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RIFM fragrance ingredient safety assessment, 2-methyloctanal, CAS Registry Number 7786-29-0

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Name: 2-Methyloctanal
CAS Registry Number: 7786-29-0

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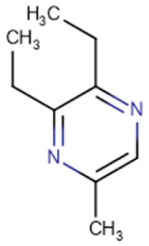

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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 (RIFM, 2015; Safford et al., 2015a; Safford et al., 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 et al., 2015), which should be referred to for clarifications.
Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.
2-Methyloctanal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on 2-methyloctanal and read-across analog 2-methyldecanal (CAS # 19009-56-4) show that 2-methyloctanal is not expected to be genotoxic. Data on read-across analog 2-methylundecanal (CAS # 110-41-8) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints 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 ultraviolet/visible (UV/Vis) spectra; 2-methyloctanal is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoints were completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; for the hazard assessment based on the screening data, 2-methyloctanal is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, 2-methyloctanal 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.

Human Health Safety Assessment
Genotoxicity: Not expected to be genotoxic. (RIFM, 2014a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 1046 mg/kg/day. RIFM (2018)

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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)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Screening-level: 3.2 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 59.8 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:** 2-Methyloctanal
2. **CAS Registry Number:** 7786-29-0
3. **Synonyms:** Methylhexylacetaldehyde; Octanal, 2-methyl-; 2-Methyloctanal
4. **Molecular Formula:** $C_9H_{18}O$
5. **Molecular Weight:** 142.24 g/mol
6. **RIFM Number:** 982
7. **Stereochemistry:** Isomer not specified. One chiral center present, and a total of 2 enantiomers possible.

2. Physical data

1. **Boiling Point:** 130 °C at 5 mm Hg (Fragrance Materials Association [FMA]), 184.21 °C (EPI Suite)
2. **Flash Point:** 156 °F; CC (FMA)
3. **Log K_{OW}:** 3.2 (EPI Suite)
4. **Melting Point**: -30.54 °C (EPI Suite)
5. **Water Solubility:** 152.1 mg/L (EPI Suite)
6. **Specific Gravity:** 0.823 (FMA)
7. **Vapor Pressure:** 0.544 mm Hg at 20 °C (EPI Suite v4.0), 0.3 mm Hg at 20 °C (FMA), 0.786 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with delicate, floral odor, delicately floral fresh, aldehydic odor much less fatty than nonanal, more rosy lily-like (Arctander, 1969).

3. Volume of use (Worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00044% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.0000020 mg/kg/day or 0.00013 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.000015 mg/kg/day (RIFM, 2017)

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

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 I, Low

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

6.2. Analogs Selected

a. **Genotoxicity:** 2-Methyldecanal (CAS # 19009-56-4)
b. **Repeated Dose Toxicity:** 2-Methylundecenal (CAS # 110-41-8)
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

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

2-Methyloctanal 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

2-Methyloctanal has been pre-registered for 2010; no dossier available as of 11/15/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-methyloctanal 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)	6.3
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 2-methyloctanal, the basis was the reference dose of 9.91 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).

cCalculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-methyloctanal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-Methyloctanal was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of 2-methyloctanal. However, read-across can be made to 2-methyldecanal (CAS # 19009-56-4; see Section VI). The mutagenic activity of 2-methyldecanal 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, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 2-methyldecanal 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 (RIFM, 2014a). Under the conditions of the study, 2-methyldecanal was not mutagenic in the Ames test, and this can be extended to 2-methyloctanal.

