Food and Chemical Toxicology 144 (2020) 111528

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 3-phenylbutanal, CAS Registry Number 16251-77-7

A.M. Api[a], D. Belsito[b], S. Biserta[a], 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], S. Gadhia[a], L. Jones[a], K. Joshi[a], A. Lapczynski[a], M. Lavelle[a], D.C. Liebler[i], M. Na[a], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], F. Rodriguez-Ropero[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], F. Siddiqi[a], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

[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*

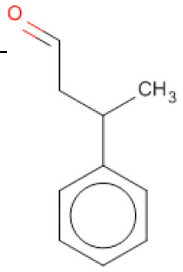
ARTICLE INFO

Keywords:
Genotoxicity
Repeated dose
Developmental
Reproductive toxicity
Skin sensitization
Phototoxicity/Photoallergenicity
Local respiratory toxicity
Environmental safety

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

https://doi.org/10.1016/j.fct.2020.111528
Received 15 April 2019; Received in revised form 16 March 2020; Accepted 11 June 2020
Available online 05 July 2020

Version: 120619. This version replaces any previous versions.



Name: 3-Phenylbutanal
CAS Registry Number: 16251-77-7

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
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
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
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

Summary: The existing information supports the use of this material as described in this safety assessment.

3-Phenylbutanal was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog isopropylphenylbutanal (CAS # 125109-85-5) show that 3-phenylbutanal is not expected to be genotoxic. Data from read-across analog 2-phenylbutanal (CAS # 93-53-8) provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on the target material provided a No Expected Sensitization Induction Level (NESIL) of 5900 μg/cm^2 for the skin sensitization endpoint. The developmental and reproductive toxicity and local respiratory toxicity endpoints were completed using the threshold of toxicological concern (TTC) for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on ultraviolet (UV) spectra; 3-phenylbutanal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 3-phenylbutanal 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, 2007a; RIFM, 1991)
Repeated Dose Toxicity: NOAEL = 10 mg/kg/day.	Pelling (1976)
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: NESIL = 5900 μg/cm^2.	RIFM (2009)
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: Critical Measured Value: 97% (OECD 301A)	RIFM (2013e)
Bioaccumulation: Screening-level: 19.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 244.2 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 244.2 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.2442 μg/L

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

1. Identification

1. **Chemical Name:** 3-Phenylbutanal
2. **CAS Registry Number:** 16251-77-7
3. **Synonyms:** Benzenepropanal, β-methyl-; 3-Phenylbutyraldehyde; 3-Phenyl-3-methylpropanal; Trifernal; フェニルアルキル(C = 1–4)アルデヒド; (RS)-3-Phenylbutanal; 3-Methyl-3-phenylpropionaldehyde; 3-Phenylbutanal
4. **Molecular Formula:** $C_{10}H_{12}O$
5. **Molecular Weight:** 148.21
6. **RIFM Number:** 1250

2. Physical data

1. **Boiling Point:** 228 ± 0.5 °C (501 ± 0.5 K) at 102.59 kPa (RIFM, 2007b), 70 °C @ 1 mm (Firmenich), 228.35 °C (EPI Suite)
2. **Flash Point:** Flash point (corrected) = 100 °C at 1013 hPa (RIFM, 2007c), 98 ± 2 °C (RIFM, 2007d), 98 °C (GHS), 170 °F/78 °C (Firmenich)

3. **Log K_{OW}**: 79.3, log10 Pow 1.90 (RIFM, 2007b), 2.45 (EPI Suite)
4. **Melting Point**: less than −20 ± 0.5 C (253 ± 0.5 K) (RIFM, 2007b), 1.2 °C (EPI Suite)
5. **Water Solubility:** 2.00 g/L of solution at 20.0 ± 0.5 °C (RIFM, 2007b), 623.9 mg/L (EPI Suite)
6. **Specific Gravity:** 0.98–1.05 @ 25/25 °C (Firmenich)
7. **Vapor Pressure:** 31 Pa at 25 °C (RIFM, 2013f), 0.0555 mm Hg @ 20 °C (EPI Suite v4.0), 0.05 mm Hg 20 °C (FMA Database), 0.0852 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 colorless liquid with a powerful, tenacious green foliage odor

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.00025% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00022 mg/kg/day or 0.016 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.00098 mg/kg/day (RIFM, 2014)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** Isopropylphenylbutanal (CAS # 125109-85-5)
   b. **Repeated Dose Toxicity:** 2-Phenylpropionaldehyde (CAS # 93-53-8)
   c. **Developmental and Reproductive Toxicity:** 2-Phenylpropionaldehyde (CAS # 93-53-8)
   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

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

3-Phenylbutanal 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. REACH dossier

Available, accessed 06/06/17 (ECHA, 2014).

