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Short review

RIFM fragrance ingredient safety assessment, methyl mercaptan, CAS Registry Number 74-93-1

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. Liebler [i], 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] *Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *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] *University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *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] *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] *The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

ARTICLE INFO

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

Version: 102820. This version replaces any previous versions.
Name: Methyl mercaptan CAS Registry Number: 74-93-1

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

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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

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

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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
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.

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

Methyl mercaptan was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog sodium methylmercaptide (CAS # 5188-07-8) show that methyl mercaptan is not expected to be genotoxic. Data on methyl mercaptan provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on read-across material sodium methylmercaptide (CAS # 5188-07-8) provide a calculated MOE >100 for the reproductive toxicity endpoint. The skin sensitization endpoint was completed using the DST for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; methyl mercaptan is not expected to be phototoxic/photoallergenic. Local respiratory toxicity was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; the exposure to methyl mercaptan is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; methyl mercaptan was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: Methanethiol; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 10 mg/kg/day.	Tansy (1981)
Reproductive Toxicity: Developmental toxicity: 45 mg/kg/day Fertility: 45 mg/kg/day.	(ECHA Reach Dossier: Methanethiol; ECHA, 2011)
Skin Sensitization: Not a concern for skin sensitization under the current, declared use levels; the 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: 3.09 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 3.162 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 747.4 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: 747.4 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.7474 μg/L

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

1. Identification

1. **Chemical Name:** Methyl mercaptan
2. **CAS Registry Number:** 74-93-1
3. **Synonyms:** Mercaptomethane; Methanethiol; Methyl sulfhydrate; Thiomethyl alcohol; Methyl mercaptan
4. **Molecular Formula:** CH_4S
5. **Molecular Weight:** 48.1
6. **RIFM Number:** 6849
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 32.01 °C (EPI Suite)
2. **Flash Point:** <-18 °C (Globally Harmonized System)
3. **Log K_{OW}:** 0.78 (EPI Suite)
4. **Melting Point:** 115.32 °C (EPI Suite)
5. **Water Solubility:** 1.54E+04 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 1280 mm Hg at 20 °C (EPI Suite v4.0), 1510 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 550 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Clear white liquid or a colorless gas with an unpleasant odor of rotten cabbage or garlic *(Arctander, Volume II, 1969)

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. **95**th **Percentile Concentration in Hydroalcoholics:** 0.000049% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.0000001 mg/kg/day or 0.0000089 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0000002 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 80%

No data are available on the skin absorption for methyl mercaptan. Therefore, dermal absorption is estimated using the Kroes approach (Kroes, 2007). Based on the molecular weight of 48.1 Da and a calculated log K_{ow} of 0.78, dermal absorption is expected to be high. Hence, conservatively, an absorption value of 80% can be used for methyl mercaptan.

Jmax Table (From the RIFM SAM model):

	Parent
Name	Methyl mercaptan
J_{max} (μg/cm^2/h)	638.37[1]
Skin Absorption Class	80%

[1] J_{max} was calculated based on calculated log K_{OW} = 0.78 (EPI Suite) and Solubility = 1.54E+04 mg/L (EPI Suite).

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 v3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Sodium methylmercaptide (CAS # 5188-07-8)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** Sodium methylmercaptide (CAS # 5188-07-8)
   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

