Food and Chemical Toxicology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

RIFM fragrance ingredient safety assessment, cinnamyl isobutyrate, CAS Registry Number 103-59-3

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

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, 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*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, 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*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

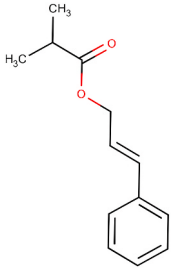
ARTICLE INFO

Handling Editor: Dr. Jose Luis Domingo

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

https://doi.org/10.1016/j.fct.2021.112457
Received 7 April 2021; Received in revised form 24 May 2021; Accepted 30 July 2021

Version: 040221. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available.



Name: Cinnamyl isobutyrate **CAS Registry Number**: 103-59-3

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
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,

(*continued on next column*)

(*continued*)

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.

Cinnamyl isobutyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog cinnamyl acetate (CAS # 103-54-8) show that cinnamyl isobutyrate is not expected to be genotoxic, provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints, and show that there are no safety concerns for cinnamyl isobutyrate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; cinnamyl isobutyrate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to cinnamyl isobutyrate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; cinnamyl isobutyrate 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, 2003; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 200 mg/kg/day. RIFM (2016a)
Reproductive Toxicity: Developmental toxicity: NOAEL = 600 mg/kg/day. Fertility: NOAEL = 600 mg/kg/day. RIFM (2016a)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use. RIFM (2018)
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: 139.9 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 8.099 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: 8.099 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.008099 µg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Cinnamyl isobutyrate
2. **CAS Registry Number:** 103-59-3
3. **Synonyms:** Cinnamyl 2-methylpropanoate; 3-Phenyl-2-propen-1-yl 2-methylpropanoate; 3-Phenyl-2-propen-1-yl isobutyrate; Propanoic acid, 2-methyl-, 3-phenyl-2-propenyl ester; ｱﾙｶﾝ酸(C = 1–6)ｼﾝﾅﾐﾙ; 3-Phenylprop-2-en-1-yl 2-methylpropanoate; Cinnamyl isobutyrate
4. **Molecular Formula:** $C_{13}H_{16}O_2$
5. **Molecular Weight:** 204.26
6. **RIFM Number:** 883
7. **Stereochemistry:** Isomer not specified. One geometric center and a total of 2 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 280.47 °C (EPI Suite)
2. **Flash Point:** >100 °C (Globally Harmonized System), >212 °F; CC (Gagnaire et al., 2002), >200 °F; CC (Fragrance Materials Association [FMA])
3. **Log K_{OW}:** 3.76 (EPI Suite)
4. **Melting Point**: 21.36 °C (EPI Suite)
5. **Water Solubility:** 25.75 mg/L (EPI Suite)
6. **Specific Gravity:** 1.01 (FMA), 1.008–1.014 (Gagnaire et al., 2002)
7. **Vapor Pressure:** 0.00339 mm Hg at 20 °C (EPI Suite v4.0), 0.002 mm Hg at 20 °C (FMA), 0.00547 mm Hg at 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} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless to slightly yellow liquid, with a sweet balsamic, fruity character (Gagnaire et al., 2002)

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance**: 0.0049% (RIFM, 2016b):
2. **Inhalation Exposure***: 0.000077 mg/kg/day or 0.0057 mg/day (RIFM, 2016b)
3. **Total Systemic Exposure****: 0.00040 mg/kg/day (RIFM, 2016b)

*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; and 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; and Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. *Cramer Classification: Class I, Low*

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v3.2
I	I	I

6.2. *Analogs Selected*

a. **Genotoxicity:** Cinnamyl acetate (CAS # 103-54-8)
b. **Repeated Dose Toxicity:** Cinnamyl acetate (CAS # 103-54-8)
c. **Reproductive Toxicity:** Cinnamyl acetate (CAS # 103-54-8)
d. **Skin Sensitization:** Cinnamyl acetate (CAS # 103-54-8)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

6.3. *Read-across Justification*

See Appendix below

7. Metabolism

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

8. Natural occurrence

Cinnamyl isobutyrate is not reported to occur in foods 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.

9. REACH dossier

Pre-registered for 2010; No dossier available as of 04/02/21.