9. Conclusion

The maximum acceptable concentrations[a] in finished products for 3-phenylbutanal are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.17
2	Products applied to the axillae	0.069
3	Products applied to the face/body using fingertips	0.023
4	Products related to fine fragrances	0.44
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.24
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.023
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.034
5D	Baby cream, oil, talc	0.0076
6	Products with oral and lip exposure	0.011
7	Products applied to the hair with some hand contact	0.023
8	Products with significant ano-genital exposure (tampon)	0.0076
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.080
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.080
10B	Aerosol air freshener	0.36
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0076
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	9.6

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 3-phenylbutanal, the basis was the reference dose of 0.1 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 5900 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. 3-Phenylbutanal was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013a). The mutagenic potential of 3-phenylbutanal 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 3-phenylbutanal at doses up to 5000 μg/plate with and without S9 metabolic activation in 2 independent experiments. There were small statistically significant increases in the number of revertant colonies for strain TA100 at concentrations of 50 and 1500 μg/plate in the absence of S9 in experiment 1 and at 150 μg/plate in the absence of S9 in experiment 2. These were considered to be not biologically relevant since the effects were not reproducible, were within the historical control range for strain TA100, and less than 2-fold above the vehicle control. Additionally, a dose response was not observed in either experiment 1 or 2. No other increases in revertant colonies were observed in any other test strain at any concentration tested (RIFM, 2007a). Under the conditions of the study, 3-phenylbutanal was not mutagenic in the Ames test.

There are no studies that have assessed the clastogenic potential of 3-phenylbutanal. The clastogenicity of read-across material isopropylphenylbutanal (CAS # 125109-85-5; see Section V) was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. Isopropylphenylbutanal was administered in phosphate buffered saline (PBS) via oral gavage to groups of male and female Fullinsdorf Moro Albino mice at doses of 1000 or 2000 mg/kg. Mice from each dose level were euthanized at 24, 48, and 72 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. Isopropylphenylbutanal did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 1991). Under the conditions of the study, isopropylphenylbutanal was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to 3-phenylbutanal.

Based on the available data, 3-phenylbutanal does not present a concern for genotoxic potential.

Additional References: RIFM, 1989a; RIFM, 2006; RIFM, 2005; RIFM, 2013b; RIFM, 2015.

Literature Search and Risk Assessment Completed On: 05/27/15.

10.1.2. Repeated dose toxicity

The margin of exposure for 3-phenylbutanal is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 3-phenylbutanal. Read-across material 2-phenylpropionaldehyde (CAS # 93-53-8; see section V) has sufficient repeated dose toxicity data. A gavage 15-week subchronic toxicity study was conducted in CFE rats with 2-phenylpropionaldehyde. Groups of 15 CFE strain rats/sex/dose were gavaged once daily with 2-phenylpropionaldehyde in corn oil at dose levels of 0, 10, 50, and 500 mg/kg/day. Hematological alterations included a significant decrease in hemoglobin concentration among high-dose males at weeks 6 and 15. The decrease in hemoglobin concentrations was also reported among mid- and high-dose females at week 15. Reticulocyte counts among high-dose females were significantly increased as compared to the controls. The reduction in hemoglobin counts among mid- and high-dose females in conjunction with increased reticulocyte counts among high-dose females were indicative of an increase in hematopoiesis and red-cell turnover. The authors reported that the alterations in hematological parameters were related to treatment with undefined causes. Thus, the authors reported a NOAEL of 10 mg/kg/day, based on alterations in hematological parameters among animals of the higher dose groups (Pelling, 1976). **Therefore, the 3-phenylbutanal MOE is equal to the 2-phenylpropionaldehyde NOAEL in mg/kg/day divided by the total systemic exposure to 3-phenylbutanal, 10/0.00098 or 10204.**

In addition, the total systemic exposure to 3-phenylbutanal (0.98 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section IX provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.1 mg/kg/day.

