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Short Review



RIFM fragrance ingredient safety assessment, (±) ethyl 3-mercaptopbutyrate, CAS Registry Number 156472-94-5

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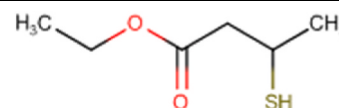
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Name: (±) Ethyl 3-mercaptopbutyrate CAS Registry Number: 156472-94-5

**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

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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., 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 et al., 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.

(±) Ethyl 3-mercaptopbutyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. The genotoxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC), and the exposure to (±) ethyl 3-mercaptopbutyrate is below the TTC (0.0025 µg/kg/day). The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to (±) ethyl 3-mercaptopbutyrate 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 µg/cm²); exposure is below the DST. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; (±) ethyl 3-mercaptopbutyrate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; (±) ethyl 3-mercaptopbutyrate 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: No data available. Exposure is below the TTC.

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.

Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.

(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Screening-level: 3.01 (BIOWIN 3)

(EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:

Screening-level: 6.3 L/kg

(EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Screening-level: Fish LC50: 350.4 mg/L

(RIFM Framework; Salvito et al., 2002)

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Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:**Screening-level:** PEC/PNEC (North America and Europe) < 1(RIFM Framework; [Salvito et al., 2002](#))**Critical Ecotoxicity Endpoint:** Fish LC50: 350.4 mg/L(RIFM Framework; [Salvito et al., 2002](#))

RIFM PNEC is: 0.3504 µg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** (±) Ethyl 3-mercaptobutyrate
2. **CAS Registry Number:** 156472-94-5
3. **Synonyms:** 3-Mercaptobutyric acid, ethyl ester; Butanoic acid, 3-mercapto-, ethyl ester; (±) Ethyl 3-mercaptobutyrate
4. **Molecular Formula:** C₆H₁₂O₂S
5. **Molecular Weight:** 148.22 g/mol
6. **RIFM Number:** 7166
7. **Stereochemistry:** No isomer is specified. One stereocenter and 2 total stereoisomers are possible.

2. Physical data

1. **Boiling Point:** Not Available
2. **Flash Point:** 71±2 °C ([RIFM, 2000](#))
3. **Log K_{ow}:** Not Available
4. **Melting Point:** Not Available
5. **Water Solubility:** Not Available
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.449 mm Hg at 20 °C (EPI Suite v4.0)
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. <0.1 metric ton per year ([IFRA, 2019](#))

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95th Percentile Concentration in Fine Fragrance:** 0.00000029% ([RIFM, 2021](#))
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day ([RIFM, 2021](#))
3. **Total Systemic Exposure**:** 0.0000001 mg/kg/day ([RIFM, 2021](#))

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model ([Comiskey et al., 2015](#); [Safford et al., 2015a](#); [Safford et al., 2017](#); and [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 et al., 2015](#); [Safford et al., 2015a](#); [Safford et al., 2017](#); and [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
I	I	I

2 Analogs Selected:

- a. **Genotoxicity:** None
- b. **Repeated Dose Toxicity:** None
- c. **Reproductive Toxicity:** None
- d. **Skin Sensitization:** None
- e. **Photoirritation/Photoallergenicity:** None
- f. **Local Respiratory Toxicity:** None
- g. **Environmental Toxicity:** None

- 3 **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

(±) Ethyl 3-mercaptobutyrate 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

Available; accessed 02/09/22.

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**

There are insufficient genotoxicity data on (±) ethyl 3-mercaptobutyrate or any read-across materials. The total systemic exposure for (±)

ethyl 3-mercaptopbutyrate is below the TTC at the current level of use.

11.1.1.1. Risk assessment. (±) Ethyl 3-mercaptopbutyrate 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). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022).