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, cinnamyl isobutyrate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Cinnamyl isobutyrate was tested using the BlueScreen assay and not found to be genotoxic with or without S9 metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. There are no studies evaluating the mutagenic or clastogenic activity of cinnamyl isobutyrate.

The mutagenic activity of read-across material cinnamyl acetate (CAS # 103-54-8; see Section VI) was assessed in an Ames study conducted in compliance with GLP requirements and in accordance with OECD TG 471 using both the standard plate incorporation and modified preincubation methods. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with cinnamyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation. No increase in the number of revertant colonies was observed in any of the test strains at the concentrations tested (RIFM, 2003). Under the conditions of the study, cinnamyl acetate was considered negative in the Ames test, and this can be extended to cinnamyl isobutyrate.

There are no studies assessing the clastogenicity of cinnamyl isobutyrate. The clastogenic activity of read-across material cinnamyl acetate (CAS # 103-54-8; see Section VI) was assessed in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes (HPBL) were treated with cinnamyl acetate in DMSO at concentrations ranging from 55.8 to 413 μg/mL in the approximate 24-h treatment without S9. The test material was also evaluated in the 3-h treatments at

244–815 μg/mL without S9 and 335–1000 μg/mL with S9. A statistically significant increase in the frequency of binucleated cells with micronuclei (BNMN) was observed at the lowest evaluated concentration (105 μg/mL) in the approximate 24-h treatment without S9. However, the BNMN frequency (1.10%) observed at this concentration is within the historical control range for this test condition. Moreover, no dose response was observed in this test condition. Therefore, the significant increase observed at 105 μg/mL in the approximate 24-h treatment without S9 was not considered biologically relevant. No significant increase in the BNMN frequencies was observed in the 3-h treatments with and without S9 (RIFM, 2015). Under the conditions of the study, cinnamyl acetate was considered to be negative for the induction of micronuclei in HPBL *in vitro* and this can be applied to cinnamyl isobutyrate.

Based on the available data, cinnamyl acetate does not present a concern for genotoxic potential, and this can be extended to cinnamyl isobutyrate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/20/20.

11.1.2. Repeated dose toxicity

The MOE for cinnamyl isobutyrate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on cinnamyl isobutyrate. Read-across material cinnamyl acetate (CAS # 103-54-8; see Section VI) has sufficient repeated dose toxicity data. An OECD 422 and GLP-compliant 28-day gavage combined repeated dose with a reproductive and developmental toxicity screening study was conducted with the test material. Groups of 10 Wistar rats/sex/dose were administered the test material via gavage at dose levels of 0, 65, 200, and 600 mg/kg/day in corn oil. An additional 14-day recovery group of 5 rats/sex assigned to the control and high-dose groups were also included. There were no treatment-related adverse effects reported among the treated animals up to the highest dose tested. Thus, the NOAEL for the repeated dose toxicity endpoint was determined to be 600 mg/kg/day, the highest dose tested (RIFM, 2016a).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 study (ECHA, 2012; Chapter R.8). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 600/3 or 200 mg/kg/day.

Therefore, the cinnamyl isobutyrate MOE for the repeated dose toxicity endpoint can be calculated by dividing the cinnamyl acetate NOAEL in mg/kg/day by the total systemic exposure to cinnamyl isobutyrate, 200/0.00040, or 500000.

In addition, the total systemic exposure to cinnamyl isobutyrate (0.40 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

* The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: Zaitsev and Rakhmanina, 1974

Literature Search and Risk Assessment Completed On: 08/13/20.

11.1.3. Reproductive toxicity

The MOE for cinnamyl isobutyrate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity or fertility data on cinnamyl isobutyrate. Read-across material cinnamyl acetate (CAS # 103-54-8; see Section VI) has sufficient developmental toxicity and fertility data. An OECD 422 and GLP-compliant 28-day gavage combined repeated dose with a reproductive and developmental toxicity screening study was conducted with the test material, cinnamyl acetate. Groups of 10 Wistar rats/sex/dose were administered the test material via gavage at dose levels of 0, 65, 200, and 600 mg/kg/day in corn oil. An additional 14-day recovery group of 5 rats/sex assigned to the control and high-dose groups were also included. The male and female mating and fertility indices were significantly lower at the 65 and 600 mg/kg/day doses when compared to controls. The changes observed at 65 mg/kg/day dose was considered incidental as the observed change was within the historical control data. The lower male and female mating and fertility indices at 600 mg/kg/day were considered treatment-related as the changes were lower than the historical control data. However, there were no effects of treatment on the reproductive organs among the treated males and females. The pup survival index was also not altered by the treatment at all dose levels tested. No treatment-related developmental toxicity effects were reported among the treated animals up to the highest dose tested. Thus, the NOAEL for the developmental toxicity endpoint was determined to be 600 mg/kg/day, the highest dose tested. The NOAEL for the reproductive toxicity endpoint was also determined to be 600 mg/kg/day since there were no effects observed on the reproductive organs among treatment-group rats (RIFM, 2016a).

