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RIFM fragrance ingredient safety assessment, 4-thujanol, CAS Registry Number 546-79-2

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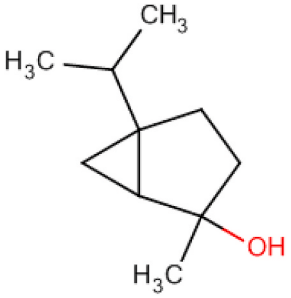
Name: 4-Thujanol
CAS Registry Number: 546-79-2



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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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al.,

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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
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, 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.

4-Thujanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4-thujanol is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 4-thujanol is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 4-thujanol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4-thujanol 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.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2016b, RIFM, 2017; RIFM, 2019)

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

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

Skin Sensitization: Not a safety concern 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: 2.4 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 59.45 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 19.2 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: 19.2 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.0192 μg/L

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

1. Identification

1. **Chemical Name:** 4-Thujanol
2. **CAS Registry Number:** 546-79-2
3. **Synonyms:** Bicyclo[3.1.0]hexan-2-ol, 2-methyl-5-(1-methylethyl)-; 2-Methyl-5-(1-methylethyl)bicyclo(3.1.0)hexan - 2-ol; Sabinenehydrate; 4 -ﾒﾁﾙ- 1 - (1 -ﾒﾁﾙｴﾁﾙ)-ﾋﾞｼｸﾛ-(3.1.0)ﾍｷｻﾝ-4-ｵｰﾙ; 5-Isopropyl-2-methylbicyclo[3.1.0]hexan-2-ol; 4-Thujanol
4. **Molecular Formula:** $C_{10}H_{18}O$
5. **Molecular Weight:** 154.25 g/mol
6. **RIFM Number:** 6260
7. **Stereochemistry:** Isomer not specified. Three stereocenters and 8 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 192.68 °C (EPI Suite)
2. **Flash Point:** 80 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.19 (EPI Suite)
4. **Melting Point**: 26.7 °C (EPI Suite)
5. **Water Solubility:** 440.5 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0563 mm Hg at 20 °C (EPI Suite v4.0), 0.0987 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not Available

3. Volume of use

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Toothpaste:** 0.0025% (RIFM, 2016a)
   (No reported use in hydroalcoholics)
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2016a)
3. **Total Systemic Exposure**:** 0.000055 mg/kg/day (RIFM, 2016a)

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	III	I

*See Appendix below for further details.

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)

4-Thujanol is reported to occur in the following foods by the VCF*:

Black currants (*Ribes nigrum* L.)	Grape (*Vitis* species)
Cardamom (*Elettaria cardamomum* Maton.)	Laurel (*Laurus nobilis* L.)
Citrus fruits	Mentha oils
Dill (*Anethum* species)	Ocimum species
Ginger (*Zingiber* species)	Origanum (Spanish) (*Coridothymus cap*. (L.) Rchb.)

*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

Pre-registered for 2010; no dossier available as of 12/14/21.

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, 4-thujanol does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 4-thujanol 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 *Escherichia coli* WP2uvrA were treated with 4-thujanol 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 (RIFM, 2016b). Under the conditions of the study, 4-thujanol was not mutagenic in the Ames test.

The clastogenic activity of 4-thujanol was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 4-thujanol in DMSO at up to 1540 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h 4-thujanol was toxic to human lymphocytes and induced statistically significant increases in the frequency of cells with micronuclei using a dose range that included a dose level that approached optimum toxicity in all 3 exposure groups. (RIFM, 2017). Under the conditions of the study, 4-thujanol was considered to be positive in the *in vitro* micronucleus test.

The clastogenic activity of 4-thujanol was evaluated in an *in vivo* micronucleus test with a comet assay in mice conducted in compliance with GLP regulations and in accordance with OECD TGs 474 and 489. The test material was administered in corn oil via oral gavage to groups of male and female CD-1 mice. Doses of 250, 500, and 1000 mg/kg body weight were administered. Mice from each dose level were euthanized at 3–4 h after the last treatment, and the bone marrow was extracted and examined for polychromatic erythrocytes. In the micronucleus assay, a significant increase in the incidence of micronuclei in reticulocyte (MnRETs) in the groups with males at 500 and 1000 mg/kg/day was observed. However, this increase was within the historical control range, and therefore not considered to be biologically significant. No statistically significant increase in the incidence of MnRETs was observed in the remaining test material-treated groups (RIFM, 2019). The test material was evaluated as non-clastogenic in the *in vivo* micronucleus test.

In the comet assay, statistically significant increases in percent tail

DNA were observed in liver cells in the test material-treated groups with males at 500 and 1000 mg/kg/day and with females at 1000 mg/kg/day. However, these increases were within the historical control range observed, and therefore were not considered to be biologically significant (RIFM, 2019). Under the conditions of the study, 4-thujanol was considered to be not clastogenic in the comet assay.

Additional References: RIFM, 2021; Kocaman et al. (2011).

Literature Search and Risk Assessment Completed On: 10/19/21.

11.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on 4-thujanol or on any read-across materials. The total systemic exposure to 4-thujanol is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4-thujanol or on any read-across materials that can support the repeated dose toxicity endpoint. The total systemic exposure to 4-thujanol (0.055 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/13/21.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on 4-thujanol or on any read-across materials. The total systemic exposure to 4-thujanol is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 4-thujanol or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 4-thujanol (0.055 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: None.

Literature Search and Risk Assessment Completed On: 10/28/21.

11.1.4. Skin sensitization

Based on the application of DST, 4-thujanol does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. There are insufficient data on 4-thujanol. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.1). Acting conservatively due to the absence of data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 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 non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 4-thujanol that present no appreciable risk for skin sensitization based on the non-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.

Table 1
Maximum acceptable concentrations for 4-thujanol that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU[b]
2	Products applied to the axillae	0.021%	NRU[b]
3	Products applied to the face using fingertips	0.41%	NRU[b]
4	Fine fragrance products	0.39%	NRU[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	NRU[b]
6	Products with oral and lip exposure	0.23%	0.0026%
7	Products applied to the hair with some hand contact	0.79%	NRU[b]
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	7.9×10^{-4}%
10	Household care products with mostly hand contact	2.7%	NRU[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	NRU[b]

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.

Literature Search and Risk Assessment Completed On: 10/21/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra, 4-thujanol 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 4-thujanol in experimental models. UV absorption spectra indicate no absorption between 290 and 400 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, 4-thujanol does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available spectra indicate no absorbance in the range of 290–400 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: 10/13/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 4-thujanol 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 4-thujanol. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is 14000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/15/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 4-thujanol 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, 4-thujanol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 4-thujanol 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).

11.2.2. Risk assessment

Based on the current VoU (2015), 4-thujanol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 4-Thujanol has been pre-registered for REACH, with no additional data at this time.

11.2.3. 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.

	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>19.2</u>			1000000	0.0192	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.19	3.19
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 0.0192 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: 12/14/21.

12. 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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **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 12/14/21.

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

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 tree.

Q1. A 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
Q4. Elements not listed in Q3 occurs only as a Na, K, Ca, Mg, N salt, sulfamate, sulfonate, sulfate, hydrochloride? 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 a detailed explanation)? Yes. Class, Low (Class I)

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