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Short Review

Update to RIFM fragrance ingredient safety assessment, terpinyl acetate (isomer mixture), CAS Registry Number 8007-35-0

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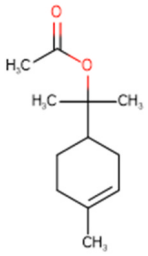

Name: Terpinyl acetate (Isomer mixture)
CAS Registry Number: 8007-35-0
Additional materials:*
80-26-2 α-Terpineol acetate
7785-54-8 *d*-\a-Terpineol acetate
*Included because the materials are isomers

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

(*continued on next column*)

(*continued*)

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprises internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.

Terpinyl acetate (isomer mixture) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that terpinyl acetate (isomer mixture) is not genotoxic. Data on terpinyl acetate (isomer mixture) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across analogs terpineol (CAS # 8000-41-7) and acetic acid (CAS # 64-19-7) provide a calculated MOE >100 for the reproductive toxicity and local respiratory toxicity endpoints. Data show that there are no safety concerns for terpinyl acetate (isomer mixture) for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; terpinyl acetate (isomer mixture) is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; terpinyl acetate (isomer mixture) was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2014b; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 400 mg/kg/day.	(Hagan et al., 1967)
Reproductive Toxicity: Developmental toxicity NOAEL = 200 mg/kg/day. Fertility NOAEL = 250 mg/kg/day.	(ECHA REACH Dossier: p-Menth-1-en-8-ol; ECHA, 2013a)
Skin Sensitization: Not a concern for skin sensitization.	RIFM (2012d)
Photoirritation/Photoallergenicity: Not expected to be a photoirritant/photoallergen.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 20 mg/m^3 (terpineol) and 12.3 mg/m^3 (acetic acid).	(ECHA REACH Dossier: 4-(1-Methoxy-1-methylethyl)-1-methylcyclohexene; ECHA, 2017a; Ernstgard et al., 2006)

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Critical Measured Value: 87% (OECD 301B) for CAS # 80-26-2 (RIFM, 1994)

Bioaccumulation:
Screening-level: 190 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Critical Ecotoxicity Endpoint: 72-h Algae EyC50: 4.3 mg/L for CAS # 80-26-2 RIFM (2013a)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito, 2002)

Critical Ecotoxicity Endpoint: 72-h algae EyC50: 4.3 mg/L for CAS # 80-26-2 RIFM (2013a)

RIFM PNEC is: 4.3 μg/L

- Revised PEC/PNECs (2019 IFRA VoU): North America and Europe <1

1. Identification

Chemical Name: Terpinyl acetate (Isomer mixture)	**Chemical Name:** α-Terpineol acetate	**Chemical Name:** d-α-Terpineol acetate
CAS Registry Number: 8007-35-0	**CAS Registry Number:** 80-26-2	**CAS Registry Number:** 7785-54-8
Synonyms: Terpineol, acetate (Isomer mixture); Terpineol acetate; ｱﾙｶﾝ酸(C = 1 ~ 5)ﾃﾙﾋﾞﾈﾙ; 1-Methyl-1-(4-methylcyclohex-3-en-1-yl)ethyl acetate; Terpinyl acetate (Isomer mixture)	**Synonyms:** α-Terpineol acetate; p-Menth-1-en-8-yl acetate; 1-Methyl-1-(4-methylcyclohex-3-en-1-yl)ethyl acetate; 3-Cyclohexene-1-methanol,α,α,4-trimethyl-, acetate; Terpinyl acetate; ｱﾙｶﾝ酸(C = 1 ~ 5)ﾃﾙﾋﾞﾈﾙ	**Synonyms:** (R)-α,α,4-Trimethylcyclohex-3-ene-1-methyl acetate; d- α -Terpineol acetate; d-p-Menth-1-en-8-ol, acetate; 1-Methyl-1-(4-methylcyclohex-3-en-1-yl)ethyl acetate; 3-Cyclohexene-1-methanol, α,α,4-trimethyl-, acetate, (R)-
Molecular Formula: $C_{12}H_{20}O_2$	**Molecular Formula:** $C_{12}H_{20}O_2$	**Molecular Formula:** $C_{12}H_{20}O_2$
Molecular Weight: 196.29 g/mol	**Molecular Weight:** 196.29 g/mol	**Molecular Weight:** 196.29 g/mol
RIFM Number: 202	**RIFM Number:** 5372	**RIFM Number:** 5366
Stereochemistry: Isomer mixture. One stereocenter and 2 total stereoisomers are possible.	**Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers are possible.	**Stereochemistry:** "d" Isomer specified. One stereocenter and 2 total stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 225 °C (Fragrance Materials Association [FMA]), 238.66 °C (EPI Suite v4.11)
2. **Flash Point:** >200 °F; closed cup (FMA), >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 4.34 (EPI Suite v4.11)
4. **Melting Point**: 21.47 °C (EPI Suite v4.11)
5. **Water Solubility:** 18.97 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 0.955 (FMA)
7. **Vapor Pressure:** 0.0319 mm Hg at 20 °C (EPI Suite v4.0), 0.02 mm Hg at 20 °C (FMA), 0.0497 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