The clastogenic activity of 2-methyloctanal was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2-methyloctanal in DMSO at concentrations up to 270 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h 2-Methyloctanal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems, except in the presence of S9 at 4-h treatment condition. A small but statistically significant increase was observed at 135 μg/mL; however, this increase was well within the vehicle historical control range and was considered to be biologically not relevant (RIFM, 2014b). Under the conditions of the study, 2-methyloctanal was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 2-methyloctanal 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 margin of exposure (MOE) for 2-methyloctanal 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 2-methyloctanal. Read-across material 2-methylundecanal (CAS # 110-41-8; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In a GLP and OECD 408-compliant study, 10 Wistar Han rats/sex/dose were administered 2-methylundecanal via diet at concentrations of 0, 1500, 5000, and 15000 ppm (equivalent to 0, 107, 346, and 1046 mg/kg/day in males; and 0, 119, 401, 1211 mg/kg/day in females; according to the study report) for 90 days. No mortality was observed throughout the study period. No treatment-related effects were seen in clinical appearance, functional observations, ophthalmoscopy, body weight, food consumption, hematology, macroscopic examination, organ weights, or histopathology. Alkaline phosphatase levels were increased in males at the mid dose and in both sexes at the high dose (statistically significant; only dose-dependent in males). However, in the absence of any other liver enzyme changes or other macroscopic or microscopic changes seen in the liver, this finding was not considered adverse. Several coagulation and biochemical parameters were altered: prothrombin time was reduced in males at the mid and high dose (statistically significant; dose-dependent), bilirubin levels were reduced in males at the high dose (statistically significant; dose-dependent), urea levels were increased in males at the high dose (statistically significant; not dose-dependent), total protein levels were reduced in females at the

high dose (statistically significant; not dose-dependent), glucose levels were increased in females at the high dose (statistically significant; not dose-dependent), and inorganic phosphate levels were increased in females at the high dose (statistically significant; not dose-dependent). However, all these effects were slight in nature and occurred without correlated macroscopic or microscopic findings. Therefore, based on no toxicologically relevant adverse effects seen up to the highest dose, the NOAEL for this study was considered to be 15000 ppm (equivalent to 1046 mg/kg/day) (RIFM, 2018).

Therefore, the 2-methyloctanal MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-methylundecanal NOAEL in mg/kg/day by the total systemic exposure for 2-methyloctanal, 1046/0.000015 or 69733333.

In addition, the total systemic exposure to 2-methyloctanal (0.015 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*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 2-methyloctanal 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 2-methyloctanal. 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, 15000 ppm (equivalent to 147, 477, 1350 mg/kg/day) 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 compared to control. However, the food consumption in 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 substance. Furthermore, the numbers of pregnant females, corpora lutea, 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, 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 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, the NOAEL for developmental toxicity was derived from a more robust OECD 414 study and was considered to be 1350 mg/kg/day.

Therefore, the 2-methyloctanal 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 2-methyloctanal, 1350/0.000015, or 90000000.

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-methyloctanal 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-methyloctanal, 991/0.000015, or 66066667.

In addition, the total systemic exposure to 2-methyloctanal (0.015 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a reference dose (RfD) of 9.91 mg/kg/day.

11.1.3.2. Derivation of RfD. The RfD for 2-methyloctanal was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 991 mg/kg/day by the uncertainty factor, 100 = 9.91 mg/kg/day.

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 analog 2-methylundecanal (CAS # 110-41-8), 2-methyloctanal 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 2-methyloctanal. Based on the existing data and read-across 2-methylundecanal (CAS # 110-41-8; see Section VI), 2-methyloctanal 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 (Toxtree v3.1.0; OECD Toolbox v4.2). Read-across 2-methylundecanal was found to be positive in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens, and U-SENS tests (Natsch et al., 2013). In a murine local lymph node assay (LLNA), 2-methyloctanal was not found to be sensitizing when tested up to 5% (1250 μg/cm^2) (RIFM, 2008). In another LLNA, read-across 2-methylundecanal was found to be sensitizing with an EC3 value of 10% (2500 μg/cm^2) (Patlewicz et al., 2003; Gerberick et al., 2005; Roberts et al., 2007). In human maximization tests, no skin sensitization reactions were observed with 2-methyloctanal or read-across 2-methylundecanal (RIFM, 1977; RIFM, 1971). In a Confirmation of No Induction in Humans (CNIH) test with 97 μg/cm^2 of 2-methyloctanal in ethanol, no reactions indicative of sensitization were observed in any of the 44

Table 1
Data summary for 2-methylundecanal as read-across for 2-methyloctanal.

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.
Additional References: RIFM, 1962; Klecak (1985).
Literature Search and Risk Assessment Completed On: 02/26/21
[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.

volunteers (RIFM, 1965). Additionally, in a CNIH 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 CNIHs 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, 1991; RIFM, 1964).