The RfD for 3-phenylbutanal was calculated by dividing the NOAEL of 10 mg/kg/day by the uncertainty factor, 100 = 0.1 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/05/17.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental or reproductive toxicity data on 3-phenylbutanal or on any read-across materials. The total systemic exposure to 3-phenylbutanal is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are insufficient developmental toxicity data on 3-phenylbutanal or on any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 3-phenylbutanal (0.98 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are insufficient reproductive toxicity data on 3-phenylbutanal or on any read-across materials that can be used to support the reproductive toxicity endpoint. A GLP study was conducted with read-across material 2-phenylpropionaldehyde (CAS # 93-53-8; see section V) administered to male Crl:CD(SD) rats only via gavage at doses of 0, 25, 75, and 250 mg/kg/day in corn oil for a period of 14 days. At the end of the treatment period, the average sperm counts and sperm density from the cauda epididymis were significantly reduced among mid- and high-dose animals. The cauda epididymal sperm count values among mid- and high-dose animals were below the ranges observed historically at the testing facility. Sperm motility and morphology were unaffected by the dose levels, up to and including 250 mg/kg/day. The absolute and relative weights of the epididymis, caudal epididymis, testes, seminal vesicles, prostate, and kidneys were comparable to the controls. There were no histopathological changes observed in the adrenals, kidneys, liver, prostate, seminal vesicles, and/or testes. The NOAEL for reproductive toxicity among male rats was considered to be 25 mg/kg/day, based on the decrease in sperm counts and density among higher dose group animals (RIFM, 2010). Since there are no female reproductive toxicity data on 2-phenylpropionaldehyde or any read-across materials, a NOAEL was not derived for the reproductive toxicity endpoint. The total systemic exposure to 3-phenylbutanal

Table 1
Data summary for 3-phenylbutanal.

LLNA Weighted Mean EC3 Value (No. Studies) μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
NA	NA	5906	NA	12500	5900

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from HRIPT or HMT.
[c] WoE NESIL limited to 2 significant figures.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/31/16.

10.1.4. Skin sensitization

Based on the existing data, 3-phenylbutanal presents a concern for skin sensitization with a defined NESIL of 5900 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, 3-phenylbutanal presents a concern for skin sensitization. The chemical structure indicates that this material is expected to react with skin proteins (Toxtree 2.6.13, OECD toolbox v3.4). 3-Phenylbutanal was found to be positive in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens, and human Cell Line Activation Test (h-CLAT) (RIFM, 2016a; RIFM, 2016b; RIFM, 2017). In guinea pigs, the Buehler test with 3-phenylbutanal did not result in reactions indicative of sensitization (RIFM, 1989b). However, in a human repeat insult patch test (HRIPT) with 12500 μg/cm^2 of 3-phenylbutanal in anhydrous alcohol, reactions indicative of sensitization was observed in 3/47 volunteers (RIFM, 1983). In another confirmatory HRIPT, no skin sensitization reactions were observed with 5906 μg/cm^2 in 1:3 ethanol:diethyl phthalate in any of the 102 volunteers (RIFM, 2009). Based on the available animal and human data, 3-phenylbutanal is considered a sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 5900 μg/cm^2 (Table 1). Section IX provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2008; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.1 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/17/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 3-phenylbutanal 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-phenylbutanal 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, 2009). Based on the lack of absorbance, 3-phenylbutanal 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/09/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 3-phenylbutanal 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-phenylbutanal. Based on the Creme RIFM Model, the inhalation exposure is 0.016 mg/day. This exposure is 87.5 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/31/16.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 3-phenylbutanal was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its Log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (US EPA, 2012b) (providing chemical class specific ecotoxicity estimates) is used, and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 3-phenylbutanal 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 v4.1 did not identify 3-phenylbutanal as either being possibly persistent nor bioaccumulative based on its structure and physical–chemical properties.

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

10.2.1.1. Risk assessment. Based on current VoU (2015), 3-phenylbutanal does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.1.1.1. Biodegradation. RIFM, 2013e: A ready biodegradability test was conducted according to the OECD 301A method. After 28 days, biodegradation of 97% was observed.

10.2.1.1.2. Ecotoxicity. RIFM, 2013c: A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-hour EC50 of 3-phenylbutanal was reported to be 14 mg/L based on time-weighted mean test concentrations.

RIFM, 2013d: An algae growth inhibition test was conducted according to the OECD 201 method. The 72-hour EC50s were reported to be 12 mg/L and 10 mg/L for growth rate and yield, respectively.

10.2.1.2. Other available data. 3-Phenylbutanal has been registered under REACH, but no additional data is available.

10.2.2. Risk assessment refinement

Since 3-phenylbutanal has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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)**	244.2			1,000,000	0.2442	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.9	1.9
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	1–10
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 0.2442 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at 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: 02/21/19.

11. 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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 03/01/19.

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.2020.111528.

