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Short Review

RIFM fragrance ingredient safety assessment, butyl 2-methylcrotonate (Z), CAS registry number 7785-64-0

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

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

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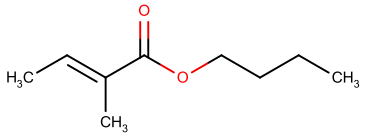

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Name: Butyl 2-methylcrotonate (Z) CAS Registry Number: 7785-64-0 ADDITIONAL CAS #: 7785-66-2 Butyl 2-methylcrotonate (E)
*Included because the materials are isomers

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

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

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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; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly 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.

Butyl 2-methylcrotonate (Z) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog hexyl tiglate (CAS # 16930-96-4) show that butyl 2-methylcrotonate (Z) is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a

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Cramer Class I material; the exposure 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 hexyl tiglate (CAS # 16930-96-4) show that there are no safety concerns for butyl 2-methylcrotonate (Z) for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; butyl 2-methylcrotonate (Z) is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; butyl 2-methylcrotonate (Z) was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 1995; RIFM, 2015b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: No concern for skin sensitization. (RIFM, 2014a; RIFM, 2015d; RIFM, 2015a)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC is available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 3.29 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:
Screening-level: 56.57 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 20.63 mg/L (RIFM Framework; Salvito et al., 2002)
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: Fish LC50: 20.63 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.02063 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable, cleared at screening-level

1. Identification

Chemical Name: Butyl 2-methylcrotonate (Z)	Chemical Name: Butyl 2-methylcrotonate (E)
CAS Registry Number: 7785-64-0	**CAS Registry Number:** 7785-66-2
Synonyms: 2-Butenoic acid, 2-methyl-, butyl ester, (Z)-; Butyl angelate; Butyl 2-methylbut-2-enoate; Butyl 2-methyl-crotonate (Z)	**Synonyms:** (E)-2-Methyl-2-butenoic acid butyl ester; 2-Butenoic acid, 2-methyl-, butyl ester, (E)- CAS; Butyl 2-methylbut-2-enoate; Butyl 2-methyl-crotonate (E); Butyl tiglate
Molecular Formula: $C_9H_{16}O_2$	**Molecular Formula:** $C_9H_{16}O_2$
Molecular Weight: 156.22 g/mol	**Molecular Weight:** 156.22 g/mol
RIFM Number: 5367	**RIFM Number:** 5368
Stereochemistry: Z isomer specified. One stereocenter and 2 total stereoisomers are possible.	**Stereochemistry:** E isomer specified. One stereocenter and 2 total stereoisomers are possible.

2. Physical data

CAS # 7785-64-0	CAS # 7785-66-2
Boiling Point: 191.54 °C (EPI Suite v4.11)	**Boiling Point:** 195 °C (EPI Suite v4.11)
Flash Point: Not Available	**Flash Point:** Not Available
Log K_{OW}: 3.16 (EPI Suite v4.11)	**Log K_{OW}:** 3.16 (EPI Suite v4.11)
Melting Point: −30.25 °C (EPI Suite v4.11)	**Melting Point**: −30.25 °C (EPI Suite v4.11)
Water Solubility: 142.2 mg/L (EPI Suite v4.11)	**Water Solubility:** 142.2 mg/L (EPI Suite v4.11)
Specific Gravity: Not Available	**Specific Gravity:** Not available

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CAS # 7785-64-0	CAS # 7785-66-2
Vapor Pressure: 0.376 mm Hg at 20 °C (EPI Suite v4.0), 0.549 mm Hg at 25 °C (EPI Suite v4.11) **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1}) **Appearance/Organoleptic:** Colorless liquid with a warm-herbaceous, winey odor and a sweet-herbaceous taste.	**Vapor Pressure:** 0.376 mm Hg at 20 °C (EPI Suite v4.0), 0.549 mm Hg at 25 °C (EPI Suite v4.11) **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1}) **Appearance/Organoleptic:** A colorless liquid that has a warm-herbaceous, diffusive, and almost grassy-ethereal odor.

3. Volume of use (Worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)***

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00086% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0000026 mg/kg/day or 0.00019 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.00010 mg/kg/day (RIFM, 2019)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure, and total exposure.

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 v4.5
I	I	I

6.2. Analogs selected

a. **Genotoxicity:** Hexyl tiglate (CAS # 16930-96-4)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Hexyl tiglate (CAS # 16930-96-4)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3.Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References: None.

8. Natural occurrence

Butyl 2-methylcrotonate (Z) (CAS # 7785-64-0) is reported to occur in the following foods by the VCF*:
Chamomile.
Chamomile flower.
Roman oil (*Anthemis nobilis* L.)
Butyl 2-methylcrotonate (E) (CAS # 7785-66-2) is reported to occur in the following foods by the VCF*:
Chamomile.
Mangifera 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

Both materials have been pre-registered for 2010; no dossiers are available as of 10/07/22.

