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Short Review

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

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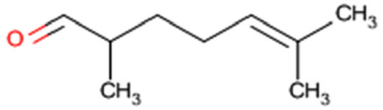

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Abbreviation/Definition list:

2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile – The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF – Assessment Factor
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
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
RIFM – Research Institute for Fragrance Materials
RQ – Risk Quotient
TTC – Threshold of Toxicological Concern
UV/Vis Spectra – Ultra Violet/Visible spectra
VCF – Volatile Compounds in Food
VoU – Volume of Use
vPvB – (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on RIFM's Criteria Document (Api et al., 2014) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
* RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as environmental assessment. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 37 mg/kg/day, based on a dietary 90-day subchronic toxicity study conducted in rats, that resulted in an MOE of 4744 assuming 100% absorption from skin contact and inhalation. An MOE of >100 is deemed acceptable.

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 2006; Wild et al., 1983)
Repeated Dose Toxicity: NOAEL = 37 mg/kg/day (Gaunt et al., 1983)
Developmental and Reproductive Toxicity: NOAEL = 300 mg/kg/day (RIFM, 1990a)
Skin Sensitization: Not sensitizing (RIFM, 1974; RIFM, 1978a; RIFM, 1981)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (RIFM Database)
Local Respiratory Toxicity: NOAEC = 34 ppm or 211.7 mg/m^3 (0.212 mg/L) (Gaworski et al., 1993)

Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 75% (OECD 301F) (RIFM, 2012)
Bioaccumulation: Screening Level: 47.0 L/Kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: 48 hr *Daphnia Magna* EC50: 2.2 mg/l (ECOSAR ver 1.11)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-Level: PEC/PNEC (North America and Europe) >1 (Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48 hr Daphnia Magna EC50: 2.2 mg/l (ECOSAR ver 1.11)
RIFM PNEC is: 0.22 μg/L
- Revised PEC/PNECs (2011 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, 2,6-Dimethyl-5-heptenal, 5-Heptenal, 2,6-dimethyl-, Melonal, 2,6-Dimethylhept-5-enal
4 **Molecular Formula:** $C_9H_{16}O$

5 **Molecular Weight:** 140.23
6 **RIFM Number:** 504

2. Physical data

1 **Boiling Point:** 65 °C @ 10 mm Hg (IFRA), 184.94 °C (EPI Suite 4.0)
2 **Flash Point:** 133 (IFRA), 60-61°C (measured)
3 **Log K_{ow}:** log P_{ow} = 3.4 (RIFM, 2000a), 3.04 (EPI Suite 4.0)
4 **Melting Point**: –39.84 °C (EPI Suite 4.0)
5 **Water Solubility:** 212 mg/L (EPI Suite 4.0)
6 **Specific Gravity:** 0.850–0.858 (IFRA), 0.848–0.856 (IFRA)
7 **Vapor Pressure:** 0.524 mmHg @ 20 °C (EPI Suite 4.0), 0.4 mm Hg 20C (IFRA), 0.759 mm Hg @ 25 °C (EPI Suite 4.0)
8 **UV Spectra:** not available
9 **Appearance/Organoleptic:** A clear, yellow liquid having a characteristic odor of melon.

3. Exposure

1 **Volume of Use (worldwide band):** <1000 metric tons per year (IFRA, 2011)
2 **Average Maximum Concentration in Hydroalcoholics:** 0.29% (IFRA, 2008)
3 **97.5th Percentile:** 0.29% (IFRA, 2008)
4 **Dermal Exposure*:** 0.0073 mg/kg/day (IFRA, 2008)
5 **Oral Exposure:** Not available
6 **Inhalation Exposures**:** 0.00045 mg/kg/day (IFRA, 2008)
7 **Total Systemic Exposure (Dermal + Inhalation):** 0.0078 mg/kg/day

* Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., antiperspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

** Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1 **Dermal:** Assumed 100%
2 **Oral:** Data not available – not considered.
3 **Inhalation:** Assumed 100%
4 **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.0078 mg/kg/day

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2 **Analogs Selected:**
- a. **Genotoxicity:** None
- b. **Repeated Dose Toxicity:** None
- c. **Developmental and Reproductive Toxicity:** Citral (CAS # 5392-40-5)
- d. **Skin Sensitization:** 2,6,10-trimethylundeca-5,9-dienal [dihydroapofarnesal], CAS# 24048-13-3
- e. **Phototoxicity/Photoallergenicity:** 2,6,10-trimethylundeca-5,9-dienal [dihydroapofarnesal], (CAS# 24048-13-3)
- f. **Local Respiratory Toxicity:** Citral (CAS# 5392-40-5)
- g. **Environmental Toxicity:** None

3 **Read-across justifications:** See Appendix 1 below

6. Metabolism

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

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

2,6-Dimethyl-5-heptenal is reported to occur in food* and as a component in some natural complex substances (NCS):

Citrus fruits
Ginger (zingiber officinale rosc.)
Lemon peel oil (citrus limon burm. F.)
Lime oil (coldpressed)
Sudachi oil (Citrus sudachi Hort. ex Shirai)

* 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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-Registered for 2010; No dossier available as of 12/13/13.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 2,6-dimethyl-5-heptenal does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic potential of the 2,6-dimethyl-5-heptenal was assessed in a bacterial reverse mutation assay performed in compliance with GLP regulations and in accordance with OECD TG (RIFM, 2006). Under the conditions of the study 2,6-dimethyl-5-heptenal was considered not mutagenic.

The clastogenic potential of 2,6-dimethyl-5-heptenal was assessed in an *in vivo* micronucleus test in which groups of male and female NMRI mice were dosed once at 3–4 dose levels up to a maximum of 1540 mg/kg b.w. in olive oil (Wild et al., 1983). Under the conditions of the study, 2,6-dimethyl-5-heptenal was considered non-clastogenic.

Taken together, 2,6-dimethyl-5-heptenal does not present a concern for genotoxic potential.

Additional References: Heck et al., 1989.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. The repeated dose toxicity data on 2,6-dimethyl-5-heptenal are sufficient for the repeated dose toxicity endpoint. A dietary 90-day subchronic toxicity study conducted in rats determined the NOAEL to be 37 mg/kg/day, based on kidney and liver effects (Gaunt et al., 1983). Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 37/0.0078 or 4744.

Additional References: RIFM, 1990b; Abramovici, 1972; Forschmidt et al., 1979; Abramovici et al., 1983; Howes et al., 2002; Ishida et al., 1989; Songkro et al., 2003; Meyer, 1965; Meyer et al., 1959; Gaworski et al., 1993; Ress et al., 2003; National Toxocology Program, 2003; Gaworski et al., 1992; York et al., 1989; Nogueira et al., 1995; Hoberman et al., 1989; Jackson et al., 1987; Dieter et al., 1993; Hagan et al., 1967; Bär et al., 1967; Abramovici et al., 1983; Sandbank et al., 1988; Abramovici et al., 1985; RIFM, 1958; Leach et al., 1956; Shillinger, 1950; Abramovici et al., 1980; Toaff et al., 1979; Geldof et al., 1992; Servadio et al., 1985; Servadio et al., 1986; Servadio et al., 1987; Abramovici et al., 1986; Scolnik et al., 1994a; Scolnik et al., 1994b; Engelstein et al., 1996; Kessler et al., 1998; Golomb et al., 2001; Diliberto et al., 1988a; Diliberto et al., 1990; Diliberto et al., 1989; Diliberto et al., 1988b; Boyer et al., 1990; Phillips et al., 1976; Barbier & Benezra, 1982.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 2,6-dimethyl-5-heptenal is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. The developmental toxicity data on 2,6-dimethyl-5-heptenal are sufficient for the developmental toxicity endpoint. A gavage developmental and reproductive toxicity screening study conducted in rats with 2,6-dimethyl-5-heptenal determined the developmental NOAEL to be 300 mg/kg/day, based on reduced pup weights and viability (RIFM, 1990a). These effects were observed at dosages that were maternally toxic. Therefore, the MOE for developmental toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.0078 or 38,462.

