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Short Review

RIFM fragrance ingredient safety assessment, 3-methylpentyl 2-methylisocrotonate, CAS Registry Number 53082-58-9

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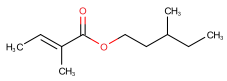


Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
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 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.

3-Methylpentyl 2-methylisocrotonate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across isopentyl 2-methylcrotonate (E) (CAS # 41519-18-0) show that 3-methylpentyl 2-methylisocrotonate is not expected to be genotoxic. The skin sensitization endpoint was completed using data from 3-methylpentyl 2-methylisocrotonate and the DST for reactive materials (64 μg/cm^2); exposure is below the DST. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to 3-methylpentyl 2-methylisocrotonate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 3-methylpentyl 2-methylisocrotonate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-methylpentyl 2-methylisocrotonate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its screening-level (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2015; RIFM, 2016)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 2.9 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 225 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 3.942 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: 3.942 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00394 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 3-Methylpentyl 2-methylisocrotonate
2. **CAS Registry Number:** 53082-58-9
3. **Synonyms:** 2-Butenoic acid, 2-methyl-, 3-methylpentyl ester, (Z)-; Iso Hexyl Angelate; Iso Hexyl Pentenoate; (Z)-2-ﾒﾁﾙ-2-ﾌﾞﾃﾝ酸 = 3-ﾒﾁﾙﾍｷｼﾁﾙ; ﾒﾁﾙ-n-ｱﾙｷﾙ(C = 2 ~ 5) = 2-ﾒﾁﾙｲｿｸﾛﾄﾅｰﾄ; 3-Methylpentyl 2-methylbut-2-enoate; 3-Methylamyl angelate; 3-Methylpentyl angelate; 3-Methylpentyl 2-methylisocrotonate
4. **Molecular Formula:** $C_{11}H_{20}O_2$
5. **Molecular Weight:** 184.79
6. **RIFM Number:** 5722
7. **Stereochemistry:** Stereoisomer not specified. Two Stereocenters and 4 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 219.01 °C (EPI Suite)
2. **Flash Point:** 184.00 °F; TCC (84.60 °C) (est)*
3. **Log K_{OW}:** 4.07 (EPI Suite)
4. **Melting Point:** −18.46 °C (EPI Suite)
5. **Water Solubility:** 17.56 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.091 mm Hg @ 20 °C (EPI Suite v4.0), 0.138 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A liquid with a woody, floral, and chamomile-like odor*

*http://www.thegoodscentscompany.com/data/rw1047181.html, 01/10/18.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00010% (RIFM, 2013b)
3. **Inhalation Exposure*:** < 0.0001 mg/kg/day or 0.0000002 mg/day (RIFM, 2013b)
4. **Total Systemic Exposure**:** 0.0000033 mg/kg/day (RIFM, 2013b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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., 2015a; Safford et al., 2017; and Comiskey et al., 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:** Isopentyl 2-methylcrotonate (E) (CAS # 41519-18-0)
   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)

3-Methylpentyl 2-methylisocrotonate 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

Pre-registered 2010; no dossier available as of 11/20/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 3-methylpentyl 2-methylisocrotonate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 3-Methylpentyl 2-methylisocrotonate was assessed in the BlueScreen assay and found negative for genotoxicity with and without metabolic activation (RIFM, 2013a). BlueScreen is a screening assay that assesses genotoxic stress through alterations in gene expressions in a human cell line. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of 3-

methylpentyl 2-methylisocrotonate; however, read-across can be made to isopentyl 2-methylcrotonate (E) (CAS # 41519-18-0; see Section 5). The mutagenic activity of isopentyl 2-methylcrotonate (E) 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 *Escherichia coli* strain WP2uvrA were treated with isopentyl 2-methylcrotonate (E) 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, 2015). Under the conditions of the study, isopentyl 2-methylcrotonate (E) was not mutagenic in the Ames test, and this can be extended to 3-methylpentyl 2-methylisocrotonate.

There are no studies assessing the clastogenic activity of 3-methylpentyl 2-methylisocrotonate; however, read-across can be made to isopentyl 2-methylcrotonate (E) (CAS # 41519-18-0; see Section 5). The clastogenic activity of isopentyl 2-methylcrotonate (E) 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 isopentyl 2-methylcrotonate (E) in DMSO at concentrations up to 1703 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. Isopentyl 2-methylcrotonate (E) 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, 2016). Under the conditions of the study, isopentyl 2-methylcrotonate (E) was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 3-methylpentyl 2-methylisocrotonate.

Based on the data available, isopentyl 2-methylcrotonate (E) does not present a concern for genotoxic potential, and this can be extended to 3-methylpentyl 2-methylisocrotonate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/31/17.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 3-methylpentyl 2-methylisocrotonate or on any read-across materials. The total systemic exposure to 3-methylpentyl 2-methylisocrotonate 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 insufficient repeated dose toxicity data on 3-methylpentyl 2-methylisocrotonate or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 3-methylpentyl 2-methylisocrotonate (0.0033 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: 08/21/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 3-methylpentyl 2-methylisocrotonate or on any read-across materials. The total systemic exposure to 3-methylpentyl 2-methylisocrotonate 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 insufficient reproductive toxicity data on 3-methylpentyl 2-methylisocrotonate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 3-methylpentyl 2-methylisocrotonate (0.0033 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/21/17.

