ^a	76.5%	1.167%	0.892%
HairSpray	10% ^b	90%	1.163%	1.047%
EAUdeToilette, EAUdeParfum	80% ^c	20%	1.171%	0.234%

^a Steiling et al., 2012

^b Api et al., 2008

^c Comiskey et al., 2017

^d Calculated via 2-box model

According to the Applicant, the ‘adjusted inhalation factor’ is a multiplication of the ‘inhalation factor’ (calculated by the 2-box model) and the ‘% available for inhalation’ for a specific product. As an example, we know that for DeoSpray 76.5% of the product that is released from the can is available for inhalation. The Inhalation Factor for DeoSpray (as calculated by the 2-box model) is 1.167%, which means that 1.167% of the product that is released into a room may be inhaled by the user. And as only 76.5% of it is available for inhalation, this results in an Adjusted Inhalation Factor of 0.892% for DeoSpray (*i.e.* 0.892% of the total amount of product released from the can may be inhaled by the user).

Some aerosol spray products, called in the model “DeoSpray – Anti-Perspirant”, can be classified as “compressed”. This describes a technology which reduces the quantity of propellant in the can and, proportionately, reduces the spray rate to ensure equivalent

product release (and hence consumer exposure) compared to standard dilute aerosols over the same duration of spray (Unilever 2015). The cosmetic companies participating in the company survey reported whether their aerosol spray products are compressed and, if so, the size of the spray rate reduction compared to standard dilute aerosols. Given that the Creme model uses exposure data for standard aerosols, the higher concentration of aluminium in the compressed product would lead to an artificially high modelled consumer exposure. In order to account for the reduced spray rate in the Creme model, the percentage of spray rate reduction is used by the exposure model as a multiplier of the aluminium concentrations to adjust exposure for compressed products. The percentages of spray rate reduction reported in the company survey are in the range 53-68%.

For aluminium, a lung bioavailability value of 3% is reported (DeVoto & Yokel, 1994), which has been considered in this 2-box model. It is generally considered that the cut-off value for droplets/particles to reach the deep lung, and be available for absorption, is $<10\text{ }\mu\text{m}$ (Steiling et al, 2014). This is known as the 'respirable fraction'. Determination of what proportion of a sprayed product is considered as the respirable fraction is based on particle size measurements. Industry data demonstrates that for aerosol spray product, approximately 20% of the spray particles are $<10\text{ }\mu\text{m}$ (unpublished industry data). The remaining 80%, known as the non-respirable fraction (or inhalable fraction) is likely deposited in the upper respiratory tract (nasopharyngeal and tracheobronchial region). For this fraction, mucociliary clearance leads to expectoration or swallowing of the aluminium trapped in the upper respiratory tract, and hence the oral absorption value of 0.1% can be applied (EFSA, 2008).

For the calculation of inhalation exposure, the Applicant used a 2-box model based on the work of Nicas & Mark (2014) and Sahmel *et al.* (2009).

Figure 1: The two-box model described in terms of relevant parameters, with descriptions of parameters (inset)

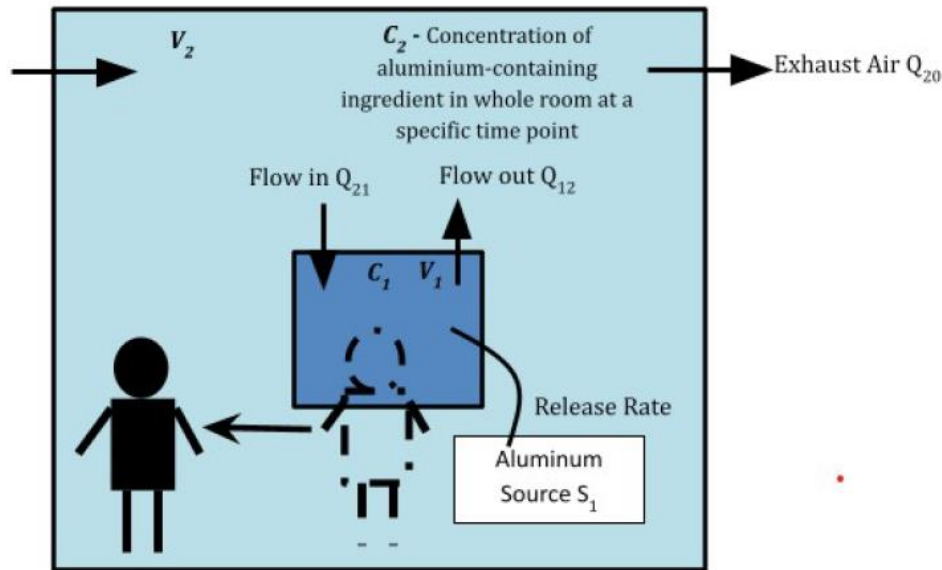


Figure 4: Two-box model described in terms of relevant parameters, with description of parameters (inset).

Where:

- C_1 – aluminium concentration in air in box 1
- C_2 – aluminium concentration in air in box 2
- S_1 – source of aluminium used in box 1
- Q_{12} – airflow from box 1 to box 2 (m^3/min)
- Q_{21} – airflow from box 2 to box 1 (m^3/min)
- Q_{02} – airflow from external world to box 2 (m^3/min) (see Section 3.2.)
- Q_{20} – airflow from box 2 to external world (m^3/min)
- V_1 – volume of box 1 (m^3)
- V_2 – volume of box 2 (m^3)

Mathematically, the mass balance can be described by:

$$\text{Zone 1 : } V_1 (dC_1/dt) = S_1 + Q_{21} C_2(t) + Q_{01} C_0 - (Q_{12} + Q_{10}) C_1(t)$$

$$\text{Zone 2 : } V_2 (dC_2/dt) = S_2 + Q_{12} C_1(t) + Q_{02} C_0(t) - (Q_{21} + Q_{20}) C_2(t)$$

The following parameter values were used for calculating the inhalation factor for input into the Crème model.

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Table 12: Parameters used for calculating the inhalation factor for input into the Crème model

Parameter	Value
Zone 1 volume (V1)	2 m ³ ^e
Time in zone 1 (t1)	2 min ^e
Zone 2 volume (V2)	10 m ³ (bathroom) ^{b,e}
Time in zone 2 (t2)	10 min ^e
Air Flow (Zone 1 -> Zone 2)	7.24 m ³ /min ^c
Air Flow (Zone 2 -> Outside)	0.1 m ³ /min ^c
Human inhalation rate (IR)	13.1 L/min ^d
Emission Duration	0.17 min (DeoSpray) ^a , 0.24 min (HairSpray) ^a , 0.08 min (EaudeParfum, EaudeToilette) ^a

^a Bremmer et al., 2006a

^b Bremmer et al., 2006b

^c ECHA, 2016

^d Salem & Katz, (2006) & Finley et al. (1994)

^e Rothe et al., 2011

Table 12A: Parameter values used for the calculation of the inhalation factor (via the 2 box model) in Scenario 1b

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Parameter	Value
Zone 1 volume (V1)	2 m ³ ^e
Time in zone 1 (t1)	2 min ^e
Zone 2 volume (V2)	10 m ³ (bathroom) ^{b, e}
Time in zone 2 (t2)	10 min ^e
Air Flow (Zone 1 -> Zone 2)	7.24 m ³ /min
Air Flow (Zone 2 -> Outside)	0 m ³ /min
Human inhalation rate (IR)	13.1 L/min
Emission Duration	0.17 min (DeoSpray) ^a , 0.24 min (HairSpray) ^a , 0.08 min (EaudeParfum, EaudeToilette) ^a
% Available for inhalation	100% DeoSpray 100% Hairspray 100% EaudeParfum, EaudeToilette

^a Bremmer et al., 2006a

^b Bremmer et al., 2006b

^c ECHA, 2016

^d Salem & Katz, (2006) & Finley et al. (1994)

^e Rothe et al., 2011

According to the Applicant, the 2-box model requires also as input the quantity of aluminium which is released into the air each minute. This value is calculated by multiplying the product's spray rate (mg/min), the emission duration (min) and aluminium concentration (%) in the product. These three parameters are also used to calculate the total amount of aluminium released (TAR). The TAR is used to estimate the inhalation factor which corresponds to the fraction of TAR that is inhaled during the exposure event, *i.e.* the model divides the total exposure by the TAR. In doing so, the model cancels out the effect of product's spray rate and aluminium concentration on the result; these two parameters can be varied but the inhalation rate remains unchanged. However, dividing the total exposure by the TAR does not completely cancel out the effect of the emission duration. The longer the length of the emission duration, the more product is released into the air and is available for inhalation by the user before the larger product particles, under the effect of gravity, drop towards the floor, exit the area surrounding the user's head, and are no longer available for inhalation. The 2-box model can calculate the exposure per unit of bodyweight by dividing the total exposure by the bodyweight. However, the model is used here to estimate the fraction of product that is typically inhaled by an adult, regardless of their bodyweight. The bodyweight was considered in the Crème model.

Table 13 contains the list of the inhalation exposure inputs used to estimate the inhalation exposure to the spray products, together with the references to the scientific literature. All these factors are applied to the exposure levels as multipliers, as explained in detail in this section.

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Table 13: Inhalation input parameters

Inhalation Factor	DeoSpray – Anti-Perspirant	DeoSpray – Pump	EaudeParfum, EaudeToilette	HairSpray
Adjusted Inhalation factor	0.892%	0.892%	0.234%	1.047%
Respirable fraction (<10 µm) (RF) ^d	20%	2%	2%	20%
Lung Bioavailability Factor for Aluminium ^a	3%	3%	3%	3%
Non-respirable fraction (NRF), calculated as 1-RF	80%	98%	98%	80%
Oral bioavailability (to account for AI from upper airways ^b)	0.1%	0.1%	0.1%	0.1%
Compression factor ^c	53-68%	NA	NA	NA

^a DeVoto & Yokel, 1994

^b EFSA, 2008

^c Values submitted in the company survey

^d Based on particle size measurements (unpublished company data).

