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RIFM fragrance ingredient safety assessment, 6-methyl-5-hepten-2-one, CAS registry number 110-93-0

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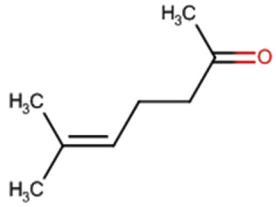

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Name: 6-Methyl-5-hepten-2-one
CAS Registry Number: 110-93-0
Additional CAS Numbers:
409-02-9 Methylheptenone (isomer unspecified)
*Included because the materials are isomers

Abbreviation/Definition List:

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(*continued*)

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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
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 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
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.

6-Methyl-5-hepten-2-one was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 6-methyl-5-hepten-2-one is not genotoxic. Data on 6-methyl-5-hepten-2-one provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog 3,5,6,6-tetramethyl-4-methyleneheptan-2-one (CAS # 81786-75-6) provide 6-methyl-5-hepten-2-one a No Expected Sensitization Induction Level (NESIL) of 4400 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on (ultraviolet/visible) UV/Vis spectra; 6-methyl-5-hepten-2-one is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 6-methyl-5-hepten-2-one is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 6-methyl-5-hepten-2-one 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 genotoxic. (ECHA REACH Dossier: 6-Methyl-5-hepten-2-one; ECHA, 2013a)

Repeated Dose Toxicity: NOAEL = 50 mg/kg/day. RIFM (2002a)

Reproductive Toxicity: Developmental toxicity: NOAEL = 200 mg/kg/day. Fertility: NOAEL = 200 mg/kg/day. (RIFM, 2002b; RIFM, 2002a)

Skin Sensitization: NESIL = 4400 μg/cm^2. RIFM (2012a)

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: 89% (301F) for CAS # 110-93-0 RIFM (1998)

Bioaccumulation:
Screening-level: 13.56 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: 96-h Algae EC50: 39.742 mg/L for CAS # 110-93-0 (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: 96-h Algae EC50: 39.742 mg/L for CAS # 110-93-0 (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 3.9742 μg/L

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

1. Identification

Chemical Name: 6-Methyl-5-hepten-2-one	Chemical Name: Methylheptenone (isomer unspecified)
CAS Registry Number: 110-93-0	**CAS Registry Number:** 409-02-9
Synonyms: 5-Hepten-2-one, 6-methyl; 2-Methyl-2-hepten-6-one; Methyl heptenone; 6 - メチル - 5 - ヘプテン - 2 - オン; 6-ﾒﾁﾙ-5-ﾍﾌﾟﾃﾝ-2-ｵﾝ; 6-Methylhept-5-en-2-one; 6-Methyl-5-hepten-2-one	**Synonyms:** 6-Methylhept-5-en-2-one; Heptenone, methyl- (isomer unspecified); Methylheptenone (isomer unspecified)
Molecular Formula: $C_8H_{14}O$	**Molecular Formula:** $C_8H_{14}O$
Molecular Weight: 126.19	**Molecular Weight:** 126.19
RIFM Number: 303	**RIFM Number:** 5171
Stereochemistry: No stereocenter present and no stereoisomer possible.	**Isomerism:** Structural isomer not specified.

2. Physical data

CAS # 110-93-0	CAS # 409-02-9
Boiling Point: 174 °C (Fragrance Materials Association [FMA]), 164.35 °C (EPI Suite)	**Boiling Point:** 157.22 °C (EPI Suite)

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CAS # 110-93-0	CAS # 409-02-9
Flash Point: 50 °C (Globally Harmonized System [GHS]), 123 °F; CC (FMA)	**Flash Point:** 52 °C (GHS)
Log K_{OW}: 1.82 (Biobyte Corp.), log Pow = 2.4 (Givaudan, 1998v), 2.06 (EPI Suite)	**Log K_{OW}:** 2.22 (EPI Suite)
Melting Point: −40.02 °C (EPI Suite)	**Melting Point:** −42.63 °C (EPI Suite)
Water Solubility: 1651 mg/L (EPI Suite)	**Water Solubility:** 1208 mg/L (EPI Suite)
Specific Gravity: 0.850 (FMA)	**Specific Gravity:** Not available
Vapor Pressure: 1.27 mm Hg at 20 °C (EPI Suite v4.0), 0.6 mm Hg at 20 °C (FMA), 1.78 mm Hg at 25 °C (EPI Suite)	**Vapor Pressure:** 2.71 mm Hg at 20 °C (EPI Suite v4.0), 3.72 mm Hg at 20 °C (EPI Suite)
UV Spectra: Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})	**UV Spectra:** N/A
Appearance/Organoleptic: Colorless, mobile, oily liquid. Oily-green, pungent-herbaceous, grassy, and diffusive odor with fresh and green-fruity notes and moderate to poor tenacity. In extreme dilution (below 5 ppm), it has a fruity, green-banana-like, or unripe berry-like taste. Higher dilutions produce harsh and pungent notes (Arctander, 1969)	**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:** 0.0021% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.000052 mg/kg/day or 0.0037 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.00022 mg/kg/day (RIFM, 2017)