Methyl mercaptan gets absorbed rapidly through the respiratory system and directly translocated to the vascular system in animals. Minimal absorption was reported through the skin and eye in animals. Methyl mercaptan binds to protein and erythrocytes. Radioactive methyl mercaptan, when administered intravenously in rats, 23% of the radioactivity was associated with plasma protein, with lesser amounts found in liver (18%), intestine (17%), lungs (12%), kidney (11%), spleen (10%), and testes (9%) within 6 h. However, no radioactivity could be traced in erythrocytes because of intraerythrocytic oxidation of methyl mercaptan to formate and sulfate (94%), which ultimately appeared in the urine. Methyl mercaptan also gets oxidized by the erythrocytes, resulting in products such as formic acid, sulfite ion, and sulfate ion. Methyl mercaptan was metabolized to dimethyl sulfide when administered intraperitoneally in mice, and both dimethyl sulfide and unchanged methyl mercaptan were reported in the exhaled air of mice. Similarly, radiolabeled methyl mercaptan when administered intraperitoneally to male rats resulted in approximately 40% of the administered dose excreted as carbon dioxide in expired air within 6 h of administration, and 6% of the administered dose excreted in expired air as unchanged methyl mercaptan in the first hour. The half-life ($T_{1/2}$) for the metabolism of methanethiol to sulfate was reported to be 1.21 h and the elimination $T_{1/2}$ for sulfate through urine was reported to be 8.47 h in rats when administered via intravenous. These above results indicate methyl mercaptan can be readily oxidized to carbon dioxide and inorganic sulfates. Methyl mercaptan has the potential to react with collagen. The metabolism of methyl mercaptan facilitates the synthesis of amino acids and proteins as a donor of methyl, sulfur, or methylthiol. Methanethiol mixed disulfides in serum are proven to be biomarkers for the exposure of methyl mercaptan in rats. Methyl mercaptan occurs endogenously as an intermediate in the catabolism of the amino acid methionine (NIH, 2020). Methyl mercaptan was found to cause interaction toxicity with a mixture of chemicals such as hydrogen sulfide, indole, and skatole when exposed to different species such as rats, mice, and monkeys for 90 days. The interaction toxicity reported across species included mortality, stress, hematological alterations, and histopathological lesions in the liver, lungs, and kidneys (Sandage, 1961a, 1961b) (see Fig. 1).

Sandage (1961a): In a 90-day subchronic toxicity study (non-GLP and non-guideline compliant) 100 male mice/group; 50 Sprague Dawley male rats/group; and 10 male Rhesus monkey/group were exposed to a mixture of chemicals hydrogen sulfide, methyl mercaptan, indole, and skatole through the inhalation route at dose levels of 0 (control) and 50.9 ppm of methyl mercaptan (equivalent to 166.8 mg/kg/day, 102.7 mg/kg/day, and 54.4 mg/kg/day, for mice, rats, and monkeys, respectively) continuously for 90 days. Parameters evaluated included mortality, body weight, hematology (hemoglobin [Hb], sulfhemoglobin, hematocrit [HCT], red blood cells [RBC], white blood cells [WBC], mean corpuscular volume [MCV], mean corpuscular hemoglobin concentration [MCHbc], differential leucocyte count, reticulocyte count, platelet count, and fragility tests) performed on 4 animals/species every day, clinical chemistry analysis (glucose, alkaline phosphatase, amylase, lipase, glutamic oxaloacetic transaminase, thymol turbidity, sodium, and potassium) performed on 4 animals/species every day and urinalysis (pH, specific gravity, urobilinogen, and total protein) performed at the end of the treatment. Stress tests (swimming until complete exhaustion) were performed on half of the animals at the end of the treatment period and these animals were euthanized thereafter. The remaining animals were euthanized after 2 weeks of the observation period. Liver function tests, necropsy, and histopathology (heart, lung, liver, kidney, and brain) were performed on 25% of animals. Mortality was reported in monkeys (80%) and mice (42%), and no mortality was reported in rats. However, mortality was also reported in the control group of mice at 22%. A significant decrease in body weight was reported in all the animals across species; however, a significant decrease in body weight was reported to be 7% in monkeys. Hematology analysis revealed a significant decrease in RBC, Hb, and HCT in rats and monkeys; a significant increase in WBC, reticulocytes, sulfhemoglobin, leucocytes in all species was reported. All these hematological changes reflected moderate hemolytic anemia, although no impairment of hematopoietic function was reported. Clinical chemistry

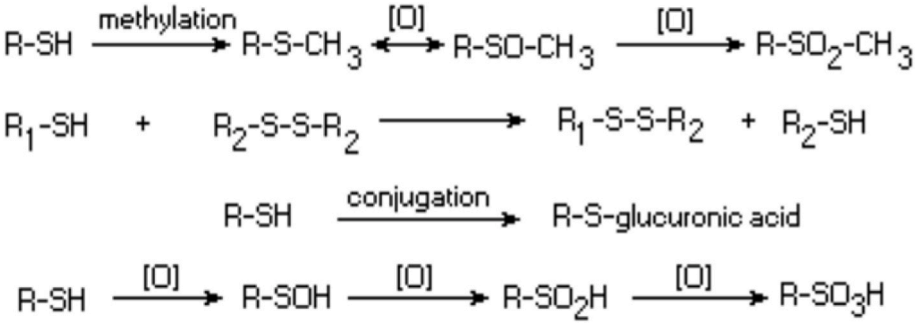


Fig. 1. Metabolism of thiols (Adapted from JECFA, 2000).