In the following, the step-wise approach used by the Applicant is described:

Step 1: the model selects each diary and retrieve the list of cosmetic products used each day. For example, the diary of subject #1 on the first day report the use of an “DeoSpray – Anti-Perspirant” deodorant and of body lotion.

Step 2: the model randomly selects one of the formulas used in “DeoSpray – Anti-Perspirant” deodorants reported by the companies. The amount sold of each formula is used as a statistical weight to determine the frequency with which each formula is selected. Let’s assume that the model selects formula F7, that was reported by company A, which contains 10% of MAGNESIUM ALUMINUM SILICATE (ARGILLA) and 15% of ALUMINUM CHLOROHYDRATE.

Step 3: the model goes in the ingredient list of company A and retrieves the aluminium concentrations related to the two aluminium ingredients used in formula F7. In case the company reported a range of aluminium concentrations, the model randomly selects a number within the range. Let’s assume in this case the concentration 2% of aluminium concentration MAGNESIUM ALUMINUM SILICATE (ARGILLA) and 12.7% to ALUMINUM CHLOROHYDRATE

Step 4: the model calculates the total aluminium concentration in formula F7 as the sum of the products between the concentration of the aluminium ingredients in the formula times the concentration of aluminium in each ingredient, as shown the following equation:

$$\text{Total-Al-concentration } (C) = 10\% * 2\% + 15\% * 12.7\% = 2.105\%$$

Step 5: the model calculates the exposure level of aluminium by entering the total aluminium concentration in equation (1). Let’s assume that the selected “DeoSpray – Anti-Perspirant” deodorant is a compressed one with compression factor equal to 53%, the used amount is 1.43 g (or 1,430 mg), which is the applied daily amount of spray deodorant recommended as default value in exposure assessments by the SCCS 10th notes of guidance (SCCS 2018), and the bodyweight of the subject is 60 kg. Then the resulting exposure level is calculated as

$$E\left(\frac{mg}{kg}\right) = \frac{1430(mg) \times 0.892\% \times 53\% \times 2.105\%}{60kg} = 0.002372$$

Step 6: the exposure level E calculated in the previous step is then split into its respirable and non-respirable components. The respirable component is equal to E multiplied times the respirable fraction RF and the lung bioavailability factors BL which are equal to 20% and 3%, respectively (see Table 25).

$$E_{respirable}\left(\frac{mg}{kg}\right) = E \times RF \times BL = 1.42E - 05$$

The non-respirable component is instead equal to E multiplied by the non-respirable fraction NF and the upper respiratory tract bioavailability factor BUA which are equal to 80% and 0.3%, respectively (see Table 25).

$$E_{non-respirable} \left(\frac{mg}{kg} \right) = E \times NF \times BUA = 5.69 E - 06$$

Step 7: the model repeats the above steps for each consumption event of the subject where a “DeoSpray – Anti-Perspirant” deodorant has been used. Then calculate the total respirable and non-respirable exposure levels and divide them by 7 (this is the number of days recorded in each diary) to calculate the average daily exposure.

The aluminium concentration for each product type is assigned at subject level, i.e. the model assumes that the subject uses the same product over the week hence the concentration does not change. For example, if a subject reported the usage of “DeoSpray – Anti-Perspirant” deodorant in three events, the model assigns the same aluminium concentration to all the three events.

The model analyses the exposure to aluminium as a single chemical, thus removing the dependence on source of the ingredient. Information about the exposure to each aluminium ingredient is stored by the model but not analysed.

Additional information provided by the Applicant after public consultation (22.09.2022)

Scenario 1b uses more conservative parameters in the Two-box model and therefore more conservative inhalation parameters which adds an additional layer of conservatism. These values are given in Table 12A.

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Table 12A: Parameter values used for the calculation of inhalation factor (via the 2-box model) in Scenario 1b

Parameter	Value
Zone 1 volume (V1)	2 m ³ ^e
Time in zone 1 (t1)	2 min ^e
Zone 2 volume (V2)	10 m ³ (bathroom) ^{b, e}
Time in zone 2 (t2)	10 min ^e
Air Flow (Zone 1 -> Zone 2)	7.24 m ³ /min
Air Flow (Zone 2 -> Outside)	0 m ³ /min
Human inhalation rate (IR)	13.1 L/min
Emission Duration	0.17 min (DeoSpray) ^a , 0.24 min (HairSpray) ^a , 0.08 min (EaudeParfum, EaudeToilette) ^a
% Available for inhalation	100% DeoSpray 100% Hairspray 100% EaudeParfum, EaudeToilette

^a Bremmer et al., 2006a

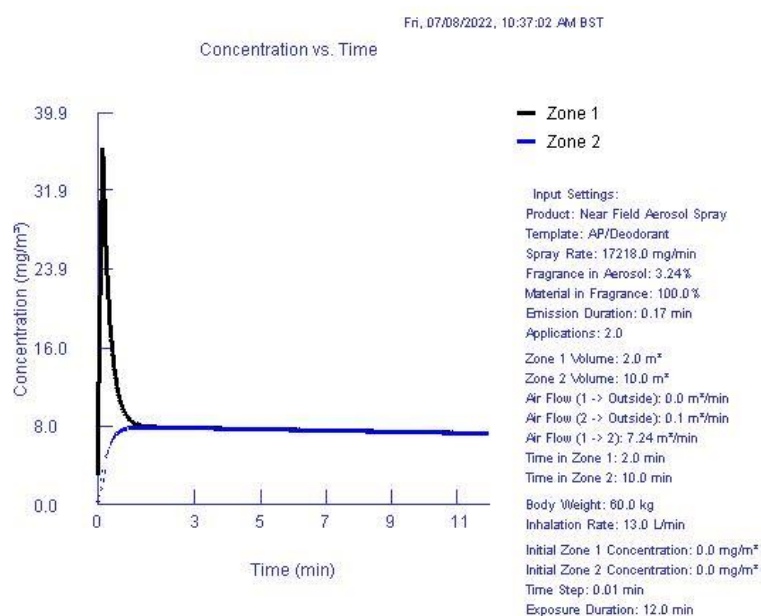
^b Bremmer et al., 2006b

^c ECHA, 2016

^d Salem & Katz, (2006) & Finley et al. (1994)

^e Rothe et al., 2011

Figure 2: Output graph from RIFM-2 box model with zone 1 to zone 2 ventilation rate set to 7.24 m³/min



SCCS comment

In the calculations of inhalation exposure, a very high airflow from zone 1 to zone 2 has been assumed, without support by literature (the reference cited (ECHA, 2016) does not report the respective value, neither can it be found in the references cited therein). However, based on the SCCS Notes of Guidance (11th Revision, SCCS/1628/21), a conservative approach is warranted, with the assumption of no ventilation. This means that the inhalation factor used in the submission dossier is too low.

A reference for the compression factor used in step 5 is not given.

The Applicant cites unpublished industry data for the assumption that approximately 20% of the spray particles are $<10\ \mu\text{m}$ for aerosol spray products. This data is not available to the SCCS and therefore cannot be evaluated.

The procedure for deriving the factor "available for inhalation" is questionable, since the experiments used to derive the dermal absorption rate aimed at deriving a worst case for dermal exposure. As explained in the comments on bioavailability, subtracting a worst-case dermal exposure from the total 100% does not result in conservative estimates for inhalation. A conservative estimate for inhalation would e.g. result from subtracting a lower estimate for dermal exposure. In consequence, the SCCS does not accept the respective factor "available for inhalation" (1-DRF) proposed in Table 11, and the proposed inhalation parameters in Table 13.

During the commenting period, the Applicant has submitted a new exposure calculation for a scenario designated as scenario 1b. In this calculation, the availability for inhalation was set to 100% and the ventilation to outside was set to zero. This results in more conservative estimates for inhalation exposure to the sprayable products. The SCCS considers that the transfer rate between the Box 1 and 2 is still too high, because - as also illustrated by the Figure submitted by the Applicant - the substance is completely distributed into Box 2 within less than 2 min. This means that the assumption of 2 min in Box 1 as suggested by Rothe *et al.*, 2011 is not observed. Therefore, for deodorant as the most important contributor an additional exposure term was added by the SCCS for the first 2 min in Box 1 based on the 2-Box model submitted in an earlier submission (see below).

3.2.4.6 Exposure calculations and Scenarios for cosmetics

According to the Applicant, a tiered approach that starts from a deterministic model up to a fully probabilistic model was used to assess the exposure to aluminium contained in personal care products, foods and medications (antacids). The aim was to estimate the total amount of aluminium to which humans are exposed from all these various sources. This amount is otherwise known as aggregate exposure.

The Creme Global model was used as the main tool to assess aggregate exposure to aluminium. The Creme tool was run first in a deterministic tier 1 mode, which simply summed the P95 exposure values for the individual products to obtain the aggregate exposure, and then in a Tier 2, probabilistic mode, to estimate the impact of the two approaches on the exposure levels related to cosmetic products.

The Creme Global model is based on the following equation for calculating the daily chemical exposure for a group of cosmetic products i and a single subject j :

$$E_{ij} = \frac{F_{ij} \times A_{ij} \times X_i \times C_{ij}}{7 \times BW_j} \quad (1)$$

Where each term on the right-hand side can be a fixed estimate or drawn from a distribution and each term is understood as follows:

E_{ij} is the systemic/internal exposure in subject j to aluminium from product group i [$\mu\text{g/kg/day}$]

F_{ij} is the frequency of applications/consumption events by subject j of product group i [day⁻¹] during the seven-day Kantar survey.

