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RIFM fragrance ingredient safety assessment, 2-methylpentanal, CAS Registry Number 123-15-9

A.M. Api [a], D. Belsito [b], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], M.A. Cancellieri [a], H. Chon [a], M.L. Dagli [e], M. Date [a], W. Dekant [f], C. Deodhar [a], A.D. Fryer [g], L. Jones [a], K. Joshi [a], M. Kumar [a], A. Lapczynski [a], M. Lavelle [a], I. Lee [a], D.C. Liebler [h], H. Moustakas [a], M. Na [a], T.M. Penning [i], G. Ritacco [a], J. Romine [a], N. Sadekar [a], T.W. Schultz [j], D. Selechnik [a], F. Siddiqi [a], I.G. Sipes [k], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [l]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Fragrance Safety, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Fragrance Safety, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Fragrance Safety, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Fragrance Safety, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[f] *Fragrance Safety, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[g] *Fragrance Safety, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[h] *Fragrance Safety, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[i] *Member of Expert Panel for Fragrance Safety, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[j] *Fragrance Safety, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[k] *Fragrance Safety, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[l] *Fragrance Safety, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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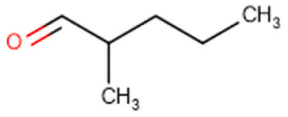

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Name: 2-Methylpentanal CAS Registry Number: 123-15-9

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)

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 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 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-Methylpentanal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-ethylhexanal (CAS # 123-05-7) show that 2-methylpentanal is not expected to be genotoxic. Data provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog 2-methylundecanal (CAS # 110-41-8) provide 2-methylpentanal 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-methylpentanal is not expected to be phototoxic/photoallergenic. Data on read-across analog isobutyraldehyde (CAS # 78-84-2) provide a calculated MOE >100 for the local respiratory endpoint. For the hazard assessment based on the screening data, 2-methylpentanal is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, 2-methylpentanal was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

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Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(ECHA REACH Dossier: 2-Methylvaleraldehyde; ECHA, 2013; Zeiger et al., 1988; ECHA REACH Dossier: 2-Ethylhexanal; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 20.8 mg/kg/day.	JECDB (2012)
Reproductive Toxicity: Developmental toxicity NOAEL: 1000 mg/kg/day. Fertility NOAEL: 1000 mg/kg/day.	JECDB (2012)
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: NOAEC = 147.4 mg/m^3.	NTP (1999)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 45% (OECD 301F)	(ECHA REACH Dossier: 2-Methylvaleraldehyde; ECHA, 2013)
Bioaccumulation: Screening-level: 6.385 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-Methylpentanal
2. **CAS Registry Number:** 123-15-9
3. **Synonyms:** 2-Methylvaleraldehyde; 2-Methylpentanal
4. **Molecular Formula:** $C_6H_{12}O$
5. **Molecular Weight:** 100.16 g/mol
6. **RIFM Number:** 1403
7. **Stereochemistry:** Isomer not specified. One chiral center and 2 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 118.3 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 1.67 (Biobyte Corp.), 1.73 (EPI Suite)
4. **Melting Point**: −66.68 °C (EPI Suite)
5. **Water Solubility:** 3930 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 17.9 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:** Not Available

3. Volume of use (Worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00003% (RIFM, 2020a)

   (No reported use in Fine Fragrance).

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2020a)
3. **Total Systemic Exposure**:** 0.0000006 mg/kg/day (RIFM, 2020a)

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

1. **Cramer Classification:** I, Low

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

2. Analogs Selected:
   a. **Genotoxicity:** 2-Ethylhexanal (CAS # 123-05-7)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-Methylundecanal (CAS # 110-41-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Isobutyraldehyde (CAS # 78-84-2)
   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

2-Methylpentanal is reported to occur in the following foods by the VCF*:

Allium Species	Gabirorba (*Campomanesia xanthocarpa*)
Beef	*Magnifera* species
Beer	Pork
Capers (*Capparis spinoza*)	Rice (*Oryza sativa* L.)
Capsicum species	Tea
Coffee	Trassi (cooked)
Desert truffle (*Terfeziaceae*)	Wheaten bread

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

9. REACH dossier

Available; accessed 02/04/21 (ECHA, 2013).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-methylpentanal 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	0.28
4	Products related to fine fragrances	0.28
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.28
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.28
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.28
5D	Baby cream, oil, talc	0.092
6	Products with oral and lip exposure	0.28
7	Products applied to the hair with some hand contact	0.28
8	Products with significant ano-genital exposure (tampon)	0.092
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.28
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.28
10B	Aerosol air freshener	0.28
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.092
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	0.28

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-methylpentanal, the basis was the subchronic reference dose of 0.208 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 2900 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

1. Human Health Endpoint Summaries:

11.1. Genotoxicity

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

11.1.1. Risk assessment

The mutagenic activity of 2-methylpentanal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in a similar manner to OECD TG 471 using the pre-incubation method. *Salmonella typhimurium* strains TA 98 and TA Mix 7001–7006 were treated with 2-methylpentanal in dimethyl sulfoxide (DMSO) at concentrations up to 7500 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2013). Under the conditions of the study, 2-methylpentanal was not mutagenic in the Ames test.