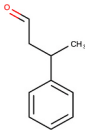
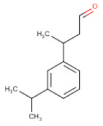
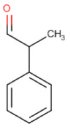
Appendix

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 Chemical 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 (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 were generated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated 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 materials	
Principal Name	3-Phenylbutanal	Isopropylphenylbutanal	2-Phenylpropionaldehyde
CAS No.	16251-77-7	125109-85-5	93-53-8
Structure			
Similarity (Tanimoto score)		0.78	0.88
Read-across endpoint		• Genotoxicity	• Repeated dose • Developmental and Reproductive
Molecular Formula	$C_{10}H_{12}O_2$	$C_{13}H_{18}O$	$C_9H_{10}O$
Molecular Weight	148.21	190.29	134.18
Melting Point (°C, EPI Suite)	1.20	09.10	−10.00
Boiling Point (°C, EPI Suite)	228.35	270.29	209.32
Vapor Pressure (Pa @ 25°C, EPI Suite)	11.4	1.14	40.4
Log Kow (KOWWIN v1.68 in EPI Suite)	2.45	3.8[2]	1.96
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2000[1]	100[3]	1877
J_{max} (μg/cm^2/h, SAM)	71.605	9.506	116.887
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.78E-001	1.90E + 000	7.37E-001
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	• Schiff base formers • Michael addition	• Schiff base formers • Michael addition	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Carcinogen (moderate reliability)	• Carcinogen (low reliability)	
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	
***In vitro* Mutagenicity (Ames test) alerts by ISS**	• Simple Aldehyde	• Simple Aldehyde	
***In vivo* mutagenicity (Micronucleus) alerts by ISS**	• Simple Aldehyde	• Simple Aldehyde	
Oncologic Classification	• Aldehyde type compound	• Aldehyde type compound	
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized		• Not categorized
Reproductive Toxicity			
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder without OH or NH_2 group		• Non-binder without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (moderate reliability)		• Toxicant (low reliability)
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

1. RIFM, 2007b.
2. RIFM, 1993b.
3. RIFM, 1993a.

Summary

There are insufficient toxicity data on the 3-phenylbutanal (CAS # 16251-77-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analogs isopropylphenylbutanal (CAS # 125109-85-5) and 2-phenylpropionaldehyde (CAS # 93-53-8) were identified as read-across materials with

data for their respective toxicity endpoints.

Conclusion

- Isopropylphenylbutanal (CAS # 125109-85-5) was used as a read-across analog for target material 3-phenylbutanal (CAS # 16251-77-7) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The target substance and the read-across analog share a phenylbutanal fragment.
  - o The key difference between the target substance and the read-across analog is that the read-across analog has a meta substitution on the benzene ring whereas the target does not have any substitution. This structural difference between the target substance and the read-across analog does not affect consideration of the toxic endpoint.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the phenylbutanal fragment. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxic endpoint.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for the genotoxicity endpoint are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog have carcinogenicity alerts by the ISS model. Both substances also have *in vivo* and *in vitro* mutagenicity alerts and DNA binding alerts by OECD. Furthermore, the target material and the read-across analog are classified as simple aldehyde type compounds. This shows that the read-across analog is predicted to have comparable reactivity with the target substance. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genetic toxicity. Therefore, the alert will be superseded by the availability of the 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 genotoxicity endpoint are consistent between the metabolites of the read-across analog and the target material.
  - o The structural differences between the target material and the read-across analog do not affect consideration of the genotoxicity endpoint.
- 2-Phenylpropionaldehyde (CAS # 93-53-8) was used as a read-across analog for target material 3-phenylbutanal (CAS # 16251-77-7) for the repeated dose and developmental and reproductive endpoints. The target substance and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The target substance and the read-across analog share a common aromatic aldehyde fragment.
  - o The key difference between the target substance and the read-across analog is that the read-across analog is a propanal whereas the target is a butanal. This structural difference between the target substance and the read-across analog does not affect consideration of the toxicity endpoint.
  - o The similarity between the target substance and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the aromatic aldehyde fragment. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o The read-across analog and the target are predicted to be toxicant by the CAESAR model for developmental toxicity. The data described in the developmental and reproductive toxicity section above shows that the read-across analog has an adequate margin of exposure at the current level of use. Therefore, the alert will be superseded by the availability of the data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

References

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.

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., Benfenati, E., 2010 July. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (S1), S4 (Springer International Publishing).

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.

ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2014. Registration dossier 3-phenylbutyraldehyde. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/11838.

