Food and Chemical Toxicology 144 (2020) 111705

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment, dimethyl sulfide, CAS Registry Number 75-18-3

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], A. Lapczynski [a], M. Lavelle [a], D.C. Liebler [i], M. Na [a], D. O'Brien [a], A. Patel [a], T.M. Penning [j], G. Ritacco [a], F. Rodriguez-Ropero [a], J. Romine [a], N. Sadekar [a], D. Salvito [a], T. W. Schultz [k], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m], S. Tsang [a]

[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), 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

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

Version: 072919. This version replaces any previous versions.

Name: Dimethyl sulfide CAS Registry Number: 75-18-3

Abbreviation/Definition List:

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

(*continued on next column*)

(*continued*)

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., 2015, 2017) compared to a deterministic aggregate approach

(*continued on next page*)

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

https://doi.org/10.1016/j.fct.2020.111705
Received 21 February 2020; Received in revised form 30 June 2020; Accepted 19 August 2020
Available online 1 September 2020

(*continued*)

DRF - Dose Range Finding
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
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.

Dimethyl sulfide was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that dimethyl sulfide is not genotoxic. Data on dimethyl sulfide provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and developmental toxicity endpoints. The fertility and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to dimethyl sulfide is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data show that there are no safety concerns for dimethyl sulfide for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; dimethyl sulfide is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; dimethyl sulfide 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.

(*continued on next column*)

(*continued*)

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: Dimethyl Sulphide; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 250 mg/kg/day.	Butterworth (1975)
Reproductive Toxicity: Developmental NOAEL = 1000 mg/kg/day; Fertility: no NOAEL available. Exposure is below the TTC.	(ECHA REACH Dossier: Dimethyl Sulphide; ECHA, 2011)
Skin Sensitization: No safety concerns at current, declared use levels.	(ECHA REACH Dossier: Dimethyl Sulphide; ECHA, 2011)
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:	
Critical Measured Value: 77% (OECD 301D)	(ECHA REACH Dossier: Dimethyl Sulphide; ECHA, 2011)
Bioaccumulation:	
Screening-level: 3.162 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 729.3 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: 729.3 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.7293 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Dimethyl sulfide
2. **CAS Registry Number:** 75-18-3
3. **Synonyms:** DMS; Methane, thiobis-; 2-Thiapropane; Methyl sulfide; 硫化ｼﾞﾒﾁﾙ; Dimethyl sulfide
4. **Molecular Formula:** C_2H_6S
5. **Molecular Weight:** 62.13
6. **RIFM Number:** 665
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 37.2 °C (Butterworth, 1975), 42.52 °C (EPI Suite)
2. **Flash Point:** < 40 °F; CC (Fragrance Materials Association [FMA]), <-30 °C (Globally Harmonized System)
3. **Log K_{OW}:** 0.92 (EPI Suite)
4. **Melting Point:** 83.2 °C (Butterworth, 1975), −107.65 °C (EPI Suite)
5. **Water Solubility:** 22490 mg/L (EPI Suite)
6. **Specific Gravity:** 0.845–0.852 (Butterworth, 1975)
7. **Vapor Pressure:** 391 mm Hg @ 20 °C (EPI Suite v4.0), 400 mm Hg 20 °C (FMA), 479 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

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

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

1. 95th Percentile Concentration in Hydroalcoholics: 0.00036% (RIFM, 2017)
2. Inhalation Exposure*: 0.0000048 mg/kg/day or 0.00034 mg/day (RIFM, 2017)
3. Total Systemic Exposure**: 0.000036 mg/kg/day (RIFM, 2017)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 5. 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, 2017; Safford et al., 2015, 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 v2.6	OECD QSAR Toolbox v3.2
I	I	I

2. Analogs Selected:
   a. Genotoxicity: None
   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: None

7. Metabolism

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

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

Dimethyl sulfide is reported to occur in the following foods by the VCF*:

Allium species	Hop (*Humulus lupulus*)
Beef	Lentils
Beer	Milk and milk products
Cabbage (*Brassica oleracea*)	Mustard (*Brassica* species)
Honey	Rapeseed

*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 07/29/19 (ECHA, 2011).

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 and use levels, dimethyl sulfide does not present a concern for genotoxic potential.

11.1.1.1. Risk assessment. The mutagenic activity of dimethyl sulfide has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with dimethyl sulfide in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2011). Under the conditions of the study, dimethyl sulfide was not mutagenic in the Ames test.

The clastogenic activity of dimethyl sulfide 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 in corn oil via oral gavage to groups of male and female ICR mice. Doses of 0, 1250, 2500, or 5000 mg/kg were administered. Mice from each dose levels were euthanized at 24, 48, or 72 h after dose administration, 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, dimethyl sulfide was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, dimethyl sulfide does not present a concern for genotoxic potential.

