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Short Review

RIFM fragrance ingredient safety assessment, 2-acetylthiophene, CAS registry number 88-15-3

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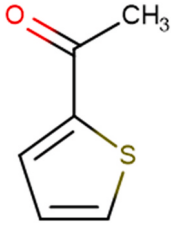
CAS Registry Number: 88-15-3



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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)

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(*continued*)

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; Safford et al., 2015a, 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $P < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment. This material has not been fully evaluated for photoallergenic potential.

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. This material has not been fully evaluated for photoallergenic potential.

2-Acetylthiophene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-acetylthiophene 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 II material, and the exposure to 2-acetylthiophene is below the TTC (0.009 mg/kg/day, 0.009 mg/kg/day, and 0.47 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. Based on data, 2-acetylthiophene is not expected to be photoirritating; 2-acetylthiophene was not evaluated for photoallergy. The environmental endpoints were evaluated; for the hazard assessment based on the screening data, 2-acetylthiophene is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, 2-acetylthiophene was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2019 IFRA Survey.

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Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2021b; RIFM, 2021a)

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

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

Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.

Photoirritation/Photoallergenicity: Not photoirritating/not evaluated photoallergenicity. (RIFM, 2020)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence:

Screening-level: 2.89 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:

Screening-level: 0.8 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:

Not applicable

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

- Not applicable; no 2019 VoU reported for EU and NA

1. Identification

1. **Chemical Name:** 2-Acetylthiophene
2. **CAS Registry Number:** 88-15-3
3. **Synonyms:** 2-Acetothiophene; Ethanone, 1-(2-thienyl)-; Methyl 2-thienyl ketone; 1-(2-Thienyl)ethanone; 2-Acetylthiophene
4. **Molecular Formula:** C_6H_6OS
5. **Molecular Weight:** 126.17 g/mol
6. **RIFM Number:** 6889
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 199.74 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 1.49 (EPI Suite)
4. **Melting Point**: 21.87 °C (EPI Suite)
5. **Water Solubility:** 8146 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.122 mm Hg at 20 °C (EPI Suite v4.0), 0.183 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm with peak absorbance at 290 nm and returning to baseline by approximately 370 nm. Molar absorption coefficients (2016, 2120, and 1751 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are above the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not available

3. Volume of use (Worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

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

1. **95th Percentile Concentration in Fine Fragrance:** 0.00019% (RIFM, 2014)
2. **Inhalation Exposure*:** 0.0000005 mg/kg/day or 0.000039 mg/day (RIFM, 2014)
3. **Total Systemic Exposure**:** 0.00037 mg/kg/day (RIFM, 2014)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015; Safford, 2015a; Safford, 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 II, Intermediate* (Expert Judgment)

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

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** None

7. Metabolism

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

8. Natural occurrence

2-Acetylthiophene is reported to occur in the following foods by the VCF*:

Asparagus (Asparagus officinalis L.)	Malt
Beef	Pork
Cabbage (*Brassica oleracea*)	Tomato (Lycopersicon esculentum Mill.)
Coffee	Wheaten bread
Krill	

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. Reach dossier

2-Acetylthiophene has been pre-registered for 2010; no dossier available as of 04/08/22.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment. This material has not been fully evaluated for photoallergenic potential.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-acetylthiophene does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2-acetylthiophene 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2-acetylthiophene in 10% dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. An increase (1.9-fold) in the mean number of revertant colonies was observed in strain WP2uvrA in the absence of S9 (RIFM, 2021b). However, this increase was not reproducible in the confirmatory study, was not dose-responsive, and was within the 99% historical control limit. Therefore, the increase was considered to be not biologically relevant, and is considered negative by OECD TG 471. Under the conditions of the study, 2-acetylthiophene was not mutagenic in the Ames test.

The clastogenic activity of 2-acetylthiophene 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 2-acetylthiophene in 10% DMSO at concentrations up to 1260 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1260 μg/mL in the presence and absence of metabolic activation. 2-Acetylthiophene did not induce binucleated cells with micronuclei when tested up to the cytotoxic or the maximum concentration, in either the presence or absence of an S9 activation system (RIFM, 2021a). Under the conditions of the study, 2-acetylthiophene was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 2-acetylthiophene does not present a concern for genotoxic potential.

Additional References: None

Literature Search and Risk Assessment Completed On: 04/01/22

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-acetylthiophene or any read-across materials. The total systemic exposure to 2-acetylthiophene is below the TTC for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-acetylthiophene or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.37 μg/kg/day) is below the TTC for 2-acetylthiophene (9 μg/kg/day; Kroes et al., 2007).