Based on the available data and read-across 2-methylundecanal, 2-methyloctanal is a weak sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (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. (2020) and a RfD of 9.91 mg/kg/day.

11.1.5. Phototoxicity/photoallergenicity

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

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

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/18/21.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on 2-methyloctanal. Based on the Creme RIFM Model, the inhalation exposure is 0.00013 mg/day. This exposure is 10769 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 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 2-methyloctanal was performed following the RIFM Environmental Framework (Salvito et al., 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, 2-methyloctanal 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 2-methyloctanal 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 et al., 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).

11.2.2. Risk assessment

Not applicable.

11.2.2.1. Key studies. ***Biodegradation***: No data available.

Ecotoxicity: No data available.

Other available data: 2-Methyloctanal has been pre-registered for REACH with no additional information available at this time.

11.2.3. Risk assessment refinement

Not applicable.

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/

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.2022.113114.

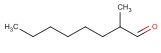
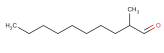
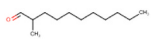
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). 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 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 (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, 2021).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2021).
- 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, 2021).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2021).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	2-Methyloctanal	2-Methyldecanal	2-Methylundecanal
CAS No.	7786-29-0	19009-56-4	110-41-8
Structure			
Similarity (Tanimoto Score)		0.91	0.83
Read-Across Endpoint		• Genotoxicity	• Skin sensitization • Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_9H_{18}O$	$C_{11}H_{22}O$	$C_{12}H_{24}O$

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Molecular Weight (g/mol)	142.24	170.30	184.32
Melting Point (°C, EPI Suite)	−30.54	−7.76	3.24
Boiling Point (°C, EPI Suite)	184.21	223.64	241.99
Vapor Pressure (Pa @ 25 °C, EPI Suite)	105	14.5	199
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	3.2	4.5[1]	4.9[4]
Log KOW	152.1	16[2]	1.3[5]
J_{max} (μg/cm^2/h, SAM)	17.644	2.70	0.22
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.93E-004	8.69E-004	1.15E-003
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found	
DNA Binding (OECDQSAR Toolbox v4.2)	• Schiff base former	• Schiff base former	
Carcinogenicity (ISS)	• Carcinogen (low reliability)	• Carcinogen (low reliability)	
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 compound	• Aldehyde type compound	
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)		• Non-toxicant (low reliability)
Skin Sensitization			
Protein Binding (OASIS v1.1)	• Schiff base formation		• Schiff base formation
Protein Binding (OECD)	• Schiff base former		• Schiff base former
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	See Supplemental Data 3

Summary

There are insufficient toxicity data on 2-methyloctanal (CAS # 7786-29-0). 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-methyldecanal (CAS # 19009-56-4) and 2-methylundecanal (CAS # 110-41-8) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 2-Methyldecanal (Cas # 19009-56-4) was used as a read-across analog for the target material, 2-methyloctanal (CAS # 7786-29-0), for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aldehydes.
  - o The target substance and the read-across analog share a common aliphatic branched aldehyde fragment.
  - o The key difference between the target substance and the read-across analog is that the target has an octane fragment, while the read-across has a decane fragment. This structural difference is toxicologically insignificant.
  - o The similarity between the target substance 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 substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The read-across analog and target material are predicted to have DNA binding alerts by OECD for genotoxicity, carcinogen by ISS, and are classified as aldehydes. All the other alerts are negative. Data superseded predictions in this case.
  - o The target substance 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, 2-methyloctanal (CAS # 7786-29-0), for the repeated dose toxicity, reproductive toxicity, and skin sensitization endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aldehydes.
  - o The target substance and the read-across analog share a common aliphatic branched aldehyde fragment.
  - o The key difference between the target substance and the read-across analog is that the target has an octane fragment, while the read-across has an undecane fragment. 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 substance 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 substance 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. $J_{max} \leq 80\%$ for the target substance 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 substance and the read-across analog.
- o The read-across analog and the target material are predicted to have positive protein binding (Schiff base formation) alerts by OASIS and OECD model for skin sensitization. All the other alerts for skin sensitization were predicted to be negative. The data on the read-across analog confirms that the analog is a skin sensitizer. Therefore, *in silico* alerts are consistent with data.
- o The target substance 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.

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