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Short Review

RIFM fragrance ingredient safety assessment, myrcene, CAS Registry Number 123-35-3

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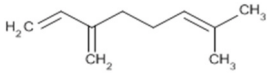

Name: Myrcene

CAS Registry Number: 123-35-3

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., 2015a; Safford et al., 2017) compared to a deterministic

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aggregate approach
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

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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.

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

Human Health Safety Assessment

Genotoxicity: Not genotoxic. NTP (2010)

Repeated Dose Toxicity: NOAEL = 25 mg/kg/day. NTP (2010)

Developmental and Reproductive Toxicity: NOAEL = 250 mg/kg/day and 300 mg/kg/day, respectively. (Delgado, 1993a; Paumgartten, 1998)

Skin Sensitization: Not sensitizing. (ECHA REACH Dossier: 7-methyl-3-methyleneocta-1,6-diene; ECHA, 2011)

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: Critical Measured Value: 76% (OECD 301 D) (ECHA REACH Dossier: 7-methyl-3-methyleneocta-1,6-diene; ECHA, 2011)
(EPI Suite v4.11; US EPA, 2012a)

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Bioaccumulation: Screening-level: 262 L/kg
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.216 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: 48-h *Daphnia magna* LC50: 0.216 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0216 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** Myrcene
2. **CAS Registry Number:** 123-35-3
3. **Synonyms:** 7-Methyl-3-methylene-1,6-octadiene; β-Myrcene; 1,6-Octadiene, 7-methyl-3-methylene-; Myrcene 90; 7 - メチル - 3 - メチレン - 1 , 6 - オクタジエン; 7-Methyl-3-methyleneocta-1,6-diene; Myrcene
4. **Molecular Formula:** $C_{10}H_{16}$
5. **Molecular Weight:** 136.23
6. **RIFM Number:** 345
7. **Stereochemistry:** Isomer not specified. Two geometric centers with 4 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 172 °C (FMA Database), 156.22 °C (EPI Suite)
2. **Flash Point:** 103 °F; CC (FMA Database)
3. **Log K_{OW}:** 5.1 at 35 °C (RIFM, 2004), 4.88 (EPI Suite)
4. **Melting Point**: −64.83 °C (EPI Suite)
5. **Water Solubility:** 6.923 mg/L (EPI Suite)
6. **Specific Gravity:** 0.793 (FMA Database)
7. **Vapor Pressure:** 1.72 mm Hg @ 20 °C (EPI Suite v4.0), 1.5 mm Hg 20 °C (FMA Database), 2.4 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance in the region 290–700 nm; molar absorption coefficient is below the benchmark (1000 L · mol^{-1} · cm^{-1}).
9. **Appearance/Organoleptic:** Colorless to very pale, straw-colored, mobile oil with a pleasant odor described as sweet, balsamic, resinous, and gum like; the taste is sweet, balsamic, and herbaceous at concentrations below 10 ppm, while higher concentrations tend to give pungency, bitterness, or a gassy taste (Arctander, 1969)

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.021% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000062 mg/kg/day or 0.0045 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00063 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, 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, 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
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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

When administered to rabbits at 670 mg/kg through oral gavage, myrcene was oxidized to 10-hydroxylinalool, 7- methyl-3-methylene-oct-6-ene-1,2-diol and uroterpineol. All were excreted in the urine (NTP, 1997).

In male rats, myrcene when administered at 5900 μmol/kg/day through gastric intubation in a 1% methanol cellulose solution for 20 days resulted in several metabolites in the urine. The metabolites were 10-hydroxylinalool, 7-methyl-3-methylene-oct-6-ene-1,2-diol, 1-hydroxymethyl-4-isopropenyl cyclohexanol, 10-carboxylinalool, and 2-hydroxy-7-methyl-3-methylene-oct-6-enoic acid. The biotransformation of myrcene involved epoxidation of the 1,2- and 3,10-double bonds, followed by hydration to yield 7-methyl-3-methylene-oct-6-ene-1,2-diol and then 10-hydroxylinalool. These diols were further oxidized and produced their respective aldehydes and hydroxy acids. The minor metabolite, 1-hydroxymethyl-4-isopropenyl cyclohexanol resulted from acid-catalyzed cyclization of 10-hydroxylinalool. Myrcene shares similarities in epoxide formation with *d*-limonene, a rat kidney carcinogen (NTP, 1997).

