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Update to RIFM fragrance ingredient safety assessment, 2,6-dimethyl-5--heptenal, CAS Registry Number 106-72-9

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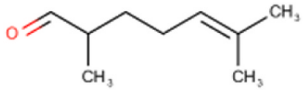

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Assessments is here: fragrancematerialsafetyresource.elsevier.com.
Name: 2,6-Dimethyl-5-heptenal
CAS Registry Number: 106-72-9

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., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015a, 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This 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.

2,6-Dimethyl-5-heptenal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog citronellal (CAS # 106-23-0) show that 2,6-dimethyl-5-heptenal is not expected to be genotoxic. Data provide a calculated MOE >100 for the repeated dose toxicity and developmental toxicity endpoints. Data from read-across analog citral (CAS # 5392-40-5) provide a calculated MOE >100 for the fertility endpoint. Data from read-across analog citronellal (CAS # 106-23-0) provided 2,6-dimethyl-5-heptenal a NESIL of 7000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; 2,6-dimethyl-5-heptenal 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 2,6-dimethyl-5-heptenal is below the TTC (1.4 mg/kg/day). The environmental endpoints were evaluated; 2,6-dimethyl-5-heptenal was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2006; RIFM, 2016a)
Repeated Dose Toxicity: NOAEL = 37 mg/kg/day.	Gaunt (1983)
Reproductive Toxicity: Developmental toxicity: NOAEL = 300 mg/kg/day. Fertility: NOAEL = 1000 mg/kg/day.	(RIFM, 1990; MHW, 1996)
Skin Sensitization: NESIL = 7000 μg/cm^2.	RIFM (2014)
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: 75% (OECD 301F)	RIFM (2012)
Bioaccumulation:	
Screening-level: 47.0 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* EC50: 2.200 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, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 2.200 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.22 μg/L	

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

1. Identification

1. **Chemical Name:** 2,6-Dimethyl-5-heptenal
2. **CAS Registry Number:** 106-72-9
3. **Synonyms:** 2,6-Dimethyl-2-hepten-7-al; Dimethylheptenal; 5-Heptenal, 2,6-dimethyl-; Melonal; 2,6-Dimethylhept-5-enal; 2,6-Dimethyl-5-heptenal
4. **Molecular Formula:** $C_9H_{16}O$
5. **Molecular Weight:** 140.22 g/mol
6. **RIFM Number:** 504
7. **Stereochemistry:** Isomer not specified. One chiral center and a total of 2 enantiomers possible.

2. Physical data

1. **Boiling Point:** 65 °C at 10 mm Hg (Fragrance Materials Association [FMA]), 184.94 °C (EPI Suite)
2. **Flash Point:** 133 (FMA), 60–61 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.4 (RIFM, 2000a), 3.04 (EPI Suite)
4. **Melting Point**: 39.84 °C (EPI Suite)
5. **Water Solubility:** 212 mg/L (EPI Suite)
6. **Specific Gravity:** 0.850–0.858 (FMA), 0.848–0.856 (FMA)
7. **Vapor Pressure:** 0.524 mm Hg at 20 °C (EPI Suite v4.0), 0.4 mm Hg at 20 °C (FMA), 0.759 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:** A clear, yellow liquid having a characteristic odor of melon

3. Volume of use (Worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.4)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.032% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.00021 mg/kg/day or 0.016 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.0018 mg/kg/day (RIFM, 2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (RIFM, 2015a; Safford, 2015; Safford, 2017; and Comiskey, 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 (RIFM, 2015a; Safford, 2015; Safford, 2017; and Comiskey, 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:** Citronellal (CAS # 106-23-0)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** Citral (CAS # 5392-40-5)
   d. **Skin Sensitization:** Citronellal (CAS # 106-23-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

2,6-Dimethyl-5-heptenal is reported to occur in the following foods by the VCF*:

Citrus fruits
Ginger (*Zingiber* species)

*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 11/15/21 (ECHA, 2017a).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2,6-dimethyl-5-heptenal 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)	0.14
2	Products applied to the axillae	0.16
3	Products applied to the face/body using fingertips	0.090
4	Products related to fine fragrances	1.1
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.36
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.045
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.090
5D	Baby cream, oil, talc	0.015
6	Products with oral and lip exposure	0.72
7	Products applied to the hair with some hand contact	0.090
8	Products with significant ano-genital exposure (tampon)	0.015
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.45
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.14
10B	Aerosol air freshener	0.99
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.015
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	23

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 2,6-dimethyl-5-heptenal, the basis was the subchronic reference dose of 0.37 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 7000 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; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2,6-dimethyl-5-heptenal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2,6-dimethyl-5-heptenal 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 and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2,6-dimethyl-5-heptenal in dimethyl sulfoxide (DMSO) 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 mix (RIFM, 2006). Under the conditions of the study, 2,6-dimethyl-5--heptenal was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 2,6-dimethyl-5-heptenal; however, read-across can be made to citronellal (CAS # 106-23-0; see Section VI).

