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RIFM fragrance ingredient safety assessment, (+/-)-4-ethyloctanal, CAS Registry Number 58475-04-0

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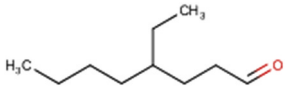
CAS Registry Number: 58475-04-0



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Abbreviation/Definition List:

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

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CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
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
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.

(+/-)-4-Ethyloctanal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 3,5,5-trimethylhexanal (CAS # 5435-64-3) show that (+/-)-4-ethyloctanal is not expected to be genotoxic and provide a calculated MOE >100 for the repeated dose toxicity endpoint. Data on analog 2-ethylhexanal (CAS # 123-05-7) provide a calculated MOE >100 for the developmental endpoint. The fertility and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material; exposure is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from analog 2-methylundecanal (CAS # 110-41-8) provided a NESIL of 2900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra from read-across analog tetrahydrogeranial (CAS # 5988-91-0); (+/-)-4-ethyloctanal is not expected to be phototoxic/photoallergenic. For the hazard assessment based on the screening data, (+/-)-4-ethyloctanal is not PBT as per the IFRA Environmental Standards. For the risk assessment, (+/-)-4-ethyloctanal was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 1980; ECHA REACH Dossier: 3,5,5-Trimethylhexanal; ECHA, 2011a)
Repeated Dose Toxicity: NOAEL = 83 mg/kg/day.	(ECHA REACH Dossier: 3,5,5-Trimethylhexanal; ECHA, 2011a)
Reproductive Toxicity: Developmental toxicity: 100 mg/kg/day. Fertility: No NOAEL available; exposure is below TTC.	(ECHA REACH Dossier: 2-Ethylhexanal; ECHA, 2011b)
Skin Sensitization: NESIL = 2900 μg/cm^2.	RIFM (2016)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic	(UV Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.17 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 126.3 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Not applicable	

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; no Volume of Use in 2015 reported for Europe and North America

1. Identification

1. **Chemical Name:** (+/-)-4-Ethyloctanal
2. **CAS Registry Number:** 58475-04-0
3. **Synonyms:** Octanal, 4-ethyl-; Excital; (+/-)-4-Ethyloctanal
4. **Molecular Formula:** $C_{10}H_{20}O$
5. **Molecular Weight:** 156.26
6. **RIFM Number:** 7178
7. **Stereochemistry:** One stereocenter and 2 possible stereoisomers

2. Physical data

1. **Boiling Point:** 98 °C at 25 mm Hg (Private communication to FEMA)
2. **Flash Point:** 173 °F (Private communication to FEMA)
3. **Log K_{OW}:** 3.69
4. **Melting Point:** −19.01 °C (EPI Suite)
5. **Water Solubility:** 50.29 mg/L at 25 °C (WSKOW v1.42 in EPI Suite)
6. **Specific Gravity:** 0.834 at 20 °C (Private communication to FEMA)
7. **Vapor Pressure:** 0.195 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** Not available
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00021% (RIFM, 2017)
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or 0.0000004 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0000012 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).

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:** 3,5,5-Trimethylhexanal (CAS # 5435-64-3)
   b. **Repeated Dose Toxicity:** 3,5,5-Trimethylhexanal (CAS # 5435-64-3)
   c. **Reproductive Toxicity:** 2-Ethylhexanal (CAS # 123-05-7)
   d. **Skin Sensitization:** 2-Methylundecanal (CAS # 110-41-8)
   e. **Phototoxicity/Photoallergenicity:** Tetrahydrogeranial (CAS # 5988-91-0)
   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

(+/-)-4-Ethyloctanal is not reported to occur in foods by the VCF*.

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

9. REACH dossier

No dossier available as of 04/19/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for (+/-)-4-ethyloctanal 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)	0.22
2	Products applied to the axillae	0.066
3	Products applied to the face/body using fingertips	1.3
4	Products related to fine fragrances	1.2
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.32
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.32
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.32
5D	Baby cream, oil, talc	0.11
6	Products with oral and lip exposure	0.73
7	Products applied to the hair with some hand contact	2.5
8	Products with significant ano-genital exposure (tampon)	0.11
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.4
10A	Household care products with mostly hand contact (hand dishwashing detergent)	8.7
10B	Aerosol air freshener	8.7
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.11
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

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 (+/-)-4-ethyloctanal, the basis was the reference dose of 0.83 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 2900 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 v3.1.1.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, (+/-)-4-ethyloctanal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic or clastogenic activity of (+/-)-4-ethyloctanal; however, read-across can be made to 3,5,5-trimethylhexanal (CAS # 5435-64-3; see Section VI).