1. >1000 metric tons per year	IFRA (2019)

4. Exposure to fragrance ingredient* (Creme RIFM aggregate exposure model v2.0)

1. 95th Percentile Concentration in Fine Fragrance: 0.15%	RIFM (2019)
2. Inhalation Exposure:** 0.0016 mg/kg/day or 0.12 mg/day	RIFM (2019)
3. Total Systemic Exposure*:** 0.0092 mg/kg/day	RIFM (2019)

*When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in fine fragrance, inhalation exposure, and total exposure.

**95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015; Safford, 2015; Safford, 2017; Comiskey, 2017).

***95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015; Safford, 2015; Safford, 2017; Comiskey, 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5 (OECD, 2021)
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** Terpineol (CAS # 8000-41-7) and acetic acid (CAS # 64-19-7)
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Terpineol (CAS # 8000-41-7) and acetic acid (CAS # 64-19-7)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

Terpinyl acetate (Isomer mixture) (CAS # 8007-35-0) is reported to occur in the following foods by the VCF*:

Buckwheat	Ginger (*Zingiber* species)
Celery (*Apium graveolens* L.)	Laurel (*Laurus nobilis* L.)
Citrus fruits	Melon
Mentha oils	*Salvia* species
Pepper (*Piper nigrum* L.)	Thyme (*Thymus* species)

α-Terpineol acetate (CAS # 80-26-2) is reported to occur in the following foods by the VCF*:

Black currants (*Ribes nigrum* L.)	Lemon balm (*Melissa officinalis* L.)
Citrus fruits	Macadamia nut (*Macadamia integrifolia*)
Cocoa category	Mentha oils
Ginger (*Zingiber* species)	Mushroom
Guava and feijoa	Star anise

d-\a-Terpineol acetate (CAS # 7785-54-8) is not reported to occur in foods by the VCF*.

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. These are partial lists.

9. REACH dossier

Terpinyl acetate (isomer mixture) (CAS # 8007-35-0) is pre-registered for 2010; no dossier available as of 02/08/23. Available for

α-terpineol acetate (CAS # 80-26-2) (ECHA, 2013b). *d*-\a-Terpineol acetate (CAS # 7785-54-8) is pre-registered for 2010; no dossier available as of 02/08/23.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, terpinyl acetate (isomer mixture) does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. α-Terpineol acetate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2014a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of the isomer α-terpineol acetate (CAS # 80-26-2) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with α-terpineol acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2014b). Under the conditions of the study, α-terpineol acetate was not mutagenic in the Ames test.