Therefore, the cinnamyl isobutyrate MOE for the reproductive toxicity endpoint can be calculated by dividing the cinnamyl acetate NOAEL in mg/kg/day by the total systemic exposure to cinnamyl isobutyrate, 600/0.00040, or 1500000.

In addition, the total systemic exposure to cinnamyl isobutyrate (0.40 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Zaitsev and Rakhmanina, 1974

Literature Search and Risk Assessment Completed On: 08/16/20.

11.1.4. Skin sensitization

Based on existing data and read-across cinnamyl acetate (CAS # 103-54-8), cinnamyl isobutyrate presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for cinnamyl isobutyrate. Based on the existing data and read-across material cinnamyl acetate (CAS # 103-54-8; see Section VI), cinnamyl isobutyrate is not considered a skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material cinnamyl acetate was found to be negative in the *in vitro* direct peptide reactivity assay (DPRA; RIFM, 2017a) and human cell line activation test (h-CLAT; RIFM, 2017b). In human maximization tests, no skin sensitization reactions were observed with cinnamyl butyrate or read-across material cinnamyl acetate (RIFM, 1976; RIFM, 1972). Additionally, in a Confirmation of No Induction in Humans (CNIH) test with 3424 μg/cm^2 of read-across material cinnamyl acetate in 1:3 ethanol:diethyl phthalate no reactions indicative of sensitization were observed in any of the 101 volunteers (RIFM, 2018).

Based on weight of evidence (WoE) from structural analysis, human studies, and read-across material cinnamyl acetate, cinnamyl isobutyrate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/06/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, cinnamyl isobutyrate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for cinnamyl 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 the lack of absorbance, cinnamyl isobutyrate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no 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: 08/07/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for cinnamyl isobutyrate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on cinnamyl isobutyrate. Based on the Creme RIFM Model, the inhalation exposure is 0.0057 mg/day. This exposure is 245.6 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: Troy (1977); UGCM, 1997; Regnault-Roger and Hamraoui, 1995; Rice and Coats, 1994; Kim et al., 2004; Johnson et al., 2005; Harth et al., 2007; RIVM et al., 2007; RIFM, 2013b; Carpenter et al., 1949; De Ceaurriz et al., 1981; Brondeau et al., 1990; Carlson (1946); Linyucheva (1971); Zissu (1995); Amdur (1961); Silver (1992); Zuskin et al., 1997; Khare et al., 1998; Helmig et al., 1999a; Helmig et al., 1999b; Montero et al., 2001; Suzuki et al., 2001; Morris and Symanowicz, 2002; Gagnaire et al., 2002; NIOSH, 2006; Cain et al., 2010; Willis et al., 2011.

Literature Search and Risk Assessment Completed On: 07/29/20.

11.2. Environmental Endpoint Summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cinnamyl isobutyrate 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, cinnamyl isobutyrate 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 cinnamyl isobutyrate 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), cinnamyl isobutyrate presents a 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

Cinnamyl isobutyrate has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.76	3.76
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 0.008099 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 VoU.

Literature Search and Risk Assessment Completed On: 08/21/20.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	8.099			1000000	0.008099	

- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/02/21.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. 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 F. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2021.112457.