10.1.4. Skin sensitization

Based on the existing data and the application of the Dermal Sensitization Threshold (DST), 3-methylpentyl 2-methylisocrotonate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v4.1). No predictive skin sensitization studies are available for 3-methylpentyl 2-methylisocrotonate. In a confirmatory human repeat insult patch test (HRIPT) with 39 μg/cm^2 or 969 μg/cm^2 of 3-methylpentyl 2-methylisocrotonate in ethanol, no reactions indicative of sensitization were observed in any of the 48 or 37 volunteers, respectively (RIFM, 1974; RIFM, 1973).

Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Roberts et al., 2015; Safford, 2008; Safford et al., 2011; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 3-methylpentyl 2-methylisocrotonate that present no appreciable risk for skin sensitization based on the reactive DST. These concentrations are not limits; they represent maximum acceptable concentrations based on the DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/03/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 3-methylpentyl 2-methylisocrotonate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 3-methylpentyl 2-methylisocrotonate 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, 3-methylpentyl 2-methylisocrotonate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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 phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/18/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of

Table 1
Maximum acceptable concentrations for 3-methylpentyl 2-methylisocrotonate that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.005%	0.000%
2	Products applied to the axillae	0.001%	0.000%
3	Products applied to the face using fingertips	0.029%	0.000%
4	Fine fragrance products	0.027%	0.001%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.239%	0.000%
6	Products with oral and lip exposure	0.016%	0.000%
7	Products applied to the hair with some hand contact	0.056%	0.000%
8	Products with significant ano-genital exposure	0.003%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	1.841%	0.000%[b]
10	Household care products with mostly hand contact	0.192%	0.000%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.107%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.000%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.001%).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

appropriate data. The exposure level for 3-methylpentyl 2-methylisocrotonate 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 3-methylpentyl 2-methylisocrotonate. Based on the Creme RIFM Model, the inhalation exposure is 0.00000020 mg/day. This exposure is at least 7,000,000 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: 08/03/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3-methylpentyl 2-methylisocrotonate 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, 3-methylpentyl 2-methylisocrotonate 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 3-methylpentyl 2-methylisocrotonate 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, 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), 3-methylpentyl 2-methylisocrotonate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.4. Other available data

3-Methylpentyl 2-methylisocrotonate has been pre-registered for REACH with no additional data at this time.

10.2.5. 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*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	3.942			1,000,000	0.00394	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.07	4.07
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 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 0.00394 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the screening-level 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: 12/14/17.

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. The links listed above were active as of 10/09/2018.

12. Conflicts of interest

The authors declare that they have no conflicts of interest.

13. Declaration of interests

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.2019.110633.

Appendix

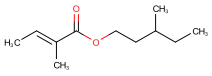
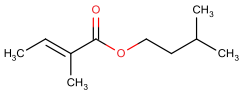
Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also 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, 2016).

- 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, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).

- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	3-Methylpentyl2-methylisocrotonate	Isopentyl 2-methylcrotonate (E)
CAS No.	53082-58-9	41519-18-0
Structure		
Similarity (Tanimoto Score)		0.9
Read-across Endpoint		• Genotoxicity
Molecular Formula	$C_{11}H_{20}O_2$	$C_{10}H_{18}O_2$
Molecular Weight	184.28	170.25
Melting Point (°C, EPI Suite)	−18.46	−29.78
Boiling Point (°C, EPI Suite)	219.01	199.53
Vapor Pressure (Pa @ 25 °C, EPI Suite)	18.4	49.2
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.07	3.58
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	17.56	25.9
J_{max} (μg/cm^2/h, SAM)	50.49	97.297
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.36E-004	7.05E-004
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v3.4)	• Michael addition – α,β-unsaturated esters	• 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)	• No alert found	• No alert found
Oncologic Classification	• Acrylate reactive functional groups	• Acrylate reactive functional groups
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 3-methylpentyl 2-methylisocrotonate (CAS # 53082-58-9). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, isopentyl 2-methylcrotonate (E) (CAS # 41519-18-0) was identified as a read-across material with sufficient data for toxicological evaluation.

14. Conclusions

- Isopentyl 2-methylcrotonate (E) was used as a read-across analog for the target material 3-methylpentyl 2-methylisocrotonate for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic crotonate esters.
  - o The key difference between the target and the read-across analog is branching on the alcohol portion. The difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score.
  - o According to the OECD QSAR Toolbox v3.4, the structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o Both the target material and the read-across analog have an alert for Michael addition. This is due to the α,β-unsaturated acid portion of the ester. An initial Michael addition mechanism has been suggested to be primarily responsible for the ability of these chemicals to alkylate DNA. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genetic toxicity. Therefore, based on structural similarity and data for the read-across analog, the alert is superseded by data.
  - o Both the read-across analog and the target substance are classified as Acrylate reactive functional groups under oncologic classification. The SAR mainly confirms carcinogenicity of carbonyl compounds with α,β-vinyl groups. The terminal double bond is highly sensitive to any substitution, and even a small alkyl group added to the double bond can substantially diminish or abolish the carcinogenic potential. There is evidence that a small methacrylate is not carcinogenic. The carboxyl end is relatively less sensitive, but the substitution of hydrogen by bulky groups or highly hydrophilic groups may also abolish the carcinogenic potential. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genetic toxicity. Therefore, based on structural similarity and data for the read-across analog, the alert is superseded by data.
  - o The target substance 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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