A_{ij} is the amount used by subject j per application/consumption event of product group i [μg]

X_i represents the exposure factors, reported in Section 3.9, for product group i [%] multiplied one by each other. These are independent of the subject.

C_{ij} is the concentration of aluminium in product group i [unitless] assigned to subject j , BW_j is the consumer's bodyweight [kg]

A group of products is one for which all included products are considered equivalent. For example, various brands and colours of lipstick, etc. are assessed together under the product group lipstick.

Aggregate aluminium exposure for each individual subject is estimated by

$$SE_j = \sum_{i=1}^n E_{ij} \quad (2)$$

Where:

SE_j is the total (or aggregated) systemic/internal exposure to aluminium from all products [$\mu\text{g/kg/day}$] for subject j

E_{ij} is the systemic/internal exposure to aluminium from product group i [$\mu\text{g/kg/day}$] for subject j

The population-level exposure can then be calculated from the individual subject-level exposures. The population can be defined in two ways. The first is the Total Population, *i.e.* all subjects in the survey, and the other is the Exposed Population, *i.e.* only those consumers who are exposed to aluminium. Given that there are two potential populations that can be used to characterise exposure, an immediate question posed is to determine which one is most appropriate. One guiding principle is that for aggregate exposure resulting from multiple sources that are used by most of the population (e.g. all categories of cosmetics and personal care products or most foods in the diet), then exposure is well represented by the Total Population. However, if exposure is due to a small number of products or is due to an infrequently occurring substance, then the Exposed Population is likely the more appropriate set to use. This is so that there is not inappropriate dilution of exposure statistics by the inclusion of large number of zero values in their calculation.

Then the population daily exposure (PE) can be written as:

$$PE = Stat(E_1, E_2, \dots, E_N) \quad (4)$$

where E_j is the daily exposure for individual j , and the $Stat()$ function is typically something like the 95th percentile.

The main differences in the values of the model parameters that were used in the three scenarios are summarized in Table 14.

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Table 14: Summary of the differences in value of the main model parameters used in the three scenarios

Table 18: Summary of the differences in value of the main model parameters used in the three scenarios.

	Product as labelled in the model	Conservative, screening analysis based on single value estimates at P95 for cosmetics	Probabilistic model		
		Scenario 1 Max Concentration	Scenario 1 Occurrence	Scenarios 2 & 3 Concentration	Scenario 2 Occurrence Scenario 3 Occurrence
1	AfterShave	2.150%	100%	Distribution (see Table 6)	30%
2	BarSoap	0.070%			35%
3	BodyLotion	3.810%			30%
4	BodySpray	1.180%			5%
5	DeoRollOn – Stick	7.730%			75%
6	DeoRollOn – RollOn	5.630%			95%
7	DeoRollOn – Gel	6.180%			100%
8	DeoRollOn – Wipes	0.000%			80%
9	DeoSpray – AP	3.240%			90%
10	DeoSpray – Pump	4.876%			100%
11	EaudeParfum, EaudeToilette	0.050%			40%
12	EyeShadow	43.310%			100%
13	FaceMoisturizer	10.590%			35%
14	HairSpray	0.000%			5%
15	HairStyling	1.190%			15%
16	HandCream	0.860%			30%
17	Lipstick	14.620%			90%
18	LiquidHandSoap	0.000%			50%
19	LiquMakeupFoundation	6.590%			95%
20	Mascara	3.130%			35%
21	Mouthwash	0.000%			60%
22	RinseoffConditioner	7.140%			35%
23	Shampoo	7.140%			40%
24	Showergel	0.890%			50%
25	Toothpaste	3.18%			55%
26	EyeLiner	15.760%			60%
27	MakeupRemover	10.590%			25%
28	Food and drinking water	see Table 10	100%		100%
29	Antacids	see Table 12	100%		100%

Deterministic calculation for Scenario 1:

Based on point estimates of each parameter of the model, the exposure was calculated by multiplying the factors as in equation (1) above for each product individually; however, the calculation cannot be carried out at subject level but only at population level.

The point estimates of the different factors are worst-case estimates (upper percentiles of the value distributions). Creme Global, in accordance with the Aluminium Consortium, decided to use as default values for the model parameters:

- the maximum concentration value of aluminium in each product category
- the 95th percentiles of the value distributions retrieved from the above-mentioned surveys and databases for all the other parameters.
- set the aluminium occurrence equal to 100% for each product category.

To calculate the systemic exposure in a deterministic model, a basic method is to simply sum up the population exposures from the individual products as:

$$SE = Stat(E_1) + Stat(E_2) + \dots + Stat(E_M) \quad (5)$$

where the $Stat(E_i)$ terms are the population exposure statistics for a single product E_i . The expectation here was that the sum of these statistics would provide a good estimate of the corresponding statistic for the aggregate statistic for the systemic exposure. However, for most statistics, there is little mathematical reason to suggest that this summation would be a good estimate.

The model analysed the exposure to aluminium as a chemical from each formulation, by taking into consideration all ingredients which might contribute aluminium to the formulation, thus removing the dependence on the source of the ingredient. Information about the exposure to each Al-ingredient was stored by the model but not analysed. Equation (1) was used to estimate the dermal and oral exposure levels.

The oral route is applicable to lipsticks and toothpaste products which can be ingested. In this case, the X_i factor corresponds to the oral bioavailability factor.

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Table 15: Summary statistics of the exposure to Al from the use of cosmetics per route of exposure for the three different scenarios provided by the Applicant

Route	Statistics	Exposed Population			Total Population		
		Scenario 1	Scenario 2	Scenario 3	Scenario 1	Scenario 2	Scenario 3
Dermal	Count	104780	104780	101364	104836	104836	104836
	Mean*	0.01657	0.002565	0.001727	0.01656	0.002562	0.001663
	P50*	0.01004	0.001087	0.0004282	0.01003	0.001085	0.0003614
	P95*	0.0529	0.0102	0.007553	0.05283	0.01019	0.007370
Ingestion	Count	95760	95760	61064	104836	104836	104836
	Mean*	0.03174	0.0006820	0.0006595	0.02861	0.0006146	0.0003831
	P50*	0.02617	0.0002215	0.0001798	0.02342	0.0001711	2.65e-05
	P95*	0.07635	0.002450	0.002386	0.07404	0.002314	0.001617
Inhalation Non-Respirable	Count	73328	73328	48984	104836	104836	104836
	Mean*	0.002787	0.000932	0.001324	0.00192	0.0006423	0.0005856
	P50*	5.4e-06	3.80e-06	0.0002713	2.3e-06	1.1e-06	0.0
	P95*	0.013054	0.004840	0.005737	0.01089	0.003906	0.003656
Inhalation Respirable	Count	73328	73328	48984	104836	104836	104836
	Mean*	0.019	0.006355	0.008920	0.013084	0.004383	0.003944
	P50*	3.4e-06	6.14e-06	0.0007796	1.43e-06	8.0e-07	0.0
	P95*	0.09735	0.03445	0.04123	0.0804	0.02746	0.02528
Total Systemic (Combined Oral, Dermal & Inhalation)	Count	104780	104780	101413	104836	104836	104836
	Mean*	0.06024	0.00821	0.006820	0.06018	0.008200	0.006577
	P50*	0.04486	0.002665	0.001384	0.0448	0.002659	0.001219
	P95*	0.1671	0.03647	0.03317	0.1671	0.03647	0.03238

* Units for Mean, P50 and P95 are µg/kg bw/day.

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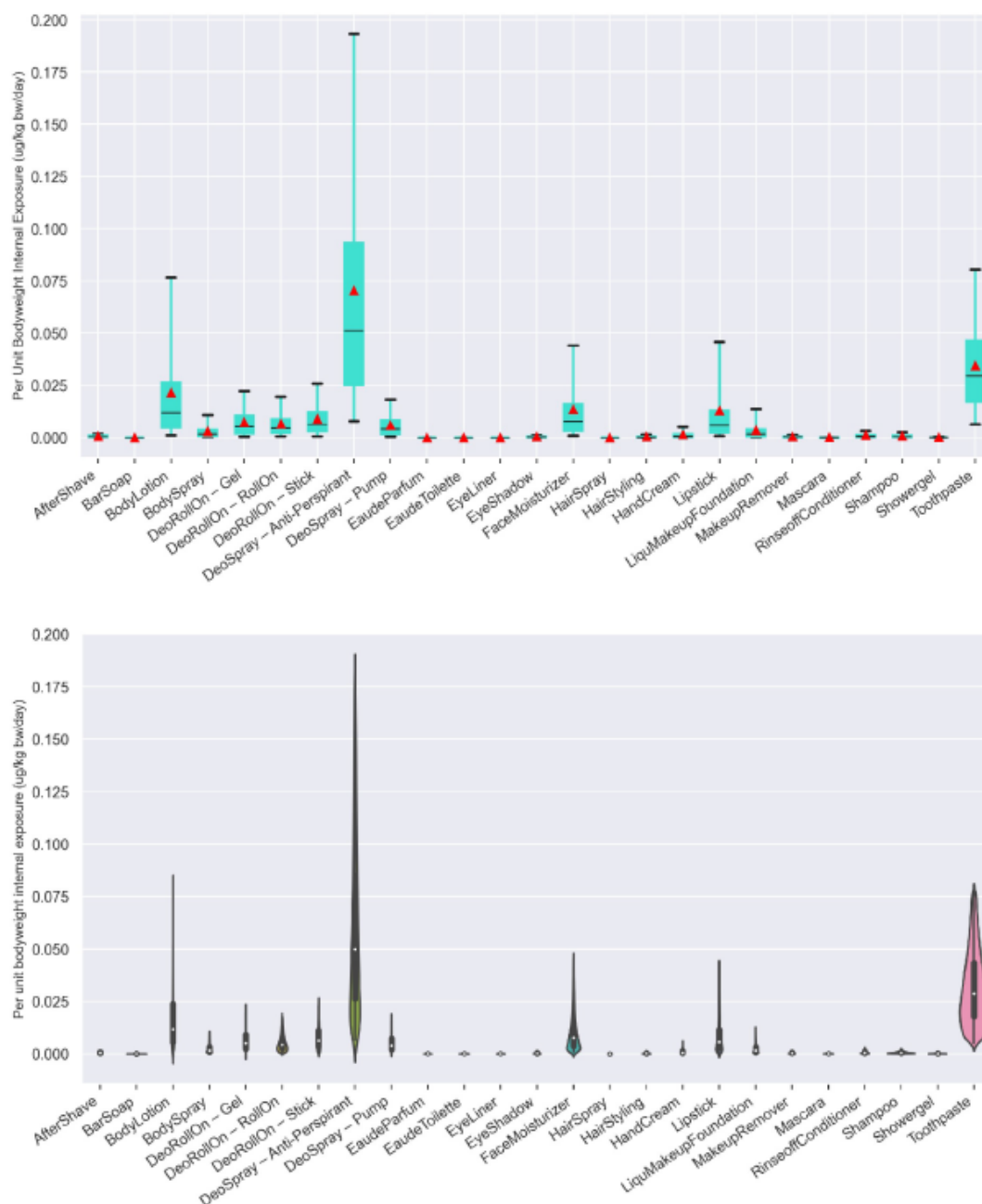