*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).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in Hydroalcoholics or 97.5th percentile, inhalation exposure, and total exposure.

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer classification

Class II, Intermediate* (Expert Judgment)

Expert Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
II	I	I

*Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978). See the Appendix below for further details.

6.2. Analogs selected

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 3,5,6,6-Tetramethyl-4-methyleneheptan-2-one (CAS # 81786-75-6)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. Read-across Justification

See Appendix below

7. Metabolism

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

8. Natural occurrence

6-Methyl-5-hepten-2-one is reported to occur in the following foods by the VCF*:
Annatto (*Bixa orellana* L.)
Apricot (*Prunus armeniaca* L.)
Cheese, various types.
Ginger (*Zingiber* species).
Guava and feyoa.
Lemongrass oil (*Cymbopogon*).
Mastic (*Pistacia lentiscus*).
Papaya (*Carica papaya* L.)
Strawberry (*Fragaria* species).
Tea.

Methylheptenone (isomer unspecified) is reported to occur in the following foods by the VCF*:
Cardamom (*Elettaria cardamomum* Maton.)
Citrus fruits.
Ginger (*Zingiber* species).
Guava and feyoa.
Katsuobushi (dried bonito).
Pepper (*Piper nigrum* L.)
Rice (*Oryza sativa* L.)
Thyme (*Thymus* species).
Tomato (*Lycopersicon esculentum* Mill.)
Wine.

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data. This is a partial list.

9. REACH dossier

Dossier available for 6-methyl-5-hepten-2-one, accessed 09/23/19 (ECHA, 2013a); methylheptenone (isomer unspecified) is pre-registered for 2010 with no dossier available as of 09/23/19.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 6-methyl-5-hepten-2-one 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)	0.34
2	Products applied to the axillae	0.10
3	Products applied to the face/body using fingertips	0.33
4	Products related to fine fragrances	0.82
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.48
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.041
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.12
5D	Baby cream, oil, talc	0.014
6	Products with oral and lip exposure	0.77
7	Products applied to the hair with some hand contact	0.16
8	Products with significant ano-genital exposure (tampon)	0.014
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.65
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.3
10B	Aerosol air freshener	2.2
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.014
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

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 6-methyl-5-hepten-2-one, the basis was the reference dose of 0.50 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 4400 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, 6-methyl-5-hepten-2-one does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 6-methyl-5-hepten-2-one 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 methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 6-methyl-5-hepten-2-one 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 (ECHA, 2013a). Under the conditions of the study, 6-methyl-5-hepten-2-one was not mutagenic in the Ames test.

The clastogenic activity of 6-methyl-5-hepten-2-one was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in olive oil via the intraperitoneal route to groups of male NMRI mice. Doses of 200, 400, and 800 mg/kg body weight were administered. Mice from each dose level were euthanized, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2013a). Under the conditions of the study, 6-methyl-5--hepten-2-one was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 6-methyl-5-hepten-2-one does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/28/21.