Due to the lack of strains tested in the Ames test and the lack of studies on the clastogenic activity of 2-methylpentanal, read-across can be made to 2-ethylhexanal (CAS # 123-05-7; see Section VI).

The mutagenic activity of 2-ethylhexanal has been evaluated in a bacterial reverse mutation assay conducted equivalent to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 were treated with 2-ethylhexanal in DMSO at concentrations up to 666 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (Zeiger, 1988). Under the conditions of the study, 2-ethylhexanal was not mutagenic in the Ames test, and this can be extended to 2-methylpentanal.

The clastogenic activity of 2-ethylhexanal 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 body weight were administered. Mice from each dose level were euthanized at 1, 2, 4, 6, or 24 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011). Under the conditions of the study, 2-ethylhexanal was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to 2-methylpentanal.

Based on the data available, 2-ethylhexanal does not present a concern for genotoxic potential, and this can be extended to 2-methylpentanal.

Additional References: Florin et al., 1980.

Literature Search and Risk Assessment Completed On: 03/11/21.

11.2. Repeated dose toxicity

The MOE for 2-methylpentanal is adequate for the repeated dose toxicity endpoint at the current level of use.

11.2.1. Risk assessment

There are sufficient repeated dose toxicity data on 2-methylpentanal. In a GLP-compliant study designed similarly to OECD 422 guidelines, 12 Crl:CD(SD) rats/sex/dose were administered 2-methylpentanal via gavage at doses of 0, 62.5, 250, and 1000 mg/kg/day. Males were treated for 42 days, while females were treated for 2 weeks before mating, the period of mating and pregnancy, and up to day 4 of nursing (41–47 days total). An additional 5 Crl:CD(SD) rats/sex/dose at 0 and 1000 mg/kg/day were maintained as recovery groups for 14 days after the treatment period. Transient increases in body weight were observed in males at the mid dose and in females at the mid dose and high dose; these were not accompanied by any changes in body weight. Ambulation count and rearing count decreased in females at the high dose. Spleen weight was increased in females at the high dose. Hyperkeratinization, hyperplasia of the squamous epithelial cell layer, infiltration of inflammatory cells into the submucosa, and edema of the lamina propria and submucosa in the forestomach were observed in both sexes at the mid dose and high dose. Focal erosion was observed in females at the high dose. Most effects were reversed except for those observed in the forestomach, which lessened in severity. Based on the histopathological changes observed in the stomach in both sexes at the mid dose and high dose, the NOAEL for this study was considered to be 62.5 mg/kg/day (JECDB, 2012).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 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 62.5/3, or 20.8 mg/kg/day.

Therefore, the 2-methylpentanal MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-methylpentanal NOAEL in mg/kg/day by the total systemic exposure for 2-methylpentanal, 20.8/0.0000006, or 34666666.

In addition, the total systemic exposure to 2-methylpentanal (0.0006 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.

11.2.1.1. 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, 2020c) and a subchronic RfD of 0.208 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 2-methylpentanal was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 20.8 mg/kg/day by the uncertainty factor, 100 = 0.208 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: 03/13/21.

11.3. Reproductive toxicity

The MOE for 2-methylpentanal is adequate for the reproductive toxicity endpoint at the current level of use.

11.3.1. Risk assessment

There are sufficient reproductive toxicity data on 2-methylpentanal that can be used to support the reproductive toxicity endpoint. An OECD 422/GLP combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats with 2-methylpentanal. Groups of 12 rats/sex/dose were exposed to the test material 2-methylpentanal at doses of 0, 62.5, 250, and 1000 mg/kg/day in corn oil via oral gavage. Female rats were treated for 14 days prior to mating and continuing through lactation day 4, and male rats were treated for 42 days. In addition, 0 and 1000 mg/kg satellite groups of non-mating females (10 animals per group) were prepared, with 5 animals of each group necropsied after 42 days of administration. No treatment-related mortality was observed during the study. No treatment-related effects were seen with respect to reproductive parameters in males or females. No adverse effects with respect to histopathology of reproductive organs were observed. Further, no treatment-related effects were seen on offspring. Hence, fertility and developmental toxicity NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (JECDB, 2012).