The reproductive toxicity data on 2,6-dimethyl-5-heptenal are insufficient for the reproductive toxicity endpoint. The 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 feed consumption (RIFM, 1990a). There are no male reproductive data on 2,6-dimethyl-5-heptenal. Read across material citral (CAS # 5392-40-5; see Section 5) has an OECD 421 gavage reproduction toxicity screening test conducted in rats which determined the NOAEL for reproductive toxicity of the parental generation males and females to be 1000 mg/kg/day, the highest dosage tested (RIFM, 1996). The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE for reproductive toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 300/0.0078 or 38,462.

Additional References: RIFM, 1990b; Abramovici, 1972; Forschmidt et al., 1979; Abramovici et al., 1983; Howes et al., 2002; Ishida et al., 1989; Songkro et al., 2003; Meyer, 1965; Meyer et al., 1959; Gaworski et al., 1993; Ress et al., 2003; National Toxocology Program, 2003; Gaworski et al., 1992; York et al., 1989; Nogueira et al., 1995; Hoberman et al., 1989; Jackson et al., 1987; Dieter et al., 1993; Hagan et al., 1967; Bär et al., 1967; Abramovici et al., 1983; Sandbank et al., 1988; Abramovici et al., 1985; RIFM, 1958; Leach et al., 1956; Shillinger, 1950; Abramovici et al., 1980; Toaff et al., 1979; Geldof et al., 1992; Servadio et al., 1985; Servadio et al., 1986; Servadio et al., 1987; Abramovici et al., 1986; Scolnik et al., 1994a; Scolnik et al., 1994b; Engelstein et al., 1996; Kessler et al., 1998; Golomb et al., 2001; Diliberto et al., 1988a; Diliberto et al., 1990; Diliberto et al., 1989; Diliberto et al., 1988b; Boyer et al., 1990; Phillips et al., 1976; Barbier & Benezra, 1982 http://rifmdatabase.rifm.org/RifmDatabase/Studies/5002.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.4. Skin sensitization

Based on the available data for the read across analog 2,6,10-trimethylundeca-5,9-dienal [dihydroapofarnesal] (CAS# 24048-13-3) and material specific data, 2,6-dimethyl-5-heptenal does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the available data for the read across analog 2,6,10-trimethylundeca-5,9-dienal [dihydroapofarnesal] (CAS# 24048-13-3; see Section 5) and material specific data, 2,6-dimethyl-5-heptenal does not present a concern for skin sensitization. Based on the chemical structure of these materials they are expected to react directly with skin proteins (Roberts et al., 2007, Toxtree 2.5.0; OECD toolbox v3.1). However, in a Buehler guinea pig test, no results indicative of sensitization were observed with the read across material (RIFM, 1978a http://rifmdatabase.rifm.org/RifmDatabase/Studies/37736). Furthermore, no reactions indicative of skin sensitization were observed in human maximization tests conducted with 2,6-dimethyl-5-heptenal (RIFM, 1974, 1981).

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.5. Phototoxicity/photoallergenicity

Based on the UV spectra for the read across analog 2,6,10-trimethylundeca-5,9-dienal [dihydroapofarnesal] (CAS# 24048-13-3), 2,6-dimethyl-5-heptenal does not present a concern for phototoxicity.