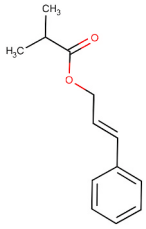
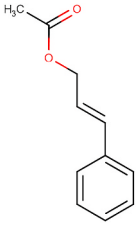
Appendix

Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Cinnamyl isobutyrate	Cinnamyl acetate
CAS No.	103-59-3	103-54-8
Structure		
Similarity (Tanimoto Score)		0.84
Endpoint		• Genotoxicity • Skin sensitization • Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_{13}H_{16}O_2$	$C_{11}H_{12}O_2$
Molecular Weight	204.269	176.215
Melting Point (°C, EPI Suite)	21.36	20.45
Boiling Point (°C, EPI Suite)	280.47	265.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.29E-01	1.61E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.58E+01	2.12E+02
Log K_{OW}	3.76	2.85
J_{max} (μg/cm^2/h, SAM)	1.88	8.91
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.84E+00	1.04E+00
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	AN2|AN2 ≫ Schiff base formation after aldehyde release|AN2 ≫ Schiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found
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	Not classified	Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	Styrene (Renal Toxicity) Alert	Coumarin (Hepatotoxicity) Alert|Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group	Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (good reliability)	Non-toxicant (low reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters
Protein Binding (OECD)	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom|SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom|SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Michael Acceptor identified	Alert for Michael Acceptor identified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There is insufficient toxicity data on cinnamyl butyrate (CAS # 103-61-7). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, cinnamyl acetate (CAS # 103-54-8) was identified as a read-across material with data for the respective toxicity endpoints.

Conclusion

- Cinnamyl acetate (CAS # 103-54-8) could be used as a structurally similar read-across analog for target material cinnamyl butyrate (CAS # 103-61-7) for the genotoxicity, skin sensitization, repeated dose toxicity, and reproductive toxicity endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of α,β-unsaturated aliphatic esters with an aryl moiety in extended conjugation.
  - The target material and the read-across analog have a cinnamyl alcohol substructure common among them.
  - The key difference between the target material and the read-across analog is that the target material is a propionate ester, while the read-across analog is an acetate ester. The read-across analog contains the structural features of the target material that are relevant to the endpoints and is expected to have an equal or greater potential for toxicity as compared to the target material.
  - Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010). The Tanimoto score is mainly driven by the cinnamyl propionate fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicity endpoint perspective.
  - The target material and the read-across analog have similar physical–chemical properties. Any differences in some of the physical–chemical properties of the target material and the read-across analog are estimated to be toxicologically insignificant for the genotoxicity, reproductive toxicity, and repeated dose toxicity endpoints.
  - The read-across analog has AN2, SN2, SN1 reaction alerts for genotoxicity by OASIS under QSAR Toolbox. The alert is because the read-across analog is an acetate ester. The QSAR Toolbox confirms that the training set for this alert had esters of acetic acid with a diverse extended fragment attached. The role of acetic acid is not completely known, and necessary conditions for eliciting direct or indirect DNA interaction, described in this general mechanistic profile, are met. However, the specific structural boundaries providing sufficiency for interaction to DNA may not be identified. These specific structural boundaries are examined in the corresponding endpoint-specific profile. The data for the read-across analog confirms that the analog does not pose a concern for genetic toxicity. Therefore, the alert is superseded by the data.
  - The target material has an alert for aldehyde-type by the oncologic classification scheme in OECD QSAR Toolbox. This alert is given because the target material is a formate ester, and the substructure matches the aldehyde substructure. The formate ester would release formic acid as a metabolite. However, the reversible conversion of formic acid to formaldehyde is not accepted to be efficient and probabilistic. There are many esters of formic acid proven to be safe under current levels of exposure. Therefore, based on the structural similarity between the target material and the read-across analog and data for the read-across analog, the alert is superseded by the data.
  - The target material has an alert for styrene and toluene renal toxicity. The read-across analog has coumarin hepatotoxicity and styrene and toluene renal toxicity alerts. These alerts are given because of structural similarity scores >0.5 with the expert judgment rules under HESS. The mechanistic domain is not met with the target material or the read-across analog. The data on the read-across analog confirms that the MOE is adequate under the current level of use. Therefore, the alert is superseded by the data.
  - The read-across analog and the target material have an alert for SN2 reaction and Michael acceptor alert by several models for skin sensitization. This is because of the α,β-unsaturation of the carbonyl group in the read-across analog. The target material has the same sub-structural feature but does not have the alert. However, the data on the read-across analog confirms that the read-across analog presents no concern for skin sensitization under the current, declared levels of use. Therefore, based on the structural similarity between the target material and the read-across analog, and the data on the read-across analog, the *in silico* alert is superseded by the data.
  - The target material and the read-across analog are expected to be similarly metabolized as shown by a metabolism simulator.
  - The structural alerts for genotoxicity, reproductive toxicity, and repeated dose toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.