11.1.2. Repeated dose toxicity

The MOE for 6-methyl-5-hepten-2-one 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 6-methyl-5-hepten-2-one. An OECD 408/GLP oral gavage 90-day subchronic study was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered 6-methylhept-5-en-2-one (Methylheptenon) via oral gavage at doses of 0, 50, 200, or 1000 mg/kg/day in olive oil for 13 weeks. At 1000 mg/kg/day, there was a statistically significant reduction in food consumption (up to 13%) in females from days 28–49. The body weight of high-dose males was decreased throughout the study period, with a maximum decrease of 7.2% on day 91. The body weight change of these high-dose males also decreased continuously, though it did not reach statistical significance. Body weight in high-dose females was statistically significantly decreased (6.7%) on day 63 only, whereas the bodyweight change in females of this dose group was statistically significantly decreased (up to 16.4%) from day 35 to day 84, with the exception of day 70. There was a statistically significant decrease in food efficiency among high-dose males on days 21, 35, 63, and 77. High-dose animals were reported to have increased platelet counts, increased plasma levels of calcium, total protein, albumin and cholesterol, and a decrease in plasma aspartate aminotransferase levels. There were increases in alkaline phosphatase, cloudy urine specimens, urinary blood, renal tubular, epithelial cells, degenerated transitional epithelial cells, granular casts, and epithelial cell casts in high-dose males. Furthermore, increased inorganic phosphate, urea, total bilirubin, globulins and magnesium, and a decrease in chloride levels were observed in high-dose females. There was a dose-related statistically significant increase in the absolute and relative kidney weight in males of the high-dose (absolute: 28.0%; relative: 38.7%), mid-dose (absolute: 16.5%; relative: 16.3%), and low-dose groups (absolute: 14.3%; relative: 11.6%) and in females of the high-dose group (absolute: 14.3%; relative: 21.6%). There was a statistically significant increase in the absolute (males: 29.6%; females: 21.9%) and relative (male: 40.7%; females: 29.7%) liver weights among both sexes of the high-dose group. Centrilobular hypertrophy of liver cells was observed in all animals of the high-dose group. At 200 mg/kg/day, increased calcium, total protein, albumin, and cholesterol levels in males and increased platelet counts in females were observed. The increased kidney weights in all treated males corresponded to an

increased accumulation of α-2u-globulin in the renal cortex of all-male rats (confirmed with Mallory-Heidenhain stain). These kidney changes were consistent with documented changes of α-2u-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman, 1992; Lehman-McKeeman, 1990). Under the conditions of the study, the NOAEL was considered to be 50 mg/kg/day, based on increased platelet counts among mid-dose females and high-dose animals as well as decreased body weights among high-dose animals (RIFM, 2002a).

Therefore, the 6-methyl-5-hepten-2-one MOE for the repeated dose toxicity endpoint can be calculated by dividing the 6-methylhept-5-en-2-one NOAEL in mg/kg/day by the total systemic exposure to 6-methylhept-5-en-2-one, 50/0.00022, or 227272.

In addition, the total systemic exposure to 6-methyl-5-hepten-2-one (0.22 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.

11.1.2.1.1. 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 0.5 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 6-methyl-5-hepten-2-one was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 50 mg/kg/day by the uncertainty factor, 100 = 0.5 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/29/21.

11.1.3. Reproductive toxicity

The MOE for 6-methyl-5-hepten-2-one is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. An OECD 414/GLP oral gavage prenatal developmental toxicity study was conducted in Wistar rats. Groups of 25 time-mated female rats/dose were administered 6-methylhept-5-en-2-one (methylheptenon) via oral gavage at doses of 0, 50, 200, or 1000 mg/kg/day in olive oil on days 6–19 post coitum. At 1000 mg/kg/day, there was a statistically significant decrease in food consumption (7%) when compared to the control group. A statistically significant reduction in bodyweight gain was also observed in the high-dose group animals (14%) when compared to the control group for days 6–19 post coitum, along with a statistically significant decrease in the corrected bodyweight gain (29% below the controls). The placental and fetal body weights were statistically significantly decreased (13% and 9% below the controls, respectively). The rates of fetuses/litters with certain skeletal variations (i.e., delays in the ossification of parts of the skull, vertebral column, and sternum) were significantly increased for the high-dose group dams. There were signs of maternal toxicity at 1000 mg/kg/day, predominantly substantiated by adverse clinical findings (i.e., transient occurrences of abdominal position, unsteady gait, and/or ataxia) and statistically significant impairments in food consumption and bodyweight gains. However, there were no treatment-related adverse effects on the gestational parameters up to the highest dose level. Conception rate, the mean number of corpora lutea, total implantations, resorptions, live fetuses, fetal sex ratio, or pre- and post-implantation losses were not affected by treatment. The mean placental and fetal body weights were statistically significantly reduced (13% and 9% below the controls, respectively). Correspondingly, the rates for certain skeletal variations were statistically significantly increased and outside historical control ranges. Thus, the NOAEL for maternal and prenatal developmental toxicity was considered to be 200 mg/kg/day, based on decreased placental and fetal body weights and increased skeletal variations observed at the highest dose group (RIFM, 2002b). **Therefore, the 6-methyl-5-hepten-2-one MOE for the developmental toxicity endpoint can be calculated by dividing the 6-methylhept-5-en-2-one NOAEL in mg/kg/day by the total systemic exposure to 6-methyl-5-hepten-2-one, 200/0.00022, or 909091.**