The mutagenic activity of 3,5,5-trimethylhexanal has been evaluated in a bacterial reverse mutation assay using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 3,5,5-trimethylhexanal in dimethyl sulfoxide (DMSO) at concentrations up to 10 μL/plate (8710 μg/plate). No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 1980). Considering that this study did not follow OECD

guidelines, the lack of use of the strains TA102 and/or *Escherichia coli* (which are mainly included in the test battery to detect oxidizing mutagens, cross-linking agents, and hydrazines) is a deviation. However, for a material in the aldehyde class, the lack of these strains is not considered to be an issue; hence, this study can be considered as sufficient to make a conclusion on mutagenic potential. Under the conditions of the study, 3,5,5-trimethylhexanal was not mutagenic in the Ames test, and this can be extended to (+/-)-4-ethyloctanal.

The clastogenic activity of 3,5,5-trimethylhexanal was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and according to OECD TG 474. The test material was administered in corn oil via oral gavage to groups of male and female NMRI mice. Doses of 2000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 and 48 h, 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, 2011a). Under the conditions of the study, 3,5,5-trimethylhexanal was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to (+/-)-4-ethyloctanal.

Based on the data available, 3,5,5-trimethylhexanal does not present a concern for genotoxic potential, and this can be extended to (+/-)-4-ethyloctanal.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/15/20.

11.1.2. Repeated dose toxicity

The MOE for (+/-)-4-ethyloctanal is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on (+/-)-4-ethyloctanal. Read-across material 3,5,5-trimethylhexanal (CAS # 5435-64-3; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. A 28-day OECD 407/GLP subchronic oral toxicity study was conducted in Wistar rats. Groups of 5 rats/sex/dose were administered 3,5,5-trimethylhexanal via oral gavage at doses of 0, 50, 150, or 500 mg/kg/day for 28 days. Post-exposure satellite groups were also assigned to the control and high-dose groups to serve as the 14-day treatment-free recovery groups. Treatment-related clinical signs of piloerection and squatting/hunchback position were observed in the male and female high-dose group after the administration of the test material at 500 mg/kg/day. Two female animals of the high-dose groups died overnight and were subsequently replaced by substitutes. The highest dose was reduced to 250 mg/kg/day as a result of mortality and adverse clinical signs. After the reduction of the high dose to 250 mg/kg/day, only animals of this dose group showed clinical signs on the second day. On the third day, 1 female of the high-dose group died most likely as a result of the administration of 500 mg/kg/day on the first day of the study. During the recovery period, no clinical signs were observed in the high-dose group (250 mg/kg/day). There was also a statistically significant decrease in body weight and a slightly reduced group mean weekly body weight in high-dose females at the end of the treatment period; however, these findings were reversible in the recovery groups. Centrilobular hypertrophy of the liver in correlation with statistically significantly higher relative and absolute liver weights and focal periportal vacuolation in treated females were considered to be treatment related. However, histopathological examination of the livers did not reveal any signs of necrotic changes of hepatocytes. The liver changes observed were considered to be an expression of a reversible adaptive response to the test material and were not deemed as an adverse effect. Thus, the NOAEL for repeated dose toxicity was considered to be 250 mg/kg/day, the highest dose tested (ECHA, 2011a).

A default safety factor of 3 was used when deriving a NOAEL from a 28-day OECD 407 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 250/3 or 83 mg/kg/day.

Therefore, the (+/-)-4-ethyloctanal MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3,5,5-trimethylhexanal NOAEL in mg/kg/day by the total systemic exposure for (+/-)-4-ethyloctanal, 83/0.0000012, or 69166667.

In addition, the total systemic exposure to (+/-)-4-ethyloctanal (0.0012 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.

