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RIFM fragrance ingredient safety assessment, propyl 2-methylbutyrate, CAS Registry Number 37064-20-3

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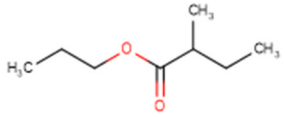
CAS Registry Number: 37064-20-3



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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.,

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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.

Propyl 2-methylbutyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl-2-methylbutyrate (CAS # 7452-79-1) show that propyl 2-methylbutyrate is not expected to be genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from analog hexyl 2-methylbutyrate (CAS # 10032-15-2) provided a No Expected Sensitization Induction Level (NESIL) of 7000 μg/cm^2 for the skin sensitization endpoint. Based on ultraviolet/visible (UV/Vis) spectra, propyl 2-methylbutyrate is not expected to be phototoxic/photoallergenic. The respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; for the hazard assessment based on the screening data, propyl 2-methylbutyrate is not Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards. For the risk assessment, propyl 2-methylbutyrate 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.	(RIFM, 2000a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	(ECHA REACH Dossier: Ethyl 2-methylbutyrate; ECHA, 2013)
Reproductive Toxicity: Developmental toxicity NOAEL: 1000 mg/kg/day. Fertility NOAEL: 1000 mg/kg/day.	(ECHA REACH Dossier: Ethyl 2-methylbutyrate; ECHA, 2013)
Skin Sensitization: NESIL = 7000 μg/cm^2.	RIFM (2018)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.02 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 30.54 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:** Propyl 2-methylbutyrate
2. **CAS Registry Number:** 37064-20-3
3. **Synonyms:** Butanoic acid, 2-methyl-, propyl ester; Propyl 2-methylbutanoate; Propyl 2-methylbutyrate
4. **Molecular Formula:** $C_8H_{16}O_2$
5. **Molecular Weight:** 144.21 g/mol
6. **RIFM Number:** 7171
7. **Stereochemistry:** Isomer not specified. One chiral center present, and 2 total enantiomers possible.

2. Physical data

1. **Boiling Point:** 157.09 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 2.76 (EPI Suite)
4. **Melting Point**: −43.92 °C (EPI Suite)
5. **Water Solubility:** 356.7 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 2.06 mm Hg at 20 °C (EPI Suite v4.0), 2.88 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 tons per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in AirFreshPlugIns:** 0.0010% (RIFM, 2019)

(No reported use in Fine Fragrance).

2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00043 mg/kg/day (RIFM, 2019)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015, 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, 2017; Safford, 2015, 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:** Ethyl-2-methylbutyrate (CAS # 7452-79-1)
b. **Repeated Dose Toxicity:** Ethyl-2-methylbutyrate (CAS # 7452-79-1)
c. **Reproductive Toxicity:** Ethyl-2-methylbutyrate (CAS # 7452-79-1)
d. **Skin Sensitization:** Hexyl 2-methylbutyrate (CAS # 10032-15-2)
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

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

Apple brandy (Calvados)	Durian (*Durio zibethinus*)
Apple fresh (*Malus* species)	Hop (*Humulus lupulus*)
Apple processed (*Malus* species)	Melon
Apricot (*Prunus armeniaca* L.)	Mentha oils
Asian pear (*Pyrus serotina, Pyrus pyrifolia*)	Sea buckthorn (*Hippophae rhamnoides* L.)
Camomile	Starfruit (*Averrhoa carambola* L.)

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*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

Pre-registered for 2010; not available as of 12/08/21.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for propyl 2-methylbutyrate 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)	0.54
2	Products applied to the axillae	0.16
3	Products applied to the face/body using fingertips	3.2
4	Products related to fine fragrances	3.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.76
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.76
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.76
5D	Baby cream, oil, talc	0.25
6	Products with oral and lip exposure	1.8
7	Products applied to the hair with some hand contact	6.1
8	Products with significant ano-genital exposure (tampon)	0.25
9	Products with body and hand exposure, primarily rinse-off (bar soap)	5.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	21
10B	Aerosol air freshener	21
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.25
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 propyl 2-methylbutyrate, the basis was the subchronic reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 7000 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, propyl 2-methylbutyrate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Propyl 2-methylbutyrate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a read-across material were considered to fully assess the potential mutagenic and clastogenic effects of the target material.

There are no studies assessing the mutagenic and clastogenic activity of propyl 2-methylbutyrate; however, read-across can be made to ethyl 2-methylbutyrate (CAS # 7452-79-1; see Section VI).

The mutagenic activity of ethyl 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with ethyl 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, 2000a). Under the conditions of the study, ethyl 2-methylbutyrate was not mutagenic in the Ames test, and this can be extended to propyl 2-methylbutyrate.

