Food and Chemical Toxicology 122 (2018) S218–S224

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short review

RIFM fragrance ingredient safety assessment, methyl benzoate, CAS Registry Number 93-58-3

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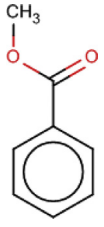
Version: 050818. This version replaces any previous versions.
Name: Methyl benzoate CAS Registry Number: 93-58-3



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 aggregate approach

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https://doi.org/10.1016/j.fct.2018.08.053
Received 9 May 2018; Received in revised form 10 July 2018; Accepted 22 August 2018
Available online 23 August 2018
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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 under the limits 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 use of this material under current conditions is supported by existing information.

Methyl benzoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that methyl benzoate is not genotoxic nor is it a safety concern under the current, declared levels of use for the skin sensitization endpoint. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using TTC for a Cramer Class I material, and the exposure to methyl benzoate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; methyl benzoate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; methyl benzoate was not found to be PBT as per 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.	(Zeiger et al., 1992; RIFM, 2013)
Repeated Dose Toxicity: No NOAEL available.	Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available.	Exposure is below the TTC
Skin Sensitization: No safety concerns under the current, declared levels of use.	(ECHA REACH Dossier: Methyl benzoate, accessed 6/14/17)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available.Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 95% (OECD 301B)	(RIFM, 1995)
Bioaccumulation: Screening-level: 11.6 mg/L	(EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 21.26 mg/L	(ECOSAR; US EPA, 2012b)

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: 96-h algae EC50: 21.26 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 2.126 μg/L
•**Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: < 1

1. Identification

1. **Chemical Name:** Methyl benzoate
2. **CAS Registry Number:** 93-58-3
3. **Synonyms:** Benzoic acid, methyl ester; Methyl benzenecarboxylate; Niobe oil; 安息香酸ｱﾙｷﾙ(C = 1 ~ 8); Methyl benzoate
4. **Molecular Formula:** $C_8H_8O_2$
5. **Molecular Weight:** 136.15
6. **RIFM Number:** 174

2. Physical data

1. **Boiling Point:** 199.5 °C (RIFM, 2012b), 200 °C (FMA), 195.93 °C (EPI Suite)
2. **Flash Point:** 77 °C (GHS), 77 °C (RIFM, 2012a), 180 °F; CC (FMA)
3. **Log K_{OW}:** LogK pdms/w = 1.882 (n = 12) (Xia et al., 2007), 1.83 (EPI Suite)
4. **Melting Point:** −11.87 °C (EPI Suite)
5. **Water Solubility:** 1344 mg/L (EPI Suite)
6. **Specific Gravity:** 1.084–1.090 (FMA), 1.09 (RIFM, 1995), 1.082–1.088 (FMA)
7. **Vapor Pressure:** 0.257 mm Hg @ 20 °C (EPI Suite v4.0), 0.3 mm Hg 20 °C (FMA), 0.379 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:** Colorless liquid with a pungent heavy-sweet deep floral odor of moderate to poor tenacity; fruity undertones resemble prunes and blackcurrant, while heavy floral tones recall notes of tuberose or longoza (Arctander Volume II, 1969)

3. Exposure

1. **Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.024% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00014 mg/kg/day or 0.0098 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00093 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 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., 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 (OECD, 2012)
I	I	I

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

6. Metabolism

Not considered for this risk assessment.

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

Menthyl benzoate is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):

Acerola (*Malpighia emarginata*)
Apple brandy (Calvados)
Banana (*Musa sapientum* L.)
Black choke berry juice (*Aronia melanocarpa* Ell.)
Black currants (*Ribes nigrum* L.)
Cape gooseberry (*Physalis peruviana* L.)
Capers (*Capparis spinoza*)
Cashew apple (*Anacardium occidentale*)
Ceriman, pinanona (*Monstera deliciosa* Liebm.)
Cheese, various types
Cherimoya (*Annona cherimolia* Mill.)
Cherry (*Prunus avium* [sweet], *Pr. cerasus* [sour])
Cinnamomum species
Citrus fruits
Cloudberry (*Rubus chamaemorus* L.)
Cloves (*Eugenia caryophyllata* Thunberg)
Coffee
Crowberry (*Empetrum nigrum* Coll.)
Date (*Phoenix dactylifera* L.)
DILL (*Anethum* species)
Grape (*Vitis* species)
Grape brandy
Guava and feyoa
Hog plum (*Spondias mombins* L.)
Honey
Hop (*Humulus lupulus*)
Katsobushi (dried bonito)
Kiwifruit (*Actinidia chinensis,* syn. *A. Deliciosa*)