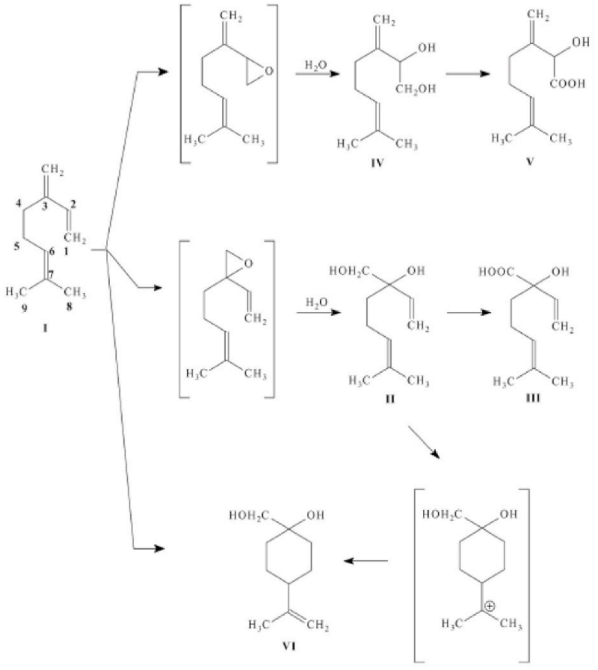
In a pharmacokinetic study, high blood levels of myrcene (Cmax of 14.1 ± 3 μg/mL) myrcene was detected after 1 h of oral administration to female rats at a dose of 1 g/kg (7300 μmol/kg). The elimination half-life was reported to be 285 min. At necropsy, myrcene was detected in the adipose tissue, brain, liver, kidneys, and testes (NTP, 1997; NTP, 2010) (see Fig. 1).

Additional References: Miyashita (1980); Krotoszynski (1982); Ishida (1981); Ishida (1980); Madhava-Madyastha and Srivatsan, 1987; Ishida (1979); De-Oliveira (1997); Schebler et al., 2006.

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

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

Calabash nutmeg (*Monodora myristica* Dunal)	Mastic (*Pistacia lentiscus*)
Citrus fruits	Pimento (Allspice) (*Pimenta dioica* L. Merr.)
Hop (*Humulus lupulus*)	Pistacia atlantica
Lemon grass oil (*Cymbopogon*)	Pistacia palaestina (*Pistacia terebinthus* L.)
Rosemary (*Rosmarinus officinalis* L.)	Wormwood oil (*Artemisia absinthium* L.)



I. Myrcene; II. 10-hydroxylinalool; III. 10-carboxylinalool; IV. 7-methyl-3-methylene-oct-6-ene-1,2-diol;

V. 2-hydroxy-7-methyl-3-methylene-oct-6-enoic acid; VI. 1-hydroxymethyl-4-isopropenyl cyclohexanol

Fig. 1. Metabolic fate of myrcene in rat (adapted from NTP, 2010).

*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.

8. REACH dossier

Available; accessed 05/20/19.

9. Conclusion

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

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. The mutagenic activity of myrcene has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA 97, TA98, TA100, and TA1535, and *Escherichia coli* strain WP2uvrA were treated with myrcene in buffer at concentrations up to 10000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (NTP, 2010). Under the conditions of the study, myrcene was not mutagenic in the Ames test.

The clastogenic activity of myrcene was evaluated in an *in vivo* micronucleus test conducted by the National Toxicology Program (NTP). The test material was administered in corn oil via oral gavage to groups of male and female B6C3 mice. Doses of 250, 500, 1000, or 2000 mg/kg body weight were administered. Mice from each dose level were euthanized, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (NTP, 2010). Under the conditions of the study, myrcene was considered to be not clastogenic in the *in vivo* micronucleus test.

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

Additional References: Kauderer (1991); Roscheisen (1991); Gomes-Carneiro (2005); Mitic-Culafic (2009);

Literature Search and Risk Assessment Completed On: 11/08/18.

