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Short Review

RIFM fragrance ingredient safety assessment, dipropyl disulfide, CAS Registry Number 629-19-6

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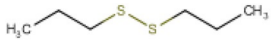
Version: 121218. This version replaces any previous versions.



Name: Dipropyl disulfide
CAS Registry Number: 629-19-6
Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union

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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
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.

Dipropyl disulfide was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog dimethyl disulfide (CAS # 624-92-0) show that dipropyl disulfide is not expected to be genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; dipropyl disulfide is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to dipropyl disulfide is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; dipropyl disulfide was found not to be persistent, bioaccumulative, and toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (ECHA Dossier: Dimethyl disulphide; ECHA, 2010)
Repeated Dose Toxicity: NOAEL = 5.5 mg/kg/day. (ECHA Dossier: Dimethyl disulphide; ECHA, 2010)
Reproductive Toxicity: Developmental toxicity: NOAEL = 20 mg/kg/day. Fertility: NOAEL = 80 mg/kg/day. (ECHA Dossier: Dimethyl disulphide; ECHA, 2010)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use. 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: 2.9 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 7.2 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 5.0834 mg/L (RIFM Framework; Salvito et al., 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 et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 5.0834 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.005083 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Dipropyl disulfide
2. **CAS Registry Number:** 629-19-6
3. **Synonyms:** Disulfide, dipropyl; Propyldithiopropane; 1,1′-Disulfanediyldipropane; Propyl disulfide; Dipropyl disulfide
4. **Molecular Formula:** $C_6H_{14}S_2$
5. **Molecular Weight:** 150.30
6. **RIFM Number:** 6815
7. **Stereochemistry:** No stereocenter and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 195 °C (Fragrance Materials Association [FMA] Database), 200.42 °C (EPI Suite)
2. **Flash Point:** 100 °F; CC (FMA Database)
3. **Log K_{OW}:** 3.84 (EPI Suite)
4. **Melting Point**: −21.81 °C (EPI Suite)
5. **Water Solubility:** 39.94 mg/L (EPI Suite)
6. **Specific Gravity:** 0.96 (FMA Database)
7. **Vapor Pressure:** 0.34 mm Hg @ 20 °C (EPI Suite v4.0), 0.4 mm Hg 20 °C (FMA Database), 0.498 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. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.000003% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.000058 mg/kg/day or 0.0043 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.000066 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; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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 et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	III	III

2. Analogs Selected:
   a. **Genotoxicity:** Dimethyl disulfide (CAS # 624-92-0)
   b. **Repeated Dose Toxicity:** Dimethyl disulfide (CAS # 624-92-0)
   c. **Reproductive Toxicity:** Dimethyl disulfide (CAS # 624-92-0)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

6.1. Additional References

None.

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

Dipropyl disulfide is reported to occur in the following foods by the VCF*:

Allium species	Durian (*Durio zibethinus*)
Apple brandy (Calvados)	Grape brandy
Beef	Peanut (*Arachis hypogaea* L.)
Cabbage (*Brassica oleracea*)	

*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.

8. REACH dossier

Pre-registered; no dossier available as of 03/24/20.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, dipropyl disulfide does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of dipropyl disulfide; however, read-across can be made to dimethyl disulfide (CAS # 624-92-0; see Section V).

The mutagenic activity of dimethyl disulfide 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/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with dimethyl disulfide in solvent 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, 2010). Under the conditions of the study, dimethyl disulfide was not mutagenic in the Ames test (and this can be extended to dipropyl disulfide).

The clastogenic activity of dimethyl disulfide 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 Sprague Dawley rats. Concentrations of 650 and 750 mg/kg body weight were administered. Rats from each dose level were euthanized at approximately 18–24 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, 2010). Under the conditions of the study, dimethyl disulfide was considered to be not clastogenic in the *in vivo* micronucleus test (and this can be extended to dipropyl disulfide).

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/20/18.

10.1.2. Repeated dose toxicity

The margin of exposure for dipropyl disulfide is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeat dose toxicity data on dipropyl disulfide. Read-across material dimethyl disulfide (CAS # 624-92-0; see Section V) has sufficient repeat dose toxicity data. In an OECD 413/GLP-compliant subchronic inhalation toxicity study, 20 Sprague Dawley rats/sex/group were exposed to dimethyl disulfide through whole-body inhalation at concentrations of 0, 10, 50, 150, and 250 ppm (equivalent to 0, 10, 50, 150, and 250 mg/kg/day) for 6 h/day, 5 days/week, for 13 weeks. No treatment-related mortality was observed during the study. Initially, treatment-related salivation, lacrimation or reduced activity, and dyspnea were observed at the 150 and 250 ppm doses. At 10, 50, and 250 ppm concentrations, a treatment-related effect on nasal mucosa characterized by squamous metaplasia was observed. Additionally, in groups receiving 50 and 250 ppm doses, squamous metaplasia was accompanied by atrophy and micro cavitation in the anterior olfactory epithelium. At the end of the recovery period, metaplasia was reversed in the 10 ppm group but not in groups treated with higher doses. Hence, the no observed adverse effect level (NOAEL) was considered to be 10 mg/kg/day (ECHA, 2010).