10.1.5.1. Risk assessment. Based on the UV spectra for the read across analog 2,6,10-trimethylundeca-5,9-dienal [dihydroapofarnesal] (CAS# 24048-13-3; see Section 5), 2,6-dimethyl-5-heptenal does not present a concern for phototoxicity. The available UV absorption spectrum for the analog demonstrate that this material would not significantly absorb in the region of 290–700 nm and therefore is not expected to present a concern for phototoxicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.1.6. Local respiratory toxicity

The margin of exposure is adequate for the respiratory endpoint at the current level of use.

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. There are no inhalation data available on 2,6-dimethyl-5-heptenal. Read across material citral (CAS# 5392-40-5; see Section 5) has an inhalation developmental toxicity study conducted in rats which only stated that maternal toxicity was observed at 68 ppm, but did not evaluate local respiratory tract effects following exposure (Gaworski et al., 1992). In an inhalation 21-day repeated dose toxicity study conducted in rats breathing effects and nasal discharge were noted at 68 ppm, thus a NOAEC of 34 ppm or 211 mg/m^3 for citral by vapor inhalation was determined (Gaworski et al., 1993).

This latter NOAEC expressed in mg/kg lung weight/day is:

- (211 mg/m3) (1m3/1000 L) = 0.211 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat × duration of exposure of 360 minutes per day (min/day) (according to GLP study guidelines) = 61.2 L/d
- (0.211 mg/L) (61.2 L/d) = 12.91 mg/d

- (12.91 mg/d) / (0.0016 kg lung weight of rat*) = 8068.75 mg/kg lw/day

Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile of fragrance ingredient in fragrance oil was reported to be 0.29%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.027 mg/day as calculated based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual using RIFM's 2-Box/MPPD in silico models. To compare this estimated exposure with the Gaworski NOAEC expressed in mg/kg lung weight/day this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.041 mg/kg lung weight/day resulting in an MOE of 196798 (i.e., [8068.75 mg/kg lw/day]/[0.041 mg/kg lung weight/day]).

Additionally, the calculated exposure of 0.027 mg/day is below the Cramer Class I TTC level of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009) and is deemed safe for use at the reported level of 0.29% in all product types as indicated above.

Since the exposure is below the TTC and the read across analog MOE is significantly greater than 100, without the adjustment for specific uncertainty factors related to inter-species and intra-species variation, the exposure to 2,6-dimethyl-5-heptenal by inhalation at 0.29% in a combination of the products noted above is deemed to be safe under the most conservative consumer exposure scenario.

* Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2nd Ed. 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy", subsection, "Comparative Airway Anatomy."

Additional References: RIFM, 1978b; York et al., 1989; Boyd et al., 1970; Cattarelli et al., 1977; RIFM, 1997; Buchbauer et al., 1993; Komori et al., 1995; Ellis et al., 1997; Rice et al., 1994.

Literature Search and Risk Assessment Completed on: 01/31/14.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 2,6-dimethyl-5-heptenal was performed following the RIFM Environmental Framework (Salvito et al., 2002) that provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Following the RIFM Environmental Framework 2,6-dimethyl-5-heptenal was identified as a fragrance material with potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC >1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify 2,6-dimethyl-5-heptenal as persistent or bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver 4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current VoU (2011), 2,6-dimethyl-5-heptenal presents a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. 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 a biodegradation of 75% was observed (RIFM, 2012).

In a modified Manometric Respirometry Test 2,6-dimethyl-5-heptenal underwent 72% biodegradation after 39 days and 68% biodegradation after 28 days under the test conditions (RIFM, 2000b).

Ecotoxicity: No data available.

Other available data: 2,6-Dimethyl-5-heptenal has been pre-registered for REACH with no additional data at this time.

10.2.3. 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.

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)**	11.45 mg/l			1,000,000	0.01145 µg/l	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.288 mg/l	2.2 mg/l	4.247 mg/l	10,000	0.22 µg/l	Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	13.42 mg/l	8.36 mg/l	9.29 mg/l			Neutral Organic SAR (Baseline toxicity)

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

Exposure	Europe	North America
Log K_{ow} used	3.4	
Biodegradation Factor Used	1	
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	10–100
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.22 µg/L. The revised PEC/PNECs for EU and NA <1 and, therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 01/31/14.