11.1.3. Derivation of reference dose (RfD)

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020) and a reference dose of 0.83 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 (+/-)-4-ethyloctanal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 83 mg/kg/day by the uncertainty factor, 100 = 0.83 mg/kg/day.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/19/20.

11.1.4. Reproductive toxicity

The MOE for (+/-)-4-ethyloctanal is adequate for the developmental toxicity endpoint at the current level of use. There are insufficient fertility data on (+/-)-4-ethyloctanal or any read-across materials. The total systemic exposure to (+/-)-4-ethyloctanal is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.4.1. Risk assessment. There are no developmental toxicity data on the (+/-)-4-ethyloctanal; hence, read-across material 2-ethylhexanal (CAS # 123-05-7; see Section VI) is considered. There are sufficient data available on developmental toxicity for 2-ethylhexanal. In a GLP (OECD 414) compliant prenatal developmental toxicity study, groups of 25 pregnant rats (Crj: CD [SD]) were dosed with 2-ethylhexanal by oral gavage at 0 (controls), 100, 300, and 800 mg/kg/day in corn oil for gestation days 6–19. Maternal effects seen at 800 mg/kg/day included: clinical signs of toxicity (salivation, piloerection, reduced activity, hunched posture, and partly closing of eyes), decreased body weight and food consumption, and changes in placenta (decreased weight, swelling, enlargement, and presence of clotted blood around, pale coloration). Findings at 300 mg/kg/day were limited to salivation and placental effects. Salivation was the only effect observed at 100 mg/kg/day. Significant fetal toxicity (visceral and skeletal) was seen at 800 mg/kg/day, characterized by dilated ventricles in the brain, absent or rudimentary thyroid, partially undescended thymus, cardiovascular abnormalities, rudimentary/absent renal papillae, left umbilical artery, subcutaneous edema, irregularly ossified ribs, tail abnormalities related to abnormalities within the termination of the vertebral column, vertebral configuration abnormalities, thoracic and lumbar vertebral abnormalities, incomplete ossification of cranial centers, cervical and sacrocaudal vertebral arches, pelvic bones, metacarpals, metatarsals and sternebrae, and cleft palate. Based on the maternal and fetal effects, the NOAEL for maternal and developmental toxicity as determined by the ECHA dossier and the BGRCI toxicological evaluation was considered to be 300 mg/kg/day. However, since there were visceral findings at 300 mg/kg/day

that included an increase in the number of fetuses displaying rudimentary/absent renal papillae, dilated ureter, and displaced testis along with skeletal effects that included incompletely ossified sternebrae and sacrocaudal vertebral arches, the 2-ethylhexanal NOAEL for developmental toxicity was conservatively considered to be 100 mg/kg/day (ECHA, 2011b; BG RCI, 2005). **Therefore, the (+/-)-4-ethyloctanal MOE for the developmental toxicity endpoint can be calculated by dividing the 2-ethylhexanal NOAEL in mg/kg/day by the total systemic exposure to (+/-)-4-ethyloctanal, 100/0.0000012, or 83333333.**

In addition, the total systemic exposure to (+/-)-4-ethyloctanal (0.0012 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on (+/-)-4-ethyloctanal, or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure (0.0012 μg/kg/day) is below the TTC for (+/-)-4-ethyloctanal (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/05/20.

11.1.5. Skin sensitization

Based on the existing data and read-across material 2-methylundecanal (CAS # 110-41-8), (+/-)-4-ethyloctanal is considered a skin sensitizer with a defined NESIL of 2900 μg/cm^2.

11.1.5.1. Risk assessment. No skin sensitization studies are available for (+/-)-4-ethyloctanal. Based on read-across material 2-methylundecanal (CAS # 110-41-8; see Section VI), (+/-)-4-ethyloctanal is considered a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, 2-methylundecanal, was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, and U937-CD86 test (Natsch, 2013). In a murine local lymph node assay (LLNA), read-across material 2-methylundecanal was found to be sensitizing with an EC3 value of 10% (2500 μg/cm^2) (Patlewicz, 2003; Roberts, 2007). In a human maximization test, no skin sensitization reactions were observed with read-across material 2-methylundecanal (RIFM, 1971). Additionally, in a Confirmation of No Induction in Humans (CNIH) test with 2953 μg/cm^2 of read-across material 2-methylundecanal in 1:3 ethanol: diethyl phthalate, no reactions indicative of sensitization were observed in any of the 102 volunteers (RIFM, 2016). In 2 additional CNIHs with 969 and 388 μg/cm^2 of 2-methylundecanal in ethanol, no reactions indicative of sensitization were observed in any of the 40 volunteers (EPA, 1991; RIFM, 1964).

