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Short Review

RIFM fragrance ingredient safety assessment, 2-phenylpropionaldehyde, CAS Registry Number 93-53-8

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A B S T R A C T

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

2-Phenylpropionaldehyde was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on read-across analogs 3-phenylbutanal (CAS # 16251-77-7) and isopropylphenylbutanal (CAS # 125109-85-5) show that this material is not expected to be genotoxic. Data from the target material provide a calculated margin of exposure (MOE) >100 for the repeated dose toxicity endpoint and a No Expected Sensitization Induction Level (NESIL) of 380 μg/cm^2 for the skin sensitization endpoint. The developmental and reproductive toxicity and the 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 endpoints were evaluated based on ultraviolet (UV) spectra; 2-phenylpropionaldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-phenylpropionaldehyde 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.

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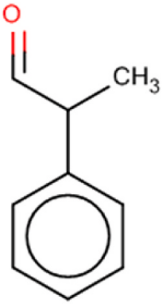


Name: 2-Phenylpropionaldehyde
CAS Registry Number: 93-53-8

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; Safford et al., 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 et al., 2015), which should be referred to for clarifications.

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

(*continued on next column*)

(*continued*)

*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.

2-Phenylpropionaldehyde was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data on read-across analogs 3-phenylbutanal (CAS # 16,251-77-7) and isopropylphenylbutanal (CAS # 125,109-85-5) show that this material is not expected to be genotoxic. Data from the target material provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity endpoint and a No Expected Sensitization Induction Level (NESIL) of 380 μg/cm^2 for the skin sensitization endpoint. The developmental and reproductive toxicity and the 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 endpoints were evaluated based on ultraviolet (UV) spectra; 2-phenylpropionaldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-phenylpropionaldehyde 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 et al., 1976)

Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: NESIL = 380 μg/cm^2. (EPA, 1991; RIFM, 1964; RIFM, 1971a; Gerberick et al., 2005)

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: 80% (OECD 301B) RIFM (1995)

Bioaccumulation: Screening-level: 9.1 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 196.1 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; #40315)

Critical Ecotoxicity Endpoint: LC50: 196.1 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.1961 μg/L

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

1. Identification

1. **Chemical Name:** 2-Phenylpropionaldehyde
2. **CAS Registry Number:** 93-53-8
3. **Synonyms:** Benzeneacetaldehyde, α-methyl-; Hydratropaldehyde; Hydratropic aldehyde; α-Methylphenylacetaldehyde; α-Methyl-tolualdehyde; 2-Phenylpropanal; α-Phenylpropionaldehyde; α - メチル - α - フェニルアセトアルデヒド; フェニルアルキル（Ｃ＝１～４）アルデヒド; 2-Phenylpropionaldehyde
4. **Molecular Formula:** $C_9H_{10}O$
5. **Molecular Weight:** 134.18
6. **RIFM Number:** 165

2. Physical data

1. **Boiling Point:** 204 °C (FMA Database), 209.32 °C (EPI Suite)
2. **Flash Point:** 170 °F; CC (FMA Database)
3. **Log K_{OW}:** 1.96 (EPI Suite)

4. **Melting Point**: −10 °C (EPI Suite)
5. **Water Solubility:** 1877 mg/L (EPI Suite)
6. **Specific Gravity:** 1.010–1.020 (FMA Database), 1.012–1.022 (FMA Database)
7. **Vapor Pressure:** 0.204 mm Hg @ 20 °C (EPI Suite v4.0), 0.2 mm Hg 20 °C (FMA Database), 0.303 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with a fresh fruity scent

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.00012% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0085 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.00047 mg/kg/day (RIFM, 2015)

*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 IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** 3-Phenylbutanal (CAS # 16,251-77-7); isopropylphenylbutanal (CAS # 125,109-85-5)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across justification: See Appendix below

6. Metabolism

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)

2-Phenylpropionaldehyde is reported to occur in the following foods by the VCF*:Cocoa category, Mushroom, Tea.

*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 06/02/17 (ECHA, 2016a).

9. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-phenylpropionaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.029
2	Products applied to the axillae	0.0087
3	Products applied to the face/body using fingertips	0.096
4	Products related to fine fragrances	0.16
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.041
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.041
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.041
5D	Baby cream, oil, talc	0.014
6	Products with oral and lip exposure	0.096
7	Products applied to the hair with some hand contact	0.19
8	Products with significant ano-genital exposure (tampon)	0.014
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.32
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.32
10B	Aerosol air freshener	0.77
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.014
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	31

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 2-phenylpropionaldehyde, 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 380 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

10. Summary

10.1. Human health endpoint summaries

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

10.1.1. Risk assessment

There are no studies assessing the mutagenicity of 2-phenylpropionaldehyde. The mutagenic potential of read-across material 3-phenylbutanal (CAS # 16,251-77-7) 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. *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. Coli* strain WP2 uvrA 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 historical control range for that strain TA100, and less than 2 times 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, and this can be applied to 2-phenylpropionaldehyde.

There are no studies assessing the clastogenic potential of 2-phenylpropionaldehyde. The clastogenicity of read-across material isopropylphenylbutanal (CAS # 125,109-85-5) 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 single oral gavage to groups of male and female Fullinsdorf Moro Albino mice. Doses of 1000 or 2000 mg/kg were administered. Mice from each dose level were euthanized at 24 h; 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 2-phenylpropionaldehyde.