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, butyl 2-methylcrotonate (Z) does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Butyl 2-methylcrotonate (Z) was assessed in the BlueScreen assay and found negative for both genotoxicity and cytotoxicity (positive: <80% relative cell density) with and without metabolic activation (RIFM, 2014b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material. The read-across material, hexyl tiglate, was assessed in the BlueScreen assay and found negative for genotoxicity and positive for cytotoxicity (positive: <80% relative cell density), with and without metabolic activation (RIFM, 2015c).

There are no studies assessing the mutagenic activity of butyl 2-methylcrotonate (Z); however, read-across can be made to hexyl tiglate (CAS # 16930-96-4). The mutagenic activity of read-across material hexyl tiglate has been evaluated in a *Salmonella typhimurium*/mammalian microsome 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 TA1538 were treated with hexyl tiglate in solvent acetone 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, 1995). Under the conditions of the study, hexyl tiglate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of butyl 2-methylcrotonate (Z); however, read-across can be made to hexyl tiglate (CAS # 16930-96-4). The clastogenic activity of read-across material hexyl tiglate 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 hexyl tiglate in dimethyl sulfoxide (DMSO) at concentrations up to 1843 μg/mL in the dose range finding (DRF) study, and micronuclei analysis was conducted up to 250 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. Hexyl tiglate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2015b). Under the conditions of the study, hexyl tiglate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data on read-across material hexyl tiglate data, butyl 2-methylcrotonate (Z) does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/01/22.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on butyl 2-methylcrotonate (Z) or any read-across materials. The total systemic exposure to butyl 2-methylcrotonate (Z) 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 butyl 2-methylcrotonate (Z) or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.1 μg/kg/day) to butyl 2-methylcrotonate (Z) is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material (30 μg/kg/day; Kroes et al., 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/02/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on butyl 2-methylcrotonate (Z) or any read-across materials. The total systemic exposure to butyl 2-methylcrotonate (Z) 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 butyl 2-methylcrotonate (Z) or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.1 μg/kg/day) to butyl 2-methylcrotonate (Z) is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/02/22.

11.1.4. Skin sensitization

Based on the existing data on the target material and read-across material hexyl tiglate, butyl 2-methylcrotonate (Z) presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for butyl 2-methylcrotonate (Z). Therefore, read-across analog hexyl tiglate (CAS # 16930-96-4; see Section VI) was used for the risk assessment of butyl 2-methylcrotonate (Z). The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, butyl 2-methylcrotonate (Z) is not considered a skin sensitizer. The chemical structures 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; OECD Toolbox v4.5). Read-across material hexyl tiglate was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA), positive in KeratinoSens, and negative in the human cell line activation test (h-CLAT) (RIFM, 2014a; RIFM, 2015d; RIFM, 2015a). Therefore, it was concluded to be non-sensitizing according to OECD TG 497 (OECD, 2021a). In a human maximization test, no skin sensitization reactions were observed with read-across material hexyl tiglate at 8280 μg/cm^2 (RIFM, 1976). Additionally, in 2 Confirmation of No Induction in Humans tests (CNIHs) with 110 μg/cm^2 of hexyl tiglate in EtOH:DEP (1:3) and 194 μg/cm^2 read-across material hexyl tiglate in alcohol SDA 39c, no reactions indicative of sensitization were observed in any of the 108 or 42 volunteers, respectively (RIFM, 2013; RIFM, 1973).

Based on the weight of evidence (WoE) from structural analysis, *in vitro* studies, and human studies on the read-across material as well as the target material, butyl 2-methylcrotonate (Z) does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/02/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis spectra, butyl 2-methylcrotonate (Z) would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photoirritation studies available for butyl 2-methylcrotonate (Z) 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 photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, butyl 2-methylcrotonate (Z) 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 significant 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: 03/08/22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for butyl 2-methylcrotonate (Z) is below the Cramer Class I TTC value for inhalation exposure local effects.

Table 1
Summary of existing data on hexyl tiglate as a read-across for butyl 2-methylcrotonate (Z).

WoE Skin Sensitization Potency Category[a]	Human Data				Animal 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	LLNA[d] Weighted Mean EC3 Value μg/cm^2	GPMT[e]	Buehler[e]
No evidence of sensitization[g]	194	8820	NA	NA	NA	NA	NA
	***In vitro* Data[f]**				***In silico* protein binding alerts (OECD Toolbox v4.5)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	Negative	Positive	Negative		No alert found	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization 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, 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 (Api et al., 2015).