In an OECD-413/GLP-compliant subchronic inhalation toxicity study, Fischer 344 rats (10 animals/sex/group) were exposed to dimethyl disulfide (purity: 99%) through whole-body inhalation at concentrations of 0 (control: dilution air), 5, 25, and 125 ppm (equivalent to 5.5, 27.4, and 137 mg/kg/day) for 6 h/day, 5 days/week, for 13 weeks (65 exposures). Based on decreased bodyweight gain and food intake in males at 25 ppm and decreased bodyweight gain and food intake at 125 ppm in both sexes, the NOAEL was considered to be 5.5 mg/kg/day (ECHA, 2010) **Therefore, the dipropyl disulfide MOE for the repeated dose toxicity endpoint can be calculated by dividing the dimethyl disulfide NOAEL in mg/kg/day by the total systemic exposure to dipropyl disulfide, 5.5/0.000066 or 83333.**

In addition, the total systemic exposure to dipropyl disulfide (0.066 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: NCBI, 2005; HSDB, 2014; US EPA, 2010; ECHA, 2017; EFSA, 2010; US EPA, 2012c; Posternak et al., 1969.

Literature Search and Risk Assessment Completed On: 11/19/18.

10.1.3. Reproductive toxicity

The MOE for dipropyl disulfide is adequate for the reproductive toxicity endpoint at the current level of use.

Table 1
Summary.

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
GDs 6–28, 6 h/day, 7 days/week	GLP/OECD 414	Female New Zealand White rabbits (24/ group)	Inhalation vapor whole-body	0, 15, 45, and 135 ppm (equal to 0, 8, 24, 71, using standard minute volume and body weight values for female New Zealand rabbits; US EPA, 1998)	NOAEC (rabbits) (maternal and developmental toxicity) = 135 ppm or 71 mg/kg/day)	No effects reported up to the highest dose tested.	ECHA, 2010 (accessed 11/02/18)
GDs 6–15, 6 h/day	GLP/OECD 414	Female Sprague Dawley rats (30/ group)	Inhalation vapor whole-body	0, 5, 15, or 50 ppm (equal to 0, 5, 15, and 51 mg/kg/day, using standard minute volume and body weight values for female Sprague Dawley rats)	NOAEC (maternal toxicity) = 5 ppm or 5 mg/kg/day NOAEC (developmental toxicity) = 15 ppm or 15 mg/kg/day	Decreased bodyweight gain at ≥ 15 ppm Reduced litter and fetal weights and a higher incidence of retarded ossification at 50 ppm.	ECHA, 2010 (accessed 11/02/18)
6 h/day, 7 days/ week	GLP/OECD 421	Sprague Dawley rats (12/sex/group)	Inhalation vapor whole-body	0, 5, 50, and 150 ppm (equal to 0, 5, 51 and 153 mg/kg/day, using standard minute volume and body weight values for female Sprague Dawley rats; US EPA, 1998)	NOAEC (repro toxicity) = 150 ppm or 153 mg/kg/day NOAEC (systemic toxicity) = 5 ppm or 5 mg/kg/day NOAEC (developmental toxicity) = 5 ppm or 5 mg/kg/day	No effects on reproduction at any exposure concentration. Decreased bodyweight gain in the 50 ppm (males only) and 150 ppm groups. Reduced F1 pup body weights and bodyweight gains at ≥ 50 ppm.	ECHA, 2010 (accessed 11/02/18)

10.1.3.1. Risk assessment. There are no reproductive toxicity data on dipropyl disulfide. Read-across material dimethyl disulfide (CAS # 624-92-0; see Section V) has sufficient reproductive toxicity data.

