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RIFM fragrance ingredient safety assessment, 3,5,5-trimethylhexanal, CAS Registry Number 5435-64-3

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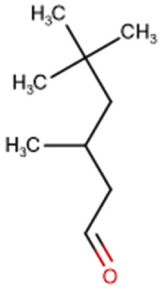
Name: 3,5,5-Trimethylhexanal

CAS Registry Number: 5435-64-3



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

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

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable

(*continued on next column*)

(*continued*)

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.

3,5,5-Trimethylhexanal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 3,5,5-trimethylhexanal is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across analog 2-methylundecanal (CAS # 110-41-8) provide a calculated MOE >100 for the reproductive toxicity endpoint and a No Expected Sensitization Induction Level (NESIL) of 2900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; 3,5,5-trimethylhexanal 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 I material, and the exposure to 3,5,5-trimethylhexanal is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 3,5,5-trimethylhexanal 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.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(ECHA REACH Dossier: 3,5,5-Trimethylhexanal; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 83 mg/kg/day.	(ECHA REACH Dossier: 3,5,5-Trimethylhexanal; ECHA, 2011)
Reproductive Toxicity: Developmental toxicity NOAEL: 1350 mg/kg/day Fertility NOAEL: 991 mg/kg/day.	(RIFM, 2019a; RIFM, 2019b)
Skin Sensitization: NESIL = 2900 μg/cm^2.	RIFM, (2016)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database; RIFM, 1979; RIFM, 1982)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Critical Measured Value: 80% (OECD 301F)	RIFM, (2013a)
Bioaccumulation:	
Screening-level: 50.5 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 48-h *Daphnia magna* LC50: 2.057 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 2.057 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.2057 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU)**: North America and Europe <1	

1. Identification

1. **Chemical Name:** 3,5,5-Trimethylhexanal
2. **CAS Registry Number:** 5435-64-3
3. **Synonyms:** Hexanal, 3,5,5-trimethyl-; Isononyl aldehyde; Vandor B; Verdinal; アルカナール(C = 4~19); Aldehyde C9 isononylic; 3,5,5-Trimethylhexanal
4. **Molecular Formula:** $C_9H_{18}O$
5. **Molecular Weight:** 142.24 g/mol
6. **RIFM Number:** 701
7. **Stereochemistry:** Isomer not specified. One chiral center present, and a total of 2 enantiomers possible.

2. Physical data

1. **Boiling Point:** >200 °C (Fragrance Materials Association [FMA]), 163.16 °C (EPI Suite)
2. **Flash Point:** 34 °C (Globally Harmonized System), 113 °F; CC (FMA)
3. **Log K_{OW}:** 2.9 (RIFM, 2013b), 3.09 (EPI Suite)
4. **Melting Point**: −35.47 °C (EPI Suite)
5. **Water Solubility:** 189.2 mg/L (EPI Suite)
6. **Specific Gravity:** 0.822 (FMA)
7. **Vapor Pressure:** 0.949 mm Hg at 20 °C (EPI Suite v4.0), 0.8 mm Hg at 20 °C (FMA), 1.35 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient (12 L mol^{-1} • cm^{-1}, condition not specified) is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless oily, water-white liquid with an aldehydic odor

3. Volume of use (Worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.03% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.00015 mg/kg/day or 0.010 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0012 mg/kg/day (RIFM, 2018)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (RIFM, 2015; Safford, 2015; Safford, 2017; Comiskey, 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (Expert Judgment)

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

*See Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** 2-Methylundecanal (CAS # 110-41-8)
   d. **Skin Sensitization:** 2-Methylundecanal (CAS # 110-41-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

3,5,5-Trimethylhexanal is not reported to occur in foods by the VCF*.

