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RIFM fragrance ingredient safety assessment, isopropyl 2-methylbutyrate, CAS Registry Number 66576-71-4

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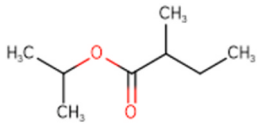


Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest 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.
Isopropyl 2-methylbutyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that isopropyl 2-methylbutyrate is not genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to isopropyl 2-methylbutyrate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog 1,3-dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5) show that there are no safety concerns for isopropyl 2-methylbutyrate for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; isopropyl 2-methylbutyrate is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; isopropyl 2-methylbutyrate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current Volume of Use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 1999b; ECHA REACH Dossier: Isopropyl 2-methylbutyrate; ECHA, 2018)

Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: No concern for skin sensitization.
(ECHA REACH Dossier: 1,3-Dimethylbut-3-enyl isobutyrate; ECHA, 2016)
Photoirritation/Photoallergenicity: Not photoirritating/photoallergenic. (UV/Vis Spectra; RIFM Database; RIFM, 1982)

(*continued on next page*)

(*continued*)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical Measured Value: 63% (OECD 301F)	RIFM (1998a)
Bioaccumulation:	
Screening-level: 27.3 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: 96-h Algae EC50: 5.692 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 96-h Algae EC50: 5.692 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.5692 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: <1	

1. Identification

1. **Chemical Name:** Isopropyl 2-methylbutyrate
2. **CAS Registry Number:** 66576-71-4
3. **Synonyms:** Butanoic acid, 2-methyl-, 1-methylethyl ester; Isopropyl 2-methylbutanoate; Isopropyl 2-methylbutyrate
4. **Molecular Formula:** $C_8H_{16}O_2$
5. **Molecular Weight:** 144.21 g/mol
6. **RIFM Number:** 6826
7. **Stereochemistry:** Isomer not specified. One stereocenter and a total of 2 stereoisomers are possible.

2. Physical data

1. **Boiling Point:** 143.81 °C (EPI Suite)
2. **Flash Point:** 33 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.3 at 35 °C (RIFM, 1998b), 2.68 (EPI Suite)
4. **Melting Point**: −55.3 °C (EPI Suite)
5. **Water Solubility:** 412.1 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 3.88 mm Hg at 20 °C (EPI Suite v4.0), 4.0 mm Hg at 20 °C (Fragrance Materials Association), 5.34 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)

1.10–100 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.000% (RIFM, 2020)
2. **Inhalation Exposure*:** 0.00020 mg/kg/day or 0.015 mg/day (RIFM, 2020)
3. **Total Systemic Exposure**:** 0.0023 mg/kg/day (RIFM, 2020)

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

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:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** 1,3-Dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5)
e. **Photoirritation/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

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

Strawberry (*Fragaria* species)

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that

have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed on 01/27/22 (ECHA, 2018).

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of isopropyl 2-methylbutyrate 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 and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA97, and TA102 were treated with isopropyl 2-methylbutyrate 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 concentration in the presence or absence of S9 (RIFM, 1999b). Under the conditions of the study, isopropyl 2-methylbutyrate was not mutagenic in the Ames test.

The clastogenicity of isopropyl 2-methylbutyrate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with isopropyl 2-methylbutyrate in DMSO. The main study was conducted at concentrations up to 1444 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2018). Under the conditions of the study, isopropyl 2-methylbutyrate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, isopropyl 2-methylbutyrate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/21/22.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on isopropyl 2-methylbutyrate or any read-across materials. The total systemic exposure to isopropyl 2-methylbutyrate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on isopropyl 2-methylbutyrate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to isopropyl 2-methylbutyrate (2.3 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/13/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on isopropyl 2-methylbutyrate or any read-across materials. The total systemic exposure to isopropyl 2-methylbutyrate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on isopropyl 2-methylbutyrate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to isopropyl 2-methylbutyrate (2.3 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: 01/13/22.

11.1.4. Skin sensitization

Based on the existing data and the read-across material 1,3-dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5), isopropyl 2-methylbutyrate does not present a safety concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for isopropyl 2-methylbutyrate. Therefore, read-across material 1,3-

Table 1
Summary of existing data on 1,3-dimethylbut-3-enyl isobutyrate as a read-across for isopropyl 2-methylbutyrate.

WoE Skin Sensitization Potency Category[a]	Human Data NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	Animal Data LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
No evidence of sensitization[g]	6202	NA	NA	NA	25000	NA	NA
	***In vitro* Data[f]**				***In silico* protein binding alerts (OECD Toolbox v4.2)**		
	KE 1	**KE 2**	**KE 3**		**Target**	**Autoxidation simulator**	**Metabolism simulator**
	NA	NA	NA		No alert found	Michael addition	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[e] Studies conducted according to the OECD TG 406 are included in the table.