Based on weight of evidence (WoE) from structural analysis and data on the read-across material 2-methylundecanal, (+/-)-4-ethyloctanal is a sensitizer with a WoE NESIL of 2900 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 0.83 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/14/20.

Table 1
Data summary for 2-methylundecanal as read-across material for (+/-)-4-ethyloctanal.

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
2500 [1]	Weak	2953	2760	NA	2900

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.

11.1.6. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra for the structurally related material, tetrahydrogeranial (CAS # 5988-91-0), (+/-)-4-ethyloctanal would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.6.1. Risk assessment. There are no phototoxicity studies available for (+/-)-4-ethyloctanal in experimental models. UV/Vis absorption spectra were not available for (+/-)-4-ethyloctanal. UV/Vis absorption spectra on the structurally related material, tetrahydrogeranial (CAS # 5988-91-0), 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 significant absorbance for the structurally related analog, (+/-)-4-ethyloctanal does not present a concern for phototoxicity or photoallergenicity.

11.1.7. UV spectra analysis

UV/Vis absorption spectra were not available for the target material (+/-)-4-ethyloctanal. UV/Vis absorption spectra (OECD TG 101) were available for the structurally related read-across analog tetrahydrogeranial (CAS # 5988-91-0). 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).

Literature Search and Risk Assessment Completed On: 10/06/20.

11.1.8. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for (+/-)-4-ethyloctanal is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.8.1. Risk assessment. There are no inhalation data available on (+/-)-4-ethyloctanal. Based on the Creme RIFM Model, the inhalation exposure is 0.0000004 mg/day. This exposure is 3500000 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: 04/14/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of (+/-)-4-ethyloctanal 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. 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, (+/-)-4-ethyloctanal was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify (+/-)-4-ethyloctanal 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 $\geq$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).

Risk Assessment: Not applicable.

11.2.2. Key studies

11.2.2.1. Biodegradation. No data available.

11.2.2.2. Ecotoxicity. No data available.

11.2.2.3. Other available data. (+/-)-4-Ethyloctanal has been pre-registered for REACH with no additional information available at this time.

Risk Assessment Refinement: Not applicable.

Literature Search and Risk Assessment Completed On: 04/08/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/19/21.

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.2021.112627.

Appendix

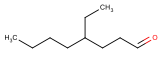
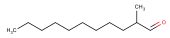
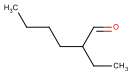
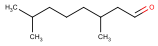
Read-across Justification

Methods

The read-across analogs were 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	Read-across Material	Read-across Material	Read-across Material
Principal Name	(+/-)-4-Ethyloctanal	3,5,5-Trimethylhexanal	2-Methylundecanal	2-Ethylhexanal	Tetrahydrogeranial
CAS No.	58475-04-0	5435-64-3	110-41-8	123-05-7	5988-91-0
Structure					
Similarity (Tanimoto Score)		0.74	0.87	0.82	0.87
Endpoint		• Genotoxicity • Repeated dose toxicity	• Skin sensitization	• Developmental toxicity	• Phototoxicity
Molecular Formula	$C_{10}H_{20}O$	$C_9H_{18}O$	$C_{12}H_{24}O$	$C_8H_{16}O$	$C_{10}H_{20}O$
Molecular Weight	156.27	142.24	184.32	128.22	156.269
Melting Point (°C, EPI Suite)	−19.01	−35.47	3.24	−42.32	−30.03
Boiling Point (°C, EPI Suite)	204.38	173.00	171.00	163	192.33
Vapor Pressure (Pa @ 25°C, EPI Suite)	38.66	10.67	198.65	266.64	7.04E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	50.29	189.20	5.37	400	58.1
Log K_{OW}	3.69	3.09	4.67	3.07	3.62
J_{max} (μg/cm^2/h, SAM)	6.87	19.97	0.87	51.20	7.60
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	66.27	49.95	116.52	85.11	66.3
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			
Repeated Dose Toxicity					
Repeated Dose (HESS)	Not categorized	Not categorized			
Reproductive Toxicity					
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure			Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)			Toxicant (moderate reliability)	
Skin Sensitization					
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base		Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base		

