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Short Review

RIFM fragrance ingredient safety assessment, 2-methyldecanal, CAS Registry Number 19009-56-4

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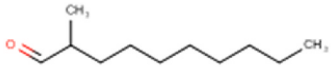

Name: 2-Methyldecanal

CAS Registry Number: 19009-56-4

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., 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; 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

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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-Methyldecanal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on 2-methyldecanal and read-across analog 2-methyloctanal (CAS # 7786-29-0) show that 2-methyldecanal is not expected to be genotoxic. Data on read-across analog 2-methylundecenal (CAS # 110-41-8) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data on 2-methyldecanal provided a No Expected Sensitization Induction Level (NESIL) of 5900 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-methyldecanal 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 2-methyldecanal is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2-methyldecanal 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 expected to be genotoxic.	(RIFM, 2014a; RIFM, 2014f)
Repeated Dose Toxicity: NOAEL = 1046 mg/kg/day.	RIFM (2018)
Reproductive Toxicity: Developmental toxicity NOAEL: 1350 mg/kg/day. Fertility NOAEL: 991 mg/kg/day.	(RIFM, 2019a; RIFM, 2019b)
Skin Sensitization: NESIL = 5900 μg/cm^2.	RIFM (2016a)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic.	(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 80% after 36 days (OECD 301F)	(ECHA REACH Dossier: 2-Methyldecan-1-al; ECHA, 2018; RIFM, 2011)
Bioaccumulation: Critical Measured Value: 11.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 0.382 mg/L	(ECOSAR; US ECHA, 2012b; RIFM, 2014e)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* EC50: 0.382 mg/L	(ECOSAR; US US EPA, 2012b)

RIFM PNEC is: 0.0382 μg/L

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

1. Identification

1. **Chemical Name:** 2-Methyldecanal

2. **CAS Registry Number:** 19009-56-4
3. **Synonyms:** Aldehyde C11 MOA; Decanal, 2-methyl-; Methyl octyl acetaldehyde; ｱﾙｶﾅｰﾙ(C = 4～19); Aldehyd C11 MOA; 2-Methyldecanal
4. **Molecular Formula:** $C_{11}H_{22}O$
5. **Molecular Weight:** 170.29
6. **RIFM Number:** 641
7. **Stereochemistry:** Isomer not specified. One chiral center and a total of 2 enantiomers possible.

2. Physical data

1. **Boiling Point:** 204.9 °C (478.1 K) at 102.2 kPa (RIFM, 2013c), 170 °C (Fragrance Materials Association [FMA]), 223.64 °C (EPI Suite)
2. **Flash Point:** 81 °C (Globally Harmonized System), 178 °F; CC (FMA)
3. **Log K_{OW}:** 4.5 (RIFM, 2013b), 5.4 (RIFM, 2014b), 4.18 (EPI Suite)
4. **Melting Point**: −36 °C at 102.3 kPa (RIFM, 2013d), −7.76 °C (EPI Suite)
5. **Water Solubility:** 16 mg/L at 20 °C (RIFM, 2014d), 16.49 mg/L (EPI Suite)
6. **Specific Gravity:** 0.824 (FMA)
7. **Vapor Pressure:** 5.39 Pa, $4.0 \times 10^{(-2)}$ mm Hg at 20 °C (RIFM, 2014c), 8.24 Pa, $6.2 \times 10^{(-2)}$ mm Hg at 25 °C (RIFM, 2014c), 56.36 Pa, $4.2 \times 10^{(-1)}$ mm Hg at 50 °C (RIFM, 2014c), 0.0713 mm Hg at 20 °C (EPI Suite v4.0), 0.04 mm Hg at 20 °C (FMA), 0.109 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient (6 L $mol^{-1} \bullet cm^{-1}$, condition not specified) is below the benchmark (1000 L $mol^{-1} \bullet cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless liquid powerful refreshing dry citrusy odor of moderate tenacity (Arctander, 1969)