10.1.2. Repeated dose toxicity

The MOE for myrcene is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient data on myrcene for the repeated dose toxicity endpoint. Several studies have been performed to assess the toxicity of the target material in rats and mice, including subchronic and chronic NTP studies. In a 2-year rat study using concentrations 0 mg/kg/day, 250 mg/kg/day, 500 mg/kg/day, and 1000 mg/kg/day (NTP, 2010), there was clear evidence of myrcene carcinogenicity in male rats based on the increased incidences of renal tubule adenoma and/or carcinoma at the 250 and 500 mg/kg/day doses. In females, although the incidence of renal tubule adenoma was not significant compared to their respective controls, it was slightly above the historical control range in the highest dose group. The marginal increase in renal tubule adenoma incidence was considered to be equivocal evidence of carcinogenicity in females. Moreover, myrcene administration also resulted in increased incidence and/or severity of a number of non-neoplastic renal lesions, including nephrosis and exacerbation of chronic progressive nephropathy in both sexes and papillary mineralization in the males. Specifically, significantly increased papillary mineralization in males that received the 250 and 500 mg/kg/day doses and were found within the loop of Henle as linear accumulations of angular to stippled basophilic material, and was considered to be a chronic manifestation of α-2u-globulin nephropathy, an effect also seen during chronic studies of the structurally related compound *d*-limonene (NTP, 1990). Nephrosis observed during chronic administration of myrcene in rats was more severe in males than females. The co-localization of nephrosis with the renal tubule necrosis in the outer medulla (in the 90-day study) combined with the proliferative nature of the lesion (karyomegaly and tubule hyperplasia) suggest that it is an adverse event in response to repeated renal tubule injury, primarily in the proximal tubules. However, it is unknown if this unusual regenerative response could lead ultimately to neoplasia, either directly or through exacerbation of chronic progressive nephropathy (CPN). The presence of renal neoplasms in female rats also suggests a mechanism of carcinogenesis that may be related to nephrosis and distinct from the α-2u-globulin mechanism. However, the underlying mechanism of myrcene-induced renal carcinogenesis in male and female rats continues to be unknown (NTP, 2010). Additional treatment-related toxicity included olfactory epithelium degeneration in rats of both sexes at a dose of 2000 mg/kg/day for 90 days and a dose-dependent increase in nasal inflammation in male rats during the 2-year study. Moreover, liver weights were significantly increased in animals at all does during the 90-day study. In B6C3F1 mice, the incidences of liver neoplasms were significantly increased in animals receiving the 250 (both sexes) and 500 mg/kg/day (males only) doses for 2 years. Liver neoplasms included hepatocellular adenoma and hepatocellular carcinoma in males and females, and hepatoblastoma in males. In addition, significant increases in hepatocellular hypertrophy incidences were observed in the 500 mg/kg/day dose group, along with increased incidences of mixed cell foci in females. Reported observations from these subchronic and chronic studies suggest that liver and kidney are the most susceptible organs to myrcene treatment in rodents. Based on the available data and the observed effects in kidneys, liver, and nasal epithelium at the lowest dose, a LOAEL of 250 mg/kg/day was determined for the repeated dose toxicity endpoint.

Myrcene is a non-genotoxic carcinogen in rats and mice (NTP, 2010). The carcinogenicity data on myrcene have been reviewed by the Expert Panel of the Flavor and Extracts Manufacturing Association (Adams, 2011) as well as in the scientific opinion on flavoring group evaluation (EFSA, 2015). In addition, myrcene has been listed on California's Proposition 65 list, but a safe harbor level (NSRL/MADL) has not been determined (OEHHA, 2015). Due to 100% incidence of nephropathy in males at the lowest dose, a benchmark dose level (BMDL) could not be determined from these studies (EFSA, 2015).

The NOAEL was derived by dividing the LOAEL by a safety factor of 10, which is equal to 25 mg/kg/day. **Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 25/0.00063 or 39683.**

In addition, the total systemic exposure to myrcene (0.63 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: ECB, 2000; Imaizumi (1985); Russin (1988); Russin (1989); Schebler et al., 2006; Ishida (1979); Ishida (1980); Ishida (1981); Madhava-Madyastha and Srivatsan, 1987; Schmitt (2010); Schmitt (2009).

Literature Search and Risk Assessment Completed On: 05/05/

19.

10.1.3. Developmental and reproductive toxicity

The MOE for myrcene 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 myrcene.

In a developmental toxicity study (similar to OECD 414/non-GLP-compliant), pregnant Wistar rats (16 females/group in the control, low-, and mid-dose groups and 29 females in the high-dose group) were administered myrcene via oral gavage at doses of 0, 250, 500, or 1200 mg/kg/day in corn oil during gestation days (GDs) 6–15. On GD 20, females were euthanized, gravid uterus was weighed, and the numbers of implantation sites, living and dead fetuses, resorptions, and corpora lutea were recorded. Fetuses were weighed and examined for external malformations and fixed for visceral examinations or cleared and stained with Alizarin Red S for skeletal evaluation. At 1200 mg/kg/day, mortality was reported in 1 dam on GD 11 after progressive and severe bodyweight loss, which started on the first day of treatment (GD 6). Furthermore, a statistically significant decrease in maternal weight gain was reported in high-dose dams, which resulted in significant reduction in the gravid uterus weight. Statistically significant reductions in the number of implantation sites, live fetuses, and individual fetal weights were reported at 1200 mg/kg/day. Additionally, high-dose group fetuses exhibited a higher rate of irregularly positioned hind paws and significantly higher incidences of delayed ossification; the most pronounced effects were reported in the skull bones (9.6%), caudal vertebrae (37.8%), metacarpus (9.1%), and metatarsus (29.2%). The NOAEL for maternal toxicity was considered to be 500 mg/kg/day, based on mortality and decreased maternal weight gain among high-dose group dams. The NOAEL for developmental toxicity was considered to be 500 mg/kg/day, based on increased incidences of skeletal malformations reported in high-dose group fetuses (Delgado, 1993b).