11.1.6.1. Risk assessment. There are no inhalation data available on butyl 2-methylcrotonate (Z). Based on the Creme RIFM Model, the inhalation exposure is 0.00019 mg/day. This exposure is 7368 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/23/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of butyl 2-methylcrotonate (Z) was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, butyl 2-methylcrotonate (Z) was identified as a fragrance material with no 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 butyl 2-methylcrotonate (Z) as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2019), butyl 2-methylcrotonate (Z) presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation

No data available.

Ecotoxicity

No data available.

Other available data

Butyl 2-methylcrotonate (Z) has been pre-registered for REACH, with no additional data available 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)**	20.63			1000000	0.02063	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.16	3.16
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band*	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

*Combined Regional Volume of Use for both CAS #s.

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

The RIFM PNEC is 0.02063 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 03/28/22.

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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/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 10/03/22.

CRediT authorship contribution statement

G. Sullivan: Writing – review & editing.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.114405.

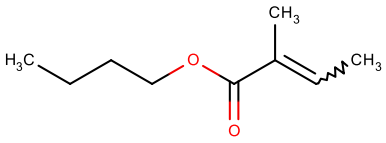
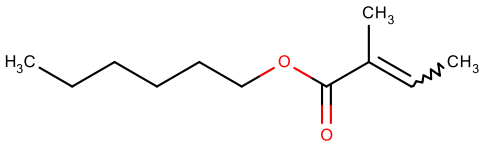
Appendix

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 Chemicals 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 v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- 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 v4.5 (OECD, 2021b).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Butyl 2-methylcrotonate (Z)	Hexyl tiglate
CAS No.	7785-64-0	16930-96-4
Structure		
Similarity (Tanimoto Score)		0.87
Endpoint		• Genotoxicity • Skin sensitization
Molecular Formula	$C_9H_{16}O_2$	$C_{11}H_{20}O_2$
Molecular Weight (g/mol)	156.22	184.28
Melting Point (°C, EPI Suite)	−30.25	−7.66
Boiling Point (°C, EPI Suite)	191.54	230.32
Vapor Pressure (Pa @ 25°C, EPI Suite)	73.19	10.25
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	142.20	15.20
Log K_{OW}	3.16	4.14
J_{max} (μg/cm²/h, SAM)	12.77	1.98
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	53.80	94.84
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.5)	Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition ≫ α, β-unsaturated esters	Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition ≫ α, β-unsaturated esters
Carcinogenicity (ISS)	No alert found	No alert found
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)**	Alert for Schiff base formation identified.	Alert for Schiff base formation identified.
Oncologic Classification	Acrylate Reactive Functional Groups	Acrylate Reactive Functional Groups
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	Michael addition|Michael addition ≫ Polarized Alkenes|Michael addition ≫ Polarized Alkenes ≫ Polarized alkene - esters	Michael addition|Michael addition ≫ Polarized Alkenes|Michael addition ≫ Polarized Alkenes ≫ Polarized alkene - esters
Protein Binding Potency	Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN)|Slightly reactive (GSH)|Slightly reactive (GSH) ≫ Methacrylates (MA)|Slightly reactive (GSH) ≫ Tiglates (MA)	Moderately reactive (GSH)|Moderately reactive (GSH) ≫ Alkenes and cycloalkenes (AN)|Slightly reactive (GSH)|Slightly reactive (GSH) ≫ Methacrylates (MA)|Slightly reactive (GSH) ≫ Tiglates (MA)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.	Alert for Schiff base formation identified.
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on butyl 2-methylcrotonate (Z) (CAS # 7785-64-0). 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, hexyl tiglate (CAS # 16930-96-4) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Hexyl tiglate (CAS # 16930-96-4) was used as a read-across analog for the target material, butyl 2-methylcrotonate (Z) (CAS # 7785-64-0), for the skin sensitization and genotoxicity endpoints.
  - o The target material and the read-across analog belong to a class of tiglate esters.
  - o The target material and the read-across analog share a tiglic acid moiety.
  - o The key difference between the target material and the read-across analog is that the target material has a butanol alcohol moiety, whereas the read-across has a hexanol alcohol moiety. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. 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 v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and the read-across analog are polarized α,β-unsaturated esters, which can undergo a Michael addition by a nucleophile attack at the β-carbon atom. The Michael addition mechanism has been suggested to be primarily responsible for the ability of these chemicals to alkylate DNA and to interact with biological nucleophiles such as cysteine or lysine amino acids. Both materials have an alert as Acrylate Reactive Functional Groups within the Oncologic Classification. This alert can be, however, ignored because tiglates are not part of the training set for this scheme. The data described in the genotoxicity and skin sensitization sections show that the MOE is adequate at the current level of use. Therefore, the predictions are superseded by the data.
  - 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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