Food and Chemical Toxicology 134 (2019) 110615

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, methyl acetoacetate, CAS Registry Number 105-45-3

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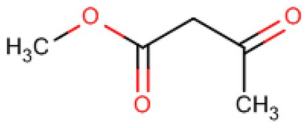
ARTICLE INFO

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

Version: 073018. This version replaces any previous versions.
Name: Methyl acetoacetate
CAS Registry Number: 105-45-3



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., 2015, 2017) compared to a deterministic

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https://doi.org/10.1016/j.fct.2019.110615
Received 20 August 2018; Received in revised form 21 May 2019; Accepted 19 June 2019
Available online 22 June 2019
0278-6915/

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 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 assesment.

Methyl acetoacetate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl acetoacetate is not genotoxic. Data show that there are no safety concerns for methyl acetoacetate for skin sensitization under the current, declared levels of use. Data on methyl acetoacetate provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to methyl acetoacetate is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; methyl acetoacetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methyl acetoacetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: Methyl acetoacetate)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(ECHA REACH Dossier: Methyl acetoacetate)
Developmental and Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	(ECHA REACH Dossier: Methyl acetoacetate)
Skin Sensitization: No safety concerns at current, declared use levels.	(ECHA REACH dossier: Methyl acetoacetate)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM DB)

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

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 95% (OECD 301F)	(ECHA REACH Dossier: Methyl acetoacetate; accessed 11/2017)
Bioaccumulation: Screening-level: 3.16 L/kg	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 2-160 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: 2-160 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 2.16 µg/L

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

1. Identification

1. **Chemical Name:** Methyl acetoacetate
2. **CAS Registry Number:** 105-45-3
3. **Synonyms:** Butanoic acid, 3-oxo-, methyl ester; Methyl acetyl acetate; Methyl 3-oxobutanoate; Methyl acetoacetate
4. **Molecular Formula:** $C_5H_8O_3$
5. **Molecular Weight:** 116.12
6. **RIFM Number:** 764
7. **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 169 °C (FMA), 147.34 °C (EPI Suite)
2. **Flash Point:** 64 °C (GHS), 158 °F; CC (FMA)
3. **Log K_{ow}:** 0.69 (EPI Suite)
4. **Melting Point**: 31.21 °C (EPI Suite)
5. **Water Solubility:** 406000 mg/L (EPI Suite)
6. **Specific Gravity:** 1.076 (FMA Database)
7. **Vapor Pressure:** 0.785 mm Hg @ 20 °C (EPI Suite v4.0), 1.24 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark ($1000\ L\ mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Merck Index (1976): colorless liquid, ethereal-green winey odor of moderate to poor tenacity; Arctander Volume II (1969): Sweet-ethereal somewhat green-fruity winey taste

3. EXPOSURE

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 3.0% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0034 mg/kg/day or 0.25 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.046 mg/kg/day (RIFM, 2016)

*95th percentile calculated exposure derived from concentration

survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015; Safford et al., 2015; 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 4. 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., 2015; 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	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and 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

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Methyl acetoacetate is reported to occur in the following foods*:
Wine.

*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. IFRA standard

None.

9. REACH dossier

3 dossiers available, accessed 12/5/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, methyl acetoacetate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Methyl acetoacetate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014a). BlueScreen is a screening assay that assesses genotoxic stress through alterations in gene expressions in a human cell line. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects on the target material.

The mutagenic activity of methyl acetoacetate 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 TA1535, TA1537, TA1538, TA98, and TA100 were treated with methyl acetoacetate in distilled water at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA REACH Dossier). Under the conditions of the study, methyl acetoacetate was not mutagenic in the Ames test.

The clastogenic activity of methyl acetoacetate 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 methyl acetoacetate in dimethyl sulfoxide (DMSO) at concentrations up to 1170 μg/mL in the presence and absence of metabolic activation (S9) for 3-h and 24-h timepoints. Methyl acetoacetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels or the maximum concentration recommended in either non-activated or S9-activated test systems (RIFM, 2014b). Under the conditions of the study, methyl acetoacetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, methyl acetoacetate does not present a concern for genotoxic potential.

Additional References: Shimizu et al., 1985; Kusakabe et al., 2002.

