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Short Review



RIFM fragrance ingredient safety assessment, S-(1-methylpropyl) 3-methylbut-2-enethioate, CAS Registry Number 34322-09-3

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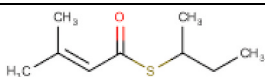
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Name: S-(1-Methylpropyl) 3-methylbut-2-ene-thioate CAS Registry Number: 34322-09-3



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

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., 2015a, 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

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.

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 comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

(continued)

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

S-(1-Methylpropyl) 3-methylbut-2-ene-thioate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that S-(1-methylpropyl) 3-methylbut-2-ene-thioate is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to S-(1-methylpropyl) 3-methylbut-2-ene-thioate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials ($64 \mu\text{g}/\text{cm}^2$); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra for read-across analog S-1-methylethyl 3-methylbut-2-ene-thioate (CAS # 34365-79-2); S-(1-methylpropyl) 3-methylbut-2-ene-thioate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; S-(1-methylpropyl) 3-methylbut-2-ene-thioate 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 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, 2017a; RIFM, 2016)

Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.

Reproductive Toxicity: No NOAEL available. Exposure is below TTC.

Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.

Phototoxicity/Photoallergenicity: (UV Spectra; RIFM Database)
Not expected to be phototoxic/photoallergenic.

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Screening-level: 2.81 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 74.02 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 15.87 mg/L (RIFM Framework; Salvito, 2002)

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: Fish LC50: 15.87 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.01587 $\mu\text{g}/\text{L}$

• **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: Not applicable; cleared at screening-level

1. Identification

- Chemical Name:** S-(1-Methylpropyl) 3-methylbut-2-ene-thioate
- CAS Registry Number:** 34322-09-3
- Synonyms:** 2-Butenethioic acid, 3-methyl-, S-(1-methylpropyl) ester; sec-Butyl 3-methyl-2-butenethioate; S-sec-Butyl 3-methylbut-2-ene-thioate; S-(1-Methylpropyl) 3-methylbut-2-ene-thioate
- Molecular Formula:** $\text{C}_9\text{H}_{16}\text{OS}$
- Molecular Weight:** 172.29
- RIFM Number:** 5668
- Stereochemistry:** Isomer not specified. One chiral center present and 2 total enantiomers possible.

2. Physical data

- Boiling Point:** 229.6 °C (EPI Suite)
- Flash Point:** Not Available
- Log Kow:** 3.34 (EPI Suite)
- Melting Point:** -5.64 °C (EPI Suite)
- Water Solubility:** 84.61 mg/L (EPI Suite)
- Specific Gravity:** Not Available

(continued on next column)

7. **Vapor Pressure:** 0.0519 mm Hg at 20 °C (EPI Suite v4.0), 0.0798 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Not Available
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95th Percentile Concentration in Fine Fragrance:** 0.0008% (RIFM, 2017b)
2. **Inhalation Exposure*:** 0.000011 mg/kg/day or 0.000073 mg/day (RIFM, 2017b)
3. **Total Systemic Exposure**:** 0.000019 mg/kg/day (RIFM, 2017b)

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

| Expert Judgment | Toxtree v 3.1 | OECD QSAR Toolbox v 3.2 |
|-----------------|---------------|-------------------------|
| I | I | III |

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See the Appendix below for further details.

2. **Analogs Selected:**
 - a. **Genotoxicity:** None
 - b. **Repeated Dose Toxicity:** None
 - c. **Reproductive Toxicity:** None
 - d. **Skin Sensitization:** None
 - e. **Phototoxicity/Photoallergenicity:** S-1-Methylethyl 3-methylbut-2-enethioate (CAS # 34365-79-2)
 - f. **Local Respiratory Toxicity:** None
 - 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

S-(1-Methylpropyl) 3-methylbut-2-enethioate 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.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 01/29/21.

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, S-(1-methylpropyl) 3-methylbut-2-enethioate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. S-(1-methylpropyl) 3-methylbut-2-enethioate was assessed in the BlueScreen assay and found negative for cytotoxicity (positive: <80% relative cell density) without metabolic activation, positive for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of S-(1-methylpropyl) 3-methylbut-2-enethioate 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 and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2uvrA were treated with S-(1-methylpropyl) 3-methylbut-2-enethioate 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 concentration in the presence or absence of S9 (RIFM, 2017a). Under the conditions of the study, S-(1-methylpropyl) 3-methylbut-2-enethioate was not mutagenic in the Ames test.