analysis revealed a decrease in glucose levels in mice. A significant decrease in swimming time in the stress test was reported in rats. Microscopic examination of liver revealed severe swelling and flocculation of cytoplasm and hyperemia in mice (60%), lesions in rats (25%), and mild to moderate edema, associated with congestion and/or accumulation of inflammatory cells in monkeys (30%). Microscopic examination of kidneys revealed chronic and acute focal interstitial nephritis including controls (12% in the treatment group and 33% in control). Some of the animals were reported to have perivascular and peri pelvic lymphocyte infiltration in mice, lesions in rats (10%), and mild to moderate edema, associated with congestion and/or accumulation of inflammatory cells in monkeys (20%). Microscopic examination of lungs revealed focal hemorrhages accompanied with peribronchial and perivascular mononuclear infiltration, which reflected chronic bronchitis and stood as a cause of mortality (75%) in mice, pulmonary emphysema associated with patchy atelectasis in almost all rats, and mild to moderate edema, associated with congestion and/or accumulation of inflammatory cells in monkeys (30%).

Sandage (1961b): In a 90-day subchronic toxicity study (non-GLP and non-guideline compliant) 100 male mice/group, 50 Sprague Dawley male rats/group, and 10 male Rhesus monkey/group were exposed to a mixture of chemicals hydrogen sulfide, methyl mercaptan, indole, and skatole through the inhalation route at dose levels of 0 (control) and 50 ppm of methyl mercaptan (equivalent to 163.8 mg/kg/day, 100.8 mg/kg/day, and 54.4 mg/kg/day, for mice, rats, and monkeys, respectively) continuously for 90 days. Parameters evaluated included mortality, body weight, hematology (Hb, sulfhemoglobin, HCT, RBC, WBC, MCV, MCHbc, differential leucocyte count, reticulocyte count, and platelet count) performed before treatment and at 30-day intervals thereafter, clinical chemistry analysis (glucose, alkaline phosphatase, sodium, and potassium) performed before treatment and at 30-day intervals thereafter, and urinalysis (pH, specific gravity, urobilinogen, and total protein) performed before treatment and at 30-day intervals thereafter. Stress tests (swimming until complete exhaustion) were performed on half of the animals at the end of the treatment period, and these animals were euthanized thereafter. The remaining animals were euthanized after 2 weeks of the observation period. Liver function tests, necropsy, and histopathology (heart, lung, liver, kidney, and brain) were performed on 25% of animals. Mortality was reported in the majority of animals (60%–80%) across all the species in mice, rats, and monkeys. A significant decrease in body weight was reported in mice and rats, whereas a significant increase in body weight was reported in monkeys. Hematology analysis revealed a significant decrease in platelets and MCHbc, and a significant increase in hematocrit and hemoglobin was reported, which revealed hemolytic processes across all species. Heinz body formation was reported in mice, but it was expected to be due to indole as similar changes were reported with administration of indole alone and not with other compounds in the mixture. A decrease (statistical significance not specified) in swimming time in the stress test was reported in mice. Clinical chemistry analysis revealed a decrease (statistical significance not specified) in glucose levels in mice and rats, whereas a significant increase in glucose and alkaline phosphatase was reported in monkeys. Urinalysis revealed a significant increase in urobilinogen in both rats and monkeys. Microscopic examination evidenced lesions in liver and kidney for mice, bronchopneumonia with no hemorrhage, central degeneration in the liver, lesions in the kidney for rats, and treatment-related pathological alterations in lungs (80% of animals), such as mild to moderate edema, associated with congestion and/or accumulation of inflammatory cells in the liver (10% of animals) in monkeys.

Additional References: None.

8. Natural occurrence (discrete chemical) or composition (NCS)

Methyl mercaptan is reported to occur in the following foods by the VCF*:

Allium species	Garlic (*Allium sativum* L.)
Asparagus (*Asparagus officinalis* L.)	Kohlrabi
Boletus edulis (dried)	Mushroom
Cabbage (*Brassica oleracea*)	Onion (*Allium cepa* L.)
Cheddar cheese chicken (fried)	Sake

*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. This is a partial list.

9. REACH dossier

Available; accessed 01/16/20.

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, methyl mercaptan does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of methyl mercaptan; however, read-across can be made to sodium methylmercaptide (CAS # 5188-07-8; see Section VI).

