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RIFM fragrance ingredient safety assessment, dihydromyrcene, CAS Registry Number 2436-90-0

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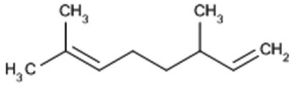

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Name: Dihydromyrcene
CAS Registry Number: 2436-90-0

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

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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., 2020)
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, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Dihydromyrcene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from dihydromyrcene and read-across analog myrcene (CAS # 123-35-3) show that dihydromyrcene is not expected to be genotoxic. Data on read-across material myrcene (CAS # 123-35-3) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from dihydromyrcene provided a No Expected Sensitization Induction Level (NESIL) of 10000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV/Vis) spectra; dihydromyrcene is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to dihydromyrcene is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; dihydromyrcene was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2000a; NTP, 2010)
Repeated Dose Toxicity: NOAEL = 25 mg/kg/day.	NTP (2010)
Reproductive Toxicity: Developmental toxicity NOAEL = 250 mg/kg/day. Fertility NOAEL = 300 mg/kg/day.	(Delgado, 1993a; Paumgartten, 1998)
Skin Sensitization: NESIL = 10000 μg/cm^2.	RIFM (2015)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra, RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 71% (OECD 301D)	(ECHA REACH Dossier: 3,7-Dimethylocta-1,6-diene; ECHA, 2011)
Bioaccumulation: Screening-level: 774 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 15 mg/L	RIFM (2000c)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 15 mg/L	RIFM (2000c)

RIFM PNEC is: 3 μg/L

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

1. Identification

1. **Chemical Name:** Dihydromyrcene
2. **CAS Registry Number:** 2436-90-0
3. **Synonyms:** 3,7-Dimethylocta-1,6-diene; 1,6-Octadiene, 3,7-dimethyl-; 2,6-ｼﾞﾒﾁﾙ-2,7-ｵｸﾀｼﾞｴﾝ; Citronellene; Dihydromyrcene
4. **Molecular Formula:** $C_{10}H_{18}$
5. **Molecular Weight:** 138.25
6. **RIFM Number:** 1055
7. **Stereochemistry:** The material has 1 chiral center and 2 geometric centers, making 8 possible isomers in all. The isomers were not specified.

2. Physical data

1. **Boiling Point:** 155.0 °C (RIFM, 2000b), 158 °C (Fragrance Materials Association [FMA] Database), 150.63 °C (EPI Suite)
2. **Flash Point:** 93 °F; CC (FMA Database)
3. **Log K_{OW}:** 4.88 (EPI Suite)
4. **Melting Point**: 66.11 °C (EPI Suite)
5. **Water Solubility:** 1.669 mg/L (EPI Suite)
6. **Specific Gravity:** 0.760 (FMA Database)
7. **Vapor Pressure:** 3.66 mm Hg at 20 °C (EPI Suite v4.0), 4.99 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra**: No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Not available

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.21% (RIFM, 2016)
2. **Inhalation Exposure*:** 0.0016 mg/kg/day or 0.11 mg/day (RIFM, 2016)
3. **Total Systemic Exposure**:** 0.0040 mg/kg/day (RIFM, 2016)

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

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** Myrcene (CAS # 123-35-3)
   b. **Repeated Dose Toxicity:** Myrcene (CAS # 123-35-3)
   c. **Reproductive Toxicity:** Myrcene (CAS # 123-35-3)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

Dihydromyrcene is not reported to occur in foods by the VCF*.

*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

Available; accessed on 09/02/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for dihydromyrcene are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.0063
2	Products applied to the axillae	0.23
3	Products applied to the face/body using fingertips	0.013
4	Products related to fine fragrances	3.4
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.85
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.019
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.14
5D	Baby cream, oil, talc	0.0063
6	Products with oral and lip exposure	0.0063
7	Products applied to the hair with some hand contact	0.87
8	Products with significant ano-genital exposure (tampon)	0.0063
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.5
10A	Household care products with mostly hand contact (hand dishwashing detergent)	11
10B	Aerosol air freshener	2.6
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0063
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	49

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For dihydromyrcene, the basis was the reference dose of 0.25 mg/kg/day, a predicted skin absorption value of 10%, and a skin sensitization NESIL of 10000 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. Dihydromyrcene 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, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of dihydromyrcene 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 TA1537,

TA98, TA1535, TA100, and TA102 were treated with dihydromyrcene in ethanol at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2000a). Under the conditions of the study, dihydromyrcene was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of dihydromyrcene. Read-across can be made to myrcene (CAS # 123-35-3; see Section VI). 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 at doses of 250, 500, 1000, or 2000 mg/kg body weight. 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, and this can be extended to dihydromyrcene.

