



Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short Review

RIFM fragrance ingredient safety assessment, 3-(methylthio)-1-hexanol, CAS Registry Number 51755-66-9



A.M. Api^a, D. Belsito^b, S. Biserta^a, D. Botelho^a, M. Bruze^c, G.A. Burton Jr.^d, J. Buschmann^e, M. A. Cancellieri^a, M.L. Dagli^f, M. Date^a, W. Dekant^g, C. Deodhar^a, A.D. Fryer^h, S. Gadhia^a, L. Jones^a, K. Joshi^a, M. Kumar^a, A. Lapczynski^a, M. Lavelle^a, I. Lee^a, D.C. Lieblerⁱ, H. Moustakas^a, M. Na^a, T.M. Penning^j, G. Ritacco^a, J. Romine^a, N. Sadekar^a, T.W. Schultz^k, D. Selechnik^a, F. Siddiqi^a, I.G. Sipes^l, G. Sullivan^{a,*}, Y. Thakkar^a, Y. Tokura^m

^a Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA

^b Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA

^c Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden

^d Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA

^e Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany

^f Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil

^g Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany

^h Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA

ⁱ Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA

^j Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA

^k Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

^l Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

^m Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

ARTICLE INFO

Handling editor: Dr. Jose Luis Domingo

Keywords:

Genotoxicity
Repeated dose, developmental, and reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

* Corresponding author.

E-mail address: gsullivan@rifm.org (G. Sullivan).

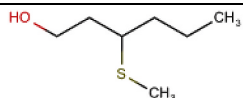
<https://doi.org/10.1016/j.fct.2021.112204>

Received 30 October 2020; Received in revised form 8 February 2021; Accepted 8 April 2021

Available online 16 April 2021

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Version: 081219. This version replaces any previous versions.
 Name: 3-(Methylthio)-1-hexanol CAS Registry Number: 51755-66-9



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
Crete RIFM Model - The Crete 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 Observable 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
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.

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

3-(Methylthio)-1-hexanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity,

(continued)

skin sensitization, and environmental safety. Data from read-across analogs 2-(ethylthio)ethanol (CAS # 110-77-0) and 3-(methylthio)propanol (CAS # 505-10-2) show that 3-(methylthio)-1-hexanol is not expected to be 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 3-(methylthio)-1-hexanol 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 (UV) spectra; 3-(methylthio)-1-hexanol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-(methylthio)-1-hexanol 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 expected to be genotoxic. (ECHA REACH Dossier: 2-(Ethylthio)ethanol; ECHA, 2011; RIFM, 2020)

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

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

Skin Sensitization: No safety concerns at current, declared use levels. Exposure is below the DST.

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

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.03 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 7.561 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 275.6 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: 275.6 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.2756 $\mu\text{g}/\text{L}$

• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

- Chemical Name:** 3-(Methylthio)-1-hexanol
- CAS Registry Number:** 51755-66-9
- Synonyms:** 3-(Methylmercapto)-1-hexanol; 3-(Methylsulfanyl)hexan-1-ol; 3-(Methylthio)-1-hexanol
- Molecular Formula:** $\text{C}_7\text{H}_{16}\text{OS}$
- Molecular Weight:** 148.26
- RIFM Number:** 6782
- Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

- Boiling Point:** 225.06 $^{\circ}\text{C}$ (EPI Suite)
- Flash Point:** Not Available
- Log K_{OW} :** 1.84 (EPI Suite)
- Melting Point:** -3.27 $^{\circ}\text{C}$ (EPI Suite)
- Water Solubility:** 2087 mg/L (EPI Suite)
- Specific Gravity:** Not Available
- Vapor Pressure:** 0.0095 mm Hg at 20 $^{\circ}\text{C}$ (EPI Suite v4.0), 0.01 mm Hg at 20 $^{\circ}\text{C}$ (FMA), 0.0158 mm Hg at 25 $^{\circ}\text{C}$ (EPI Suite)

(continued on next column)

8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark ($1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$)

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 Hydroalcoholics:** 0.01% (RIFM, 2017)

2. **Inhalation Exposure*:** 0.00002 mg/kg/day or 0.0014 mg/day (RIFM, 2017)