The clastogenic activity of terpinyl acetate (Isomer mixture) was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with terpinyl acetate (isomer mixture) in DMSO at concentrations up to 1963 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 300 μg/mL in the presence and absence of metabolic activation. Terpinyl acetate (Isomer mixture) did not induce binucleated cells with micronuclei in either the presence or absence of an S9 activation system (RIFM, 2015). Under the conditions of the study, terpinyl acetate (isomer mixture) was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, terpinyl acetate does not present a concern for genotoxic potential.

Additional References: Oda (1978); RIFM, 2012c; RIFM, 2013b; RIFM, 2013c; RIFM, 2014c.

Literature Search and Risk Assessment Completed On: 01/27/23.

11.1.2. Repeated dose toxicity

The MOE for terpinyl acetate (isomer mixture) is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on terpinyl acetate (isomer mixture). A dietary 20-week chronic toxicity study was conducted in Osborne-Mendel rats. Groups of 10 rats/sex/dose were administered diets containing 0, 1000, 2500, or 10000 ppm terpinyl acetate (isomer mixture), equivalent to targeted doses of 0, 50, 250, or 500 mg/kg/day, for 20 weeks. No effects on growth and no alterations in hematology, macroscopic, or microscopic changes were observed up to the highest dose of 10000 ppm. The animals exposed to 10000 ppm in the diet consumed between 400 and 500 mg/kg/day terpinyl acetate. Thus, the NOAEL for repeated dose toxicity was considered to be 10000 ppm or 400 mg/kg/day (Hagan et al., 1967; Bar, 1967; ECHA, 2013a). **Therefore, the terpinyl acetate (isomer mixture) MOE for the repeated dose toxicity endpoint can be calculated by dividing the terpinyl acetate (isomer mixture) NOAEL in mg/kg/day by the total systemic exposure to terpinyl acetate, 400/0.0092, or 43478.**

In addition, the total systemic exposure to terpinyl acetate (isomer mixture) (9.2 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/01/23.

11.1.3. Reproductive toxicity

The MOE for terpinyl acetate (isomer mixture) is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on terpinyl acetate (isomer mixture) or any of the materials listed under Section I of the safety assessment. Terpinyl acetate is expected to hydrolyze to terpineol (CAS # 8000-41-7; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI). Based on the available data (NICNAS, 2013; WHO, 2006; US FDA, 2023), acetic acid does not show specific developmental toxicity. Thus, acetic acid does not pose any systemic (repeated dose), developmental, or reproductive toxicity to human health when used in fragrances.

The metabolite terpineol has an OECD 422 gavage combined repeated dose toxicity study with a reproduction/developmental toxicity screening test conducted in Sprague Dawley rats. The rats were administered via gavage with test material terpineol at doses of 0, 60, 250, or 750 mg/kg/day in corn oil. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at the top dose: 5 males/dose). The toxicity subgroup consisted of 5 females/dose and 10 males. Main-phase males and toxicity-phase females were dosed daily for a minimum of 5 consecutive weeks. An additional 10 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for 5 weeks and then given 2 weeks of recovery before termination. There were no adverse effects on the development of the fetus up to 250 mg/kg/day. At 750 mg/kg/day, no females became pregnant. It was considered that the testicular and epididymal effects observed in males receiving 750 mg/kg/day would have been sufficient to prevent fertilization. Thus, the NOAEL for the developmental toxicity endpoint was considered to be 250 mg/kg/day (ECHA, 2013a).

In an OECD 414-compliant study, groups of 20 mated female Sprague Dawley rats/dose were administered terpineol multi-constituent via gavage (vehicle: corn oil) at doses of 0, 60, 200, and 600 mg/kg/day from days 6–19 after mating. Male and female fetal weights were significantly reduced at the high dose. Placental weights were slightly but significantly reduced at the high dose. There were no treatment-related major and minor abnormalities or skeletal variations. Thus, based on reduced fetal weights and placental weights at 600 mg/kg/day, the developmental toxicity NOAEL for this study was determined to be 200 mg/kg/day (ECHA, 2013a). The more conservative NOAEL of 200 mg/kg/day was selected for the developmental toxicity endpoint.