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

9. REACH dossier

Available; accessed on 11/05/21 (ECHA, 2011).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 3,5,5-trimethylhexanal 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	0.89
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	0.45
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)	2.2
10B	Aerosol air freshener	8.5
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 3,5,5-trimethylhexanal, the basis was the subchronic 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; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 3,5,5-trimethylhexanal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 3,5,5-trimethylhexanal 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/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with 3,5,5-trimethylhexanal 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 dose in the presence or absence of S9 (ECHA, 2011). Under the conditions of the study, 3,5,5-trimethylhexanal was not mutagenic in the Ames test.

The clastogenic activity of 3,5,5-trimethylhexanal 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 corn oil via oral gavage to groups of male and female NMRI mice. Doses of 0 or 2000 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h; 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, 2011). Under the conditions of the study, 3,5,5-trimethylhexanal was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 3,5,5-trimethylhexanal does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/21.

11.1.2. Repeated dose toxicity

The MOE for 3,5,5-trimethylhexanal 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 3,5,5-trimethylhexanal to support the repeated dose toxicity endpoint. A 28-day OECD/GLP 407 subchronic oral toxicity study was conducted in Wistar rats. Groups of 5 rats/sex/dose were administered via oral gavage test material, 3,5,5-trimethylhexanal, 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 the aforementioned adverse clinical signs. After the reduction of the high dose to 250 mg/kg/day, only animals of this dose group showed these clinical signs. 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 bodyweight 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 degenerative or 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, 2011).

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 3,5,5-trimethylhexanal 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 3,5,5-trimethylhexanal, 83/0.0012, or 69167.

In addition, the total systemic exposure to 3,5,5-trimethylhexanal (1.2 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.

11.1.2.2. Derivation of subchronic 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, 2020b) and a subchronic RfD 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 subchronic RfD for 3,5,5-trimethylhexanal 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: 03/08/21.

11.1.3. Reproductive toxicity

The MOE for 3,5,5-trimethylhexanal is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on 3,5,5-trimethylhexanal. Read-across material, 2-methylundecanal (CAS # 110-41-8; see Section VI), has sufficient data to support the reproductive toxicity endpoint.

In an OECD 414/GLP prenatal developmental toxicity study, 22 female Wistar Han rats/group were administered dose levels of 0, 1500, 5000, and 15000 ppm (equivalent to 0, 147, 477, and 1350 mg/kg/day, respectively) in diet from gestation days (GDs) 6–21. No mortality was observed. No treatment-related clinical signs of toxicity were observed in any dose groups. A lower test-diet consumption at the start of treatment was observed in the mid- and high-dose groups as compared to control. However, the food consumption in the mid- and high-dose groups over the remaining treatment period and the overall mean was similar to the control. Histopathological examination at the end of the administration period showed no abnormalities due to the test material. Furthermore, the numbers of pregnant females, corpora lutea and implantation sites, and pre-implantation loss were comparable in the control and test groups. Thus, the NOAEL for developmental toxicity was considered to be 15000 ppm (equivalent to 1350 mg/kg/day), the highest dose tested (RIFM, 2019a).

Another OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were exposed to the test material 2-methylundecanal at dose levels of 0, 1500, 5000, 15000 ppm (mg/kg/day equivalency in males: 0,

96–108, 313–360, and 991–1093, respectively; in females: 0, 97–292, 339–995, and 1005–2527, respectively) in diet. Males were treated for 29 days (up to and including the day before scheduled necropsy) and females were treated for 51–63 days (2 weeks prior to mating, during mating, and 14–16 days after delivery, up to and including the day of scheduled necropsy). No parental toxicity was observed up to the highest dose. There were no treatment-related developmental toxicity effects seen at any dose levels. Thus, the NOAEL for developmental toxicity was considered to be 15000 ppm (equivalent to 991 mg/kg/day), the highest dose tested (RIFM, 2019b).

Thus, NOAEL for developmental toxicity was derived from a more robust OECD 414 study and was considered to be 1350 mg/kg/day.

Therefore, the 3,5,5-trimethylhexanal MOE for the developmental toxicity endpoint can be calculated by dividing the 2-methylundecanal NOAEL in mg/kg/day by the total systemic exposure for 3,5,5-trimethylhexanal, 1350/0.0012, or 1125000.