The clastogenic activity of citronellal was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with citronellal in DMSO at concentrations up to 1540 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 300 μg/mL in the presence and absence of metabolic activation. Citronellal did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2016a). Under the conditions of the study, citronellal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2,6-dimethyl-5-heptenal.

Based on the data available, citronellal does not present a concern for genotoxic potential, and this can be extended to 2,6-dimethyl-5-heptenal.

Additional References: Heck (1989).

Literature Search and Risk Assessment Completed On: 02/09/21.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for 2,6-dimethyl-5-heptenal is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 2,6-dimethyl-5-heptenal for the repeated dose toxicity endpoint. A dietary 90-day subchronic toxicity study was conducted in rats. Groups of 15 Wistar rats/sex/group were treated with test material DMH (DMH was an isomeric mixture of 2,6-dimethylhept-5-en-1-al) at dose levels of 0, 9, 37, and 150 mg/kg/day for 13–14 weeks. The NOAEL was determined to be 37 mg/kg/day, based on kidney and liver effects at a dose of 150 mg/kg/day (Gaunt, 1983). **Therefore, the 2,6-dimethyl-5-heptenal MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2,6-dimethyl-5-heptenal NOAEL in mg/kg/day by the total systemic exposure to 2,6-dimethyl-5-heptenal, 37/0.0018, or 20555.**

In addition, the total systemic exposure to 2,6-dimethyl-5-heptenal (1.8 μg/kg/day) is below the Threshold of Toxicological Concern (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.

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, 2020b) and a subchronic reference dose (RfD) of 0.37 mg/kg/day.

11.1.2.1.1. Derivation of subchronic RfD. 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 subchronic RfD for 2,6-dimethyl-5-heptenal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 37 mg/kg/day by the uncertainty factor, 100 = 0.37 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/15/20.

11.1.3. Reproductive toxicity

The MOE for 2,6-dimethyl-5-heptenal is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on 2,6-dimethyl-5-heptenal for the developmental toxicity endpoint. A gavage developmental and reproductive toxicity screening study was conducted in rats. Groups of 10 female CD (SD) BR rats were first administered 2,6-dimethyl-5-heptenal in corn oil at dosages of 0, 300, 1500, or 3000 mg/kg/day for 7 days, followed by cohabitation with untreated males for a maximum of 7 days. The dams were allowed to deliver and nurse their litters during a 4-day lactation period (day 1 of lactation/post-parturition was defined as the day the first pup was delivered), and all dams and their pups were euthanized on day 4 of lactation. The NOAEL for developmental toxicity was determined to be 300 mg/kg/day, based on reduced pup weights and viability among the higher dose group animals (RIFM, 1990). These effects were observed at dosages that were maternally toxic. Thus, the NOAEL for developmental toxicity was determined to be 300 mg/kg/day. **Therefore, the 2,6-dimethyl-5-heptenal MOE for the developmental toxicity endpoint can be calculated by dividing the 2,6-dimethyl-5-heptenal NOAEL in mg/kg/day by the total systemic exposure to 2,6-dimethyl-5-heptenal, 300/0.0018, or 166666.**

There are insufficient data on 2,6-dimethyl-5-heptenal for the fertility endpoint. A gavage developmental and reproductive toxicity screening study conducted in rats determined the maternal NOAEL to be 300 mg/kg/day, based on clinical signs, body weight, and food consumption (RIFM, 1990). However, there are no male reproductive toxicity data on 2,6-dimethyl-5-heptenal. The read-across material citral (CAS # 5392-40-5; see Section VI) has an OECD 421 gavage reproduction toxicity screening test conducted in Crj:CD (SD) rats. Citral was administered to rats via gavage at dose levels of 0, 40, 200, and 1000 mg/kg/day in males for 46 days and in females for 39–50 days, including before and through mating and gestation periods and until day 3 of lactation. The NOAEL for fertility of the parental generation males and females was determined to be 1000 mg/kg/day, the highest dose tested. There were no statistically significant effects detected in reproductive ability, organ weights, or histopathology of the reproductive organs of both sexes (MHW, 1996). In another study, a reproductive toxicity screening study conducted on 30 female Sprague Dawley rats/group were administered citral via gavage at dose levels of 0 (corn oil), 50, 160, and 500 mg/kg/day for 2 weeks prior to mating through gestation day 20. The female fertility and reproductive system remained unaffected after treatment with citral up to the highest dose tested (Hoberman, 1989). Thus, the NOAEL for the fertility endpoint was determined to be 1000 mg/kg/day. **Therefore, the 2,6-dimethyl-5--heptenal MOE for the fertility endpoint can be calculated by dividing the citral NOAEL in mg/kg/day by the total systemic exposure to 2,6-dimethyl-5-heptenal, 1000/0.0018, or 555555.**

In addition, the total systemic exposure to 2,6-dimethyl-5-heptenal (1.8 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: Gaworski (1992); Nogueira (1995); Hoberman (1989).