3. Volume of use (worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.2)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.025% (RIFM, 2020a)
2. **Inhalation Exposure*:** 0.00017 mg/kg/day or 0.012 mg/day (RIFM, 2020a)
3. **Total Systemic Exposure**:** 0.0012 mg/kg/day (RIFM, 2020a)

*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-Methyloctanal (CAS # 7786-29-0)
b. **Repeated Dose Toxicity:** 2-Methylundecenal (CAS # 110-41-8)
c. **Reproductive Toxicity:** 2-Methylundecanal (CAS # 110-41-8)
d. **Skin Sensitization:** None
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-Methyldecanal 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 (ECHA, 2018); accessed 11/10/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-methyldecanal 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)	0.25
2	Products applied to the axillae	0.14
3	Products applied to the face/body using fingertips	2.7
4	Products related to fine fragrances	2.5
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.64
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.64
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.64
5D	Baby cream, oil, talc	0.21
6	Products with oral and lip exposure	0.25

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(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
7	Products applied to the hair with some hand contact	5.2
8	Products with significant ano-genital exposure (tampon)	0.21
9	Products with body and hand exposure, primarily rinse-off (bar soap)	4.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	18
10B	Aerosol air freshener	18
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.21
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-methyldecanal, the basis was the reference dose of 9.91 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 5900 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, 2-methyldecanal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 2-Methyldecanal was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013a). 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.

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.

There are no studies assessing the clastogenic activity of 2-methyldecanal. However, read-across can be made to 2-methyloctanal (CAS # 7786-29-0; see Section VI). 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 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 small but statistically significant increase was observed at 135 μg/mL; however, these increases were well within vehicle historical control range and were considered to be biologically not relevant (RIFM, 2014f). Under the conditions of the study, 2-methyloctanal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-methyldecanal.

Based on the available data, 2-methyldecanal 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 2-methyldecanal 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-methyldecanal. 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, and 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 doses (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-methyldecanal 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-methyldecanal, 1046/0.0011, or 950909.

In addition, the total systemic exposure to 2-methyldecanal (1.1 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-methyldecanal 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-methyldecanal. 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, and 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 as compared to the 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 2-methyldecanal 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-methyldecanal, 1350/0.0011 or 1227273.

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, 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-methyldecanal 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-methyldecanal, 991/0.0011, or 900909.

In addition, the total systemic exposure to 2-methyldecanal (1.1 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. (RIFM, 2020c) and a reference dose (RfD) of 9.91 mg/kg/day.

Derivation of RfD

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for 2-methyldecanal was calculated by dividing the lowest NOAEL (from the Repeated Dose and 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, 2-methyldecanal is considered a skin sensitizer with a defined NESIL of 5900 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, 2-methyldecanal is a weak sensitizer with a NESIL of 5900 μg/cm^2. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). 2-Methyldecanal was found to be positive in *in vitro* Direct Peptide Reactivity Assay (DPRA) and human cell line activation test (h-CLAT), but negative in the KeratinoSens (RIFM, 2016b; RIFM, 2016c; RIFM, 2017). In a murine local lymph node assay (LLNA), 2-methyldecanal was found to be sensitizing with an EC3 value of 23.6% (5900 μg/cm^2) (RIFM, 2010). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1975). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 5905 μg/cm^2 of 2-methyldecanal in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 102 volunteers (RIFM, 2016a). In another CNIH with 388 μg/cm^2 of 2-methyldecanal in ethanol, no reactions indicative of sensitization were observed in any of the 39 volunteers (RIFM, 1965).

Based on weight of evidence (WoE) from structural analysis and animal and human studies, 2-methyldecanal is a weak sensitizer with a WoE NESIL of 5900 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, 2020c) and a reference dose of 9.91 mg/kg/day.

Additional References: RIFM, 1970.

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

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-methyldecanal 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-methyldecanal in experimental models. UV/Vis absorption spectra indicate minor 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-methyldecanal 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

Table 1
Data summary for 2-methyldecanal.

