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Short Review

RIFM fragrance ingredient safety assessment, 1,3-dimethylbut-3-enyl isobutyrate, CAS Registry Number 80118-06-5

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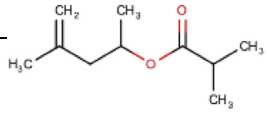
Version: 031618. This version replaces any previous versions

Name: 1,3-Dimethylbut-3-enyl isobutyrate
CAS Registry Number: 80118-06-5



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
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
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

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LOEL - Lowest Observable 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
QRA - Quantitative Risk Assessment
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 under the limits described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

1,3-Dimethylbut-3-enyl isobutyrate was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 1,3-dimethylbut-3-enyl isobutyrate is not genotoxic and does not have skin sensitization potential. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; 1,3-dimethylbut-3-enyl isobutyrate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment
Genotoxicity: Not genotoxic (RIFM, 2016b; RIFM, 2016c)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization. (ECHA REACH Dossier: 1,3-dimethylbut-3-enyl isobutyrate)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC

Environmental Safety Assessment
Hazard Assessment:
Persistence: Critical Measured Value: 80% (OECD 301F) (RIFM, 2009b)
Bioaccumulation: Screening-level: 107.5 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h algae EC50: 1.527 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 et al., 2002)
Critical Ecotoxicity Endpoint: 96-h algae EC50: 1.527 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.1527 μg/L
· Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1

1. Identification

1. **Chemical Name:** 1,3-Dimethylbut-3-enyl isobutyrate
2. **CAS Registry Number:** 80118-06-5
3. **Synonyms:** Propanoic acid, 2-methyl-, 1,3-dimethyl-3-butenyl ester; アルカン酸（C = 1 ~ 6 ）アルケニル（C = 4 ~ 8 ）; 4-Methyl-4-penten-2-yl isobutyrate; Isopentyrate; 1,3-Dimethylbut-3-enyl isobutyrate
4. **Molecular Formula:** $C_{10}H_{18}O_2$
5. **Molecular Weight:** 170.52
6. **RIFM Number:** 5994
7. **Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 179.45 °C (EPI Suite)
2. **Flash Point:** 62 °C (GHS)
3. **Log KOW:** 3.4 (RIFM, 2009a), 3.58 (EPI Suite)
4. **Melting Point:** -41.49 °C (EPI Suite)
5. **Water Solubility:** 53.36 mg/L (EPI Suite)
6. **Specific Gravity:** 0.86000 @ 25.00 °C.*
7. **Vapor Pressure:** 0.992 mm Hg @ 25 °C (EPI Suite), 0.69 mm Hg @ 20 °C (EPI Suite 4.0)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol-1 · cm-1)
9. **Appearance/Organoleptic:** colorless clear liquid (est), natural fruity floral herbal chamomile (Luebke, William tgsc, 1987)*

*http://www.thegoodscentscompany.com/data/rw1028271.html.

3. Exposure

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.011% (RIFM, 2016a)
3. **Inhalation Exposure*:** 0.00013 mg/kg/day or 0.0098 mg/day (RIFM, 2016a)
4. **Total Systemic Exposure**:** 0.0015 mg/kg/day (RIFM, 2016a)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. 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 et al., 2015, 2017; Safford et al., 2015, 2017).

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

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

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

7. Natural occurrence (discrete chemical) or composition (NCS)

1,3-Dimethylbut-3-enyl isobutyrate is not reported to occur in food by the VCF.*

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

8. IFRA standard

None.

9. REACH dossier

Available; accessed 07/31/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1,3-dimethylbut-3-enyl isobutyrate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 1,3-Dimethylbut-3-enyl isobutyrate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). The mutagenic activity of 1,3-dimethylbut-3-enyl isobutyrate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 1,3-dimethylbut-3-enyl isobutyrate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2016b). Under the conditions of the study, 1,3-dimethylbut-3-enyl isobutyrate was not mutagenic in the Ames test.

The clastogenic activity of 1,3-dimethylbut-3-enyl isobutyrate 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 1,3-dimethylbut-3-enyl isobutyrate in DMSO at concentrations up to 540 μg/mL in the presence

and absence of metabolic activation (S9) for 4 and 24 h 1,3-Dimethylbut-3-enyl isobutyrate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2016c). Under the conditions of the study, 1,3-dimethylbut-3-enyl isobutyrate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 1,3-dimethylbut-3-enyl isobutyrate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/26/2018.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 1,3-dimethylbut-3-enyl isobutyrate or any read-across materials. The total systemic exposure to 1,3-dimethylbut-3-enyl isobutyrate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 1,3-dimethylbut-3-enyl isobutyrate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 1,3-dimethylbut-3-enyl isobutyrate (1.5 μg/kg/day) is below the TTC (30 μg/kg bw/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: 07/25/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 1,3-dimethylbut-3-enyl isobutyrate or any read-across materials. The total systemic exposure to 1,3-dimethylbut-3-enyl isobutyrate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 1,3-dimethylbut-3-enyl isobutyrate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 1,3-dimethylbut-3-enyl isobutyrate (1.5 μg/kg/day) is below the TTC (30 μg/kg bw/day) (Kroes et al., 2007) 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: 07/25/17.

10.1.4. Skin sensitization

Based on the existing data, 1,3-dimethylbut-3-enyl isobutyrate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data, 1,3-dimethylbut-3-enyl isobutyrate does not present a concern for skin sensitization. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay 1,3-dimethylbut-3-enyl isobutyrate was found to be non-sensitizing up to 100% (ECHA dossier accessed 6/30/2017). In 2 separate confirmatory human repeat insult patch tests (HRIPT) with 54 and 43 subjects, no skin sensitization reactions were observed with 20% (6202 μg/cm^2) 1,3-dimethylbut-3-enyl isobutyrate in white petrolatum (RIFM, 1979) or 2.5% (1938 μg/cm^2) 1,3-dimethylbut-3-enyl isobutyrate in alcohol SDA 39c (RIFM, 1973), respectively. Based on the weight of evidence from structural analysis and human studies, 1,3-dimethylbut-3-enyl isobutyrate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/01/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, 1,3-dimethylbut-3-enyl isobutyrate would not be expected to present a concern for phototoxicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 1,3-dimethylbut-3-enyl isobutyrate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, 1,3-dimethylbut-3-enyl isobutyrate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD Test Guideline 101) were obtained. The spectra indicate no significant 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: 07/12/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 1,3-dimethylbut-3-enyl isobutyrate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 1,3-dimethylbut-3-enyl isobutyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.0098 mg/day. This exposure is 143 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: 12/15/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1,3-dimethylbut-3-enyl isobutyrate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers 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, 1,3-dimethylbut-3-enyl isobutyrate 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 1,3-dimethylbut-3-enyl isobutyrate as possibly being either persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WOE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), 1,3-Dimethylbut-3-enyl isobutyrate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2009b: The ready biodegradability of the test material was evaluated in a Manometric Respirometry Test according to the OECD 301F method. Under the conditions of the study, biodegradation of 80% was observed after 28 days.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. 1,3-Dimethylbut-3-enyl isobutyrate has been registered for REACH with no additional data available.

10.2.3. 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)**	13.92			1,000,000	0.01392	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.706	4.748	1.527	10,000	0.1527	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	5.290	3.477	4.741			Neutral Organic

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

Exposure	Europe	North America
Log K_{ow} Used	3.4	3.4
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.1527 µg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 7/31/17.

11. Literature search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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