Therefore, the terpinyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the terpineol NOAEL in mg/kg/day by the total systemic exposure to terpinyl acetate, 200/0.0092, or 21739.

There are no fertility data on terpinyl acetate (isomer mixture) or any of the materials listed under Section I of the safety assessment. Terpinyl

acetate is expected to hydrolyze to terpineol (CAS # 8000-41-7; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI). Based on the available data (NICNAS, 2013; WHO, 2006; US FDA, 2023), acetic acid does not show specific reproductive toxicity. Thus, acetic acid does not pose any systemic (repeated dose), developmental, or reproductive toxicity to human health when used in fragrances.

The metabolite terpineol has an OECD 422 gavage combined repeated dose toxicity study with a reproduction/developmental toxicity screening test conducted in Sprague Dawley rats. The rats were administered via gavage with test material terpineol at doses of 0, 60, 250, or 750 mg/kg/day in corn oil. The reproductive subgroup (main phase) consisted of 10 males and 10 females/dose (except for control males and at the top dose: 5 males/dose). The toxicity subgroup consisted of 5 females/dose and 10 males. Main-phase males and toxicity-phase females were dosed daily for a minimum of 5 consecutive weeks. An additional 10 rats/sex/dose were dosed with the vehicle or 750 mg/kg/day for 5 weeks and then given 2 weeks of recovery before termination. Testis weight was markedly lower in males receiving 750 mg/kg/day (58% of controls), and there was also an indication of low epididymal weights at this dose. This effect was also seen in the recovery group males. At 750 mg/kg/day, reduced numbers or complete absence of spermatozoa, accompanied by the presence of degenerate spermatogenic cells in the ducts, were observed in the epididymides and were still present following the 2-week recovery period. Spermatocele granulomata that were seen in 2 males receiving 750 mg/kg/day and 1 receiving 60 mg/kg/day were not seen at the end of the recovery period. The significance of this change in the single male receiving 60 mg/kg/day is uncertain, as spermatocele granuloma(ta) can occur spontaneously in rats of this age. Considering the absence of other degenerative changes in the testes or epididymides of this animal and the fact that no such changes were observed at a dose of 250 mg/kg/day, this finding is considered incidental. Moderate to severe seminiferous tubular atrophy/degeneration was seen in the testes of all animals dosed at 750 mg/kg/day, accompanied by minimal to moderate spermatid giant cells and minimal to slight seminiferous tubular vacuolation. Similar findings were still evident following the 2-week recovery period but at a lower incidence and severity, suggesting a degree of recovery. There were no alterations in the female reproductive cycles or the reproductive organs up to the highest dose tested. Thus, the NOAEL for the fertility endpoint was considered to be 250 mg/kg/day, based on the impairment of male

Table 1
Summary of existing data on terpinyl acetate (isomer mixture).

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL (induction) µg/cm²	WoE NESIL µg/cm²	LLNA[2] Weighted Mean EC3 Value µg/cm²	GPMT	Buehler
No evidence of sensitization[3]	N/A	3450	N/A	N/A	Negative up to 25000	N/A	N/A
	In vitro Data				*In silico* protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	N/A	N/A	N/A		No alert found	Radical reactions; SN2; Nucleophilic addition	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available.
1WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
2Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
3Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

fertility at 750 mg/kg/day (ECHA, 2013a). **Therefore, the terpinyl acetate (isomer mixture) MOE for the fertility endpoint can be calculated by dividing the terpineol NOAEL in mg/kg/day by the total systemic exposure to terpinyl acetate (isomer mixture), 250/0.0092, or 27174.**

In addition, the total systemic exposure to terpinyl acetate (isomer mixture) (9.2 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/27/23.

11.1.4. Skin sensitization

Based on the existing data, terpinyl acetate (isomer mixture) presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, terpinyl acetate (isomer mixture) is not considered a skin sensitizer. The data are summarized in Table 1. This material is predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). In a murine local lymph node assay (LLNA), isomer α-terpineol acetate was found to be non-sensitizing when tested up to 100% (25000 μg/cm^2) (RIFM, 2012d). In a human maximization test, no skin sensitization reactions were observed when terpinyl acetate (isomer mixture) was tested at 3450 μg/cm^2 (RIFM, 1971).