References

Amdur, M.O., 1961. The respiratory response of Guinea pigs to the inhalation of acetic acid vapor. Am. Ind. Hyg. Assoc. J. 22 (1), 1–5.

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Brondeau, M.T., Bonnet, P., Guenier, J.P., Simon, P., DeCeaurriz, J., 1990. Adrenal-dependent leucopenia after short-term exposure to various airborne irritants in rats. J. Appl. Toxicol. 10 (2), 83–86.

Cain, W.S., Dourson, M.L., Kohrman-Vincent, M.J., Allen, B.C., 2010. Human chemosensory perception of methyl isothiocyanate: chemesthesis and odor. Regul. Toxicol. Pharmacol. 58 (2), 173–180.

Carlson, G.W., 1946. Aplastic anemia following exposure to products of the sulfite pulp industry: a report of one case. Ann. Intern. Med. 24, 277–284.

Carpenter, C.P., Smyth Jr., H.F., Pozzani, U.C., 1949. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Toxicol. 31 (6), 343–346.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

De Ceaurriz, J.C., Micillino, J.C., Bonnet, P., Guenier, J.P., 1981. Sensory irritation caused by various industrial airborne chemicals. Toxicol. Lett. 9, 137–143.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2017. Read-across Assessment Framework (RAAF). https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

Gagnaire, F., Marignac, B., Hecht, G., Hery, M., 2002. Sensory irritation of acetic acid, hydrogen peroxide, peroxyacetic acid and their mixture in mice. Ann. Occup. Hyg. 46 (1), 97–102.

Harth, V., Merget, R., Altmann, L., Bruning, T., 2007. Bronchial challenge testing to fragrance component as further diagnostic approach to non-immune immediate contact reactions. Contact Dermatitis 56 (3), 175–177.

Helmig, D., Klinger, L.F., Guenther, A., Vierling, L., Geron, C., Zimmerman, P., 1999a. Biogenic volatile organic compound emissions (BVOCs). I. Identifications from three continental sites in the U.S. Chemosphere 38 (9), 2163–2187.

Helmig, D., Klinger, L.F., Guenther, A., Vierling, L., Geron, C., Zimmerman, P., 1999b. Biogenic volatile organic compound emissions (BVOCs). II. Landscape flux potentials from three continental sites in the U.S. Chemosphere 38 (9), 2189–2204.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Johnson, B.A., Farahbod, H., Leon, M., 2005. Interactions between odorant functional group and hydrocarbon structure influence activity in glomerular response modules in the rat olfactory bulb. J. Comp. Neurol. 483 (2), 205–216.

Khare, P., Kumar, N., Satsangi, G.S., Maharaj Kumari, K., Srivastava, S.S., 1998. Formate and acetate in particulate matter and dust fall at Dayalbagh, Agra (India). Chemosphere 36 (14), 2993–3002.

Kim, H.-K., Kim, J.-R., Ahn, Y.-J., 2004. Acaricidal activity of cinnamaldehyde and its congeners against tyrophagus putrescentiae(Acari: Acaridae). J. Stored Prod. Res. 40 (1), 55–63.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Linyucheva, L.A., 1971. Effects of the acetic acid inhalation on the citrate metabolism in the liver of albino rats. Farmakologiia i Toksikologiia 34 (4), 481–483.

Montero, L., Vasconcellos, P.C., Souza, S.R., Pires, M.A.F., Andrade, O.R., Carvalho, L.R. F., 2001. Measurements of atmospheric carboxylic acids and carbonyl compounds in Sao Paulo City, Brazil. Environ. Sci. Technol. 35 (15), 3071–3081.

Morris, J.B., Symanowicz, P.T., 2002. Immediate responses of mouse nose to inspired irritants. Toxicologist 66 (1-S), 98.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2020. Fragrance Skin Sensitization Evaluation and Human Testing, Dermatitis: November 16, 2020. Volume Publish Ahead of Print Issue. https://doi.org/10.1097/DER.0000000000000684.

National Institute for Occupational Safety and Health, Kanwal, R., Kullman, G., Fedan, K., Kreiss, K., 2006. NIOSH Health Hazard Evaluation Report. Unpublished.

OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA(2015)7. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. http://www.qsartoolbox.org/.

Regnault-Roger, C., Hamraoui, A., 1995. Fumigant toxic activity and reproductive inhibition induced by monoterpenes on Acanthoscelides obtectus (Say) (Coleoptera), a bruchid of kidney bean (Phaseolus vulgaris L.). J. Stored Prod. Res. 31 (4), 291–299.

Rice, P.J., Coats, J.R., 1994. Insecticidal properties of several monoterpenoids to the house fly (Diptera: muscidae), red flour beetle (Coleoptera: tenebrionidae) and southern corn rootworm (Coleoptera: chrysomelidae). J. Econ. Entomol. 87 (5), 1172–1179.

RIFM (Research Institute for Fragrance Materials, Inc), 1972. The Contact-Sensitization Potential of Fragrance Materials by Maximization Testing in Humans. Report to RIFM. RIFM Report Number 1804. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1976. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1796. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2003. Evaluation of the Mutagenic Activity of Cinnamyl Acetate in the Salmonella typhimurium Reverse Mutation Assay. Unpublished Report from Givaudan. RIFM Report Number 42155. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013a. Evaluation of Nose-Only Inhalation Exposure to Aerosolized Cinnamal in Sprague-Dawley Rats. RIFM Report Number 64503. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013b. Report on the Testing of Cinnamyl Isobutyrate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 65349. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2015. Cinnamyl Acetate: in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM Report Number 68481. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016a. Combined Repeated Dose Toxicity Study with the Reproduction/developmental Toxicity Screening Test with Cinnamyl Acetate (Cinnamylacetat) by Oral Gavage in Wistar Rats. Unpublished Report from RIFM Report Number 71062. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016b. Exposure Survey 12, August 2016.

RIFM (Research Institute for Fragrance Materials, Inc), 2017a. Cinnamyl Acetate (Cinnamylacetat): Direct Peptide Reactivity Assay. Unpublished Report from Symrise. RIFM Report Number 72219. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2017b. Cinnamyl Acetate (Cinnamylacetat): in Vitro Skin Sensitization Test - Human Cell Line Activation Test (H-CLAT). Unpublished Report from Symrise. RIFM Report Number 72650. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2018. Cinnamyl Acetate: Repeated Insult Patch Test (RIPT). RIFM Report Number 73720. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2020. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM Report Number 76272. RIFM, Woodcliff Lake, NJ, USA.

RIVM., Rijksinstituut voor Volksgezondheid en M (National Institute for Public Health and Environment), Ezendam, J., De Klerk, A., Cassee, F.R., Van Loveren, H., de Jong, W.H., 2007. Immune Effects of Respiratory Exposure to Fragrance Chemicals. Pilot Studies with Isoeugenol and Cinnamal. Unpublished. RIVM Report 340301001/2007.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. In: Annals of the New York Academy of Sciences, vol. 641, pp. 152–163.

Suzuki, Y., Kawakami, M., Akasaka, K., 2001. (1)H NMR Application for characterizing water-soluble organic compounds in urban atmospheric particles. Environ. Sci. Technol. 35 (13), 2656–2664.

The Union of German Candle Manufacturers, 1997. Investigation of Oxidation Gases from Paraffin Aromatic Candles in Toxicological Relevance to Classes of Damaging Materials. Unpublished.

Troy, W.R., 1977. Doctoral Dissertation: the Comparative Respiratory Irritation Potential of Fourteen Fragrance Raw Materials. Unpublished.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.

Willis, D.N., Lin, B., Ha, M.A., Jordt, S.-E., Morris, J.B., 2011. Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. Faseb. J. 25 (12), 4434–4444.

Zaitsev, A.N., Rakhmanina, N.L., 1974. Some data on the toxic properties of phenylethanol and cinnamic alcohols. Vopr. Pitan. 6, 48–53.

Zissu, D., 1995. Histopathological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. J. Appl. Toxicol. 15 (3), 207–213.

Zuskin, E., Mustajbegovic, J., Schachter, E.N., Pavicic, D., Budak, A., 1997. A follow-up study of respiratory function in workers exposed to acid aerosols in a food-processing industry. Int. Arch. Occup. Environ. Health 70, 413–418.