The clastogenic activity of ethyl 2-methylbutyrate 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 ethyl 2-methylbutyrate in DMSO at concentrations up to 1300 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1300 μg/mL in the presence and absence of metabolic activation. Ethyl 2-methylbutyrate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels or the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2014b). Under the conditions of the study, ethyl 2-methylbutyrate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to propyl 2-methylbutyrate.

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

Additional References: None.

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

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on propyl 2-methylbutyrate. Read-across material ethyl 2-methylbutrate (CAS # 7452-79-1; see Section VI) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. In an OECD 422 combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 10 Sprague Dawley rats/sex/dose were administered ethyl 2-methylbutyrate via oral gavage at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil. Males were treated for 28–41 days, and females were treated for 40–51 days (maximum of 51 days, males and females). Males were euthanized on day 14 after mating, and females (with offspring) were euthanized on day 5 postpartum. No treatment-related adverse effects were reported for mortality, clinical signs, neurobehavior, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, pathological findings during necropsy, or histopathological examination. The NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013). 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*. The derived NOAEL for the repeated dose toxicity data is 1000/3, or 333 mg/kg/day.

Therefore, the propyl 2-methylbutyrate MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethyl 2-methylbutyrate NOAEL in mg/kg/day by the total systemic exposure to propyl 2-methylbutyrate, 333/0.00043, or 774418.

In addition, the total systemic exposure to propyl 2-methylbutyrate (0.43 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.2. Derivation of subchronic reference dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a subchronic RfD of 3.33 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 propyl 2-methylbutyrate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 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: 02/23/21.

11.1.3. Reproductive toxicity

The MOE for propyl 2-methylbutyrate 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 propyl 2-methylbutyrate. Read-across material ethyl 2-methylbutrate (CAS # 7452-79-1; see Section VI) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint. In an OECD 422 combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 10 Sprague Dawley rats/sex/dose were administered ethyl 2-methylbutyrate via oral gavage at doses of 0, 250, 500, or 1000 mg/kg/day in corn oil. Males were treated for 28–41 days, and females were treated for 40–51 days (maximum of 51 days, males and females). Males were euthanized on day 14 after mating, and females (with offspring) were euthanized on day 5 postpartum. There were no treatment-related effects on mating performance, fertility, conception, gestation length, parturition, survival, litter size, or litter weight. In the F1 generation, no treatment-related effects were reported for mortality, clinical signs, body weight, and bodyweight changes during necropsy. Furthermore, no gross abnormalities were reported in pups. Therefore, the NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013).

Therefore, the propyl 2-methylbutyrate MOE for the reproductive toxicity endpoint can be calculated by dividing ethyl 2-methylbutrate NOAEL in mg/kg/day by the total systemic exposure to propyl 2-methylbutyrate, 1000/0.00043, or 2325581.

In addition, the total systemic exposure to propyl 2-methylbutyrate

(0.43 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/01/21.

11.1.4. Skin sensitization

Based on read-across to hexyl 2-methylbutyrate (CAS # 10032-15-2), propyl 2-methylbutyrate is considered a skin sensitizer with a defined NESIL of 7000 μg/cm^2.

11.1.4.1. Risk assessment. No data on skin sensitization studies are available for propyl 2-methylbutyrate. Based on read-across material hexyl 2-methylbutyrate (CAS # 10032-15-2; see Section VI), propyl 2-methylbutyrate is considered a skin sensitizer. The chemical structure of these materials indicates that they would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material, hexyl 2-methylbutyrate, was found to be negative in the *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens assay (RIFM, 2015b; RIFM, 2015a). In a murine local lymph node assay (LLNA), read-across material hexyl 2-methylbutyrate was found to be sensitizing with an EC3 value of 54.8% (13700 μg/cm^2) (RIFM, 2000b). However, the results from this LLNA may be suboptimal since the test was conducted in the unvalidated range (>25%) of the OECD guideline (Kolle, 2020). In a guinea pig open epicutaneous test (OET), read-across material, hexyl 2-methylbutyrate, did not present reactions indicative of sensitization (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with read-across material, hexyl 2-methylbutyrate, at 10% (6900 μg/cm^2) in petrolatum (RIFM, 1977). Additionally, in Confirmation of No Induction in Humans tests (CNIHs) with read-across material, hexyl 2-methylbutyrate at 7086 μg/cm^2 in 3:1 diethyl phthalate:EtOH or 967 μg/cm^2 in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 109 or 38 volunteers, respectively (RIFM, 2018; RIFM, 1972).

Based on the weight of evidence (WoE) from structural analysis and data on the read-across material hexyl 2-methylbutyrate, propyl 2-methylbutyrate is a sensitizer with a WoE NESIL of 7000 μg/cm^2 (see Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a subchronic RfD of 3.33 mg/kg/day.

Additional References: Natsch (2007); McKim (2010).