Figure 1: Distribution of internal exposure levels per cosmetic product, scenario 1

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In a previous dossier (Cosmetics Europe, 2016), the Applicant had provided a deterministic 2-Box-Model calculation for the systemic body burden of aluminium via the lung. When aluminium chlorohydrate was used in spray/aerosol antiperspirants, a 2-Box exposure model was used. The 2-Box model calculation was performed using the input parameters given in Table 16.

Table 16: Parameter values used for the calculation of lung exposure in the 2-Box model (Cosmetics Europe, 2016)

		Reference
Distribution volume at time point 1 (V1)	2 m ³	Rothe <i>et al.</i> , 2011
Exposure time 1 (t1)	2 min	Rothe <i>et al.</i> , 2011
Distribution volume at time point 2 (V2)	10 m ³	Rothe <i>et al.</i> , 2011
Exposure time 2 (t2)	10 min	Rothe <i>et al.</i> , 2011
Human breath minute volume (BR)	13.1 l/min	Finley <i>et al.</i> , 1994; Salem & Katz, 2006
Mean human body weight (BW)	60 kg	SCCS (2015), 9th notes of guidance
Airborne Fraction (AF)*	76.5%	Steiling <i>et al.</i> , 2012
Respirable Fraction (<10 µm) (RF)	20%	based on particle size measurements (unpublished company data) The cut-off value for droplets/particles reaching the deeper lung is set as <10 µm - SCCS (2015), 9th notes of guidance
Non-Respirable fraction (NRF)	80%	The inhaled Al that is trapped in the upper respiratory tract (and does not reach the deeper lung) is also considered
Lung deposition rate	20%	Lippmann (1977)
Gas exchange factor	75%	Rothe <i>et al.</i> , 2011
Concentration of Al in spray formulation incl. propellant (C)	2.86%	Maximum value reported by industry
Amount sprayed per day (A)	6.1 g	Hall <i>et al.</i> , 2007 (6.1 g is the 90 th percentile value of daily deo/ap spray usage (including the propellant and solvent))
Bioavailability of Al from alveoli	3%	DeVoto & Yokel, 1994
Bioavailability of Al from upper airways	0.3%	EFSA J (754), 1-34, 2008 (typical value for oral bioavailability)

* It should be noted that ACH is not a volatile substance and the fraction that is present on the skin would not become volatile and be available for inhalation.

Calculation of the substance amount relevant for exposure (EA)

The amount of Al that will be available for inhalation after spraying is calculated as follows:

$$EA [g] = A [g] \times C [\%] \times AF [\%] \times RF [\%] / NRF [\%]$$

The Applicant further calculated the systemic exposure dose for aluminium upon inhalation as follows:

For the respirable fraction:

$$EA [g] = A [g] \times C [\%] \times AF [\%] \times RF [\%]$$

$$EA_{resp} = 6.1 \text{ g} \times 0.0286 \times 0.765 \times 0.2 = 0.02669 \text{ g}$$

For the non-respirable fraction:

$$EA [g] = A [g] \times C [\%] \times AF [\%] \times NRF [\%]$$

$$EA_{non-resp} = 6.1 \text{ g} \times 0.0286 \times 0.765 \times 0.8 = 0.10677 \text{ g}$$

Calculation of the Exposure Dose (ED)

The inhaled amounts (IM) at time point 1 and 2 (IM 1/2, 2/10 min) are calculated with the following formula:

$$IM_{1/2} [mg] = (EA [mg] / V_{1/2} [l]) \times BR [l/min] \times t_{1/2} [min]$$

For the respirable fraction:

$$\text{first 2 minutes: } IM_1 [mg] = (26.69 / 2000) \times 13.1 \times 2 = 0.350$$

$$\text{following 10 minutes: } IM_2 [mg] = (26.69 / 10000) \times 13.1 \times 10 = 0.350$$

For the non-respirable fraction:

$$\text{first 2 minutes: } IM_1 [mg] = (106.77 / 2000) \times 13.1 \times 2 = 1.399$$

$$\text{following 10 minutes: } IM_2 [mg] = (106.77 / 10000) \times 13.1 \times 10 = 1.399$$

The ED is then calculated as follows:

$$ED_{(inhal)} [mg/kg \text{ bw/d}] = (IM_1 + IM_2 \text{ mg}) / BW [kg]$$

$$ED_{(resp)} [mg/kg \text{ bw/d}] = (0.350 + 0.350) / 60 = 0.01167$$

$$ED_{(non-resp)} [mg/kg \text{ bw/d}] = (1.399 + 1.399) / 60 = 0.04663$$

$$ED_{(total)} [mg/kg \text{ bw/d}] = 0.01167 + 0.04663 = 0.0583$$

Thus, the total amount of Al exposure via inhalation within 12 minutes after spraying of an antiperspirant spray in a 10 m³ room according to this calculation is 0.0583 mg/kg bw/day.

Additional information provided by the Applicant after public consultation (22.09.2022)

Calculations with scenario 1b result in exposure estimates highlighted in Table 18A.

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Table 15A: Summary statistics of the exposure to Al from the use of cosmetics per route of exposure for the four different scenarios provided by the Applicant

Route	Statistic	Exposed Population				Total Population			
		Scenario 1	Scenario 1b	Scenario 2	Scenario 3	Scenario 1	Scenario 1b	Scenario 2	Scenario 3
Dermal	Count	104780	104780	104780	101364	104836	104836	104836	104836
	Mean*	0.01657	0.01858	0.002565	0.001727	0.01656	0.01857	0.002562	0.001663
	P50*	0.01004	0.01102	0.001087	0.0004282	0.01003	0.011	0.001085	0.0003614
	P95*	0.0529	0.05988	0.0102	0.007553	0.05283	0.05987	0.01019	0.007370
Ingestion	Count	95760	95760	95760	61064	104836	104836	104836	104836
	Mean*	0.03174	0.03179	0.0006820	0.0006595	0.02861	0.02866	0.0006146	0.0003831
	P50*	0.02617	0.02611	0.0002215	0.0001798	0.02342	0.02342	0.0001711	2.65e-05
	P95*	0.07635	0.07683	0.002450	0.002386	0.07404	0.07471	0.002314	0.001617
Inhalation Non-Respirable	Count	73328	73328	73328	48984	104836	104836	104836	104836
	Mean*	0.002787	0.003756	0.000932	0.001324	0.00192	0.00259	0.0006423	0.0005856
	P50*	5.4e-06	1.712e-04	3.80e-06	0.0002713	2.3e-06	1.58e-05	1.1e-06	0.0
	P95*	0.013054	0.01761	0.004840	0.005737	0.01089	0.01473	0.003906	0.003656
Inhalation Respirable	Count	73328	73328	73328	48984	104836	104836	104836	104836
	Mean*	0.019	0.02592	0.006355	0.008920	0.013084	0.01786	0.004383	0.003944
	P50*	3.4e-06	7.25e-04	6.14e-06	0.0007796	1.43e-06	9.74e-06	8.0e-07	0.0
	P95*	0.09735	0.13124	0.03445	0.04123	0.0804	0.10971	0.02746	0.02528
Total Systemic (Combined Oral, Dermal & Inhalation)	Count	104780	104780	104780	101413	104836	104836	104836	104836
	Mean*	0.06024	0.0677	0.00821	0.006820	0.06018	0.06767	0.008200	0.006577
	P50*	0.04486	0.04785	0.002665	0.001384	0.0448	0.04781	0.002659	0.001219
	P95*	0.1671	0.19911	0.03647	0.03317	0.1671	0.19906	0.03647	0.03238

* Units for Mean, P50 and P95 are µg/kg bw/day.