(continued on next page)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
	formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes		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	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on (+/-)-4-ethyloctanal (CAS # 58475-04-0). 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, 3,5,5-trimethylhexanal (CAS # 5435-64-3), 2-methylundecanal (CAS # 110-41-8), tetrahydrogeranial (CAS # 5988-91-0), and 2-ethylhexanal (CAS # 123-05-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 3,5,5-Trimethylhexanal (CAS # 5435-64-3) was used as a read-across analog for the target material (+/-)-4-ethyloctanal (CAS # 58475-04-0) for the genotoxicity and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The key difference between the target material and the read-across analog is in the branching of the methyl or ethyl groups on different positions on the aliphatic chain. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target material.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score presented in the table above. The differences in the structures which are responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.
  - 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 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 Both target and read-across are predicted to have an alert for genotoxic carcinogenicity. Based on existing data and read-across, (+/-)-4-ethyloctanal does not pose any concern for genotoxicity. Therefore, based on the structural similarity between the target material and the read-across analog, and the data for the read-across analog, the *in silico* alerts for the target and read-across are superseded by 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 endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-Methylundecanal (CAS # 110-41-8) was used as a read-across analog for the target material (+/-)-4-ethyloctanal (CAS # 58475-04-0) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The key difference between the target material and the read-across analog is that the target has an ethyl substituent on the fourth position whereas the read-across has a methyl substituent on the second position. Moreover, the main carbon chain in the target material is 3 carbons shorter than in the read-across. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score presented in the table above. The differences in the structures which are responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.
  - 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 According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.

- The target material and the read-across analog have alerts for Schiff base formation by the protein Binding (OASIS v1.1 QSAR Toolbox v4.2) and skin sensitization reactivity domains (Toxtree v2.6.13) *in silico* models for skin sensitization. A chemical with this structural alert could cause a skin sensitization effect as a result of Schiff base formation with aldehydes. Aldehydes are highly reactive molecules, many of which are strong sensitizers, and their direct conjugation to protein nucleophiles is thought to be responsible. Simple aldehydes react readily with the amino groups of lysine residues on proteins to form imines or Schiff bases. Based on the existing data and read-across to 2-methylundecanal (CAS # 110-41-8), (+/-)-4-ethyloctanal is considered a skin sensitizer with a defined NESIL of 2900 μg/cm^2. Therefore, based on the structural similarity between the target material and the read-across analog, and the data for the read-across analog, the *in silico* alerts on both materials are superseded by the data.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- 2-Ethylhexanal (CAS # 123-05-7) was used as a read-across analog for the target material (+/-)-4-ethyloctanal (CAS # 58475-04-0) for the developmental toxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - The key difference between the target material and the read-across analog is that the target has an ethyl substituent on the fourth position whereas the read-across has the same substituent on the second position. Moreover, the main carbon chain in the target material is 2 carbons longer than in the read-across. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score presented in the table above. The differences in the structures which are responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The read-across has a toxicant (moderate reliability) alert for developmental Toxicity (CAESAR v2.1.6). This implies that the read-across is more reactive than the target. The MOE for (+/-)-4-ethyloctanal is adequate for the developmental toxicity endpoint at the current level of use. Therefore, based on the structural similarity between the target material and the read-across analog, and the data for the read-across analog, the *in silico* alert on read-across material is superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Tetrahydrogeranial (CAS # 5988-91-0) was used as a read-across analog for the target material (+/-)-4-ethyloctanal (CAS # 58475-04-0) for the phototoxicity/photoallergenicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - The key difference between the target material and the read-across analog is in the branching of the methyl or ethyl groups on different positions on the aliphatic chain. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have an equal or greater potential for toxicity as compared to the target material.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score presented in the table above. The differences in the structures which are responsible for a Tanimoto score <1 are not relevant from a toxicological perspective.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - There is no substructural feature on the target material and the read-across analog is expected to be a chromophore in absorbing UVVIs range of interest. Both substances are not expected to absorb.

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