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

Table 1
Data summary for hexyl 2-methylbutyrate as read-across material for propyl 2-methylbutyrate.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
13700 [1]	Weak	7086	6900	NA	7000

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

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

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, propyl 2-methylbutyrate 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 propyl 2-methylbutyrate 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, 2009). Based on the lack of absorbance, propyl 2-methylbutyrate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

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

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for propyl 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 propyl 2-methylbutyrate. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 mg/day. This exposure is at least 1400 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/12/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of propyl 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, propyl 2-methylbutyrate was not able to be risk screened as there were no reported volumes of use for either North America or Europe in the 2015 IFRA Survey.

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify propyl 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, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Not applicable.

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

Ecotoxicity: No data available.

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

11.2.3. Risk assessment refinement

Not applicable.

Literature Search and Risk Assessment Completed On: 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.2022.112950.

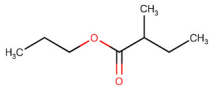
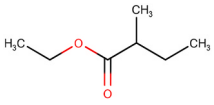
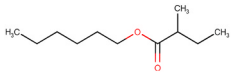
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (Schultz, 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 alert system.

	Target Material	Read-across Material	Read-across Material
Principal Name	Propyl 2-methylbutyrate	Ethyl 2-methylbutyrate	Hexyl 2-methylbutyrate
CAS No.	37064-20-3	7452-79-1	10032-15-2
Structure			
Similarity (Tanimoto Score)		0.87	0.81
Endpoint		Genotoxicity Repeated dose toxicity Reproductive toxicity	Skin sensitization
Molecular Formula	$C_8H_{16}O_2$	$C_7H_{14}O_2$	$C_{11}H_{22}O_2$
Molecular Weight (g/mol)	144.214	130.187	186.295
Melting Point (°C, EPI Suite)	−43.92	−56.05	−9.14
Boiling Point (°C, EPI Suite)	157.09	134.87	218.34
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.84E+02	1.07E+03	1.91E+01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	3.57E+02	1.07E+03	1.26E+01
Log K_{OW}	2.76	2.26	4.23
J_{max} (μg/cm^2/h, SAM)	25.85	55.11	1.68
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.33E+01	5.52E+01	1.71E+02
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	
Carcinogenicity (ISS)	Structural alert for nongenotoxic carcinogenicity|Substituted n-alkylcarboxylic acids (Nongenotox)	Structural alert for nongenotoxic carcinogenicity|Substituted n-alkylcarboxylic acids (Nongenotox)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	
Oncologic Classification	Not classified	Not classified	
Repeated Dose Toxicity			
Repeated Dose (HESS)	Not categorized	Urethane (Renal toxicity) Alert	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)	
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found		No alert found
Protein Binding (OECD)	No alert found		No alert found
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)	No alert found		No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified.		No skin sensitization reactivity domain alerts 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

Summary

There are insufficient toxicity data on propyl 2-methylbutyrate (CAS # 37064-20-3). 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, ethyl 2-methylbutyrate (CAS # 7452-79-1) and hexyl 2-methylbutyrate (CAS # 10032-15-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Ethyl 2-methylbutyrate (CAS # 7452-79-1) was used as a read-across analog for the target material propyl 2-methylbutyrate (CAS # 37064-20-3) for the genotoxicity, reproductive toxicity, and repeated dose toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to a class of aliphatic esters.
  - o The key difference between the target substance and the read-across analog is in the chain length of the alcohol portion. 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.

- 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 a structural alert for the nongenotoxic carcinogen. Substances belonging to this chemical class are potentially reactive as peroxisome proliferators (PPs). PPs are a diverse group of chemicals, including hypolipidemic drugs, plasticizers, and herbicides, that were found to cause liver cancer when chronically administered to rats and mice. These chemicals are considered non-genotoxic agents, given generally negative results in genotoxicity assays. Even if the mechanism by which these chemicals cause tumors is not fully understood, peroxisome proliferator-activated receptor alpha (PPAR a) is thought to mediate most of the PP effects in the rodent liver. Two hypotheses have been proposed to account for PP-induced hepatocarcinogenesis in rodents: (i) increase in DNA damage through induction of oxidative stress, and (ii) alteration of hepatocyte growth control by enhanced cell proliferation or decreased apoptosis. The read-across analog and the target substance are out of the structural domain from the training set used to generate this alert. The data on the read-across analog confirm that the analog does not pose a concern for genetic toxicity under 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.

- Hexyl 2-methylbutyrate (CAS # 10032-15-2) was used as a read-across analog for the target material propyl 2-methylbutyrate (CAS # 37064-20-3) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to a class of aliphatic esters.
  - The key difference between the target substance and the read-across analog is in the chain length of the alcohol portion. 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.
  - 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.
  - There are no structural alerts for the skin sensitization endpoint for 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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