There are sufficient fertility data on 2-methylundecanal. An OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose were exposed to the test material 2-methylundecanal at dose levels of 0, 1500, 5000, and 15000 ppm (mg/kg/day equivalency in males: 0, 96–108, 313–360, and 991–1093, respectively; in females: 0, 97–292, 339–995, and 1005–2527, respectively) in diet. Males were treated for 29 days (up to and including the day before scheduled necropsy), and females were treated for 51–63 days (2 weeks prior to mating, during mating, and 14–16 days after delivery, up to and including the day of scheduled necropsy). No treatment-related effects were seen for gestation, viability and lactation indices, duration of gestation, parturition, sex ratio, live litter size, maternal care, clinical signs, body weight, anogenital distance, areola/nipple retention, serum level of T4 thyroid hormone, and macroscopic examination. Thus, the NOAEL for fertility was considered to be 15000 ppm (equivalent to 991 mg/kg/day), the highest dose tested (RIFM, 2019b).

Therefore, the 2-methylpentanal MOE for the fertility endpoint can be calculated by dividing the 2-methylundecanal NOAEL in mg/kg/day by the total systemic exposure for 2-methylpentanal, 991/0.0012, or 825833.

In addition, the total systemic exposure to 3,5,5-trimethylhexanal (1.2 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: 03/05/21.

11.1.4. Skin sensitization

Based on the existing data and read-across material 2-methylundecanal (CAS # 110-41-8), 3,5,5-trimethylhexanal is considered a skin sensitizer with a defined NESIL of 2900 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 3,5,5-trimethylhexanal. Based on the existing data and read-across material 2-methylundecanal (CAS # 110-41-8; see Section VI), 3,5,5-trimethylhexanal is considered a skin sensitizer with a defined NESIL of 2900 μg/cm^2. The chemical structure of these materials indicates that they would be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across material 2-methylundecanal was found to be positive in the *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens test, and U-SENS test (Natsch, 2013). In a murine local lymph node assay (LLNA), 3,5,5-trimethylhexanal was not found to be sensitizing when tested up to 50% (12500 μg/cm^2) (RIFM, 2014). In another LLNA, read-across material 2-methylundecanal was found to be sensitizing with an EC3 value of 10% (2500 μg/cm^2) (Patlewicz, 2003; Gerberick, 2005; Roberts, 2007). In human maximization tests, no skin sensitization reactions were observed with 3,5,5-trimethylhexanal or read-across 2-methylundecanal (RIFM, 1975; RIFM, 1971). In a Confirmation of No Induction in Humans (CNIH) test with 7752 μg/cm^2 of 3,5,5-trimethylhexanal in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 39 volunteers (EPA, 1991a). Additionally, in a CNIH test with 2953 μg/cm^2 of read-across 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 other CNIH tests with 969 μg/cm^2 of read-across 2-methylundecanal in ethanol, no reactions indicative of sensitization were observed in any of the 40 volunteers (EPA, 1991b; RIFM, 1964c).

Based on the weight of evidence (WoE) from the available data and read-across analog 2-methylundecanal, 3,5,5-trimethylhexanal is a weak sensitizer with 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, 2020b) and a subchronic RfD of 0.83 mg/kg/day.

Additional References: Klecak (1979); Klecak (1985); EPA, 1964; RIFM, 1979; RIFM, 1964b; RIFM, 1964a; RIFM, 1972; EPA, 1991a.

Literature Search and Risk Assessment Completed On: 02/26/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra and available study data, 3,5,5-trimethylhexanal would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). A rat phototoxicity study was conducted with undiluted 3,5,5-trimethylhexanal, and there was no evidence of phototoxicity (RIFM, 1982). A photo-CNIH test was conducted with 5% 3,5,5-trimethylhexanal, and there were no reactions during induction or challenge (RIFM, 1979). Based on the lack of significant absorbance in the critical range and study data, 3,5,5-trimethylhexanal 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 (12 L mol^{-1} • cm^{-1}, condition not specified) 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: 03/01/21.