In an OECD 414/GLP prenatal developmental toxicity study, female Sprague Dawley rats (27/group) were exposed to dimethyl disulfide via whole-body inhalation at concentrations of 0, 5, 20, or 80 ppm (equivalent to 0, 5, 20, 82 mg/kg/day, respectively, using standard minute volume and body weight values for female Sprague Dawley rats) 6 h/day for gestation days (GDs) 6–19. At 80 ppm, maternal food consumption was statistically significantly lower than the control group throughout the exposure period, which corresponded to bodyweight loss and lower bodyweight gains reported for this group. The bodyweight loss was associated to a statistically significant decrease in gravid uterine weight in the 80 ppm dose group dams. The mean fetal weight in the 80 ppm group was statistically significantly lower than the control group and was outside the historical control data. Skeletal malformations/variations were noted in the 80 ppm group fetuses, which were considered to be treatment-related since they corresponded to the reduced fetal body weight at 80 ppm, indicating developmental delay. Therefore, the NOAEC for maternal toxicity was considered to be 20 ppm or 20 mg/kg/day, based on lower maternal bodyweight gains and food consumption observed at 80 ppm. The NOAEC for developmental toxicity was considered to be 20 ppm or 20 mg/kg/day, based on decreased fetal weight and increased incidences of skeletal variations reported at 80 ppm (ECHA, 2010; also available at Kirkpatrick et al., 2007).

In another OECD 414/GLP prenatal developmental toxicity study, female Sprague Dawley rat (30/group) were exposed to dimethyl disulfide in similar doses as compared to the above rat study (27/group), in which adverse effects were observed at the highest dose of 51 mg/kg/day. The developmental toxicity NOAEL was considered to be 15 mg/kg/day (ECHA, 2010; details of the study are included in Table 1 below).

In another OECD 414/GLP prenatal developmental toxicity study, female New Zealand White rabbits (24/group) were exposed to dimethyl disulfide, and the developmental toxicity NOAEL was determined to be 71 mg/kg/day, the highest dose tested (ECHA, 2010; details of the study are included in Table 1 below).

Since there were no effects observed in the mid-dose level for both rat studies, the higher NOAEL of 20 mg/kg/day was selected for the developmental toxicity endpoint. **Therefore, the dipropyl disulfide MOE for the developmental toxicity endpoint can be calculated by dividing the dimethyl disulfide NOAEL in mg/kg/day by the total systemic exposure to dipropyl disulfide, 20/0.000066 or 303030.**

In an OECD 416/GLP 2-generation reproduction toxicity study, Sprague Dawley Rats (30 animals/sex/group) were exposed to dimethyl disulfide via whole-body inhalation at concentrations of 0, 5, 20, or 80 ppm (equivalent to 0, 5, 20, and 80 mg/kg/day, respectively, using standard minute volume and body weight values for male and female Sprague Dawley rats) for 6 h/day, 7 days/week, for at least 70 consecutive days prior to mating for the F0 and F1 generations. The offspring selected to become the F1 parental generation were exposed following weaning (beginning on postnatal day [PND] 28). General systemic toxicity was evident in the ≥20 ppm dose group of F0 and F1 parental males and females with persistent statistically significant decreases in body weights, bodyweight gains, and/or food consumption. Potential treatment-related effects on the adrenal glands (an increase in the incidence of vacuolization of the adrenal cortex or increased relative adrenal gland weights) were reported in the F0 and F1 parental animals in the 80 ppm group. Therefore, the NOAEC for parental systemic toxicity was considered to be 5 ppm or 5 mg/kg/day, based on decreases in body weights, bodyweight gains, and/or food consumption at ≥20 ppm and increased incidence of vacuolization of the adrenal cortex or increased adrenal gland weights in the 80 ppm dose group animals. There were no effects on reproduction (e.g., estrous cycles, mating and fertility indices, number of days between pairing and coitus, gestation length, spermatogenetic parameters, ovarian primordial follicles) in any treatment group for both F0 and F1 generations. There were no adverse effects observed on pups born to exposed dams (F1 and F2 generation) and no effect on postnatal growth prior to weaning with exposure of the lactating dams in any treatment groups. Thus, the NOAEC for effects on fertility and the development of pups was considered to be 80 ppm or 80 mg/kg/day, the highest dose tested. (ECHA, 2010). In an OECD/GLP 421 reproduction and developmental toxicity screening test, Sprague Dawley rats were exposed to dimethyl disulfide, and the fertility NOAEL was considered to be 153 mg/kg/day, the highest dose tested (ECHA, 2010; details of the study are included in Table 1 above).

The NOAEL of 80 mg/kg/day was selected from the more robust OECD 416 study for the fertility endpoint. **Therefore, the dipropyl**

Table 2
Maximum acceptable concentrations for dipropyl disulfide that present no appreciable risk for skin sensitization based on the 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%	6.0×10^{-7}%
3	Products applied to the face using fingertips	0.029%	NRU[b]
4	Fine fragrance products	0.027%	3.0×10^{-6}%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	7.0×10^{-7}%
6	Products with oral and lip exposure	0.016%	5.6×10^{-9}%
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%	1.8×10^{-7}%
10	Household care products with mostly hand contact	0.19%	0.12%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.00%

Nleote.
[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.

disulfide MOE for the fertility endpoint can be calculated by dividing the dimethyl disulfide NOAEL in mg/kg/day by the total systemic exposure to dipropyl disulfide, 80/0.000066 or 1212121.