An OECD 408/GLP oral gavage 90-day subchronic study was conducted in Wistar rats. Groups of 10 rats/sex/dose were administered 6-methylhept-5-en-2-one (Methylheptenon) via oral gavage at doses of 0, 50, 200, or 1000 mg/kg/day in olive oil for 13 weeks. In addition to systemic toxicity parameters, estrous cycle assessment of all females and sperm parameters from all males were evaluated. Vaginal smears for estrous cycle determination among the female animals were prepared and evaluated each day during the last 4 weeks of the study. At 1000 mg/kg/day, there was a statistically significant reduction in spermatozoa in the cauda epididymis and spermatids in the testis, with an increase in morphologically abnormal sperm in 3 out of 10 males. Furthermore, 3 high-dose group male rats revealed extreme diffuse atrophy of the testes, which was associated with aspermia and luminal debris in the epididymides, and 2 other male rats experienced minimal to slight focal tubular atrophy in the testes. There were no treatment-related adverse effects on estrous cycle determinations conducted from days 63–91. Thus, the NOAEL for reproductive toxicity was considered to be 200 mg/kg/day, based on testicular toxicity affecting spermatogenesis among males of the high-dose group (RIFM, 2002a). **Therefore, the 6-methyl-5-hepten-2-one MOE for the fertility endpoint can be calculated by dividing the 6-methylhept-5-en-2-one NOAEL in mg/kg/day by the total systemic exposure to 6-methyl-5-hepten-2-one, 200/0.00022, or 909091.**

In addition, the total systemic exposure to 6-methyl-5-hepten-2-one (0.22 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: None.

Literature Search and Risk Assessment Completed On: 04/29/21.

11.1.4. Skin sensitization

Based on existing data and read-across material 3,5,6,6-tetramethyl-4-methyleneheptan-2-one (CAS # 81786-75-6), 6-methyl-5-hepten-2-one is considered a skin sensitizer with a defined NESIL of 4400 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 6-methyl-5-hepten-2-one. Based on the existing data and read-across material 3,5,6,6-tetramethyl-4-methyleneheptan-2-one (CAS # 81786-75-6; see Section VI), 6-methyl-5-hepten-2-one is considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins (Roberts, 2007; Toxtree 3.1.0; OECD Toolbox v4.3).In a murine local lymph node assay (LLNA), read-across material 3,5,6,6-tetramethyl-4-methyleneheptan-2-one was found to be sensitizing with an EC3 value of 64% (16000 μg/cm^2) (ECHA, 2013b; RIFM, 2012b). In a guinea pig open epicutaneous test (OET), 6-methyl-5-hepten-2-one at 3% did not present reactions indicative of sensitization (ECHA, 2013a; Klecak, 1985). In a modified Draize test, no skin sensitization reactions were observed (ECHA, 2013a; Sharp, 1978). In a human maximization test, no skin sensitization reactions were observed with 6-methyl-5-hepten-2-one at 3% (2070 μg/cm^2) (RIFM, 1972). Additionally, in a confirmatory Confirmation of No Induction in Humans test (CNIH) with 8% (4408 μg/cm^2) of read-across material 3,5,6,6-tetramethyl-4-methyleneheptan-2-one in 1:3 ethanol:diethyl phthalate (EtOH:DEP), no reactions indicative of sensitization were observed in any of the 100 volunteers (RIFM, 2012a).

Based on WoE from structural analysis, animal and human studies, and data on the read-across material 3,5,6,6-tetramethyl-4-methyleneheptan-2-one, 6-methyl-5-hepten-2-one is a weak sensitizer with a WoE NESIL of 4400 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 0.5 mg/kg/day.

Additional References: ECHA, 2013a; OECD, 2003.