Additional References: Nakamura (1990); OECD, 2006.

Literature Search and Risk Assessment Completed On: 08/28/19.

11.1.2. Repeated dose toxicity

The MOE for dimethyl sulfide 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 dimethyl sulfide that can be used to support the repeated dose toxicity endpoint. In an OECD 408 repeated dose toxicity study, groups of 15 Wistar rats/sex/dose were administered the test material dimethyl sulfide daily via oral gavage at dose levels of 0, 2.5, 25, and 250 mg/kg/day in corn oil for 14 weeks. Additional groups of 5/sex/dose were given daily doses of 0.25 and 250 mg/kg/day for 2 and 6 weeks. No treatment-related effects were reported for mortality, clinical signs, body weights, food consumption, water consumption, hematology, and clinical chemistry. Examination of organ weights demonstrated a significant increase in relative brain weights of female rats in the high-dose group at

the 2-week interval, but it was not considered to be a treatment-related adverse effect since the effect was not reported in their male counterparts or in female animals at the end of the study. At 14 weeks, the absolute small intestine weights in male rats were significantly higher at all dose levels, but the relative small intestine weights were only increased at the mid and high doses. High-dose females displayed lower absolute and relative thyroid weights (by 23%), while high-dose males displayed higher relative thyroid weights(by 19%). All organ weight changes were considered incidental and not treatment-related adverse effects, due to the lack of correlated histopathological findings. No treatment-related adverse effects were observed up to the highest tested level; thus, the NOAEL was considered to be 250 mg/kg/day (Butterworth, 1975; also available at ECHA, 2011; OECD, 2006; Health Canada, 2017; EFSA, 1988).

Therefore, the dimethyl sulfide MOE for the repeated dose toxicity endpoint can be calculated by dividing the dimethyl sulfide NOAEL in mg/kg/day by the total systemic exposure to dimethyl sulfide, 250/0.000036, or 6944444.

In addition, the total systemic exposure to dimethyl sulfide (0.036 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: 10/02/19.

11.1.3. Reproductive Toxicity

The MOE for dimethyl sulfide is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient fertility data on dimethyl sulfide or on any read-across materials. The total systemic exposure to dimethyl sulfide is below the TTC for the fertility endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data that can be used to support the developmental toxicity endpoint. An OECD/GLP 414 developmental toxicity study was conducted in Crl:CD (SD)IGS BR rats. Groups of 25 mated female rats were administered the test material (dimethyl sulfide) via oral gavage at doses of 0, 100, 500, and 1000 mg/kg/day in corn oil during gestation days 6 through 19. No treatment-related effects on clinical signs, maternal body weight (absolute or corrected for gravid uterine weight), food consumption, or intrauterine growth were reported. No treatment-related effects were reported on fetal numbers, fetal weight, survival, sex ratio, fetal external, visceral or skeletal malformations, or developmental variations. Thus, the NOAEL for maternal and developmental toxicity was considered to be 1000 mg/kg/day, based on the absence of adverse effects on the dams and development of offspring up to the highest dose tested (ECHA, 2011; also available at OECD, 2006; Health Canada, 2017). This is consistent with a range-finding study conducted with dimethyl sulfide at dose levels of 333, 666, and 1000 mg/kg/day, which reported no effects at any dose (ECHA, 2011). **Therefore, the dimethyl sulfide MOE for the developmental toxicity endpoint can be calculated by dividing the dimethyl sulfide NOAEL in mg/kg/day by the total systemic exposure to dimethyl sulfide, 1000/0.000036, or 27777778**.

In addition, the total systemic exposure to dimethyl sulfide (0.036 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are limited fertility data on dimethyl sulfide. In an OECD 408 repeated dose toxicity study, groups of 15 Wistar rats/sex/dose were administered daily via oral gavage test material, dimethyl sulfide at dose levels of 0, 2.5, 25, and 250 mg/kg/day in corn oil for 14 weeks. None of the doses had any effect on the weights or microscopic appearance of the gonads (Butterworth, 1975; see the Repeated Dose Toxicity section). However, because there was no information on spermatology or the estrous cycle, a NOAEL could not be derived for the fertility endpoint. There are no data on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to dimethyl sulfide (0.036 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/02/19.

11.1.4. Skin sensitization

Based on existing data, dimethyl sulfide does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, dimethyl sulfide does not present a concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.3). No predictive *in vitro* skin sensitization studies are available for dimethyl sulfide. In a murine local lymph node assay (LLNA), dimethyl sulfide was not found to be sensitizing up to 100% (ECHA, 2011). In a human maximization test, no skin sensitization reactions were observed with 1% or 690 μg/cm^2 of dimethyl sulfide (RIFM, 1975).