In addition, the total systemic exposure to dipropyl disulfide (0.066 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Hazleton-UK Study no. 6142–514/8, May 1991 (Cited in US EPA, 1991).

Literature Search and Risk Assessment Completed On: 11/14/18.

10.1.4. Skin sensitization

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

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (OECD toolbox v3.4). No predictive skin sensitization studies are available for dipropyl disulfide. Acting conservatively, due to the absence of data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/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 maximum acceptable concentrations for dipropyl disulfide that present no appreciable risk for skin sensitization based on the reactive DST. These concentrations are not limits; they represent maximum acceptable concentrations based on the DST approach. 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: 10/26/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, dipropyl disulfide would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for dipropyl disulfide in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, dipropyl disulfide does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/17/18.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on dipropyl disulfide. Based on the Creme RIFM Model, the inhalation exposure is 0.0043 mg/day. This exposure is 326 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: 11/01/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of dipropyl disulfide 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 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, dipropyl disulfide was identified as a fragrance material with the 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 dipropyl disulfide 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, 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 $\geq$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).

10.2.2. Risk assessment

Based on the current Volume of Use (2015), dipropyl disulfide does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.4. Other available data

Dipropyl disulfide has been registered under REACH and the additional data is not available at this time.

10.2.5. 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.

	(mg/L)	(*Daphnia*) (mg/L)	(mg/L)			
RIFM Framework Screening-level **(Tier 1)**	5.0834			1,000,000	0.005083	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.84	3.84
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.005083 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/13/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 5/20/2019.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111423.

Appendix

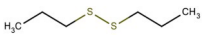
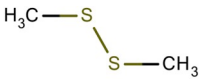
Read-across Justification

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 Chemical Agency read-across assessment framework (ECHA, 2016).

- 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 substance and the read-across analogs were calculated using EPI Suite v4.11 (US ECHA, 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	Dipropyl disulfide	Dimethyl disulfide
CAS No.	629-19-6	624-92-0
Structure		
Similarity (Tanimoto Score)		0.35
Read-across Endpoint		• Genotoxicity • Repeated Dose Toxicity • Reproductive Toxicity
Molecular Formula	$C_6H_{14}S_2$	$C_2H_6S_2$
Molecular Weight	150.3	94.19
Melting Point (°C, EPI Suite)	−85.6	−84.67
Boiling Point (°C, EPI Suite)	193.5	109.72
Vapor Pressure (Pa @ 25 °C, EPI Suite)	68.3	3.83E+003
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.84	1.77
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	39.94	3000
J_{max} (μg/cm^2/h, SAM)	36.63	176.08
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.82E+002	1.23E+002
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (moderate reliability)
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
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Thiocarbamates/Sulfides (Hepatotoxicity) No rank	• Thiocarbamates/Sulfides (Hepatotoxicity) No rank
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)	• Toxicant (low reliability)	• Non-toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD Q-SAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on dipropyl disulfide (CAS # 629-19-6). 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, dimethyl disulfide (CAS # 624-92-0) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Dimethyl disulfide (CAS # 624-92-0) was used as a read-across analog for the target material dipropyl disulfide (CAS # 629-19-6) for the genotoxicity, reproductive toxicity, and repeated dose toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to a class of dialkyl disulfides.
  - o The target substance and the read-across analog share a disulfide group.
  - o The key difference between the target substance and the read-across analog is that the target substance has 2 propyl groups as the alkyl substituents, whereas the read-across analog has 2 methyl groups. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance 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 substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog have been categorized as Thiocarbamates/Sulfides without rank. This alert is due to the fact that the target substance and the read-across analog have structural similarity of more than 50% with 4 key compounds bearing Thiocarbamate

and Sulfide (or Disulfide) which are known to induce adverse effects in the liver. Although structural similarity is more than 50% between toxicants and the target substance, the sub-structural features are different. The toxicants predominantly bear carbamodithoate, which is not present in the target substance or the read-across analog. The data described in the repeated dose toxicity confirm that the margin of exposure for the read-across analog is adequate at the current level of use. Therefore, the predictions are superseded by data.

- o The target substance 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.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision.

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? Yes
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes
Q21. 3 or more different functional groups? No
Q18. One of the list (see Cramer et al., 1978 for detailed explanation on list of categories)? No, Class I (Low Class)

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