Additional References: None

Literature Search and Risk Assessment Completed On: 03/02/22

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 2-acetylthiophene or any read-across materials. The total systemic exposure to 2-acetylthiophene is below the TTC for the reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-acetylthiophene or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.37 μg/kg/day) is below the TTC for 2-acetylthiophene (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None

Literature Search and Risk Assessment Completed On: 03/02/22

11.1.4. Skin sensitization

Based on existing data and the application of DST, 2-acetylthiophene does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for 2-acetylthiophene (Table 1). This material was not found to be reactive with skin proteins *in silico*; however, based on expert judgment, the parent target is expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford, 2011; Roberts et al., 2015; Safford, 2015b). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 2 provides the supported concentrations for 2-acetylthiophene that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent supported concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None

Literature Search and Risk Assessment Completed On: 03/15/22

11.1.5. Photoirritation/photoallergenicity

Based on the available *in vitro* study data, 2-acetylthiophene would not be expected to present a concern for photoirritation. 2-Acetylthiophene was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of 2-acetylthiophene.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate significant absorption between 290 and 700 nm, with peak absorbance at 290 nm and returning to baseline by 370 nm. The corresponding molar absorption coefficients are above the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). In an *in vitro* 3T3-Neutral Red uptake photoirritation assay (OECD TG 432), 2-acetylthiophene was not predicted to have any photoirritating potential (RIFM, 2020). Based on the available *in vitro* study data, 2-acetylthiophene would not be expected to present a concern for photoirritation. 2-Acetylthiophene was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of 2-acetylthiophene.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate significant absorbance between 290 and 700 nm, with peak absorbance at 290 nm and returning to baseline by approximately 370 nm. Molar absorption coefficients (2016, 2120, and 1751 L mol^{-1} • cm^{-1} under neutral, acidic, and basic conditions, respectively) are above the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None

Literature Search and Risk Assessment Completed On: 04/01/22

11.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2-acetylthiophene is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-acetylthiophene. Based on the Creme RIFM Model, the inhalation exposure is 0.000039 mg/day. This exposure is 12051 times lower than the Cramer Class III* TTC value of 0.47 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.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None

Literature Search and Risk Assessment Completed On: 03/28/22

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-acetylthiophene was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1,

Table 1
Summary of existing data on 2-acetylthiophene.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
Human potency category unknown; Current exposure level below the DST for reactive materials.	NA	NA	NA	NA	NA	NA	NA
	***In vitro* Data**[f]			***In silico* protein binding alerts (OECD Toolbox v4.2)**			
	KE 1	**KE 2**	**KE 3**	**Target Materials**	**Autoxidation simulator**	**Metabolism simulator**	
	NA	NA	NA	No alert found	No alert found	No alert found	

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

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

[e] Studies conducted according to the OECD TG 406 are included in the table.

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

Table 2
Supported concentrations for 2-acetylthiophene that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Supported Concentrations[b] (%) in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049	NRU[c]
2	Products applied to the axillae	0.0015	NRU[c]
3	Products applied to the face using fingertips	0.029	NRU[c]
4	Fine fragrance products	0.027	NRU[c]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070	NRU[c]
6	Products with oral and lip exposure	0.016	NRU[c]
7	Products applied to the hair with some hand contact	0.056	NRU[c]
8	Products with significant ano-genital exposure	0.0029	No Data[d]
9	Products with body and hand exposure, primarily rinse-off	0.054	0.0060
10	Household care products with mostly hand contact	0.19	NRU[c]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11	No Data[d]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	NRU[c]

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

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, 2-acetylthiophene was not assessed as no Volume of Use was reported

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) identified 2-acetylthiophene as possibly being 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, 2017a). 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).

11.2.2. Risk assessment

Not applicable.

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. 2-Acetylthiophene has been pre-registered for REACH with no data available.

11.2.3. Risk assessment refinement

Not applicable.

Literature Search and Risk Assessment Completed On: 03/31/22

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA ChemView:** https://chemview.epa.gov/chemview/
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/17/23.

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 (Cramer et al., 1978).

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? No
Q23. Aromatic? No
Q24. Monocarbocyclic with simple substituents? No
Q25. Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26. Monocycloalkanone or a bicyclo compound? Yes, Intermediate (Class II)

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