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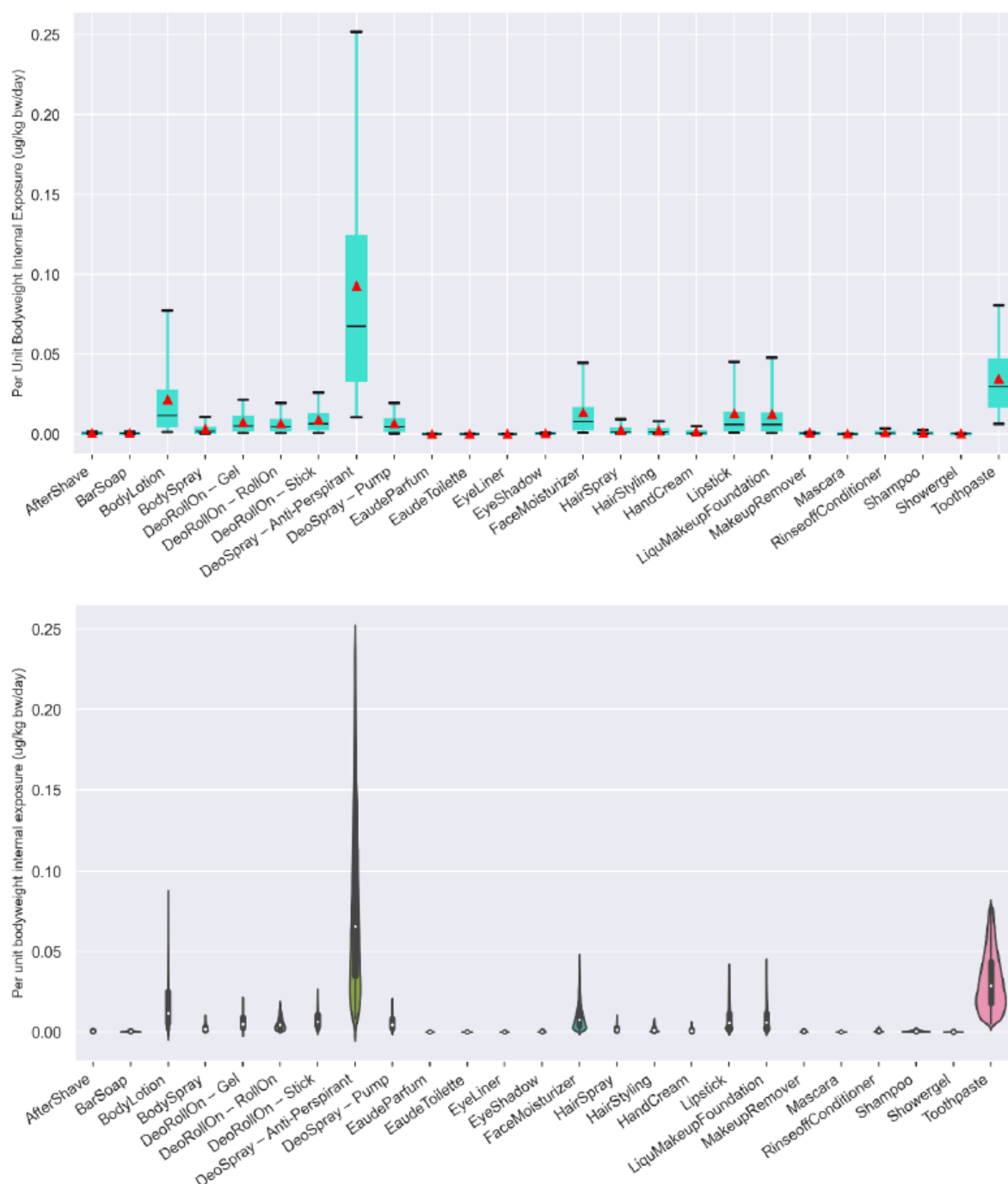


Figure 15A Distribution of internal exposure levels per cosmetic product, scenario 1b

SCCS comment

Of the presented scenarios, only Scenario 1 can be accepted according to the SCCS Notes of guidance (SCCS/1628/21), because Scenarios 2 and 3 use distributions for the concentrations in products and not the maximum levels. Scenario 3 in addition uses occurrence data that may change over time.

The SCCS in principle accepts the new inhalation exposure estimates calculated for Scenario 1b for sprayable products. However, since the transfer rate from Box 1 to Box 2 results in

less than 2 min residence time of the substance in Box 1 for the most relevant product deodorant, the SCCS adds an exposure estimate for the first 2 min based on the calculations in a previous dossier. For the other sprayable products this amount is considered to be covered by other conservatisms in the assumptions.

Adding up the respirable and non-respirable amounts from the first 2 min yields 1.749 mg, divided by 60 kg and with an AF of 100% instead of 76.4% (which is not accepted due to derivation from a dermally conservative value) yields 0.038 mg/kg BW /day.

However, since in Scenario 1b maximal amounts were changed for some product categories without justification, for dermal and oral exposure SCCS will use the original exposure assessment from Scenario 1 and derive the aggregate exposure over routes by adding the inhalation contribution from Scenario 1b.

3.2.4.7 Aggregate exposure with food and antacids

According to the Applicant, concentrations of aluminium in food were defined based on the 2006 UK Total Diet Study (Rose, *et al.*, 2010) which outlines aluminium concentration levels in 20 food groups, based on measurements. The 20 food groups were defined from the British Total Diet Study for Monitoring Food Constituents from 1981 (Peattie, 1983). Drinking water is the only food group not studied in Peattie, 1983. The aluminium concentration value of drinking water has been retrieved from the EU Drinking Water Directive 98/83/EC of 3 November 1985, which set a concentration limit of 0.2 mg/L. The WHO Drinking Water Guidelines (WHO, 2011) explain that it is reasonable to expect municipal drinking water treatment plants to contain between 0.1-0.2 mg/L. Estimates of aluminium in foods are for the element itself rather than an Al-ingredient, so a breakdown by Al-ingredient was not required.

According to the Applicant, the concentrations of aluminium in antacids are drawn from Micromedex data (Webb, 2000) and individual product websites. The Al-amount in one dosing ranges from 48.5 – 207 mg for different products.

Frequency of use and co-use in food was taken from the Dutch (DNFCS), Irish (NSIFCS) and UK (NDNS) national dietary surveys. The NSIFCS and NDNS surveys are 7-day semi-weighted food diaries and the DNFCS comprises 2 non-consecutive 24-hour diaries. Co-use of foods is automatically taken care of in the food consumption diaries.

Frequency of use data for antacids was not identified for European consumers and so US data was used as a proxy. Frequency of use data of antacids comes from a 30-day weighted US National Health and Nutrition Examination Survey (NHANES) 2007-2008 survey on supplement use. The results are based on a representative sample of 10,537 people in the US. Antacids are independent of all other products because the model does not assume any correlation between the consumption of antacids and the consumption of foods and cosmetics. Also, not all the subjects were considered as antacid-consumers by the model; only those subjects randomly matched with antacid-consumer subjects from the NHANES survey were considered as such. Hence, it is useful to contrast exposure estimates for the general population, which models less than 5% of consumers using antacids, and the 'exposed population' which assumes that antacid use is 100%.

The data of aluminium concentrations in food and drinking water are presented for aluminium as a standalone chemical not bounded to any specific compound, while antacids may contain different Al-ingredients. To make sure that the results obtained from all the different sources are comparable, the analyses must be carried out on the final concentrations of aluminium in every media.

The calculation of the exposure levels related to foods and antacids follows the same process previously described for cosmetics. The only difference is in the equation to calculate the exposure levels; exposure from foods and antacids must take in account other factors so equation (1) is to be substituted with two proper equations.

The aluminium exposure levels from food are calculated as

$$E_{ij} = \frac{F_{ij} \times A_{ij} \times X \times C_{ij}}{n \times BW} \quad (6)$$

Where each term on the right-hand side can be a fixed estimate or drawn from a distribution

and each term is understood as follows:

E_{ij} is the systemic/internal exposure to aluminium from food group i [$\mu\text{g}/\text{kg}/\text{day}$]

F_{ij} is the frequency of consumption events of food group i [day^{-1}] during the survey of length n days

A_{ij} is the amount consumed at each consumption event of food group i [μg]

X is the oral bioavailability factor [%]

C_{ij} is the concentration of aluminium in food group i [unitless]. Food groups according to the Applicant were: Bread, Miscellaneous cereals, carcass meat, offal, meat products, poultry, fish, oils and fats, eggs, sugars &

BW is the consumer's bodyweight [kg]

The aluminium exposure levels from antacids are calculated as:

$$E_{ij} = \frac{F_{ij} \times A_{ij} \times X \times C_{ij} \times P_{ij}}{30 \times BW} \quad (7)$$

Where each term on the right-hand side can be a fixed estimate or drawn from a distribution and each term is understood as follows:

E_{ij} is the systemic/internal exposure to aluminium from antacid of brand i [$\mu\text{g}/\text{kg}/\text{day}$]

F_{ij} is the frequency of consumption events of antacid of brand i [day^{-1}] during the survey of length 30 days

A_{ij} is the recommended serving size of antacid of brand i [μg]

X is the oral bioavailability factor [%]

P_{ij} is the occurrence of aluminium in antacid of brand i [unitless]

C_{ij} is the concentration of aluminium in antacid i [unitless]

BW is the consumer's bodyweight [kg]

Table 17: Summary statistics of the internal exposure to Al per route for Scenario 1

Route	Statistics	Exposed Population				
		Ingestion	Dermal	Inhalation Respirable	Inhalation Non-Respirable	Total
All Ingested Al**	Count	104836	0	0	0	104836
	Mean*	0.1175	0.0000	0.0000	0.0000	0.1175
	P95*	0.1966	0.0000	0.0000	0.0000	0.1966
Antacids	Count	4264	0	0	0	4264
	Mean*	0.2341	0.0000	0.0000	0.0000	0.2341
	P95*	1.0391	0.0000	0.0000	0.0000	1.0391
Cosmetics	Count	95760	104780	73328	73328	104780
	Mean*	0.03174	0.01657	0.01899	0.002786	0.06023
	P95*	0.07636	0.05288	0.09733	0.01306	0.16715
Food	Count	104836	0	0	0	104836
	Mean*	0.0749	0.0000	0.0000	0.0000	0.0749
	P95*	0.1253	0.0000	0.0000	0.0000	0.1253

* Units for Mean and P95 are µg/kg bw/day.