In a peri- and postnatal developmental toxicity study, pregnant Wistar rats (12–20 females/group) were administered myrcene via oral gavage at doses of 0, 250, 500, 1000, or 1500 mg/kg/day in corn oil from GD 15 through parturition and lactation up to weaning (postnatal day [PND] 21). All F1 generation pups were examined at birth and up to weaning for mortality, weight gain, and physical signs of postnatal development (e.g., ear unfolding, incisor eruption, fur development, and eye opening). On PND 21, all dams (parental generation) were euthanized. The reproductive capacity of pups (F1 generation) was evaluated after reaching maturity (120 days) by mating 1:3 (male:female) progeny from the same treatment group of different litters for 15 days. On PND 4, the number of male and female live pups per litter were counted (F2 generation), and the number of implantation sites for each F1 pregnant female was also evaluated. Male reproductive organs (testes, cauda epididymis, and prostate) were excised and weighed with the concomitant evaluation of spermatozoa in the testes and cauda epididymis from F1 males. Mortality was reported in 5 pregnant females (parental generation) at 1500 mg/kg/day. A statistically significant decrease in body weight was reported in pregnant females on GD 20 (parental generation) at ≥1000 mg/kg/day, and decreased body weight persisted up to delivery (PND 1) at 1500 mg/kg/day. A higher rate of stillbirths was reported at the 1000 mg/kg/day dose. Increased labor duration was reported at 500 mg/kg/day (for 1 dam) and 1000 mg/kg/day (for 3 dams), which could be attributed to myrcene. The increased stillbirths and labor duration at ≥500 mg/kg/day reflects how myrcene could induce parturition disturbance. A statistically significant increase in pup mortality (F1 generation) was reported at ≥500 mg/kg/day during the first week of lactation. A statistically significant decrease in pup weight (F1 generation) was reported at >500 mg/kg/day, which recovered for all treatment groups at PND 21. Delayed appearance of developmental landmarks such as primary coat was reported at ≥500 mg/kg/day, and ear unfolding and eye opening were reported at ≥1000 mg/kg/day. A statistically significant decrease in fertility (after 120 days maturation) was reported in F1 generation females when treated with doses ≥1000 mg/kg/day. The NOAEL for maternal toxicity was considered to be 1000 mg/kg/day, due to mortality in pregnant rats (parental generation) and persisted decreased body weight up to PND 1 (F1 generation) at 1500 mg/kg/day. The NOAEL for developmental toxicity was considered to be 250 mg/kg/day, based on decreased pup bodyweight, increased pup mortality, parturition disturbance, and delayed appearance of developmental landmarks at ≥500 mg/kg/day. The NOAEL for reproductive toxicity was considered to be 500 mg/kg/day, based on impaired fertility in F1 females. which resulted from dams treated at ≥1000 mg/kg/day (Delgado, 1993a).

In a 1-generation reproduction toxicity study (similar to OECD 415/non-GLP-compliant), Wistar rats (15 males/group and 45 females/group) were administered myrcene via oral gavage at doses of 0, 100, 300, or 500 mg/kg/day in peanut oil. Male rats were treated for 91 days prior to mating and during the mating period, and females were treated continuously for 21 days before mating, during mating and pregnancy, and throughout lactation up to PND 21. On GD 21, one-third of the females of each group were euthanized and subjected to cesarean section. The remaining dams gave birth to their offspring. The progeny were examined at birth and subsequently up to PND 21. Males were euthanized at the end of the mating period, and no treatment-related effects were reported on the number of spermatids in the testis or on the number of spermatozoa in the cauda epididymis at any dose levels. Fertility indices (such as mating index and pregnancy index) were not affected at any dose levels. No signs of maternal toxicity and no increase in externally visible malformations were observed at any dose. At 500 mg/kg/day, a statistically significant increase in the resorption rate and a parallel statistically significant decrease in the ratio of live fetuses per implantation site were reported. Furthermore, the frequency of skeletal malformations such as fused or zygomatic, dislocated sternum (non-aligned sternebrae) and extra lumbar ribs were increased in the high-dose group pups. No treatment-related effects were reported on postnatal weight gain, but day of primary coat appearance, incisor eruption, and eye opening were slightly delayed in the exposed offspring. The NOAEL for reproductive toxicity was considered to be 300 mg/kg/day, based on increased resorption rate and a parallel decrease in the ratio of live fetuses per implantation site in the high-dose group. The NOAEL for developmental toxicity was considered to be 300 mg/kg/day, based on the increased frequency of skeletal malformations among high-dose group pups (Paumgartten, 1998).