The mutagenic activity of sodium methylmercaptide 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 methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with sodium methylmercaptide in distilled water 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 (ECHA, 2011). Under

the conditions of the study, sodium methylmercaptide was not mutagenic in the Ames test, and this can be extended to methyl mercaptan.

The clastogenic activity of methyl mercaptan was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered via inhalation to groups of male and female Swiss Webster mice. Doses of 0, 114, 258, and 512 ppm were administered. Mice from each dose level were euthanized at 24, 48, and 72 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011). Under the conditions of the study, methyl mercaptan was considered to be not clastogenic in the *in vivo* micronucleus test.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/04/20.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for methyl mercaptan is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on methyl mercaptan. In a subchronic repeated dose toxicity study (OECD TG 413, non-GLP), 31 male CR Sprague Dawley rats/dose were exposed to methyl mercaptan via whole-body inhalation at concentrations of 0, 2, 17, and 57 ppm (equivalent to 0, 1.18, 10, and 33.52 mg/kg/day, respectively) for 3 months (7 h/day, 5 days/week; 65 exposures). A subset of 10 animals/dose was designated for special metabolic performance testing. Average terminal body weights were lower for all treated rats; however, it only attained statistically significant at the 57 ppm dose and showed a statistically significant dose-related trend, which was apparent for the metabolic subsets as well at 57 ppm. No significant differences were reported in metabolic performance. No treatment-related effects were reported for mortality, clinical signs, food consumption, water consumption, clinical chemistry, or organ weights at any dose level. No histopathological changes were reported for the heart, small intestine, or kidneys at any dose level. Based on the significant decrease in average terminal body weight (15%) at 57 ppm, the no observed adverse effect concentration (NOAEC) was considered to be 17 ppm. Using standard minute volume (MV) and bodyweight values for male Sprague Dawley rats, the calculated no observed adverse effect level (NOAEL) for repeated dose toxicity is 10 mg/kg/day.

Therefore, the methyl mercaptan MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl mercaptan NOAEL in mg/kg/day by the total systemic exposure for methyl mercaptan, 10/0.0000002 or 50000000.

In addition, the total systemic exposure to methyl mercaptan (0.0002 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.

Duration in detail	GLP/ Guideline	No. of animals/dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/ LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
3 months (7 h/day, 5 days/week; 65 exposures)	OECD TG 413, Non-GLP	31 male CR Sprague Dawley rats/dose	Inhalation (whole-body)	0, 2, 17, and 57 ppm (equivalent to 0, 1.18, 10, and 33.52 mg/kg/day)	17 ppm (equivalent to 10 mg/kg/day)	Decreased body weight	Tansy (1981)
13 weeks (24 h/day)	Non-GLP and non-guideline	10 male Rhesus monkeys	Inhalation	50 ppm (equivalent to 54.4 mg/kg/day)	LOAEL: 54.4 mg/kg/day	Based on mortality (80%), hematological analysis evidenced a significant decrease in RBC, Hb, MCH, MCHbc, and histopathology examination revealed treatment-related pathological alterations in lungs (80% of animals) such as mild to moderate edema, associated with congestion and/or accumulation of inflammatory cells, liver (10% of animals)	Sandage (1961b)
8 weeks (3 days/week and 2 h/day)	Non-GLP and non-guideline	11 male healthy mice (strain not reported)	Inhalation	300 ppm (equivalent to 83.7 mg/kg/day)	LOAEL- 300 ppm	Mortality	Horiguchi (1960a)
13 weeks (24 h/day)	Non-GLP and non-guideline	50 male Sprague Dawley rats	Inhalation	50 ppm (equivalent to 100.83 mg/kg/day)	LOAEL-100.83 mg/kg/day	64% mortality. Low-grade hemolytic process was reported, weight loss, bronchopneumonia, central degeneration in the liver, and lesions kidney	Sandage (1961b)
13 weeks (24 h/day)	Non-GLP and non-guideline	100 male mice (strain not reported)	Inhalation	50 ppm (equivalent to 163.84 mg/kg/day)	LOAEL-163.84 mg/kg/day	99% mortality. Low-grade hemolytic process was reported, weight loss, lung hemorrhage, decrease in swimming time, lesions in the liver, and kidney	Sandage (1961b)
13 weeks (24 h/day)	Non-GLP and non-guideline	10 male Rhesus monkeys	Inhalation	50.9 ppm (equivalent to 54.4 mg/kg/day)	LOAEL-54.4 mg/kg/day	Based on high mortality, decreased bodyweight, treatment-related alterations in hematology, clinical chemistry, and histopathology examination revealed lesions in lung, kidneys, and liver	Sandage (1961a)
13 weeks (24 h/day)	Non-GLP and non-guideline	50 male Sprague Dawley rats	Inhalation	50.9 ppm (equivalent to 102.68 mg/kg/day)	LOAEL-102.68 mg/kg/day	Based on high mortality, decreased bodyweight, treatment-related alterations in hematology, clinical chemistry, decreased swimming time, and histopathology examination revealed lesions in lung, kidneys, and liver	Sandage (1961a)
13 weeks (24 h/day)	Non-GLP and non-guideline	100 male mice (strain not reported)	Inhalation	50.9 ppm (equivalent to 166.83 mg/kg/day)	LOAEL-166.83 mg/kg/day	Based on high mortality, decreased bodyweight, treatment-related alterations in hematology, clinical chemistry, and histopathology examination revealed lesions in lung, kidneys, and liver	Sandage (1961a)