Literature Search and Risk Assessment Completed On: 01/14/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for methyl acetoacetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on methyl acetoacetate. An OECD 407/GLP oral gavage repeated dose toxicity study was conducted in Sprague Dawley rats. Groups of 5 rats/sex/dose were gavaged with methyl acetoacetate at doses of 0, 100, 300, or 1000 mg/kg/day daily for 4 weeks. Additional groups of 5 rats/sex/dose were assigned to the control and high dose group to serve as the 14-day treatment-free recovery groups. There were no treatment-related adverse effects observed in any of the treatment groups. Thus, the NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA Dossier: Methyl acetoacetate; data also available at EPA HPV Robust Summaries - Methyl acetoacetate, 2006). In another study, an OECD 422/GLP combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Crj:CD(SD) rats. Groups of 12 rats/sex/dose were gavaged with methyl acetoacetate at doses of 0, 100, 300, or 1000 mg/kg/day. Males were treated for 49 days (2 weeks prior to mating, during mating, and up to termination) while females were treated 2 weeks prior to mating to day 3 of lactation. No treatment-related adverse effects were reported up to the highest dose groups.

Thus, the NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day, the highest dose tested (JECDB Study report, 2000, JECDB Study Abstract; data also available at EPA HPV Robust Summaries - Methyl acetoacetate, 2006, and ECHA Dossier: Methyl acetoacetate). A NOAEL of 1000 mg/kg/day was determined from both OECD 407 and OECD 422 studies. A default safety factor of 3 was used when deriving a NOAEL from OECD 407 or 422 studies. The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the methyl acetoacetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the methyl acetoacetate NOAEL in mg/kg/day by the total systemic exposure for methyl acetoacetate, 333/0.046 or 7239.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/01/17.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for methyl acetoacetate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on methyl acetoacetate. An OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was conducted in Crj:CD(SD) rats. Groups of 12 rats/sex/dose were gavaged with methyl acetoacetate at doses of 0, 100, 300, or 1000 mg/kg/day. Males were treated for 49 days (2 weeks prior to mating, during mating, and up to termination) while females were treated 2 weeks prior to mating to day 3 of lactation. There were no treatment-related effects on estrous cycle, numbers of corpora lutea and implantations, and copulation or fertility indices. No histological changes were reported in the ovary. Furthermore, gestational days, litter and live born numbers, gestation index, stillborn index, birth index, sex ratio, body weights of offspring at birth and day 4 post-partum, or viability index on day 4 were comparable between the treatment and control groups. No external malformations were reported. The NOAEL for developmental and reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (JECDB Study report, 2000; JECDB Study Abstract; data also available at EPA HPV Robust Summaries - Methyl acetoacetate, 2006, and ECHA Dossier: Methyl acetoacetate).

Therefore, the methyl acetoacetate MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the methyl acetoacetate NOAEL in mg/kg/day by the total systemic exposure for methyl acetoacetate, 1000/0.046 or 21739.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/01/17.

10.1.4. Skin sensitization

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

10.1.4.1. Risk assessment. Based on the existing data, methyl acetoacetate does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a murine Local Lymph Node Assay (LLNA), methyl acetoacetate was found to be negative up to maximum tested concentration of 100% which resulted in Stimulation Index (SI) of 0.70 (ECHA Dossier: accessed 10/19/17). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1976).

Based on weight of evidence from structural analysis as well as animal and human studies, methyl acetoacetate does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/19/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, methyl acetoacetate 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 methyl acetoacetate in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, methyl acetoacetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for methyl acetoacetate were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/12/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for methyl acetoacetate 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 methyl acetoacetate. Based on the Creme RIFM Model, the inhalation exposure is 0.25 mg/day. This exposure is 5.6 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: 12/1/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of methyl acetoacetate 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, methyl acetoacetate 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 v4.1 did not identify methyl acetoacetate as either being possibly persistent nor 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 ≥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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	2160			1,000,000	2.160	

10.2.2. Risk assessment

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

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data

Methyl acetoacetate has been registered under REACH, and the following data is available.

The ready biodegradability of the test material was evaluated according to the OECD 301F method. Biodegradation of 95% was observed after 28 days.

A 96-h fish (*Pimephales promelas*) acute toxicity study was conducted according to the OECD 203 method under static conditions. The LC50 was reported to be greater than 111.4 mg/L.

A *Daphnia magna* immobilization study was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was greater than 100 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 was reported to be greater than 100 mg/L.

10.2.3. Risk assessment refinement

Since Methyl acetoacetate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	0.6	0.6
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	Not reported	< 1
Risk Characterization: PEC/PNEC	**N/A**	**N/A**

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

The RIFM PNEC is 2.16 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: 11/30/17.

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 07/30/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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