Based on WoE from structural analysis and animal and human studies, dimethyl sulfide does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/13/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, dimethyl sulfide 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 dimethyl sulfide 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). Based on the lack of absorbance, dimethyl sulfide 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 dimethyl sulfide 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 dimethyl sulfide. Based on the Creme RIFM Model, the inhalation exposure is 0.00034 mg/day. This exposure is 4117.65 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).

Literature Search and Risk Assessment Completed On: 09/04/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of dimethyl sulfide 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, dimethyl sulfide 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).

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>729.3</u>			1000000	0.7293	

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify dimethyl sulfide 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 PBT or vPvB 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), dimethyl sulfide 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. Dimethyl sulfide has been registered for REACH with following data available at this time (ECHA, 2011):

The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 77% was observed after 28 days.

An acute fish (*Oncorhynchus mykiss*) toxicity test was conducted according to the OECD 203 guidelines under semi-static conditions. The 96-h LC50 value based on nominal concentrations was reported to be 213 mg/L (95% CI: 118–479 mg/L).

A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on initial measured concentrations was reported to be 29 mg/L (95% CI: 19–45 mg/L).

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 values for growth and yield based on initial measured concentrations were reported to be greater than 113.7 mg/L.

11.2.2.4. Risk assessment refinement. Since dimethyl sulfide has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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	0.92	0.92
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 0.7293 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: 09/09/19.

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**
- **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/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/31/20.

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.

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.

Butterworth, K.R., Carpanini, F.M.B., Gaunt, I.F., Hardy, J., Kiss, I.S., Gangolli, S.D., 1975. Short-term toxicity of dimethyl sulphide in the rat. Food Chem. Toxicol. 13 (1), 15–22.

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.

Doizaki, W.M., Zieve, L., 1973. Measurement of volatile mercaptans in whole blood. J. Lab. Clin. Med. 82 (4), 674–681.

Echa, 2011. Dimethyl Sulphide Registration Dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/13649/1.

Echa, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

Efsa, 1988. Scientific Opinion on Flavouring Group Evaluation 8, Revision 3 (FGE.08Rev3): aliphatic and alicyclic mono-, di-, tri-, and polysulphides with or without additional oxygenated functional groups from chemical groups 20 and 30, 2011 EFSA J. 9 (5), 1988. Retrieved from: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2011.1988.

Health Canada, 2017. Screening Assessment: Thiols Group. Retrieved from. http://www.ec.gc.ca/ese-ees/9DD12E69-B7A1-4D21-81D0-890BE9B4AFCC/Draft%20SAR-Thiols_clean%202017-07-18.pdf.

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), 2015. Volume of Use Survey. February 2015.

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.

Ljunggren, G., Norberg, B., 1943. On the effect and toxicity of dimethyl sulfide, dimethyl disulfide & methyl mercaptan. Acta Physiol. Scand. 5, 248–255.

Nakamura, S., Oda, Y., Ugawa, M., 1990. Induction of umu gene expression in Salmonella typhimurium TA1535/pSK1002 by dimethyl sulfoxide (DMSO). Mutation Research. Fundam. Mol. Mechan. Mutagen. 229 (1), 11–15.

Oecd, 2006. SIDS Initial Assessment Report for SIAM 22: Dimethyl Sulfide. UNEP Publications. Retrieved from: https://hpvchemicals.oecd.org/ui/handler.axd?id=08A93943-9275-4A0A-BA1E-6ABE00B29376.

Rifm (Research Institute for Fragrance Materials, Inc), 1975. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1799. RIFM, Woodcliff Lake, NJ, USA.

Rifm(Research Institute for Fragrance Materials, Inc), 2017. Expos. Surv. 16. May 2017.

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., 2015. 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.

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.

Speranskii, S.P., Spasolomskaya, A.E., 1973. Effect of gas emission in the sulfate cellulose industry. Vrach. Delo 6, 131–135.

Tansy, M.F., Kendall, F.M., Fantasia, J., Landin, W.E., Oberly, R., Sherman, W., 1981. Acute and subchronic toxicity studies of rats exposed to vapors of methyl mercaptan and other reduced-sulfur compounds. J. Toxicol. Environ. Health 8, 71–88.

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, v1.11. United States Environmental Protection Agency, Washington, DC, USA.

Zieve, L., Doizaki, W.M., Zieve, F.J., 1974. Synergism between mercaptans and ammonia or fatty acids in the production of coma: a possible role for mercaptans in the pathogenesis of hepatic coma. J. Lab. Clin. Med. 83 (1), 16–28.