Based on the weight of evidence from structural analysis and animal and human studies, terpinyl acetate (isomer mixture) does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/17/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, terpinyl acetate (isomer mixture) would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for terpinyl acetate (isomer mixture) in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, terpinyl acetate (isomer mixture) does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating or photoallergenic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/20/22.

11.1.6. Local respiratory toxicity

There are no inhalation data available on terpinyl acetate (isomer mixture); however, there are sufficient data on terpineol (CAS # 8000-41-7; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI), the ester hydrolysis products of terpinyl acetate. A Lowest Observed Adverse Effect Concentration (LOAEC) of 200 mg/m^3 was identified for terpineol in an OECD 413, 13-week inhalation exposure study (ECHA, 2017a; using terpineol data as read-across) and a NOEC of 12.3 mg/m^3 was identified for acetic acid in an inhalation exposure study in humans (Ernstgard et al., 2006).

11.1.6.1. Risk assessment. The calculated chronic inhalation exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. An OECD 413, 13-week inhalation study in CRL:CD rats identified a LOAEC of 200 mg/m^3 (ECHA, 2017a; using terpineol data as read-across). In this study, 10 rats/sex/group were exposed to terpineol via nose-only inhalation for 6 h a day, 5 days per week for 13 weeks. The test concentrations were 0, 200, 600, and 2000 mg/m^3. Standard evaluations included mortality, clinical observations, body weight, hematology, clinical chemistry, and gross and microscopic pathology. After 13 weeks of treatment, related effects were observed in the nasal turbinates and nasal pharynx. Minimal to slight severity hyperplasia of the mucous cells in nasal turbinates was observed in males from all the terpineol exposure groups (0/10, 9/10, 9/10, 10/10) and the females from all the terpineol exposure groups (0/10, 4/10, 8/10, 8/10). Minimal degeneration of olfactory epithelium, respiratory epithelium, and inflammation of the respiratory epithelium in the nasal turbinates were observed in the males and females of the high-dose group. Minimal hyperplasia of the mucous cells in the nasal pharynx was observed in the males and females of the mid- and high-dose groups. Based on the observations in the respiratory tract, the LOAEC is identified at 200 mg/m^3. Therefore, by using a safety adjustment factor of 10, a local effects NOAEC of 20 mg/m^3 is calculated for the subchronic inhalation exposure of terpineol.

This NOAEC expressed in mg/kg lung weight/day is:

- (20 mg/m^3) × (1 m^3/1000 L) = 0.02 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat* × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.02 mg/L) × (61.2 L/d) = 1.224 mg/day
- (1.224 mg/day)/(0.0016 kg lung weight of rat**) = 765 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.12 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015; Safford, 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.18 mg/kg lung weight/day resulting in a MOE of 4250 (i.e., [765 mg/kg lung weight of rat/day]/[0.18 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.12 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

In an inhalation study to evaluate potential acute irritation during controlled exposure to vapors of acetic acid, 6 healthy female and 6 healthy male volunteers (age range 21–41) were exposed to 0 ppm (control exposure), 12.3, and 24.6 mg/m^3 acetic acid vapor for 2 h at rest (Ernstgard et al., 2006). In the qualitative, self-report portion of the study, the individuals indicated subjective ratings of nasal irritation and smell increased significantly with exposure level using the visual analog scale (VAS). VAS is a psychometric response scale typically used in questionnaires to describe subjective characteristics that cannot be directly measured. Except for the smell, all average ratings at 24.6 mg/m^3 were at the lower end of the 0–100 mm VAS and did not exceed the verbal expression “somewhat” (26 mm). Quantitative pulmonary function measurements included: vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), peak expiratory flow (PEF), and forced expiratory flow in 25%, 50%, and 75% of FVC (FEF25, FEF50, FEF75). The highest value of the 3 measurements was used. Secondary parameters calculated from the spirogram were FEV1/FVC and FEV1/VC. The measurements were performed using a spirometer (Vitalograf 21210; Buckingham, UK) along with designated computer software (Spirotrac 3, v2.0). Pulmonary function parameters