There are no studies assessing the mutagenicity or clastogenicity of (±) ethyl 3-mercaptopbutyrate or any read-across materials that can be used to support the genotoxicity endpoint. The total systemic exposure for (±) ethyl 3-mercaptopbutyrate (0.0001 µg/kg/day) is below the TTC for genotoxicity (0.0025 µg/kg/day; Kroes et al., 2004) at the current level of use and therefore does not present a risk for toxicological concern.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/20/22.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on (±) ethyl 3-mercaptopbutyrate or any read-across materials. The total systemic exposure to (±) ethyl 3-mercaptopbutyrate 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 (±) ethyl 3-mercaptopbutyrate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to (±) ethyl 3-mercaptopbutyrate (0.0001 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: 05/06/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on (±) ethyl 3-mercaptopbutyrate or any read-across materials. The total systemic exposure to (±) ethyl 3-mercaptopbutyrate 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 (±) ethyl 3-mercaptopbutyrate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to (±) ethyl 3-mercaptopbutyrate (0.0001 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for

Table 1
Summary of existing data on (±) ethyl 3-mercaptopbutyrate.

WoE Skin Sensitization Potency Category ¹	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm ²	NOEL-HMT (induction) µg/cm ²	LOEL ² (induction) µg/cm ²	WoE NESIL ³ µg/cm ²	LLNA ⁴ Weighted Mean EC3 Value µg/cm ²	GPMT ⁵	Buehler ⁵
	NA	NA	NA	NA	NA	NA	NA
Human potency category unknown; Current exposure level below the DST for reactive materials.	<i>In vitro</i> Data ⁶				<i>In silico</i> protein binding alerts (OECD Toolbox v4.5)		
	KE 1	KE 2	KE 3		Target Material	Autoxidati on simulator	Metabolis m simulator
	NA	NA	NA		SN2	SN2	SN2

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = 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).

²Data derived from CNIH or HMT.

³WoE NESIL limited to 2 significant figures.

⁴Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

⁵Studies conducted according to the OECD TG 406 are included in the table.

⁶Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

Table 2Supported concentrations for (\pm) ethyl 3-mercaptopbutyrate that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category ^a	Description of Product Type	Supported Concentrations ^b (%) in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049	NRU ^c
2	Products applied to the axillae	0.0015	NRU ^c
3	Products applied to the face using fingertips	0.029	NRU ^c
4	Fine fragrance products	0.027	3.0×10^{-8}
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070	7.4×10^{-7}
6	Products with oral and lip exposure	0.016	NRU ^c
7	Products applied to the hair with some hand contact	0.056	NRU ^c
8	Products with significant ano-genital exposure	0.0029	No Data ^d
9	Products with body and hand exposure, primarily rinse-off	0.054	2.6×10^{-6}
10	Household care products with mostly hand contact	0.19	9.4×10^{-7}
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11	No Data ^d
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	NRU ^c

Note:

^a For a description of the categories, refer to the IFRA/RIFM Information Booklet.^b These levels represent supported concentrations based on the DST. However, additional studies may show it could be used at higher levels.^c No reported use.^d Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

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: 05/06/22.

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. Limited skin sensitization data are available for (\pm) ethyl 3-mercaptopbutyrate (see [Table 1](#) below). The chemical structure of this material indicates that it would be expected to react with skin proteins directly ([Roberts et al., 2007](#); Toxtree v3.1.0; [OECD Toolbox v4.5](#)). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 $\mu\text{g}/\text{cm}^2$ ([Safford, 2008](#); [Safford et al., 2011](#); [Roberts et al., 2015](#); [Safford et al., 2015b](#)). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. [Table 2](#) provides the supported concentrations for (\pm) ethyl 3-mercaptopbutyrate that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent supported 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: 05/04/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis spectra, (\pm) ethyl 3-mercaptopbutyrate 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 (\pm) ethyl 3-mercaptopbutyrate 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, (\pm) ethyl 3-mercaptopbutyrate 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 effects, $1000 \text{ L mol}^{-1} \bullet \text{cm}^{-1}$ ([Henry et al., 2009](#)).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/13/22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for (\pm) ethyl 3-mercaptopbutyrate 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 (\pm) ethyl 3-mercaptopbutyrate. Based on the Creme RIFM Model, the inhalation exposure is $< 0.0001 \text{ mg/day}$. This exposure is at least 14000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; [Carthew et al., 2009](#)); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of (\pm) ethyl 3-mercaptopbutyrate was performed following the RIFM Environmental Framework ([Salvito et al., 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 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, (\pm) ethyl 3-mercaptopbutyrate 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 (\pm) ethyl 3-mercaptopbutyrate 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017). 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).