Therefore, the 2-methylpentanal MOE for the fertility endpoint can be calculated by dividing the 2-methylpentanal NOAEL in mg/kg/day by the total systemic exposure for 2-methylpentanal 1000/0.0000006, or 1666666667.

In addition, the total systemic exposure to 2-methylpentanal (0.0006 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.

Additional References: None.

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

11.4. Skin sensitization

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

11.4.1. Risk assessment

Insufficient skin sensitization studies are available for 2-methylpentanal. Based on the existing data and read-across material 2-methylundecanal (CAS # 110-41-8; see Section VI), 2-methylpentanal is considered a skin sensitizer. The chemical structures of these materials indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, 2-methylundecanal, was found to be positive in an *in vitro* direct peptide reactivity assay, KeratinoSens assay, and U937-CD86 test (Natsch, 2013). In a murine local lymph node assay (LLNA), the target material 2-methylpentanal was found to be sensitizing with an EC3 value of 81.54% (20385 μg/cm^2) (ECHA, 2013). 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; Roberts et al., 2007). In a human maximization test, no skin sensitization reactions were observed with read-across material 2-methylundecanal (RIFM, 1971). Additionally, in 2 Confirmation of No Induction in Humans (CNIH) tests with 969 μg/cm^2 and 388 μg/cm^2 of read-across material 2-methylundecanal in ethanol, no reactions indicative of sensitization were observed in any of the 40 volunteers, respectively (EPA, 1991; RIFM, 1964). In an additional CNIH with 2953 μg/cm^2 of read-across material 2-methylundecanal in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 102 volunteers (RIFM, 2016).

Based on the weight of evidence (WoE) from structural analysis, animal studies, and data on the read-across material 2-methylundecanal, 2-methylpentanal is a sensitizer with a WoE NESIL of 2900 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020c) and a subchronic RfD of 0.208 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/22/21.

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

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[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
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.
[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.

11.5. Phototoxicity/photoallergenicity

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

11.5.1. Risk assessment

There are no phototoxicity studies available for 2-methylpentanal 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-methylpentanal does not present a concern for phototoxicity or photoallergenicity.

11.5.2. 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.

11.6. Local respiratory toxicity

There are no inhalation data available on 2-methylpentanal; however, in a 2-year inhalation exposure study for the read-across analog isobutyraldehyde (CAS # 78-84-2; see Section VI), a LOAEC of 1474.44 mg/m^3 is reported (Abdo, 1998).

11.6.1. Risk assessment

The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a chronic carcinogenicity study (according to GLP and similar to OECD 451), 50 F344/N rats/sex/group were exposed via inhalation to 0, 1474.44, 2948.88, and 5897.75 mg/m^3 of isobutyraldehyde vapors for 6 h/day, 5 days/week, for 2 years (Abdo, 1998; NTP, 1999). A complete necropsy was carried out on all animals. Exposure-related effects were localized in the nasal region. Respiratory epithelium squamous metaplasia was observed in 1/50, 1/49, 10/49, and 44/50 males and in 1/49, 11/50, 9/49, and 44/50 females from the 0, 1474.44, 2948.88, and 5897.75 mg/m^3 exposure groups, respectively. Suppurative inflammation was seen in 5/50, 3/49, 6/49, and 15/50 males and 2/49, 3/50, 5/49, and 11/50 females from the 0, 1474.44, 2948.88, and 5897.75 mg/m^3 exposure groups, respectively. Olfactory epithelium degeneration was observed in 0/50,0/49, 3/49, and 44/50 males and 0/49, 0/50, 2/49, and 45/50 females from the 0, 1474.44, 2948.88, and 5897.75 mg/m^3 exposure groups, respectively. Females were more sensitive to the effects in the respiratory epithelium, as seen at the lowest exposure group. Therefore, the LOAEC for the local respiratory effects was identified at 1474.44 mg/m^3. A NOAEC of 147.4 mg/m^3 is calculated using the safety factor of 10.

This NOAEC expressed in mg/kg lung weight/day is:

- (147.4 mg/m^3) × (1 m^3/1000 L) = 0.1474 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.1474 mg/L) × (61.2 L/day) = 9.02 mg/day
- (9.02 mg/day)/(0.0016 kg lung weight of rat*) = 5637.5 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be < 0.0001 mg/day; this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015; Safford et al.,

2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.00015 mg/kg lung weight/day resulting in a MOE of at least 37583333 (i.e., [5637.5 mg/kg lung weight of rat/day]/[0.00015 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at <0.0001 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/11/21.