ECHA, 2016. Read-across assessment framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

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.

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.

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

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

Pelling, D., Gaunt, I.F., Butterworth, K.R., Hardy, J., Lansdown, A.B.G., Gangolli, S.D., 1976. Short-term toxicity of hydratropic aldehyde in rats. Food Chem. Toxicol. 14 (4), 249–253.

RIFM (Research Institute for Fragrance Materials, Inc.), 1983. Clinical Safety Evaluation of 3-phenylbutanal. Repeated Insult Patch Test. Unpublished report from Firmenich SA. RIFM report number 40514. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1989. Mutgenicity Test on Isopropylphenylbutanal (Florhydral) in the Ames Salmonella/microsome Reverse Mutation Assay. Unpublished report from Givaudan. RIFM report number 41941. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1989. Delayed Dermal

Sensitisation Test of 3-phenylbutanal in the guinea Pig. Unpublished report from Firmenich SA. RIFM report number 40513. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1991. Micronucleus Test in Mouse Bone Marrow after Oral Administration of the Fragrance Ingredient Isopropylphenylbutanal (Florhydral). Unpublished report from Givaudan. RIFM report number 41942. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1993. Ready Biodegradability of Isopropylphenylbutanal (Florhydral). Unpublished report from Givaudan. RIFM report number 55921. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1993. Isopropylphenylbutanal (Florhydral): Determination of the Partition Coefficient N-Octanol/water. Unpublished report from Givaudan. RIFM report number 55924. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2005. In Vitro Chromosome Aberration Test in Chinese Hamster V79 Cells with Isopropylphenylbutanal (Florhydral). Unpublished report from Givaudan. RIFM report number 55923. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Escherichia coli Reverse Mutation Assay with Isopropylphenylbutanal (Florhydral). Unpublished report from Givaudan. RIFM report number 55922. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2007. 3-Phenylbutanal (Trifernal): Reverse Mutation Assay "Ames Test" Using Salmonella typhimurium and Escherichia coli. Unpublished report from Firmenich. RIFM report number 67754. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2007. 3-Phenylbutanal (Trifernal): Determination of General Physico-Chemical Properties. Unpublished report from Firmenich. RIFM report number 67756. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2007. 3-Phenylbutanal (Trifernal): Determination of Flash Point. Unpublished report from Firmenich. RIFM report number 67755. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2007. 3-Phenylbutanal (Trifernal): Determination of Flash Point (Non-GLP). Unpublished report from Firmenich. RIFM report number 67752. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients. RIFM report number 55663. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Repeated Insult Patch Test with 3-phenylbutanal. RIFM report number 57513. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2010. An Oral (Gavage) Repeated Dose 14-day Toxicity Study of 3 Alpha Substituted, 1 Beta Substituted and 2 Unsubstituted Test Substances in Male Rats, Including an Evaluation of the Reproductive Organs. RIFM report number 59712. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of 3-phenylbutanal in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65407. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Isopropylphenylbutanal in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 66009. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. 3-Phenylbutanal (Trifernal): Daphnia Magna 48-hour Acute Immobilization Test. Unpublished report from Firmenich. RIFM report number 67749. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. 3-Phenylbutanal (Trifernal): Algal Growth Inhibition Test. Unpublished report from Firmenich. RIFM report number 67751. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. 3-Phenylbutanal (Trifernal): Assessment of Ready Biodegradability. Unpublished report from Firmenich. RIFM report number 67753. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013. 3-Phenylbutanal (Trifernal): Determination of Vapor Pressure. Unpublished report from Firmenich. RIFM report number 67757. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2014. Exposure Survey 04. July 2014.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015. Isopropylphenylbutanal (Florhydral): Chromosome Aberrations in Chinese Hamster Ovary Cells in Vitro. Unpublished report from Givaudan. RIFM report number 68778. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016. Direct Peptide Reactivity Assay (DPRA) in Fragrance Materials. RIFM report number 72226. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2016. Induction of Antioxidant-Response-Element Dependent Gene Activity and Cytotoxicity (Using Mtt) in the Keratinocyte Are-Reporter Cell Line Keratinosens. RIFM report number 72233. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2017. 3-Phenylbutanal: in Vitro Sensitization: Dendritic Cell Line Activation Assay Human Cell Line Activation Test (H-CLAT). RIFM report number 72757. RIFM, Woodcliff Lake, NJ, USA.
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., Cronin, M.T.D., 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 (12), 164–176.
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, v1.11. United States Environmental Protection Agency, Washington, DC, USA.