11.2.1.1. Risk assessment. Based on the current VoU (2019), (\pm) ethyl 3-mercaptopbutyrate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. Biodegradation:

No data available.

Ecotoxicity:

No data available.

11.2.1.3. Other available data. (\pm) Ethyl 3-mercaptopbutyrate has been registered for REACH, with no additional data available at this time.

11.2.2. 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.72	1.72
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU 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 0.3504 $\mu\text{g/L}$. 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: 05/16/22.

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's Toxicology Information Services:** <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 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://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 10/12/22.

	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>350.4</u>			1000000	0.3504	

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.

References

- Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. *Food Chem. Toxicol.* 82, S1–S19.
- Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. *Food Chem. Toxicol.* 47 (6), 1287–1295.
- Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. *Regul. Toxicol. Pharmacol.* 72 (3), 660–672.
- Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. *Regul. Toxicol. Pharmacol.* 88, 144–156.
- Cottrez, F., Boitel, E., Ourlin, J.C., Peiffer, J.L., et al., 2016. A 3D reconstituted epidermis based model for quantifying chemical sensitization potency: reproducibility and predictivity results from an inter-laboratory study. *Toxicol. Vitro* 32, 248–260. Apr.
- ECHA, 2017. *Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.11: PBT Assessment*. Retrieved from: <https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>.
- Forreryd, A., Zeller, K.S., Lindberg, T., Johansson, H., Linstedt, M., 2016. From genome-wide arrays to tailor-made biomarker readout - progress towards routine analysis of skin sensitizing chemicals with GARD. *Toxicol. Vitro* 37, 178–188.
- Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? *J. Photochem. Photobiol. B Biol.* 96 (1), 57–62.
- IFRA (International Fragrance Association), 2019. *Volume of Use Survey, January–December 2019*.
- Kroes, R., Renwick, A.G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J.G., Wurtzen, G., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food Chem. Toxicol.* 42 (1), 65–83.
- Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. *Food Chem. Toxicol.* 45 (12), 2533–2562.
- Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. *Regul. Toxicol. Pharmacol.* 62 (1), 160–182.
- Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. *Dermatitis* 32 (5), 339–352, 2021 Sep-Oct 01.
- OECD, 2021. *The OECD QSAR Toolbox, v3.2–4.5*. Retrieved from: <http://www.qsartoolbox.org/>.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2000. (+/-) Ethyl 3-mercaptopbutyrate: Determination of Flash Point. Unpublished Report from IFF. RIFM Report Number 68641. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2014. *Report on the Testing of (+/-) Ethyl 3-mercaptopbutyrate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation)*. RIFM Report Number 67442. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2021. *Exposure Survey 31*. March 2021.
- Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. *Regul. Toxicol. Pharmacol.* 72 (3), 683–693.
- Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. *Chem. Res. Toxicol.* 20 (7), 1019–1030.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015b. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. *Regul. Toxicol. Pharmacol.* 72, 673–682.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. *Regul. Toxicol. Pharmacol.* 86, 148–156.
- Safford, R.J., 2008. The dermal sensitisation threshold—A TTC approach for allergic contact dermatitis. *Regul. Toxicol. Pharmacol.* 51 (2), 195–200.
- Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015a. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. *Regul. Toxicol. Pharmacol.* 72 (3), 694–701.
- Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. *Regul. Toxicol. Pharmacol.* 60 (2), 218–224.
- Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. *Environ. Toxicol. Chem.* 21 (6), 1301–1308.
- Thakkar, Y., Joshi, K., Hickey, C., Wahler, J., et al., 2022. The BlueScreen HC assay to predict the genotoxic potential of fragrance materials. *Mutagenesis* 37 (1), 13–23, 2022.
- US EPA, 2012a. *Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11*. United States Environmental Protection Agency, Washington, DC, USA.
- US EPA, 2012b. *The ECOSAR (ECOLOGical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0*. United States Environmental Protection Agency, Washington, DC, USA.