3. **Total Systemic Exposure**:** 0.000013 mg/kg/day (RIFM, 2017)

*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	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. **Analogs Selected:**

a. **Genotoxicity:** 2-(Ethylthio)ethanol (CAS # 110-77-0); 3-(methylthio)propanol (CAS # 505-10-2)

b. **Repeated Dose Toxicity:** None

c. **Reproductive Toxicity:** None

d. **Skin Sensitization:** None

e. **Phototoxicity/Photoallergenicity:** None

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

3-(Methylthio)-1-hexanol is reported to occur in the following foods by the VCF*:

Artocarpus species

Passion fruit (*Passiflora* species)

*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

3-(Methylthio)-1-hexanol has been pre-registered for 2010; no dossier available as of 08/12/19.

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, 3-(methylthio)-1-hexanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 3-(Methylthio)-1-hexanol was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014).

There are no studies assessing the mutagenic activity of 3-(methylthio)-1-hexanol; however, read-across can be made to 2-(ethylthio)ethanol (CAS # 110-77-0; see Section VI). The mutagenic activity of 2-(ethylthio)ethanol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent to OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 2-(ethylthio)ethanol in dimethyl sulfoxide (DMSO) at concentrations up to 10 $\mu\text{L}/\text{plate}$. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2011). Under the conditions of the study, 2-(ethylthio)ethanol was not mutagenic in the Ames test, and this can be extended to 3-(methylthio)-1-hexanol.

There are no studies assessing the clastogenic activity of 3-(methylthio)-1-hexanol; however, read-across can be made to 3-(methylthio)propanol (CAS # 505-10-2; see Section VI). The clastogenic activity of 3-(methylthio)propanol 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 3-(methylthio)propanol in DMSO at concentrations up to 1060 $\mu\text{g}/\text{mL}$ in the DRF study; micronuclei analysis was conducted at concentrations up to 1060 $\mu\text{g}/\text{mL}$ in the presence and absence of metabolic activation. 3-(Methylthio)propanol did not induce binucleated cells with micronuclei when tested up to maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2020). Under the conditions of the study, 3-(methylthio)propanol was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 3-(methylthio)-1-hexanol.

Based on the data available on the read-across materials, 3-(methylthio)-1-hexanol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/24/19.

11.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 3-(methylthio)-1-hexanol or any read-across materials. The total systemic exposure to 3-(methylthio)-1-hexanol 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 3-(methylthio)-1-hexanol or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3-(methylthio)-1-hexanol (0.013 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes, 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: 10/01/19.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on 3-(methylthio)-1-hexanol or on any read-across materials. The total systemic exposure to 3-(methylthio)-1-hexanol 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 3-(methylthio)-1-hexanol or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 3-(methylthio)-1-hexanol (0.013 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes, 2007; Laufersweiler, 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: 08/28/19.

11.1.4. Skin sensitization

Based on existing data and the application of DST, 3-(methylthio)-1-hexanol does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins while its metabolite is expected to be reactive (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for 3-(methylthio)-1-hexanol. Acting conservatively, due to insufficient 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 3-(methylthio)-1-hexanol 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: 08/28/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 3-(methylthio)-1-hexanol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 3-(methylthio)-1-hexanol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009).

Table 1

Maximum acceptable concentrations for 3-(methylthio)-1-hexanol 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%	NRU ^b
3	Products applied to the face using fingertips	0.029%	NRU ^b
4	Fine fragrance products	0.027%	0.010%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	NRU ^b
6	Products with oral and lip exposure	0.016%	2.0 × 10 ⁻⁴ %
7	Products applied to the hair with some hand contact	0.056%	NRU ^b
8	Products with significant anogenital exposure	0.0029%	No Data ^c
9	Products with body and hand exposure, primarily rinse-off	0.054%	1.1 × 10 ⁻⁶ %
10	Household care products with mostly hand contact	0.19%	NRU ^b
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	0.030%

^aNote.

^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.