The most conservative NOAEL of 250 mg/kg/day from the peri- and postnatal developmental toxicity study was selected for the developmental toxicity endpoint. **Therefore, the myrcene MOE for the developmental toxicity endpoint can be calculated by dividing the myrcene NOAEL in mg/kg/day by the total systemic exposure to myrcene, 250/0.00063 or 396825.**

A NOAEL of 300 mg/kg/day from the 1-generation reproduction toxicity study was selected for the reproductive toxicity endpoint. **Therefore, the myrcene MOE for the reproductive toxicity endpoint can be calculated by dividing the myrcene NOAEL in mg/kg/day by the total systemic exposure to myrcene, 300/0.00063 or 476190.**

In addition, the total systemic exposure to myrcene (0.63 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2013; NTP, 2011; US EPA, 2006 (accessed 11/14/18).

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

10.1.4. Skin sensitization

Based on the existing data, myrcene 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, myrcene is not considered a skin sensitizer. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD toolbox v4.2). In a murine local lymph node assay, myrcene was found to be non-sensitizing up to 50% (ECHA, 2011). In a human maximization test, no skin sensitization reactions were observed with myrcene at 4% (2760 μg/cm^2) (RIFM, 1972a).

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

Additional References: RIFM, 1972b; Friedrich (2007); Hausen (1999).bib_Hausen_et_al_1999

Literature Search and Risk Assessment Completed On: 11/07/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, myrcene 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 myrcene 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, 2009). Based on the lack of absorbance, myrcene does not present a concern for phototoxicity or photoallergenicity.

Key Studies

There are no studies available for myrcene in experimental models.

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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/18/18.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are insufficient inhalation data available on myrcene. Based on the Creme RIFM Model, the inhalation exposure is 0.0045 mg/day. This exposure is 311 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Key Studies: None.

Additional References: Kovar (1987): Coats (1991): Helmig (1999a): Helmig (1999b):

Literature Search and Risk Assessment Completed On: 10/23/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of myrcene 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, myrcene was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC >1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify myrcene 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). 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 VoU (2015), myrcene presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Key Studies. ***Biodegradation***

RIFM, 2005: The ready biodegradability of the test material was determined by the Manometric Respirometry Test according to the OECD 301F method. Myrcene underwent 31% biodegradation after 28 days (and 31% after 29 days) in the test conditions.

RIFM, 2009: The CO_2 headspace test according to OECD 310 guidelines was conducted to evaluate the biodegradability of the test material under aerobic conditions. Under the conditions of the study, the biodegradation at day 28 was 73%.

Ecotoxicity

Union Carbide Corporation Chemicals and Plastics Company, 1991**:** The toxicity of the test material was determined using *Daphnia magna*. The 48-h LC50 was reported to be 31 mg/L.

Other available data

Myrcene has been registered under REACH and the following additional data is available.

The ready biodegradability study was conducted according to the OECD 301D method, and biodegradation of 76% was observed after 28 days.

A 96-h fish (*Cyprinus carpio*) acute toxicity study was conducted according to the OECD 203 method, and the LC50 was reported to be greater than the limit of solubility.

A *Daphnia magna* immobilization study was conducted according to the OECD 202 method, and the 48-h EC50 was reported to be 1.47 mg/L, based on mean measured concentrations.

An algae inhibition study was conducted according to the OECD 201 method, and the 72-h ErC50 (growth rate) was reported to be 0.342 mg/L (ECHA, 2011).

10.2.3. Risk assessment refinement

Since myrcene 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.3692			1,000,000	0.000369	
ECOSAR Acute	0.292	0.216	0.485	10,000	0.0216	Neutral
Endpoints **(Tier 2)** ***Ver 1.11***						Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	5.1	5.1
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0216 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environmental at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 11/07/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** 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 05/20/19.

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.

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