LLNA weighted mean EC3 value μg/cm^2 [No. Studies]	Potency Classification Based on Animal ata[1]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[2] (induction)μg/cm^2	WoE NESIL[3] μg/cm^2
5900 []	Weak	5905	6900	N/A	5900

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.
[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2] Data derived from CNIH or HMT.
[3] WoE NESIL limited to 2 significant figures.

of 290–700 nm. The molar absorption coefficient (6 L mol^{-1} • cm^{-1}, condition not specified) 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: 03/01/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-methyldecanal 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-methyldecanal. Based on the Creme RIFM Model, the inhalation exposure is 0.012 mg/day. This exposure is 116.7 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-methyldecanal 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. 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, 2-methyldecanal 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 2-methyldecanal 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 ≥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), 2-methyldecanal presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation

RIFM, 2011: The ready biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D method. Under the conditions of the study, the test material was found to be biodegradable by 41% over a period of 28 days.

Ecotoxicity

RIFM, 2014e: A fish (*Oryzias latips*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions and in a closed system. The 96-h LC50 based on the mean measured concentration was reported to be 1.819 mg/L.

Other available data

2-Methyldecanal has been registered for REACH with the following additional information available at this time (ECHA, 2018):

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 77% was observed after 28 days and 80% after 36 days.

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on a time-weighted average concentration was reported to be 31.8 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guidelines under static conditions. The 72-h EC50 values based on time-weighted average concentration for growth rate and yield were reported to be 30.5 mg/L and 9.4 mg/L, respectively. The 72-h EC10 values based on a time-weighted average for growth rate and yield were reported to be 6.15 mg/L and <0.248 mg/L, respectively.

11.2.3. Risk assessment refinement

Since 2-methyldecanal has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)		EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.253				1000000	0.000253	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	0.702	0.382		0.955	10000	0.0382	Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.540	1.069		1.831			Neutral Organic SAR

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 Framework: Salvito et al., 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	5.4	5.4
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 additional assessment is necessary.

The RIFM PNEC is 0.0382 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: 03/08/21.

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 11/10/21.

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.2023.113899.

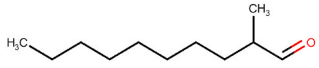
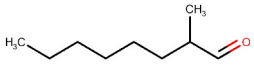
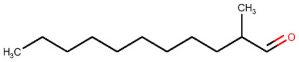
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020b). These criteria follow 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 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, oncologic classification, ER binding, and repeat dose categorization predictions 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).
- 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-Methyldecanal	2-Methyloctanal	2-Methylundecanal
CAS No.	19009-56-4	7786-29-0	110-41-8
Structure			
Similarity (Tanimoto Score)		1.00	1.00
Endpoint		• Genotoxicity	• Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_{11}H_{22}O$	$C_9H_{18}O$	$C_9H_{18}O$
Molecular Weight	170.30	142.24	142.24
Melting Point (°C, EPI Suite)	−7.76	−30.54	−35.47
Boiling Point (°C, EPI Suite)	223.64	184.21	163.16
Vapor Pressure (Pa @ 25°C, EPI Suite)	14.5	105	180
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	16.5	152.1	5.4
Log K_{OW}	4.2	3.2	4.7
J_{max} (μg/cm^2/h, SAM)	2.70	17.644	16.59
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	8.69E-004	4.93E-004	4.93E-004
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			

(*continued on next page*)

(*continued*)

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

Conclusions

- 2-Methyloctanal (CAS # 7786-29-0) was used as a read-across analog for the target material, 2-methyldecanal (CAS # 19009-56-4), for the genotoxicity endpoint.
  - 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 a decane fragment while the read-across has an octane fragment. This structural difference is toxicologically insignificant.
  - o 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. 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 The physical–chemical properties of the target material 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 material and the read-across analog.
  - o The read-across analog and target material are predicted to have DNA binding alerts by OECD for genotoxicity, carcinogenicity by ISS, and are classified as aldehydes. All the other alerts are 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.
- 2-Methylundecanal (CAS # 110-41-8) was used as a read-across analog for the target material, 2-methyldecanal (CAS # 19009-56-4), for the repeated dose toxicity and reproductive toxicity 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 while the target material 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 material.
  - o 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 According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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