Additional References: NCBI, 2020; ECHA, 2011; Tansy (1981).

Literature Search and Risk Assessment Completed On: 02/24/20.

11.1.3. Reproductive toxicity

The MOE for methyl mercaptan is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on methyl mercaptan. Read-across material sodium methylmercaptide (CAS # 5188-07-8; see Section VI) has sufficient reproductive toxicity data.

In an OECD TG 422 and GLP-compliant combined repeated dose toxicity study with a reproduction and development toxicity screening test, 10 Sprague Dawley (SD) rats/sex/dose were treated with sodium methyl mercaptide via gavage at doses of 0 (vehicle: water), 5, 15, and 45 mg/kg/day. Males were treated once daily for 28 days before mating, during the mating and post-mating periods until sacrifice (approximately 8 weeks). Females were treated once daily for 28 days before mating, during the mating period, during pregnancy, and lactation until day 4 post-partum (approximately 8–9 weeks). No treatment-related adverse effects were reported for mortality, clinical signs, body weight, food consumption, mating index, pre-coital time, fertility index, gestation period, gestation index, conception/pregnant female number, post-natal and neo-natal losses, necropsy, organ weights, or microscopic examination at any dose level. A significant decrease in bodyweight gain was reported in males (18%) and females (36%) at 45 mg/kg/day. However, the decreased bodyweight gain was considered to be transient in nature and not toxicologically relevant. No treatment-related effects were reported on mortality, clinical signs, gross external abnormalities, body weight, or sex ratio in pups at any dose level. Based on a lack of treatment-related adverse effects up to the highest tested dose, the NOAEL for developmental and reproductive toxicity was considered to be 45 mg/kg/day (ECHA, 2011).

Therefore, the methyl mercaptan MOE for the fertility endpoint can be calculated by dividing the sodium methylmercaptide NOAEL in mg/kg/day by the total systemic exposure for methyl mercaptan, 45/0.0000002, or 225000000.

The methyl mercaptan MOE for the developmental toxicity endpoint can be calculated by dividing the sodium methylmercaptide NOAEL in mg/kg/day by the total systemic exposure for methyl mercaptan, 45/0.0000002, or 225000000.

In addition, the total systemic exposure to Methyl mercaptan (0.0002 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: 02/25/20.

11.1.4. Skin sensitization

Based on the application of DST, methyl mercaptan does not present a concern for skin sensitization under the current, declared use levels.

11.1.4.1. Risk assessment. No skin sensitization studies are available for methyl mercaptan. 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/cm^2 (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 methyl mercaptan 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: 02/21/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, methyl mercaptan 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 methyl mercaptan in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 550 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, methyl mercaptan does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra were obtained. The spectra indicate no significant absorbance in the range of 290–550 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: 02/18/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for methyl mercaptan is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on methyl mercaptan. Based on the Creme RIFM Model, the inhalation exposure is 0.0000089 mg/day. This exposure is 157,303 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: Ljunggren (1943); Tansy (1981); Zieve (1974); Speranskii (1973); Doizaki (1973); Horiguchi (1960b); Sandage (1961a); Sandage (1961b).