Literature Search and Risk Assessment Completed On: 02/09/21.

11.1.4. Skin sensitization

Based on the available data and read-across material citronellal (CAS

106-23-0), 2,6-dimethyl-5-heptenal is considered a skin sensitizer with a defined No Expected Sensitization Induction Level (NESIL) of 7000 μg/cm^2.

11.1.4.1. Risk assessment. Based on the available data, 2,6-dimethyl-5-heptenal is a skin sensitizer. However, no sufficient human data are available to confirm the NESIL in humans. Therefore, citronellal was used as a read-across (CAS # 106-23-0; see Section VI). The chemical structure of these materials indicates that they would be expected to react directly with skin proteins (Toxtree v3.1.0; OECD Toolbox v4.2). *In vitro*, 2,6-dimethyl-5-heptenal was not predicted to be a sensitizer in a direct peptide reactivity assay (DPRA), while it was predicted to be a sensitizer in a KeratinoSens assay (ECHA, 2017a). The read-across material citronellal was not predicted to be a sensitizer in a DPRA, while it was predicted to be a sensitizer in a KeratinoSens assay and a human cell line activation test (h-CLAT) (RIFM, 2016b; RIFM, 2020c; RIFM, 2016c). A murine local lymph node assay (LLNA) on 2,6-dimethyl-5-heptenal indicated that it is a sensitizer with an EC3 of 34% (8500 μg/cm^2) (ECHA, 2017a). The read-across material, citronellal, was not found to be sensitizing when tested up to 30% (7500 μg/cm^2) in an LLNA (RIFM, 2004). Citronellal was found to be sensitizing in guinea pig sensitization studies, including guinea pig maximization tests and Buehler tests (RIFM, 1977; Basketter, 1996). In a Confirmation of No Induction in Humans test (CNIH), no skin sensitization was observed in 110 subjects when 6% (7086 μg/cm^2) citronellal in 1:3 ethanol:diethyl phthalate (EtOH:DEP) was used for induction and challenge (RIFM, 2014). In addition, in 2 human maximization tests with 22 subjects in each test, 2, 6-dimethyl-5heptenal did not induce skin sensitization when tested at 4% and 5%, respectively (RIFM, 1981; RIFM, 1974). In another human maximization test with 4% of the read-across material, no sensitization was observed in 25 subjects (RIFM, 1973).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies 2,6-dimethyl-5-heptenal is a sensitizer with a WoE NESIL of 7000 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, 2020b) and a sub-chronic RfD of 0.37 mg/kg/day.

Additional References: Marzulli (1980); Klecak (1977); Ishihara (1986); Robinson et al. (1990); Kashima (1993a); Kashima et al. (1993b); Basketter (1996); Coutant (1999); Klecak (1985).

Literature Search and Risk Assessment Completed On: 02/04/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2,6-dimethyl-5-heptenal would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2,6-dimethyl-5-heptenal in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 2,6-dimethyl-5-heptenal does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no 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: 02/09/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2,6-dimethyl-5-heptenal is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2,6-dimethyl-5-heptenal. Based on the Creme RIFM Model, the inhalation exposure is 0.016 mg/day. This exposure is 87.5 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2,6-dimethyl-5-heptenal 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, 2,6-dimethyl-5-heptenal 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 2,6-dimethyl-5-heptenal 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).

Table 1
Data summary for citronellal as read-across for 2,6-dimethyl-5-heptenal.

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
>7500 [1]	Weak	7086	2760	NA	7000

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.

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.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 2,6-dimethyl-5-heptenal presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 2012:** The ready biodegradability of 2,6-dimethyl-5-heptenal was evaluated using the Manometric Respirometry test according to the OECD 301F method. After 28 days, biodegradation of 75% was observed.

RIFM, 2000b: In a modified manometric respirometry test according to the OECD 301F guideline, 2,6-dimethyl-5-heptenal underwent 72% biodegradation after 39 days and 68% biodegradation after 28 days under the test conditions.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 2,6-Dimethyl-5-heptenal has been registered for REACH, with the following additional data available at this time (ECHA, 2017a):

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under semi-static conditions. The 48-h EC50 value based on a time-weighted average concentration was reported to be 2.4 mg/L (95% CI: 0.53–10.4 mg/L).

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 Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.4	3.4
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	100–1000
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 0.22 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 VoU.