Literature Search and Risk Assessment Completed On: 05/12/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 6-methyl-5-hepten-2-one 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 6-methyl-5-hepten-2-one in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 6-methyl-5-hepten-2-one 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 minor 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: 04/29/21.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 6-methyl-5-hepten-2-one is below the Cramer Class III* TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on 6-methyl-5-hepten-2-one. Based on the Creme RIFM Model, the inhalation exposure is 0.0037 mg/day. This exposure is 127 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Table 1
Data summary for 3,5,6,6-tetramethyl-4-methyleneheptan-2-one as read-across material for 6-methyl-5-hepten-2-one.

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
16000 [1]	Weak	4408	NA	NA	4400

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.

Additional References: RIFM, 1974; Pinching (1974); Helmig (1999a); Helmig (1999b); Wolkoff (2013).

Literature Search and Risk Assessment Completed On: 05/03/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 6-methyl-5-hepten-2-one 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, 6-methyl-5-hepten-2-one 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 6-methyl-5-hepten-2-one as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

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

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. For CAS # 110-93-0.

RIFM, 1998: The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 89% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 6-Methyl-5-hepten-2-one (CAS #

110-93-0) has been registered for REACH with following additional data available at this time (ECHA, 2013a):

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 91% was observed after 28 days.

The acute fish (golden orfe) toxicity test was conducted according to the DIN 38 412 (1982) guidelines under static conditions. The 96-h LC50 value based on the nominal test concentration was reported to be 50 mg/L. The LC50 value was corrected based on 26% evaporation of the test material.

The acute toxicity of the test material to *Daphnia magna* was conducted according to the DIN 38412, L11 guidelines under static conditions. The 48-h EC50, based on the nominal concentration, was reported to be 74 mg/L. The EC50 value was corrected based on 35% evaporation of the test material.

The algae growth inhibition test was conducted according to the DIN 38412, L 9 guidelines under static conditions. The 72-h EC50 based on nominal concentration for growth rate was reported to be 116 mg/L. The EC50 value was corrected based on 39% evaporation of the test material.

11.2.3. Risk assessment refinement

Since 6-methyl-5-hepten-2-one has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} Used	2.4	2.4
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use.

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

The RIFM PNEC is 3.9742 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 volumes of use.

Literature Search and Risk Assessment Completed On: 05/03/21.

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
- **TOXNET:** 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 05/24/21.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	76.39			1000000	0.07639	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	91.253	52.110	39.742	10000	3.9742	Neutral Organics

Appendix G. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2021.112558.

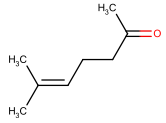
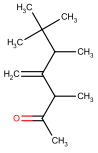
Appendix

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	6-Methyl-5-hepten-2-one	3,5,6,6-Tetramethyl-4-methyleneheptan-2-one
CAS No.	110-93-0	81786-75-6
Structure		
Similarity (Tanimoto Score)		0.35
Read-across Endpoint		• Skin Sensitization
Molecular Formula	$C_8H_{14}O$	$C_{12}H_{22}O$
Molecular Weight	126.19	182.30
Melting Point (°C, EPI Suite)	−67.10	−21.02
Boiling Point (°C, EPI Suite)	173.50	193.77
Vapor Pressure (Pa @ 25°C, EPI Suite)	237.31	92.66
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.06	3.85
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1651.00	27.84
J_{max} (μg/cm^2/h, SAM)	109.105	6.959
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.15E+001	5.65E+001
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
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)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
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 6-methyl-5-hepten-2-one (CAS # 110-93-0). 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, 3,5,6,6-tetramethyl-4-methyleneheptan-2-one (CAS # 81786-75-6) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 3,5,6,6-Tetramethyl-4-methyleneheptan-2-one (CAS # 81786-75-6) was used as a read-across analog for the target material 6-methyl-5-hepten-2-one (CAS # 110-93-0) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of unsaturated ketones.
  - o The target material and the read-across analog share a ketone functionality within a branched unsaturated aliphatic chain.
  - o The key difference between the target material and the read-across analog is that the target material has a vinylene unsaturation, whereas the read-across analog has a vinyl group. This structural difference is toxicologically insignificant.
  - 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 physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a 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 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.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree.

Q1. A normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene (see Cramer et al., 1978 for detailed explanation)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? Yes
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes
Q21.3 or more different functional groups? No
Q18. One of the lists (see Cramer et al., 1978 for a detailed explanation on the list of categories)? Yes, Intermediate (Class II)

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