The clastogenic activity of S-(1-methylpropyl) 3-methylbut-2-enethioate 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 S-(1-methylpropyl) 3-methylbut-2-enethioate in dimethyl sulfoxide (DMSO) at concentrations up to 1723 µg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 200 µg/mL in the presence and absence of metabolic activation. S-(1-methylpropyl) 3-methylbut-2-enethioate did not induce binucleated cells with micronuclei when tested in either the presence or absence of an S9 activation system (RIFM, 2016). Under the conditions of the study, S-(1-methylpropyl) 3-methylbut-2-enethioate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, S-(1-methylpropyl) 3-methylbut-2-enethioate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/21/20.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on S-(1-methylpropyl) 3-methylbut-2-enethioate or any read-across materials. The total systemic exposure to S-(1-methylpropyl) 3-methylbut-2-enethioate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on S-(1-methylpropyl) 3-methylbut-2-enethioate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.019 µg/kg/day) is below the TTC for S-(1-methylpropyl) 3-methylbut-2-enethioate (30 µg/kg/day; Kroes, 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/30/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on S-(1-methylpropyl) 3-methylbut-2-enethioate or any read-across materials. The total systemic exposure to S-(1-methylpropyl) 3-methylbut-2-enethioate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on S-(1-methylpropyl) 3-methylbut-2-enethioate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.019 µg/kg/day) is below the TTC for S-(1-methylpropyl) 3-methylbut-2-enethioate (30 µg/kg/day; Kroes, 2007; Lauferweiler, 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/03/20.

11.1.4. Skin sensitization

Based on the application of DST, S-(1-methylpropyl) 3-methylbut-2-enethioate does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. No skin sensitization studies are available for S-(1-methylpropyl) 3-methylbut-2-enethioate. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Acting conservatively due to the lack of data, the reported exposure was benchmarked utilizing the reactive DST of 64 µg/cm² (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for S-(1-methylpropyl) 3-methylbut-2-enethioate that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/04/20.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra for the structurally related material S-1-methylethyl 3-methylbut-2-enethioate (CAS # 34365-79-2), S-(1-methylpropyl) 3-methylbut-2-enethioate would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 1

Maximum acceptable concentrations for S-(1-methylpropyl) 3-methylbut-2-enethioate that present no appreciable risk for skin sensitization based on reactive DST.

| IFRA Category ^a | Description of Product Type | Maximum Acceptable Concentrations in Finished Products Based on Reactive DST | Reported 95th Percentile Use Concentrations in Finished Products |
|----------------------------|--|--|--|
| 1 | Products applied to the lips | 0.0049% | NRU ^b |
| 2 | Products applied to the axillae | 0.0015% | 1.8 × 10 ⁻⁴ % |
| 3 | Products applied to the face using fingertips | 0.029% | 2.1 × 10 ⁻⁵ % |
| 4 | Fine fragrance products | 0.027% | 0.0008% |
| 5 | Products applied to the face and body using the hands (palms), primarily leave-on | 0.0070% | 2.1 × 10 ⁻⁴ % |
| 6 | Products with oral and lip exposure | 0.016% | NRU ^b |
| 7 | Products applied to the hair with some hand contact | 0.056% | 5.4 × 10 ⁻⁵ % |
| 8 | Products with significant anogenital exposure | 0.0029% | No Data ^c |
| 9 | Products with body and hand exposure, primarily rinse-off | 0.054% | 6.5 × 10 ⁻⁵ % |
| 10 | Household care products with mostly hand contact | 0.19% | 1.8 × 10 ⁻⁴ % |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate | 0.11% | No Data ^c |
| 12 | Products not intended for direct skin contact, minimal or insignificant transfer to skin | Not restricted | 0.0065% |

Note.

^a For a description of the categories, refer to the IFRA/RIFM Information Booklet.

^b No reported use.

^c Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for S-(1-methylpropyl) 3-methylbut-2-enethioate in experimental models. UV/Vis absorption spectra for S-(1-methylpropyl) 3-methylbut-2-enethioate are also not available. UV/Vis absorption spectra for the structurally related material S-1-methylethyl 3-methylbut-2-enethioate (CAS # 34365-79-2) indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance for the structurally related analog, S-(1-methylpropyl) 3-methylbut-2-enethioate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra for the target material S-(1-methylpropyl) 3-methylbut-2-enethioate were not available. UV/Vis absorption spectra for the structurally related material S-1-methylethyl 3-methylbut-2-enethioate (CAS # 34365-79-2) were obtained. The spectra indicate minor absorbance in the range of 290–700

nm. The molar absorption coefficients (522, 0, and 568 L mol⁻¹ · cm⁻¹ under neutral, acidic, and basic conditions, respectively) are below the benchmark of concern for phototoxic effects, 1000 L mol⁻¹ · cm⁻¹ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/11/20.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for S-(1-methylpropyl) 3-methylbut-2-enethioate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on S-(1-methylpropyl) 3-methylbut-2-enethioate. Based on the Creme RIFM Model, the inhalation exposure is 0.000073 mg/day. This exposure is 19178 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/29/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of S-(1-methylpropyl) 3-methylbut-2-enethioate 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 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 Volume of Use

Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, S-(1-methylpropyl) 3-methylbut-2-enethioate was identified as a fragrance material with no 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 S-(1-methylpropyl) 3-methylbut-2-enethioate as possibly 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, 2012). 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), S-(1-methylpropyl) 3-methylbut-2-enethioate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. S-(1-Methylpropyl) 3-methylbut-2-enethioate has been pre-registered for REACH with no additional information available 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.

| | LC50 (Fish) (mg/L) | EC50 (<i>Daphnia</i>) (mg/L) | EC50 (Algae) (mg/L) | AF | PNEC (µg/L) | Chemical Class |
|---|-----------------------|--------------------------------------|---------------------------|---------|-------------|----------------|
| RIFM Framework Screening-level (Tier 1) | <u>15.87</u> | | | 1000000 | 0.01587 | |

Exposure information and PEC calculation (following RIFM Environmental Framework: [Salvito, 2002](#)).

| Exposure | Europe (EU) | North America (NA) |
|--|-------------|--------------------|
| Log K _{ow} Used | 3.34 | 3.34 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | <1 | No VoU |
| Risk Characterization: PEC/PNEC | <1 | NA |

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.01587 µg/L. The revised PEC/PNECs for EU and NA (No VoU) are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 07/28/20.

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>
- **PubMed:** <https://www.ncbi.nlm.nih.gov/pubmed>

Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria ([RIFM, 2020](#)). These criteria follow 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 Chemical Agency read-across assessment framework ([ECHA, 2017](#)).

- 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 v4.11 ([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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 ([OECD, 2020](#)).
- Developmental toxicity was predicted using CAESAR v2.1.7 ([Cassano et al., 2010](#)).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 ([OECD, 2020](#)), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 ([OECD, 2020](#)).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

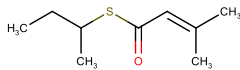
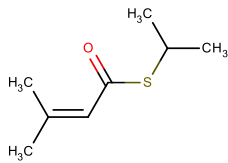
- **National Library of Medicine's Toxicology Information Services:** <https://toxnet.nlm.nih.gov/>
- **IARC:** <https://monographs.iarc.fr>
- **OECD SIDS:** <https://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/public_search_publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **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://chem.nlm.nih.gov/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 01/29/21.

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.

| | Target Material | Read-across Material |
|---|--|---|
| Principal Name | S-(1-Methylpropyl) 3-methylbut-2-enethioate | S-1-Methylethyl 3-methylbut-2-enethioate |
| CAS No. | 34322-09-3 | 34365-79-2 |
| Structure |  |  |
| Similarity (Tanimoto Score) | | 0.83 |
| Endpoint | | • Phototoxicity/photoallergenicity |
| Molecular Formula | C ₉ H ₁₆ OS | C ₈ H ₁₄ OS |
| Molecular Weight | 172.29 | 158.26 |
| Melting Point (°C, EPI Suite) | -5.64 | -16.81 |
| Boiling Point (°C, EPI Suite) | 229.60 | 210.63 |
| Vapor Pressure (Pa @ 25°C, EPI Suite) | 1.06E+01 | 2.81E+01 |
| Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite) | 8.46E+01 | 2.58E+02 |
| Log KOW | 3.34 | 2.85 |
| J_{max} (µg/cm²/h, SAM) | 6.94 | 15.82 |
| Henry's Law (Pa·m³/mol, Bond Method, EPI Suite) | 1.92E+01 | 1.44E+01 |
| Metabolism | | |
| Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2) | N/A | N/A |

Summary

There are insufficient toxicity data on S-(1-Methylpropyl) 3-methylbut-2-enethioate (CAS # 34322-09-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, S-1-methylethyl 3-methylbut-2-enethioate (CAS # 34365-79-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- S-1-Methylethyl 3-methylbut-2-enethioate (CAS # 34365-79-2) was used as a read-across analog for the target material S-(1-methylpropyl) 3-methylbut-2-enethioate (CAS # 34322-09-3) for the phototoxicity/photoallergenicity endpoint.
 - o The target material and the read-across analog are structurally similar and belong to the class of thioesters.
 - o The key difference between the target material and the read-across analog is in the branching attached to the thiol of the thioester. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target material.
 - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
 - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
 - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
 - o The target material and the read-across analog do not have a chromophore that is expected to absorb in the UV/Vis range of the electromagnetic spectrum that is of interest to human health toxicity. The data on the read-across analog confirm that the substance does not absorb in the UV/Vis range. Therefore, the structural difference between the target material and the read-across analog is toxicologically insignificant for the phototoxicity endpoint, and the target material can be predicted to not absorb in the UV/Vis range.
 - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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