were measured prior to, immediately after, and at 3 h post-exposure. Measurements before and after all exposure concentrations demonstrated that there were no effects on pulmonary function, nasal swelling, nasal airway resistance, or plasma inflammatory markers (C-reactive protein and interleukin-6). There was a non-significant tendency to increase blinking frequency, as measured continuously during exposure, after exposure to 24.6 mg/m^3 of acetic acid. The authors concluded that study data suggests a mild irritative effect at 24.6 mg/m^3 acetic acid, and no effects were observed at 12.3 mg/m^3 acetic acid. Therefore, the NOEC was determined to be the lowest exposure concentration at 12.3 mg/m^3.

This NOEC expressed in mg/kg lung weight/day is:

- (12.3 mg/m^3) × (1 m^3/1000 L) = 0.0123 mg/L
- MV of 9 L/min*** for a human (on average) × duration of exposure of 120 min per day (min/day) = 1080 L/day
- (0.0123 mg/L) × (1080 L/d) = 13.28 mg/day
- (13.28 mg/day)/(0.65 kg lung weight of human) = 20.43 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.12 mg/day — this value was derived from the concentration survey data in the Creme RIFM Exposure Model Comiskey, 2015; Safford (2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.18 mg/kg lung weight/day, resulting in an MOE of 113.5 (i.e., [20.43 mg/kg lung weight/day]/[0.18 mg/kg lung weight/day]).

The MOE is greater than 10. Without adjustment for specific uncertainty factors related to intra-species variation, the material exposure by inhalation at 0.12 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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**Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

** US EPA. (2011). Exposure Factors Handbook. Chapter 6: Inhalation Rates, Tables 6–42, p. 6–75. Retrieved from https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/23/23.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of terpinyl acetate (isomer mixture) was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio of Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, terpinyl acetate (isomer mixture) was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify terpinyl acetate (isomer mixture) as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017b). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current VoU (2019), terpinyl acetate (isomer mixture) presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. ***For CAS # 80-26-2.***

RIFM, 1996: The ready biodegradability of α-terpineol acetate has been determined by the Manometric Respirometry test according to the OECD 301F method. α-Terpineol acetate underwent 63% biodegradation after 28 days in the test conditions.

RIFM, 1994: A study was conducted to determine the ready and ultimate biodegradability of the test material using the sealed vessel test following the OECD 301B method. After 28 days, the biodegradation was 87%.

11.2.2.1.2. Ecotoxicity. **For CAS # 80-26-2.**

RIFM, 2013a: A 72-h algae acute test was conducted according to the OECD 201 guidelines under static conditions. Based on day 0 measured test concentrations, the 72-h EC50 for cell density, yield (EyC50), and growth rate (ErC50) was greater than 11 mg/L.

RIFM, 2012a: A study according to the OECD 202 method was conducted to determine the acute effects of the test material on *Daphnia magna* during a 48-h exposure period under flow-through test conditions. The EC50 was reported to be greater than 10 mg/L.

RIFM, 2012b: A 96-h fish (fathead minnow) acute test was conducted according to the OECD 203 method under flow-through conditions. Based on the mean measured concentration, an LC50 of 11 mg/L was reported.

RIFM, 2011: An algae growth inhibition test was conducted according to the OECD 201 method. Based on the geometric mean measured concentrations, the 72-h EC50 was reported to be 6.9 mg/L and 4.3 mg/L for growth rate and yield, respectively.

11.2.2.1.3. Other available data. Terpinyl acetate (isomer mixture) has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in

mg/L; PNECs in μg/L)

Endpoints used to calculate PNEC are underlined.