Literature Search and Risk Assessment Completed On: 02/28/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of methyl mercaptan 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, methyl mercaptan was identified as a fragrance material with no potential to present a possible

Table 1
Maximum acceptable concentrations for methyl mercaptan 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%	4.0×10^{-7}%
3	Products applied to the face using fingertips	0.029%	NRU[b]
4	Fine fragrance products	0.027%	4.9×10^{-5}%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	5.3×10^{-8}%
6	Products with oral and lip exposure	0.016%	4.0×10^{-6}%
7	Products applied to the hair with some hand contact	0.056%	NRU[b]
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	3.5×10^{-9}%
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	2.0×10^{-4}%

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.

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 methyl mercaptan 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).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), methyl mercaptan presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. No data available.

11.2.2.2. Ecotoxicity. No data available.

11.2.2.3. Other available data. Methyl mercaptan has been registered for REACH with no additional information available at this time.

11.2.2.4. Risk assessment refinement. Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	0.78	0.78
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 0.7474 μg/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: 02/11/20.

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
- **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 HPVIS:** https://ofmpub.epa.gov/oppthpv/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/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	747.4			1000000	0.7474	

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 05/31/20.

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.2020.111891.

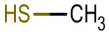
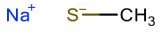
Appendix

Read-across Justification

Methods

The read-across analog was 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
Principal Name	Methyl mercaptan	Sodium methyl mercaptan
CAS No.	74-93-1	5188-07-8
Structure		
Similarity (Tanimoto Score)		0.75
Endpoint		• Genotoxicity • Reproductive toxicity
Molecular Formula	CH_4S	CH_3NaS
Molecular Weight	48.1	70.08
Melting Point (°C, EPI Suite)	−123.00	141.75
Boiling Point (°C, EPI Suite)	5.90	387.83
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.01E+05	1.44E-02

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.54E+04	1E+006
Log K_{OW}	0.78	−2.33
J_{max} (μg/cm^2/h, SAM)	638.37	111.8
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.16E+02	1.009E-08
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	Radical|Radical ≫ Radical mechanism via Reactive oxygen species (ROS) formation (indirect)|Radical ≫ Radical mechanism via ROS formation (indirect) ≫ Thiols	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found
Oncologic Classification	Not classified	Not classified
Reproductive and Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on methyl mercaptan (CAS # 74-93-1). 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, sodium methyl mercaptan (CAS # 5188-07-8) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Sodium methyl mercaptan (CAS # 5188-07-8) was used as a read-across analog for the target material methyl mercaptan (CAS # 74-93-1) for the genotoxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of organosulfur compounds.
  - o The target material and the read-across analog share a methyl mercaptan structure.
  - o The key difference between the target material and the read-across analog is that the read-across analog is a sodium salt of the target material. This structural difference is toxicologically insignificant.
  - o 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 has a radical mechanism via ROS formation (indirect)|Radical from DNA binding alert from the QSAR toolbox. This is due to the fact that the target material is a thiol and has the potential to form a sulfide bond with proteins. A characteristic feature of most thiols is their ability to act as reducing agents. ROS have a strong tendency to transfer an electron to other species, i.e, to act as oxidants. Reducing agents such as thiols act as prompt electron acceptors. Therefore, in the case of an oxidant-thiol interaction, the oxidant is neutralized to a relatively less toxic byproduct at the expense of the reducing power of thiol, which is oxidized to a disulfide. A thiyl radical is produced when a thiol loses the H-atom from the –SH group or loses an electron from sulfur, followed by a proton. Under the conditions of physiological pH, thyil radicals are unstable and may recombine to form the corresponding disulfide. In biological systems, there are specific reductases that recycle disulfides to thiols using cellular reducing equivalents such as NADH, and thus, the power of cellular metabolism is coupled to maintain a favorable redox state of thiols. If there is an imbalance in this process, favoring the generation of pro-oxidants over antioxidants occurring for any reason, this results in oxidative stress and, in some cases, mutagenic response. The read-across analog is a sodium salt of the target and similar to salts of weak acids and can dissociate to the thiolate anion, which is in equilibrium with the thiol. Therefore, the reactivity/toxicity of the read-across analog is expected to be the same as the target material. The data on the read-across analog confirm that the chemical does not pose a concern for genetic toxicity. Therefore, based on the structural similarity between the target and the read-across analog as well as the data of the read-across analog, the predictions are superseded by the data.
  - 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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