** "All Ingested Al" is the combination of exposure from food, from antacids and from ingested cosmetics.

Conclusions by the Applicant:

- Food is the principal overall source of exposure to aluminium for the majority of the population.
- The population cohort taking antacids have the highest exposure to aluminium.
- Probabilistic estimates (Scenario 2 and 3) indicate that cosmetics contribute no more than 7-9% of mean aggregate exposures to aluminium, and 20-23% of P95 aggregate exposures, suggesting cosmetics are a minor source of aggregate consumer exposure.
- While the output of this exposure estimate suggests that inhalation exposure (primarily of aerosol deodorants) appears to be the main route of exposure to aluminium from cosmetics, the 2-Box model methodology is very conservative and overestimates inhalation exposure. There is scope to further refine this estimate with experimental measurements if needed.
- Overall, the margin of safety relative to the point of departure identified by the SCCS is sufficiently protective (4900 for Scenario 2, P95).
- In the context of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) tolerable weekly intake (TWI) of 2 mg/kg bw/week, which is equivalent to an internal systemic exposure of 1.8 µg/kg bw/day, total consumer exposure represents a small contribution to the tolerable intake, with cosmetics making a minor contribution of less than 0.5% (mean) and 2% (95th percentile) of the tolerable intake.

SCCS comment

The SCCS notes that food may contribute to the aggregate exposure to aluminium in the same order of magnitude as cosmetics, when the conservative estimate for cosmetics using maximum use levels is compared to the aggregate estimates for food. Pharmaceuticals such as antacids may contribute to a higher proportion but are consumed by only a small fraction of the population under different risk-benefit considerations.

3.3 TOXICOLOGICAL EVALUATION

The data related to toxicological evaluation were assessed and commented upon by the SCCS in the previous Opinion (SCCS/1613/19). Only SCCS' comments and main conclusions are included in this section.

General toxicity

The toxicological evaluation is focused on the toxicity of aluminium compounds relevant to the risk assessment of cosmetic ingredients containing aluminium. There is an extensive body of literature on the health effects and toxicity of aluminium; a number of extensive reviews and authoritative evaluations were published before 2014 (WHO IPCS 1997; Krewski *et al.*, 2007; ATSDR, 2008; EFSA, 2008; FAO/WHO JECFA 2007; Environment Canada & Health Canada 2010; AFSSAPS 2011; FAO/WHO JECFA, 2012; VKM 2013; Willhite *et al.*, 2014). For the 2017 SCHEER Opinion on aluminium in toys, a literature search covering the period from 01/01/2008 until 31/01/2017 was performed. The evaluation by JECFA (2011) was based on new data which included a developmental toxicity study specifically evaluating neurobehavioural endpoints (Poirier *et al.*, 2011). The LOAELs identified in these studies were consistent with the body of data reviewed previously by other committees; however, the oral developmental toxicity study in rats provided a suitable and robust NOAEL for risk assessment (30 mg/kg bw/day). By applying the standard uncertainty factor of 100 to this NOAEL and considering the bioavailability of aluminium citrate, the JECFA considered it appropriate to revise the PTWI (provisional tolerable weekly intake) upward to 2 mg/kg bw/week. This new data by the JECFA Committee therefore supersedes its earlier Opinions in 2008 and does not contradict the 2008 EFSA Opinion. The SCCS agrees on the NOAEL of 30 mg/kg bw/day used by JECFA for risk assessment.

Irritation/sensitisation

Local dermal effects have been observed when aluminium compounds (10% [w/v] chloride, nitrate) have been applied to the skin of mice, rabbits and pigs over five-day periods (once per day) including epidermal damage, hyperkeratosis, acanthosis and microabscesses (Lansdown, 1973). In this study, these effects were not observed with aluminium acetate, hydroxide or chlorohydrate compounds (SCCS/1626/20 Final version Addendum to the scientific opinion SCCS/1613/19 on the safety of aluminium in cosmetic products (lipstick) - Submission II).

Aluminium compounds are widely used in antiperspirants without acute harmful effects to the skin. Some people, however, may be unusually sensitive to topically-applied aluminium compounds. Skin irritation has been reported in human subjects following the application of aluminium chloride hexahydrate in ethanol used in a high-dose (20% ACH) formulation for the treatment of axillary or palmar hyperhidrosis (excessive sweating) (Ellis and Scurr, 1979; Goh, 1990; Reisfeld & Berliner, 2008) and after use of a crystal deodorant containing alum (Gallego *et al.*, 1999).

Although some high-strength antiperspirants used in hyperhidrosis treatments, using aluminium chloride, have been associated with irritation of the axilla, the long history of cosmetic antiperspirant use would suggest that irritation of the axilla is uncommon. There are several examples of cosmetic product formulations that include raw materials that are irritant in isolation, yet acceptable amongst consumers (e.g. surfactants, menthol).

With respect to skin sensitisation, the SCCS agrees that the available animal studies show that aluminium compounds used in antiperspirants are not skin sensitising. There is limited evidence that aluminium compounds can cause contact allergy in humans. However, taking into account the widespread use of these compounds, the SCCS considers this to be a rare phenomenon.

Mutagenicity/Genotoxicity

The most commonly reported mode of genotoxic action is induction of oxidative stress by aluminium ions. The other suggested MoA is inhibition by Al ions of proteins involved in mitotic spindle function. Hence, an existence of a threshold mechanism for Al ions can be assumed. Considering all the data, the SCCS is of the opinion that under the scenarios of dermal exposure in cosmetics, aluminium is not likely to pose a risk of genotoxic effects. The SCCS is aware of the request addressed by ECHA for a combined *in vivo* mammalian erythrocyte micronucleus test and an *in vivo* mammalian Comet assay with additional specific investigation on oxidative DNA damage in rats by oral route, using aluminium sulphate.

Carcinogenicity

Carcinogenicity studies in animals have been reviewed by the SCCS and were summarised in the Annex of the previous Opinion ((SCCS/1525/14, Revision of 18 June 2014). There was no indication of carcinogenicity at high dietary doses (up to 850 mg Al/kg bw/day) in animal studies, and the SCCS considers that carcinogenicity is not expected at exposure levels that are achieved via cosmetic use.

The new submission comprised only a new exposure assessment, not a new toxicological evaluation. Therefore, only the study selected previously for the safety assessment (Poirier et al, 2011) is reported here in detail, all other studies are summarised and discussed in preceding Opinions, notably in SCCS/1613/19. Only the final SCCS statement taken from discussion of the previous Opinion is reported here for transparency.

Since the last SCCS Opinion 1613/19, two additional papers on the effects of aluminium chloride on chromosomal integrity in mammalian cells have been published, continuing the work of Sappino *et al.* (2012) and Mandriota (2016).

In the study by Mandriota *et al.* (2020) normal mouse mammary epithelial cells after long-term culture in the presence of aluminium chloride formed tumours and metastases when injected into syngeneic and immunocompetent BALB/cByJ mice. As was shown by the authors $AlCl_3$ rapidly increased chromosomal structural abnormalities in the cultured cells.

In the second study by Tenan *et al.* (2021) in V79 hamster lung fibroblasts exposed to aluminium dose-dependent increases in DNA double strand breaks, and chromosome numerical abnormalities (aneuploidy) as well as arrest in the G2/M phase of the cell cycle, were observed. Additionally, during mitosis, abnormal multipolar mitotic spindles were detected.

Additionally, García-Alegría *et al.*, 2020 investigated aluminium chloride alone and in co-treatment with MNU in female Sprague Dawley rats. They treated rats with 1mL (2000mg/L) of aluminium solution 5 days per week and sampled blood at 5, 10, and 15 days of exposure. They found significant time dependent increase in micronucleus induction as well as DNA damage measured by the comet assay. However, only one concentration of

aluminium chloride was used with three exposure time points. In study of Jalili *et al.*, 2020 acute exposure to aluminium chloride induced slight but non-significant oxidative DNA damage in peripheral blood lymphocytes. No increase of micronuclei in both bone marrow cells and in colon was observed.

Based on analysis of the whole series of 4 articles by the same group as well as additional literature, the SCCS acknowledges that aluminium ions may disturb structural and functional features of chromosomal material in the cells; however, the potential of the ions to induce such effects in the organism after exposure to cosmetic products is still unknown and rather implausible. There is no additional data available to support a link between skin penetration of aluminium and the occurrence of genotoxic effects at relevant exposure conditions. Based on the actual available information the SCCS is of the opinion that there is no concern for carcinogenicity in the context of use in cosmetics.

Fertility and reproduction toxicity

Poirier *et al.*, 2011, reported a 12-month neuro-developmental toxicity study of aluminium citrate. The study in Sprague-Dawley rats was conducted according to a double-blind, vehicle-controlled randomised design by exposing offspring to aluminium citrate in-utero, through lactation, and then via drinking water post-weaning. The study was conducted according to Good Laboratory Practice (GLP) and was conducted to distinguish between cumulative neurodegenerative and cognitive changes from aberrant neural development alterations. Three dose levels were used: 30, 100, 300 mg Al/kg bw/day, in addition to control groups that received either water or a sodium citrate solution (27.2 g/L) compared to 27.2 g sodium citrate/L in the control group. Aluminium citrate was selected for the study since it is the most soluble and bioavailable aluminium salt. It is also the salt which is likely to be formed readily in the body when absorbed aluminium reacts with endogenous citrate. Pregnant dams (n=20 per group) were exposed to aluminium citrate from gestational day 6 through lactation, and then the offspring (n = 80 per group) were exposed post-weaning until postnatal day 364.