Exposure information and PEC calculation (following RIFM Framework; Salvito, 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.34	4.34
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	100–1000	100–1000
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on read-across data, the RQ for this material is < 1. No additional assessment is necessary.

The RIFM PNEC is 4.3 μg/L. The revised PEC/PNECs for EU and NA <1. The material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 01/18/23.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/14/23.

CRediT authorship contribution statement

G. Sullivan: Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.389			1000000	0.2389	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.231	5.326	1.871			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.592	<u>1.218</u>	1.370	10000	0.1218	Neutral Organic
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	>11					
Daphnia		<u>>10</u>				
Algae		4.3		1000	4.3	

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.114363.

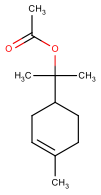
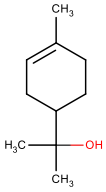
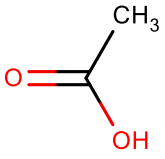
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017c).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021).
- ER binding and repeat dose categorization were generated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using the OECD QSAR Toolbox v4.5 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

Principal Name	Target Material	Read-across Material	Read-across Material
	Terpinyl acetate (isomer mixture)	Terpineol	Acetic acid
CAS No.	8007-35-0	8000-41-7	64-19-7
Structure			
Similarity (Tanimoto Score)		Not applicable*	Not applicable*
SMILES	CC(=O)OC(C)(C)C1CCC(C)=CC1	CC1CCC(CC = 1)C(C)(C)O	CC(O)=O
Endpoint		Reproductive toxicity Local Respiratory toxicity	Reproductive toxicity Local Respiratory toxicity
Molecular Formula	$C_{12}H_{20}O_2$	$C_{10}H_{18}O$	$C_2H_4O_2$
Molecular Weight (g/mol)	196.29	154.253	60.052
Melting Point (°C, EPI Suite)	21.47	33.00	16.64
Boiling Point (°C, EPI Suite)	238.66	217.50	117.90
Vapor Pressure (Pa @ 25°C, EPI Suite)	6.63E+00	2.61E+00	2.09E+03
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.90E+01	1.98E+03	1.00E+06
Log K_{OW}	3.96	3.28	−0.17
J_{max} (μg/cm^2/h, SAM)	1.89	205.45	6282.71
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.04E+02	2.26E-01	1.45E-02
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.5)	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Toxicant (good reliability)	Toxicant (low reliability)
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

*Tanimoto score not reported as the read-across analogs are metabolites of the target material and not structural analogs.

Summary

There are insufficient toxicity data on terpinyl acetate (isomer mixture) (CAS # 8007-35-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, terpineol (CAS # 8000-41-7) and acetic acid (CAS # 64-19-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the target material terpinyl acetate (isomer mixture) (CAS # 8007-35-0) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.5). The target material is predicted to be metabolized to terpineol (CAS # 8000-41-7) and acetic acid (CAS # 64-19-7) in the first step with 0.499 pre-calculated and 0.950 intrinsic probability. Hence, terpineol (CAS # 8000-41-7) and acetic acid (CAS # 64-19-7) can be used as read-across analogs for the target material. Read-across analogs terpineol (CAS # 8000-41-7) and acetic acid (CAS # 64-19-7) were in domain of the training set for the *in vivo* rat and in domain of the training set for the *in vitro* rat S9 simulator (OASIS TIMES v2.30.1.11). However, based on expert judgment, the model's domain exclusion was overridden, and a justification is provided.

Conclusions

- Read-across alcohol terpineol (CAS # 8000-41-7) and read-across acid acetic acid (CAS # 64-19-7) were used as read-across analogs for the target ester, terpinyl acetate (isomer mixture) (CAS # 8007-35-0), for the local respiratory toxicity and reproductive toxicity endpoints since they are hydrolysis products of the target material.
  - o Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v4.5, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
  - o The data described in the local respiratory toxicity sections confirm that the MOE for the read-across analogs is adequate under the current usage. Therefore, based on the structural similarity between the target material and the read-across analogs, the data is considered and applied to the target material.

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