2. Environmental Endpoint Summary:

11.7. Screening-level assessment

A screening-level risk assessment of 2-methylpentanal 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, 2-methylpentanal 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) identified 2-methylpentanal as possibly persistent but not bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.8. Risk assessment

Not applicable.

11.9. Key studies

11.9.1. Biodegradation

No data available.

11.9.2. Ecotoxicity

No data available.

11.10. Other available data

2-Methylpentanal has been registered for REACH with the following additional information available at this time (ECHA, 2013):

The ready biodegradability of the test material was evaluated using the manometric respirometry test according to the OECD 301F guideline. Biodegradation of 45% was observed after 28 days.

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 value based on the mean measured concentration was reported to be 27.7 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 value based on the arithmetic mean measured concentration for growth rate was reported to be 61 mg/L (95% CI: 28.8–32.7 mg/L).

Risk Assessment Refinement: Not applicable.

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

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 12/08/21.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113007.

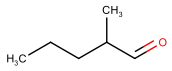
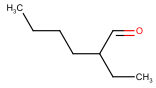
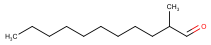
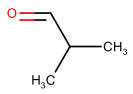
Appendix

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. (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 substance 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 choice of the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	2-Methylpentanal	2-Ethylhexanal	2-Methylundecanal	Isobutyraldehyde
CAS No.	123-15-9	123-05-7	110-41-8	78-84-2
Structure				
Similarity (Tanimoto Score)		0.79	0.68	0.60
Endpoint		Genotoxicity	Skin sensitization	Local respiratory toxicity
Molecular Formula	$C_6H_{12}O$	$C_8H_{16}O$	$C_{12}H_{24}O$	C_4H_8O
Molecular Weight (g/mol)	100.161	128.215	184.323	72.107
Melting Point (°C, EPI Suite)	−66.68	−42.32	3.24	−65.90
Boiling Point (°C, EPI Suite)	117.00	163.00	171.00	64.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.39E+03	2.67E+02	1.99E+02	2.31E+04
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	4.20E+03	4.00E+02	5.37E+00	8.90E+04
Log KOW	1.73	3.07	4.67	0.74
J_{max} (μg/cm^2/h, SAM)	203.58	51.20	0.87	1875.91
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.14E+01	8.51E+01	1.17E+02	1.82E+01
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|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers		

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
Carcinogenicity (ISS)	Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes 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		
Skin Sensitization				
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes		Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	
Protein Binding (OECD)	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls		Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	
Protein Binding Potency	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes		Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.		Alert for Schiff base formation identified.	
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on 2-methylpentanal (CAS 123-15-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, read-across materials 2-ethylhexanal (CAS 123-05-7), 2-methylundecanal (CAS # 110-41-8), and isobutyraldehyde (CAS # 78-84-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 2-Ethylhexanal (CAS 123-05-7) was used as a read-across analog for the target material, 2-methylpentanal (CAS 123-15-9), for the genotoxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to a class of aliphatic aldehydes.
  - The key difference between the target substance and the read-across analog is that the read-across analog has a longer carbon chain length compared to the target substance. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog have an alert for Schiff base formation. This is because of the aldehyde group, which can form a Schiff base with proteins. The data on the read-across analog confirm that the analog does not pose a concern for genetic toxicity under the current levels of use. Therefore, based on the structural similarity between the target substance and the read-across analog and the data on the read-across analog, the predictions are superseded by data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-methylundecanal (CAS # 110-41-8) was used as a read-across analog for the target material, 2-methylpentanal (CAS 123-15-9), for the skin sensitization endpoint.

- The target substance and the read-across analog are structurally similar and belong to a class of aliphatic aldehydes.
- The key difference between the target substance and the read-across analog is that the read-across analog has a longer carbon chain length compared to the target substance. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
- The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target substance corresponds to skin absorption $\leq$80% and J_{max} for the read-across analog corresponds to skin absorption $\leq$10%. While the percentage of 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.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- The target substance and the read-across analog have an alert for Schiff base formation. This is because of the aldehyde group, which can form a Schiff base with proteins. The data on the read-across analog confirm that the analog is a sensitizer. Therefore, *in silico* alerts are consistent with data.
- The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Isobutyraldehyde (CAS # 78-84-2) was used as a read-across analog for the target material, 2-methylpentanal (CAS 123-15-9), for the local respiratory toxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to a class of aliphatic aldehydes.
  - The key difference between the target substance and the read-across analog is that the read-across analog has a shorter carbon chain length compared to the target substance. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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