11. Literature search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed

- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

* Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

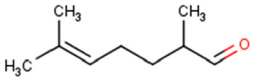
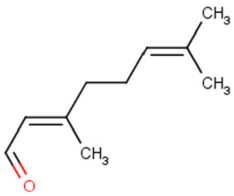
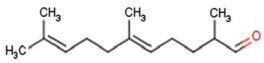
Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

Appendix 1

	Target Material	Read across Material	
Principal Name	2,6-Dimethyl-5-heptenal	Citral	2,6,10-Trimethylundeca-5,9-dienal (dihydroapofarnesal)
CAS No.	106-72-9	5392-40-5	24048-13-3
Structure			
3D Structure	http://www.thegoodscentscompany.com/opl/106-72-9.html	http://www.thegoodscentscompany.com/opl/5392-40-5.html	http://www.thegoodscentscompany.com/opl/24048-13-3.html
Read-across endpoint		Devel/Repro Respiratory	Skin sensitization Phototox
Molecular Formula	C9H16O	C10H16O	C14H24O
Molecular Weight	140.23	152.24	208.35
Melting Point (°C, EPISUITE)	–39.84	–26.74	5.72
Boiling Point (°C, EPISUITE)	184.94	217.44	277.12
Vapor Pressure (Pa @ 25 °C, EPISUITE)	101.2	12.17	0.8319
Log K_{ow} (KOWWIN v1.68 in EPISUITE)	3.04	3.45	5.34
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	212	84.71	1.099
J_{max} (mg/cm^2/h, SAM)	76.37242181	75.58388321	3.797278984
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	51.858135	38.108332	222.003075
Similarity (Tanimoto score) [a]		60%	82%
Developmental and Reproductive Toxicity			
ER binding (OECD)	Non binder, non-cyclic structure	Non binder, non-cyclic structure	
Developmental toxicity model (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 (OECD)	• 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 model (CAESAR v2.1.6)	Sensitizer (good reliability)		Sensitizer (good reliability)
Metabolism			
Rat liver S9 metabolism simulator (OECD)	See supplemental data 1	See supplemental data 2	See supplemental data 3

[a] Values calculated using OpenBabel with FP2 fingerprint (O'Boyle et al., 2011).

Summary

There are insufficient toxicity data on 2,6-Dimethyl-5-heptenal (CAS # 106-72-9). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across analogs for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- ER binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/rationale

- Citral (analog) was used as a read-across for 2,6-Dimethyl-5-heptenal (target) based on the following:
  - The target and analog both belong to the generic class of aldehydes, specifically, aldehydes/branched chain/unsaturated.
  - Both have the common substructure of isoprene units and aldehyde function groups.
  - The key differences are that the analog has a longer chain length and an α,β unsaturated aldehyde group. It makes the analog more reactive than the target.
  - They both show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - Both materials are expected to be metabolized similarly. As per the OECD Toolbox both materials are predicted to have similar metabolites.
- 2,6,10-Trimethylundeca-5,9-dienal (dihydroapofarnesal) (analog) was used as a read-across for 2,6-Dimethyl-5-heptenal (target) based on the following:
  - The target and analog both belong to the generic class of aldehydes, specifically, aldehydes/branched chain/unsaturated.
  - Both have the common substructure of isoprene units and aldehyde function groups.
  - The only difference is that the analog has two isoprene units while the target has only one. The differences between structures and physicochemical properties do not essentially change the reactivity nor raise any additional structural alerts and therefore, the skin sensitization profiles are expected to be similar.
  - They both show similar alerts for protein binding.
  - Both materials are expected to be metabolized similarly. As per the OECD Toolbox both the materials are predicted to have similar metabolites.

Appendix 2: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.fct.2015.01.007.

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