Table 1
Data summary for 2-methylundecanal as read-across for 3,5,5-trimethylhexanal.

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 test or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3,5,5-trimethylhexanal is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 3,5,5-trimethylhexanal. Based on the Creme RIFM Model, the inhalation exposure is 0.010 mg/day. This exposure is 140 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: 03/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3,5,5-trimethylhexanal 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, 3,5,5-trimethylhexanal 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 3,5,5-trimethylhexanal 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). 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), 3,5,5-trimethylhexanal presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation

RIFM, 2013a: The ready biodegradability of the test material was evaluated using a manometric respirometry test according to the OECD 301F method. Under the conditions of the study, biodegradation of 80% was observed after 28 days.

Ecotoxicity

No data available.

Other available data

3,5,5-Trimethylhexanal has been registered under REACH, and the following data is available (ECHA, 2011):

Ready biodegradation test was conducted using the modified MITI test according to the OECD 301C method, and 7% biodegradation was observed after 28 days.

11.2.3. Risk assessment refinement

Since 3,5,5-trimethylhexanal 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 (EU)	North America (NA)
Log K_{ow} Used	2.9	2.9
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.2057 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 03/04/21.

12. Literature Search*

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	31.61			1000000	0.03161	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	2.192	2.057	4.015	10000	0.2057	Aldehydes
ECOSAR Acute Endpoints **(Tier 2)** v1.11	12.33	7.745	8.737			Neutral Organic SAR

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 11/09/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113022.

Appendix

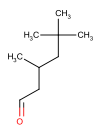
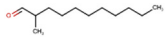
Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 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 (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	3,5,5-Trimethylhexanal	2-Methylundecanal
CAS No.	5435-64-3	110-41-8
Structure		
Similarity (Tanimoto Score)		0.53
Read-across Endpoint		• Reproductive toxicity • Skin sensitization
Molecular Formula	$C_9H_{18}O$	$C_{12}H_{24}O$
Molecular Weight (g/mol)	142.24	184.32
Melting Point (°C, EPI Suite)	−35.47	3.24
Boiling Point (°C, EPI Suite)	163.16	241.99
Vapor Pressure (Pa @ 25°C, EPI Suite)	180	199
Log Kow (KOWWIN v1.68 in EPI Suite)	2.9[1]	4.9[2]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	189.2	1.3[3]
J_{max} (mg/cm^2/h, SAM)	16.59	0.22
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.93E-004	1.15E-003
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	• Schiff base formation	• Schiff base formation
Protein Binding (OECD)	• Schiff base formers	• Schiff base formers
Protein Binding Potency	• Not possible to classify	• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• Schiff base formation	• Schiff base formation
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 3,5,5-trimethylhexanal (CAS # 5435-64-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 2-methylundecanal (CAS # 110-41-8) was identified as read-across material with sufficient data for toxicological evaluation.

Conclusions

- 2-Methylundecanal (CAS # 110-41-8) was used as a read-across analog for the target material, 3,5,5-trimethylhexanal (CAS # 5435-64-3), for the reproductive toxicity and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the class of aldehydes.
  - o The target material and the read-across analog share a common aliphatic branched aldehyde fragment.
  - o The key difference between the target material and the read-across analog is that the target has 3 methyl substitutions on the aliphatic chain, while the read-across analog has a single methyl substitution 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.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by an aliphatic branched aldehyde fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} values are $\leq$80% for the target material and $\leq$40% for the read-across analog. 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 read-across analog and the target material are predicted to have positive protein binding alerts by OASIS and OECD model for skin sensitization. All the other alerts for skin sensitization were predicted to be negative. Data superseded predictions in this case.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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. Normal constituent of the body? **No**
- Q2. Contains functional groups associated with enhanced toxicity? **No**
- Q3. Contains elements other than C, H, O, N, 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 explanation in Cramer et al., 1978)? **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 following categories? **No** Low **(Class I)**

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