Macadamia nut (*Macadamia integrifolia*)
Mangifera species
Milk and milk products
Mountain papaya (*C. candamarcensis, C. pubescens*)
Mushroom
Mustard (*Brassica* species)
Myrtle (*Myrtus communis* L.)
Naranjilla fruit (*Solanum quitoense* Lam.)
Ocimum species
Olive (*Olea europaea*)
Papaya (*Carica papaya* L.)
Passion fruit (*Passiflora* species)
Peach (*Prunus persica* L.)
Pear (*Pyrus communis* L.)
Peas (*Pisum sativum* L.)
Pepper (*Piper nigrum* L.)
Pimento (allspice) (*Pimenta dioica* L. Merr.)
Pineapple (*Ananas comosus*)
Piper betle L. Cultivars
Plum (*Prunus* species)
Plum brandy
Prickly pear (*Opuntia ficus indica*)
Rice (*Oryza sativa* L.)
Rooibos tea (*Aspalathus linearis*)
Sapodilla fruit (*Achras sapota* L.)
Soursop (*Annona muricata* L.)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species)
Tamarind (*Tamarindus indica* L.)
Tapereba, caja fruit (*Spondias lutea* L.)
Tea
Tomato (*Lycopersicon esculentum* Mill.)
Vaccinium species
Vanilla
Vinegar

*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 that contains 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

Available, accessed 06/21/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the existing data, methyl benzoate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of methyl benzoate has been evaluated in a bacterial reverse mutation assay using the preincubation method. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 were treated with methyl benzoate in dimethyl sulfoxide (DMSO) at concentrations up to 6666 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (Zeiger et al., 1992). Under the conditions of the study, methyl benzoate was not mutagenic in the Ames test.

The clastogenic activity of methyl benzoate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487 (OECD, 2015). Human peripheral blood lymphocytes were treated with methyl benzoate in DMSO at concentrations up to 1360 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 20 h. Methyl benzoate did not induce binucleated cells with micronuclei when tested up to the highest applied dose in either non-activated or S9-activated test systems (RIFM, 2013). Under the conditions of the study, methyl benzoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

Additional References: Szybalski, 1958; ECHA Reach Dossier.

Literature Search and Risk Assessment Completed On: 06/19/17.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on methyl benzoate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to methyl benzoate (0.93 μg/kg/day) is below the TTC (30 μg/kg bw/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: 06/05/17.

10.1.3. Reproductive toxicity

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

10.1.3.1. Risk assessment. There are no reproductive toxicity data on methyl benzoate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to methyl benzoate (0.93 μg/kg/day) is below the TTC (30 μg/kg bw/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: 06/05/17.

10.1.4. Skin sensitization

Based on the existing data, methyl benzoate 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 benzoate 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 could possibly react with skin proteins with little to no reaction under physiological conditions. In a murine local lymph node assay, methyl benzoate was found to be negative up to maximum tested concentration of 100% which resulted in Stimulation Index (SI) of 2.98 (ECHA REACH Dossier: Methyl benzoate, accessed 6/14/17). In guinea pigs, open epicutaneous tests and Freund's complete adjuvant tests with methyl benzoate did not present reactions indicative of sensitization (Klecak, 1985; Hausen et al., 1995). In a human maximization test, no skin sensitization reactions were observed with 4% or 2760 μg/cm^2 methyl benzoate in petrolatum (RIFM, 1970). Based on the weight of evidence from structural analysis as well as animal and human studies,

methyl benzoate 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: 06/14/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorbance spectra, methyl benzoate 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 benzoate 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 lack of absorbance in the critical range, methyl benzoate 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: 06/02/17.

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 benzoate 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 benzoate. Based on the Creme RIFM Model, the inhalation exposure is 0.0098 mg/day. This exposure is 143 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: Smyth et al., 1954: Pinching and Doving, 1974: Johnson et al., 2005.

Literature Search and Risk Assessment Completed On: 12/15/16.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of methyl benzoate 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 benzoate 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 v4.1 (US EPA, 2012a) did not identify methyl benzoate 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 ≥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.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), methyl benzoate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 1995: The ready and ultimate biodegradability of the test material was evaluated using the sealed vessel test according to the OECD 301B method. Biodegradation of 95% was observed after 28 days.

RIFM, 1992: The biological degradation of the test substance was evaluated using a Carbon Dioxide Evolution Test according to the 79/831 Method C.4-C. Under the conditions of this study, biodegradation of 62% was observed.

10.2.2.2. Ecotoxicity. RIFM, 1993: The acute toxicity of the test material on *Brachydanio rerio* (zebrafish) was evaluated according to the OECD 203 method. Under the conditions of the study, the 96-h measured LC50 was reported to be 23 mg/L.

10.2.2.3. Other available data. Methyl benzoate has been registered under REACH, and the following data is available:

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h LC50 based on growth rate was reported to be 111.9 mg/L.

10.2.3. Risk assessment refinement

Since methyl benzoate 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	274.1			1,000,000	0.2741	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	22.48	48.55	21.26	10,000	2.126	Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	159.5	89.14	62.2			Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.8	1.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
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 2.126 μg/L. The revised PEC/PNECs for EU and NA are < 1 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: 6/15/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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