Based on the lack of absorbance, 3-(methylthio)-1-hexanol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is 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: 08/13/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3-(methylthio)-1-hexanol 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 3-

(methylthio)-1-hexanol. Based on the Creme RIFM Model, the inhalation exposure is 0.0014 mg/day. This exposure is 1000 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: 09/20/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3-(methylthio)-1-hexanol 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 esti-

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), 3-(methylthio)-1-hexanol presents no risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. *Biodegradation.* No data available.

11.2.3.2. *Ecotoxicity.* No data available.

11.2.4. Other available data

3-(Methylthio)-1-hexanol has been pre-registered for REACH with no additional data available at this time.

11.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ($\mu\text{g/L}$)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>275.6</u>			1000000	0.2756	

mates. 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, 3-(methylthio)-1-hexanol 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 3-(methylthio)-1-hexanol 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

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	1.84	1.84
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	<1	<1

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

The RIFM PNEC is 0.2756 $\mu\text{g/L}$. The revised PEC/PNECs for EU and NA 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: 09/18/19.

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>
- **TOXNET:** <https://toxnet.nlm.nih.gov/>
- **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 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 10/30/20.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2021.112204>.

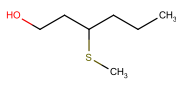
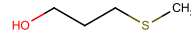
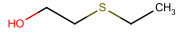
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also 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, 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), 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, 2018).

	Target Material	Read-across Material	Read-across Material
Principal Name	3-(Methylthio)-1-hexanol	3-(Methylthio)propanol	Ethyl 2-hydroxyethyl sulfide
CAS No.	51755-66-9	505-10-2	110-77-0
Structure			
Similarity (Tanimoto Score)		0.55	0.30
Read-across Endpoint		• Genotoxicity	• Genotoxicity
Molecular Formula	C ₇ H ₁₆ OS	C ₄ H ₁₀ OS	C ₄ H ₁₀ OS
Molecular Weight	148.26	106.18	106.18
Melting Point (°C, EPI Suite)	-3.27	-26.55	-100.00
Boiling Point (°C, EPI Suite)	225.06	177.54	184.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.106	37.330	24.798
Log K _{OW} (KOWWIN v1.68 in EPI Suite)	1.84	0.44	0.44
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.09E+03	4.75E+04	4.75E+04
J _{max} (µg/cm ² /h, SAM)	119.353	246.994	246.994
Henry's Law (Pa·m ³ /mol, Bond Method, EPI Suite)	1.20E-02	5.13E-03	5.13E-03

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	Target Material	Read-across Material	Read-across Material
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found	• No alert found
Carcinogenicity (ISS)	• No alert found	• No alert found	• No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	• No alert found
<i>In Vitro</i> Mutagenicity (Ames, ISS)	• No alert found	• No alert found	• No alert found
<i>In Vivo</i> Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified	• Not classified
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 3-(methylthio)-1-hexanol (CAS # 51755-66-9). 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, 3-(methylthio)propanol (CAS # 505-10-2) and ethyl 2-hydroxyethyl sulfide (CAS # 110-77-0) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 3-(Methylthio)propanol (CAS # 505-10-2) was used as a read-across analog for the target material 3-(methylthio)-1-hexanol (CAS # 51755-66-9) for the genotoxicity endpoint.
 - o The target material and the read-across analog are structurally similar and belong to a class of thioethers containing a primary alcohol.
 - o The target material and the read-across analog share a primary alcohol and a methylthio group.
 - o The key difference between the target material and the read-across analog is that the target material is a secondary thioether, whereas the read-across analog is a primary thioether. This structural difference is toxicologically insignificant.
 - 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 The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
 - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Ethyl 2-hydroxyethyl sulfide (CAS # 110-77-0) was used as a read-across analog for the target material 3-(methylthio)-1-hexanol (CAS # 51755-66-9) for the genotoxicity endpoint.
 - o The target material and the read-across analog are structurally similar and belong to a class of thioethers containing a primary alcohol.
 - o The target material and the read-across analog share a primary alcohol and thioether functionality.
 - o The key difference between the target material and the read-across analog is that the target material is a secondary thioether, whereas the read-across analog is a primary thioether. This structural difference is toxicologically insignificant.
 - 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 The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
 - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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