Aluminium citrate was generally well tolerated in the dams at all doses, except the high dose (300 mg Al/kg bw/day) where diarrhoea occurred in 8 of the treated dams. In high-dosed pups, the main toxic effects were observed in the urinary tract (damage and the formation of calculi (chalky secretions blocking the urinary tract)), resulting in high mortality in the male offspring (see Table 3 below). This caused a differential response in female and male pups. High-dose males were euthanised on study day 98 because of excessive clinical signs (including weight loss, diarrhoea, mild dehydration and poor hair coat).

In the same study, Poirier also evaluated the relative distribution of aluminium following repeated oral administration of various aluminium salts. Sprague-Dawley rats (n= 5 per sex per group) were orally gavaged with formulations of aluminium citrate, sulphate, nitrate, chloride and hydroxide, each delivering a dosage of 30 mg/kg body weight aluminium. Control animals were similarly dosed with deionised water. Animals were dosed daily for either 7 days or 14 days, followed by blood and organ collection. The distribution and concentrations of aluminium present in different tissues and organs, were measured by ICP Mass Spectrometry. From this analysis, concentrations in the blood were much lower than those that distributed heterogeneously into other tissues and organs, in both females and males. The authors state that 'of the few significant differences, concentrations of aluminium were highest for the aluminium citrate treatment.' The authors further conclude from their data that 'bioavailability of the three Al salts (chloride, sulfate and nitrate) and the Al hydroxide looks much lower than that of the Al citrate'.

However, as ²⁶Al was not used as a tracer, it is not possible to know the absolute oral bioavailability of the administered dose.

SCCS comment

Based on the results of this neurodevelopmental toxicity study, the SCCS derives a NOAEL of 30 mg/kg bw/day, which will be used for MoS calculation. This is in line with SCHEER (2017), where the same NOAEL from the same study was used to derive migration limits for Al in toys.

Furthermore, on the basis of available information on solubility (Annex 1 of SCCS/1613/19), the SCCS agrees that aluminium citrate can be regarded as the most bioavailable of the Al salts assessed in this Opinion. Therefore, the derived NOAEL can be regarded as a worst case for all aluminium salts discussed in this Opinion.

Human data

The SCCS considers that aluminium is a known neurotoxicant in animals. Circumstantial evidence has linked this metal with several neurodegenerative disorders, like Alzheimer's disease (Miu and Benga, 2006; Percy *et al.*, 2011), Parkinson's diseases (Oyanagi, 2005) and other chronic neurodegenerative diseases (Bondy, 2010), but no causal relationship has yet been proven.

3.4 SAFETY EVALUATION (including calculation of the MoS)

The new submission comprised only a new exposure assessment, not a new toxicological evaluation. Some new scientific studies on genotoxicity, which have become available lately, have been evaluated by the SCCS, but do not change the general picture. Therefore, the toxicological assessment, selected NOAEL and point of departure derived in SCCS/1613/19 remain valid.

Based on the results of the neurodevelopmental toxicity study on rats with aluminium citrate (Poirier *et al.*, 2011), the SCCS derived a NOAEL of 30 mg aluminium citrate/kg bw/day. After adjustment for the rat oral bioavailability (0.6%) of aluminium citrate (Poirier *et al.*, 2011, Zhou *et al.*, 2008), the systemic exposure at the NOAEL is estimated to be **180 µg Al/kg bw/day**. This value is used as a point of departure for the safety assessment and MoS calculation.

The provided exposure report included an aggregate exposure assessment of all Cosmetic categories containing aluminium at maximum levels (Scenario 1). The respective aggregate estimate is considered valid as aggregate value for all assessed product categories, for which the main exposure routes are dermal and oral exposure. The deterministic assessment to aluminium in sunscreens needs to be added to this aggregate assessment.

Table 18: Calculation of aggregate exposure and MoS for aluminium-containing cosmetics

Product type	Systemic Exposure (internal dose) µg Al/kg bw/day	Remarks	MOS based on POD of 180 µg Al/kg bw/day
Dermal from exposure report	0.053	P95, exposed population, Table 15	3403
Dermal sunscreen lotion, deterministic	0.484	Deterministic calculation, max. content, NoG, Table 9	372
Oral from exposure report	0.076	P95, exposed population, Table 15	2358
Inhalation from addendum (respirable + non-respirable)	0.149	P95, exposed population, Table 15A	1209
Inhalation for deodorant first 2 min	0.03		4718
Aggregation over routes	0.800		225

SCCS conclusion

Under the assumption that approximately 20% of the spray particles are <10 µm for aerosol spray products, the SCCS considers that Al is safe for use in antiperspirant and deodorant products (spray and non-spray) and all other product categories.

3.5 DISCUSSION

Physicochemical properties

Physicochemical properties of aluminium compounds that can generally be used as cosmetic ingredients have been summarised in Annex I of the previous SCCS Opinion (SCCS/1613/19). These encompass aluminium compounds in water-soluble and water-insoluble form. The water-soluble Al-containing compounds form are simple inorganic salts, simple organic salts, aluminium benzoate, and chlorohydrates, which can be used in skin care products. Water-insoluble aluminium containing ingredients can be minerals, glasses and clays, aluminium lakes, carbohydrates, fatty acid salts, which are typically added to cosmetic products as bulking agents, coloured pigments, and sometimes as mild abrasives.

The new submission presents an industry survey that indicates the substances actually in use along with their amounts. The INCI names and CAS numbers of these substances are given in Tables 2 and 3 of this Opinion. The respective physicochemical properties of the substances can be retrieved from Annex 1 of SCCS/1613/19.

On the basis of available information on solubility (Annex 1 of SCCS/1613/19), the SCCS agrees that aluminium citrate may exhibit the highest bioavailability amongst the Al salts assessed in this Opinion.

Exposure assessment & Toxicokinetics

The SCCS understands that the 'Al-concentrations' of Al-containing cosmetics ingredients mentioned in Tables 2 and 3 represent the Al-contents in terms of the stoichiometric ratios of Al in these ingredients.

It is unclear to the SCCS why a range of Al-contents ('Al-concentrations') in the Al-ingredient for some of the Al-ingredients may result from the defined stoichiometry of the chemical substance (e.g. for potassium aluminium sulphate in Table 3). However, the SCCS has calculated the Al-contents based on stoichiometry and found no underestimation of Al-content in the upper bound (max value). Therefore, risk assessment based on exposure calculations with these maximum values is considered valid.

Some products had been excluded from the aggregate exposure assessment (see Tables 5, 7) without explanation in the submitted report. Upon request, the Applicant has submitted the explanation along with additional deterministic assessment of dermal exposure from sunscreen creams and lotions. The assessment using the maximum Al level possible is considered valid by the SCCS.

The SCCS considers that sunscreen products should be included in the assessment, because on a seasonal basis they are used regularly, even daily, and due to the high amount applied may present a large exposure source. Furthermore, the presence probability of aluminium in sunscreens is 30%, which cannot be considered negligible.

Some of the products that have not been considered may also be used regularly (shaving products, eyeliner, eye contour products and lip care products). However, for these products the exposure potential is low and the tonnage of Al-containing products sold is also low. Therefore, their contribution to dermal exposure can be considered as negligible and these products can be considered safe for use.

Scenario 1 can be accepted according to the SCCS Notes of guidance (SCCS/1628/21), but not Scenarios 2 and 3, because these use distributions for the concentrations in products and not the maximal levels. Scenario 3 in addition uses occurrence data that can be specific in time.

The SCCS notes that food may contribute to the aggregate exposure to aluminium in the same order of magnitude as cosmetics, when deterministic estimates are compared across the sectors food, pharmaceuticals and cosmetics. Pharmaceuticals such as antacids may contribute to a higher degree but are consumed by only a small fraction of the population under different risk-benefit considerations.

Toxicological Evaluation

The new submission comprised only a new exposure assessment, not a new toxicological evaluation. Some new scientific studies on genotoxicity, which have become available lately, have been evaluated by the SCCS, but do not change the general picture. Therefore, the toxicological assessment, selected NOAEL and point of departure derived in SCCS/1613/19 remain valid.

Based on the results of the neurodevelopmental toxicity study, the SCCS derived a NOAEL of 30 mg/kg bw/day. After adjustment for the rat oral bioavailability (0.6%) of aluminium

citrate, the systemic exposure at the NOAEL is estimated to be 180 µg Al/kg bw/day. This value is used as a point of departure for the safety assessment and MoS calculation.

4. CONCLUSION

1. In light of the new data provided, does the SCCS consider Aluminium compounds safe when used in cosmetic products other than deodorants, antiperspirants, lipsticks and toothpastes? In the event that the estimated exposure to Aluminium from cosmetic products is found to be of concern, SCCS is asked to recommend safe concentration limits for each category.

The SCCS considers that aluminium compounds are safe when used

- in non-sprayable product categories at the maximum levels indicated in Tables 4 and 6; and
- in sprayable products, at the maximum levels indicated in Table 4, provided that the percentage of particles/droplets with a diameter of less than 10 µm does not exceed 20% of the total aerosolised particles/droplets. Since the Applicant's data submission indicated that aluminium is not used in sunscreen aerosol sprays, this Opinion does not cover sunscreen aerosol sprays.

2. Does the SCCS have any further scientific concerns regarding the use of relevant Aluminium compounds in cosmetic products taking into account the newly submitted information on aggregate exposure to Aluminium from cosmetics, medicines (e.g. antacids) and food intake?