Based on the available data, dihydromyrcene 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: 06/09/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on dihydromyrcene. Read-across material myrcene (CAS # 123-35-3; see Section VI) has sufficient data for repeated dose toxicity. Several studies have been performed to assess the toxicity of myrcene in rats and mice, including subchronic and chronic NTP studies. In the 2-year rat study, there was clear evidence of β-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, β-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. The papillary mineralization found in the loop of Henle had a linear appearance and was considered a chronic manifestation of α-2-globulin nephropathy, an effect also seen during chronic studies of the structurally related compound *d*-limonene (NTP, 1990). Nephrosis was observed during chronic administration of β-myrcene in rats and was more severe in males than in 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-2-globulin mechanism. However, the underlying mechanism of β-myrcene-induced renal carcinogenesis in male and female rats continues to be unknown (NTP, 2010). Based on the available data and the observed effects in kidneys, liver, and nasal epithelium at the lowest dose, the lowest observable adverse effect level (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 β-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, β-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 a 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, 25/0.004, or 6250.**

11.1.3. Derivation of reference dose (RfD)

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.25 mg/kg/day.

The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The reference dose for dihydromyrcene was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 25 mg/kg/day by the uncertainty factor, 100 = 0.25 mg/kg/day.

In addition, the total systemic exposure to dihydromyrcene (4.0 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: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.4. Reproductive toxicity

The MOE for dihydromyrcene is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.4.1. Risk assessment. There are no reproductive toxicity data dihydromyrcene. Read-across material myrcene (CAS # 123-35-3; see Section VI) has sufficient data that can be used to support the reproductive toxicity endpoint.

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 a 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 concentrations ≥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 β-myrcene. The increased stillbirths and labor duration at concentrations ≥500 mg/kg/day reflect how β-myrcene could induce parturition disturbance. A statistically significant increase in pup mortality (F1 generation) was reported at concentrations ≥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 concentrations ≥500 mg/kg/day, and ear unfolding and eye opening were reported at concentrations ≥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 body weight, increased pup mortality, parturition disturbance, and delayed appearance of developmental landmarks at concentrations ≥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 concentrations ≥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 were allowed to give birth to their offspring. The progeny was 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 os 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 the 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 dihydromyrcene MOE for the developmental toxicity endpoint can be calculated by dividing the myrcene NOAEL in mg/kg/day by the total systemic exposure to dihydromyrcene, 250/0.004, or 62500.**

A NOAEL of 300 mg/kg/day from the 1-generation reproduction toxicity study was selected for the fertility endpoint. **Therefore, the dihydromyrcene MOE for the fertility endpoint can be calculated by dividing the myrcene NOAEL in mg/kg/day by the total systemic exposure to dihydromyrcene, 300/0.004, or 75000.**

In addition, the total systemic exposure to dihydromyrcene (4.0 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2013b; NTP, 2011; US EPA, 2006.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.5. Skin sensitization

Based on the existing data, dihydromyrcene is considered a skin sensitizer with a defined NESIL of 10000 μg/cm^2.

11.1.5.1. Risk assessment. Based on the existing data, dihydromyrcene is 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 v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), dihydromyrcene was found to be sensitizing with an EC3 value of 41% (10250 μg/cm^2) (ECHA, 2011). In a human maximization test, no skin sensitization reactions were observed with dihydromyrcene at 4% (2760 μg/cm^2) (RIFM, 1980). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 10275 μg/cm^2 dihydromyrcene in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 109 volunteers (RIFM, 2015).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, dihydromyrcene is a weak sensitizer with a WoE NESIL of 10000 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.25 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.1.6. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, dihydromyrcene would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.6.1. Risk assessment. There are no phototoxicity data available for dihydromyrcene. UV/Vis absorption spectra indicate no absorption

Table 1
Data summary for dihydromyrcene.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human 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
10250[1]	Weak	10275	2760	NA	10000

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

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on lack of absorbance, dihydromyrcene does not present a concern for phototoxicity or photoallergenicity.