[f] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[g] Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients.

dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5; see Section VI) was used for the risk assessment of isopropyl 2-methylbutyrate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, isopropyl 2-methylbutyrate is not considered a skin sensitizer. The chemical structure of the read-across material and the target material indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay, read-across material 1,3-dimethylbut-3-enyl isobutyrate was found to be non-sensitizing up to 100% (ECHA, 2016). In guinea pigs, a maximization test with isopropyl 2-methylbutyrate did not present reactions indicative of sensitization (RIFM, 1999a). Additionally, in 2 separate Confirmation of No Induction in Humans tests (CNIH) with read-across material 1,3-dimethylbut-3-enyl isobutyrate at 6202 μg/cm^2 in white petrolatum and 1938 μg/cm^2 in alcohol SDA 39c, no sensitization reactions were observed in any of the 54 and 43 volunteers, respectively (RIFM, 1979; RIFM, 1973). In a CNIH with 20% isopropyl 2-methylbutyrate in white petrolatum, no reactions indicative of sensitization were observed in any of the 50 volunteers (RIFM, 1982).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies on the read-across material as well as the target material, isopropyl 2-methylbutyrate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/17/22.

11.1.5. Photoirritation/photoallergenicity

Based on the UV/Vis absorption spectra and available human data, isopropyl 2-methylbutyrate would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). In a photo-CNIH, photoirritation and photoallergenicity were not observed following topical application of 20% isopropyl 2-methylbutyrate in white petrolatum (RIFM, 1982). Based on the lack of absorbance and human study data, isopropyl 2-methylbutyrate does not present a concern for photoirritation or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/12/22.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for isopropyl 2-methylbutyrate 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 isopropyl 2-methylbutyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.015 mg/day. This exposure is 93.4 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: 01/21/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of isopropyl 2-methylbutyrate 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, isopropyl 2-methylbutyrate 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 isopropyl 2-methylbutyrate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2019), isopropyl 2-methylbutyrate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation:

RIFM, 1998a: The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F guidelines. Vessels containing mineral medium inoculated with activated sludge and 100 mg/L of isopropyl 2-methylbutyrate were incubated for 28 days. The biodegradation rate was 58% at the end of 10

days and 63% after 28 days.

Ecotoxicity:

No data available.

Other available data:

Isopropyl 2-methylbutyrate has been registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L)

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	14.36			1000000	0.01436	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	7.71	14.89	5.692	10000	0.5692	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	28.93	17.49	16.9			Neutral Organic

Exposure information and PEC calculation (following RIFM Framework: Salvito et al., 2002)

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.3	3.3
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	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 0.5692 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: 05/24/22.

13. 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 06/16/22.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113316.

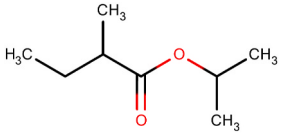
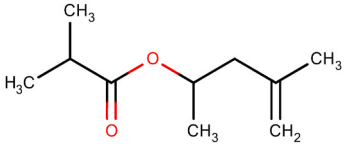
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Isopropyl 2-methylbutyrate	1,3-Dimethylbut-3-enyl isobutyrate
CAS No.	66576-71-4	80118-06-5
Structure		
Similarity (Tanimoto Score)		0.56
Endpoint		Skin sensitization
Molecular Formula	$C_8H_{16}O_2$	$C_{10}H_{18}O_2$
Molecular Weight (g/mol)	144.21	170.25
Melting Point (°C, EPI Suite)	−55.30	−41.49
Boiling Point (°C, EPI Suite)	143.81	179.45
Vapor Pressure (Pa @ 25°C, EPI Suite)	711.94	132.26
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	412.10	53.36
Log K_{OW}	2.68	3.58
J_{max} (μg/cm^2/h, SAM)	27.15	5.64
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	73.26	113.48
Skin Sensitization		
Protein Binding (OASIS v1.1)	DPRA less than 9% (DPRA 13%)|DPRA less than 9% (DPRA 13%) ≫ Non-Conjugated carboxylic acids and esters (non-reactive)	DPRA less than 9% (DPRA 13%)|DPRA less than 9% (DPRA 13%) ≫ Non-Conjugated carboxylic acids and esters (non-reactive)
Protein Binding (OECD)	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Potency	Not categorized	Not categorized
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts were identified	No skin sensitization reactivity domain alerts were 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

Summary

There are insufficient toxicity data on isopropyl 2-methylbutyrate (CAS # 66576-71-4). 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, 1,3-dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- 1,3-Dimethylbut-3-enyl isobutyrate (CAS # 80118-06-5) was used as a read-across analog for the target material, isopropyl 2-methylbutyrate (CAS # 66576-71-4), for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to the class of branched aliphatic esters.
  - o The key difference between the target material and the read-across analog is that the target material has a saturated alcohol portion, whereas the read-across analog has an unsaturated alcohol portion. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the branched saturated acid portion. 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 a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o 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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