As aluminium does not belong to substances classified as CMR 1A or B, only exposure from cosmetic uses was considered in this safety assessment with the exposure assessment based on maximum use levels for cosmetic ingredients.

However, the submission also provided a scenario where realistic exposure from non-cosmetic sources of aluminium (food and pharmaceuticals) was aggregated along with exposure from cosmetics at use levels from the year 2016. From this scenario, it can be deduced that contribution to aluminium exposure from food may be at a similar order of magnitude to that from cosmetics used for the safety assessment. Considering the conservative nature of the estimates, the aggregate exposure to aluminium from cosmetic and non-cosmetic sources may exceed safe limits for consumers at the highest exposure ranges.

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6. REFERENCES

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7. GLOSSARY OF TERMS

See SCCS/1628/21, 11th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 181.

8. LIST OF ABBREVIATIONS

See SCCS/1628/21, 11th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 181.

SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006

Version 6.8

Revision Date 02.06.2023

Print Date 21.11.2023

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 : Aluminum hydroxide

Product Number : 239186

Brand : SIGALD

REACH No. : 01-2119529246-39-XXXX

CAS-No. : 21645-51-2

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) 112
(numer alarmowy)

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

No hazard pictogram, no signal word, no hazard statement(s), no precautionary statement(s) required

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.



SECTION 3: Composition/information on ingredients

3.1 Substances

Formula	: H_3AlO_3
Molecular weight	: 78,00 g/mol
CAS-No.	: 21645-51-2
EC-No.	: 244-492-7

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

After inhalation: fresh air.

In case of skin contact

In case of skin contact: Take off immediately all contaminated clothing. Rinse skin with water/ shower.

In case of eye contact

After eye contact: rinse out with plenty of water. Remove contact lenses.

If swallowed

After swallowing: make victim drink water (two glasses at most). Consult doctor if feeling unwell.

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 extinguishing measures that are appropriate to local circumstances and the surrounding environment.

Unsuitable extinguishing media

For this substance/mixture no limitations of extinguishing agents are given.

5.2 Special hazards arising from the substance or mixture

Aluminum oxide

Not combustible.

Ambient fire may liberate hazardous vapours.

5.3 Advice for firefighters

In the event of fire, wear self-contained breathing apparatus.



5.4 Further information

none

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures

Advice for non-emergency personnel: Avoid inhalation of dusts. Evacuate the danger area, observe emergency procedures, consult an expert.

For personal protection see section 8.

6.2 Environmental precautions

No special precautionary measures necessary.

6.3 Methods and materials for containment and cleaning up

Observe possible material restrictions (see sections 7 and 10). Take up dry. Dispose of properly. Clean up affected area. Avoid generation of dusts.

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

Tightly closed. Dry.

Storage class

Storage class (TRGS 510): 13: Non Combustible Solids

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). Safety glasses

Skin protection

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please



contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).

Full contact

Material: Nitrile rubber

Minimum layer thickness: 0,11 mm

Break through time: 480 min

Material tested: KCL 741 Dermatril® L

This recommendation applies only to the product stated in the safety data sheet, supplied by us and for the designated use. When dissolving in or mixing with other substances and under conditions deviating from those stated in EN374 please contact the supplier of CE-approved gloves (e.g. KCL GmbH, D-36124 Eichenzell, Internet: www.kcl.de).

Splash contact

Material: Nitrile rubber

Minimum layer thickness: 0,11 mm

Break through time: 480 min

Material tested: KCL 741 Dermatril® L

Respiratory protection

required when dusts are generated.

Our recommendations on filtering respiratory protection are based on the following standards: DIN EN 143, DIN 14387 and other accompanying standards relating to the used respiratory protection system.

Recommended Filter type: Filter type P1

The entrepreneur has to ensure that maintenance, cleaning and testing of respiratory protective devices are carried out according to the instructions of the producer. These measures have to be properly documented.

Control of environmental exposure

No special precautionary measures necessary.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

a) Physical state	solid
b) Color	white
c) Odor	odorless
d) Melting point/freezing point	Melting point: 300 °C - Elimination of water of crystallization
e) Initial boiling point and boiling range	Not applicable
f) Flammability (solid, gas)	The product is not flammable.
g) Upper/lower flammability or explosive limits	No data available



h) Flash point	Not applicable
i) Autoignition temperature	No data available
j) Decomposition temperature	ca. 150 - 300 °C
k) pH	ca.8 - 9 at 100 g/l at 20 °C (slurry)
l) Viscosity	Viscosity, kinematic: No data available Viscosity, dynamic: No data available
m) Water solubility	at 20 °C - OECD Test Guideline 105insoluble
n) Partition coefficient: n-octanol/water	Not applicable for inorganic substances
o) Vapor pressure	< 0,1 hPa at 20 °C
p) Density	2,42 g/cm ³ at 20 °C
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	none

9.2 Other safety information

No data available

SECTION 10: Stability and reactivity

10.1 Reactivity

No data available

10.2 Chemical stability

The product is chemically stable under standard ambient conditions (room temperature) .

10.3 Possibility of hazardous reactions

Exothermic reaction with:
Strong acids

10.4 Conditions to avoid

no information available

10.5 Incompatible materials

No data available

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 - female - > 2.000 mg/kg
(OECD Test Guideline 423)

Inhalation: No data available

Dermal: No data available

Skin corrosion/irritation

Skin - Rabbit

Result: No skin irritation - 4 h
(OECD Test Guideline 404)

Serious eye damage/eye irritation

Eyes - Rabbit

Result: No eye irritation
(OECD Test Guideline 405)

Respiratory or skin sensitization

Maximization Test - Guinea pig

Result: negative
(OECD Test Guideline 406)

Germ cell mutagenicity

Test Type: In vitro mammalian cell gene mutation test

Test system: Mouse lymphoma test

Metabolic activation: with and without metabolic activation

Method: OECD Test Guideline 476

Result: negative

Test Type: In vivo micronucleus test

Species: Rat

Cell type: Bone marrow

Application Route: Oral

Method: OECD Test Guideline 474

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

Endocrine disrupting properties

Product:

Assessment

The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.

Repeated dose toxicity - Rat - male - Oral - 28 d - NOAEL (No observed adverse effect level) - 302 mg/kg

Remarks: Subacute toxicity

RTECS: BD0940000

SECTION 12: Ecological information

12.1 Toxicity

No data available

12.2 Persistence and degradability

The methods for determining the biological degradability are not applicable to inorganic substances.

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

Product:

Assessment

: The substance/mixture does not contain components considered to have endocrine disrupting properties according to REACH Article 57(f) or Commission Delegated regulation (EU) 2017/2100 or Commission Regulation (EU) 2018/605 at levels of 0.1% or higher.

12.7 Other adverse effects

No data available



SECTION 13: Disposal considerations

13.1 Waste treatment methods

No data available

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: -

14.5 Environmental hazards

ADR/RID: no

IMDG Marine pollutant: no

IATA: no

14.6 Special precautions for user

No data available

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

Full text of other abbreviations

ADN - European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways; ADR - Agreement concerning the International Carriage of Dangerous Goods by Road; AIIC - Australian Inventory of Industrial Chemicals; ASTM - American Society for the Testing of Materials; bw - Body weight; CMR - Carcinogen, Mutagen or Reproductive Toxicant; DIN - Standard of the German Institute for Standardisation; DSL - Domestic Substances List (Canada); ECx - Concentration associated with x% response; ELx - Loading rate associated with x% response; EmS - Emergency Schedule; ENCS - Existing and New Chemical Substances (Japan); ErCx - Concentration associated with x% growth rate response; GHS - Globally Harmonized System; GLP - Good Laboratory Practice; IARC - International Agency for Research on Cancer; IATA - International Air Transport Association; IBC - International Code for the Construction and Equipment of Ships carrying Dangerous Chemicals in Bulk; IC50 - Half maximal inhibitory concentration; ICAO - International Civil Aviation Organization; IECSC - Inventory of Existing Chemical Substances in China; IMDG - International Maritime Dangerous Goods; IMO - International Maritime Organization; ISHL - Industrial Safety and Health Law (Japan); ISO - International Organisation for Standardization; KECI - Korea Existing Chemicals Inventory; LC50 - Lethal Concentration to 50 % of a test population; LD50 - Lethal Dose to 50% of a test population (Median Lethal Dose); MARPOL - International Convention for the Prevention of Pollution from Ships; n.o.s. - Not Otherwise Specified; NO(A)EC - No Observed (Adverse) Effect Concentration; NO(A)EL - No Observed (Adverse) Effect Level; NOELR - No Observable Effect Loading Rate; NZIoC - New Zealand Inventory of Chemicals; OECD - Organization for Economic Co-operation and Development; OPPTS - Office of Chemical Safety and Pollution Prevention; PBT - Persistent, Bioaccumulative and Toxic substance; PICCS - Philippines Inventory of Chemicals and Chemical Substances; (Q)SAR - (Quantitative) Structure Activity Relationship; REACH - Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals; RID - Regulations concerning the International Carriage of Dangerous Goods by Rail; SADT - Self-Accelerating Decomposition Temperature; SDS - Safety Data Sheet; TCSI - Taiwan Chemical Substance Inventory; TECI - Thailand Existing Chemicals Inventory; TSCA - Toxic Substances Control Act (United States); UN - United Nations; UNRTDG - United Nations Recommendations on the Transport of Dangerous Goods; vPvB - Very Persistent and Very Bioaccumulative

Further information

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Corporation and its Affiliates shall not be held liable for any damage resulting from handling or from contact with the above product. See www.sigma-aldrich.com and/or the reverse side of invoice or packing slip for additional terms and conditions of sale.

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