11.1.7. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) for dihydromyrcene were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, 1000 L mol^{-1} • cm^{-1}, of concern for phototoxic effects (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.8. Local Respiratory Toxicity

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

11.1.8.1. Risk assessment. There are no inhalation data available for dihydromyrcene. Based on the Creme RIFM Model, the inhalation exposure is 0.11 mg/day. This exposure is 12.7 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/24/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of dihydromyrcene was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, dihydromyrcene 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 dihydromyrcene 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 v4.1). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.1.1. Risk assessment. Based on current VoU (2015), dihydromyrcene presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2. Key studies

11.2.2.1. Biodegradation. RIFM, 2000b: The biodegradability of the test material was evaluated in a closed bottle test as described in the OECD 301D guideline. The mean biodegradation for dihydromyrcene at day 28 was 3%.

11.2.2.2. Ecotoxicity. RIFM, 2000c: A *Daphnia magna* acute toxicity study was conducted according to the OECD 202I method under static conditions. The 48-h EC50 based on nominal test concentration for dihydromyrcene was reported to be 15 mg/L.

11.2.2.3. Other available data. Dihydromyrcene was registered under REACH, and the following additional data is available (ECHA, 2011):

The biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D guideline. The mean biodegradation for dihydromyrcene at day 28 was 71%.

An algae inhibition test was conducted according to the OECD 201 method. The 48-h EC50 was greater than the solubility limit.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.8	4.8
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**

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.582			1000000	0.000582	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.292	0.216	0.485	10000	0.0216	Neutral Organics
Tier 3: Measured Data						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish						
Daphnia		15		5000	3	
Algae						

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

The RIFM PNEC is 3 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volume of use.

Literature Search and Risk Assessment Completed On: 06/25/21.

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
- **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 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:** 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 09/02/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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 A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2021.112642.

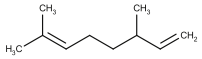
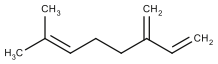
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Dihydromyrcene	Myrcene
CAS No.	2436-90-0	123-35-3
Structure		
Similarity (Tanimoto Score)		0.64
Read-across Endpoint		• Genotoxicity • Repeated Dose Toxicity • Reproductive Toxicity
Molecular Formula	$C_{10}H_{18}$	$C_{10}H_{16}$
Molecular Weight	138.25	136.23
Melting Point (°C, EPI Suite)	−66.11	−64.83
Boiling Point (°C, EPI Suite)	150.63	156.22
Vapor Pressure (Pa @ 25°C, EPI Suite)	666.00	320.00
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.88	4.88
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.67	5.05
J_{max} (μg/cm^2/h, SAM)	18.33	1.09
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.39E+004	5.30E+004
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Carcinogenicity (ISS)	• Non-Carcinogen (low reliability)	• Non-Carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Aliphatic/Alicyclic hydrocarbons (α-2u-globulin nephropathy) Rank C
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-Toxicant (low reliability)	• Non-Toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on dihydromyrcene (CAS # 2436-90-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, myrcene (CAS # 123-35-3) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Myrcene (CAS # 123-35-3) was used as a read-across analog for the target material dihydromyrcene (CAS # 2436-90-0) for the genotoxicity, repeated dose toxicity, and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of unsaturated hydrocarbons.
  - o The target material and the read-across analog share nearly identical unsaturated branched aliphatic hydrocarbon chains.
  - o The key difference between the target material and the read-across analog is the degree of unsaturation. The read-across analog contains conjugated vinyl groups, whereas one of the vinyls is saturated in the target material. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq$80%, and J_{max} for the read-across analog corresponds to skin absorption $\leq$40%. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The HESS categorization scheme has an alert of aliphatic/alicyclic hydrocarbons (α-2u-globulin nephropathy) Rank C for the read-across analog. The target material does not have an alert. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. The data described in the repeated dose toxicity section confirm that the MOE of the read-across analog is adequate at the current level of use. Therefore, data supersedes predictions in this case.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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