Literature Search and Risk Assessment Completed On: 01/05/21.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	11.45			1000000	0.01145	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	2.288	2.200	4.247	10000	0.22	Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2)** v1.11	13.42	8.36	9.29			Neutral Organic SAR (Baseline toxicity)

- **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 11/15/21.

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.2022.112965.

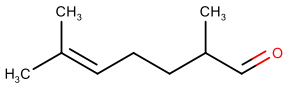
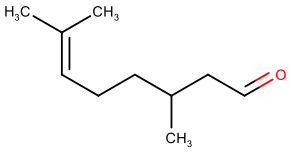
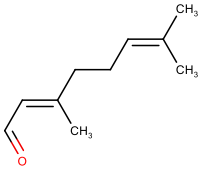
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017b).

- 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, oncologic classification, ER binding, and repeat dose categorization predictions 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).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	2,6-Dimethyl-5-heptenal	Citronellal	Citral
CAS No.	106-72-9	106-23-0	5392-40-5
Structure			
Similarity (Tanimoto Score)		0.76	0.49
Endpoint		• Genotoxicity • Skin sensitization	• Fertility
Molecular Formula	$C_9H_{16}O$	$C_{10}H_{18}O$	$C_{10}H_{16}O$
Molecular Weight (g/mol)	140.226	154.253	152.237
Melting Point (°C, EPI Suite)	−39.84	−28.33	−26.74
Boiling Point (°C, EPI Suite)	184.94	207.00	227.00

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.01E+02	3.39E+01	1.22E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.12E+02	3.89E+01	1.34E+03
Log K_{OW}	3.04	3.83	3.45
J_{max} (μg/cm^2/h, SAM)	22.07	5.87	164.13
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	5.19E+01	6.88E+01	3.81E+01
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	Schiff base formers|Schiff base formers ≫ Direct-acting Schiff Base Formers|Schiff base formers ≫ Direct-acting Schiff Base Formers ≫ Mono aldehydes	Schiff base formers|Schiff base formers ≫ Direct-acting Schiff Base Formers|Schiff base formers ≫ Direct-acting Schiff Base Formers ≫ Mono aldehydes	
Carcinogenicity (ISS)	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	Simple aldehyde	Simple aldehyde	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	Simple aldehyde	Simple aldehyde	
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds	
Fertility			
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)
Skin Sensitization			
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	
Protein Binding (OECD)	Schiff Base Formers|Schiff Base Formers ≫ Direct-acting Schiff Base Formers|Schiff Base Formers ≫ Direct-acting Schiff Base Formers ≫ Mono-carbonyls	Schiff Base Formers|Schiff Base Formers ≫ Direct-acting Schiff Base Formers|Schiff Base Formers ≫ Direct-acting Schiff Base Formers ≫ Mono-carbonyls	
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff-base formation identified.	Alert for Schiff-base formation identified.	
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There is insufficient toxicity data on 2,6-dimethyl-5-heptenal (CAS # 106-72-9). Hence *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, citronellal (CAS # 106-23-0) and citral (CAS # 5392-40-5) were identified as read-across materials with data for their respective toxicity endpoints.

Conclusion

- Citral (CAS # 5392-40-5) was used as a read-across analog for the target material 2,6-dimethyl-5-heptenal (CAS # 106-72-9) for the fertility endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aldehyde.
  - o The target material and the read-across analog have the heptanal fragment common among them.
  - o The 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 target material and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant for the respiratory endpoint.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for the respiratory endpoint are consistent between the target material and the read-across analog.

- o According to the metabolic simulator, the read-across is expected to undergo metabolism and form a Schiff base at the activated aldehyde group. The target material will not have similar metabolism as seen for the read-across analog.
- o The structural alerts for the respiratory endpoint are consistent between the metabolites of the read-across analog and the target material.
- o The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant.

- Citronellal (CAS # 106-23-0) was used as a read-across analog for the target material 2,6-dimethyl-5-heptenal (CAS # 106-72-9) for the genotoxicity and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The target material and the read-across analog have the heptanal fragment common among them.
  - o The key difference between the target material and the read-across analog is that the read-across is an α-β unsaturated aldehyde with β-methyl substitution. The target does not have α-β unsaturation to the aldehyde group. Because of the β-methyl substitution, the aldehyde functionality of the target material and the read-across analog are equivalent.
  - o The 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 target material and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant for the skin sensitization endpoint.
  - o According to the QSAR OECD Toolbox (v4.2), structural alerts for skin sensitization endpoint are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have an alert for Schiff base formation and direct-acting agent. The data on the read-across analog confirms that the substance is a sensitizer. Therefore, the *in silico* alerts are consistent with the data.
  - 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 skin sensitization endpoint are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant.

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