Based on the available data, 2-phenylpropionaldehyde does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/23/14.

10.1.2. Repeated dose toxicity

The margin of exposure for 2-phenylpropionaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. The data on 2-phenylpropionaldehyde are sufficient for the repeated dose toxicity endpoint. 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 week 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 et al., 1976). **Therefore, the 2-phenylpropionaldehyde MOE is equal to the 2-phenylpropionaldehyde NOAEL in mg/kg/day divided by the total systemic exposure to 2-phenylpropionaldehyde, 10/0.00047 or 21,277.**

In addition, the total systemic exposure to 2-phenylpropionaldehyde (0.47 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.

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, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 0.1 mg/kg/day.

The reference dose for 2-phenylpropionaldehyde 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 2-phenylpropionaldehyde or on any read-across materials. The total systemic exposure to 2-phenylpropionaldehyde 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 2-phenylpropionaldehyde or on any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to 2-phenylpropionaldehyde (0.47 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 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 2-phenylpropionaldehyde or on any read-across materials that can be used to support the reproductive toxicity endpoint. A GLP study was conducted with test material 2-phenylpropionaldehyde 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 2-phenylpropionaldehyde (0.47 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: None.

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

10.1.4. Skin sensitization

Based on the existing data, 2-phenylpropionaldehyde is considered to be a skin sensitizer with a defined NESIL of 380 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, 2-phenylpropionaldehyde is considered to be a skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree v2.6.13; OECD Toolbox v3.4). 2-Phenylpropionaldehyde was found to be positive in the *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens, and U937-CD86 test (Natsch et al., 2013; McKim et al., 2010). In addition, in a murine local lymph node assay (LLNA), 2-phenylpropionaldehyde was found to be sensitizing with an EC3 value of 6.3% (1575 μg/cm^2) (Gerberick et al., 2005; Patlewicz et al., 2003; Roberts et al., 2007). In human maximization tests, no skin sensitization reactions were observed with 1380 μg/cm^2 of 2-phenylpropionaldehyde (RIFM, 1970; RIFM, 1971b). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 382 μg/cm^2 of 2-phenylpropionaldehyde in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 38 volunteers (RIFM, 1971a). In another HRIPT with 1938 μg/cm^2 of 2-phenylpropionaldehyde in ethanol, reactions indicative of sensitization was observed in 1 of the 7 volunteers (RIFM, 1964). Based on weight of evidence from all the available data, 2-phenylpropionaldehyde is considered to be a moderate skin sensitizer with a defined NESIL of 380 μg/cm^2 (See 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, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 0.1 mg/kg/day.

Additional References: RIFM, 1962; Klecak (1985); Sharp (1978); EPA, 1991

Literature Search and Risk Assessment Completed On: 05/22/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 2-phenylpropionaldehyde does not present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-phenylpropionaldehyde in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, 2-phenylpropionaldehyde does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 2-phenylpropionaldehyde were obtained. The spectra indicate minor 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: 05/05/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 2-phenylpropionaldehyde 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 2-phenylpropionaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.0085 mg/day. This exposure is 165 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/10/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-phenylpropionaldehyde was performed following the RIFM Environmental Framework (Salvito et al., 2002; #40315), 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, 2-phenylpropionaldehyde was identified as a fragrance

Table 1
Data summary for 2-phenylpropionaldehyde.

LLNA Weighted Mean EC3 Value μg/Cm^2 [No. Studies]	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
1575 [1][d]	Moderate	388[e]	1380	1938	380[f]

NOEL=No observed effect level; HRIPT=Human Repeat Insult Patch Test; HMT=Human Maximization Test; LOEL = lowest observed effect level.

[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.

[d] EC3 value from one LLNA, not the mean.

[e] HRIPT with 38 subjects only; study with 100 subjects not done because the material is used at a low volume (1–5 metric tons).

[f] WoE NESIL based on limited subject HRIPT, which was lower than the default LLNA (1000 μg/cm^2).

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 2-phenylpropionaldehyde 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 v4.1). 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 the current VoU (2015), 2-phenylpropionaldehyde does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. **RIFM, 1995:** A study was conducted according to the OECD 301B method to determine the ready and ultimate biodegradability using the sealed vessel test. Biodegradation of 2-phenylpropionaldehyde after 28 days was 80%.

Ecotoxicity: No data available.

Other available data: No data available.

10.2.2. 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 Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.96	1.96
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 additional assessment is necessary.

The RIFM PNEC is 0.1961 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 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
- **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 08/04/20.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	196.1			1,000,000	0.1961	

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111697.

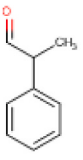
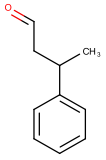
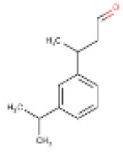
Appendix

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, 2016b).

- 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, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- 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, 2012).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target Material	Read-across Materials	
Principal Name	2-Phenylpropionaldehyde	3-Phenylbutanal	Isopropylphenylbutanal
CAS No.	93-53-8	16,251-77-7	125,109-85-5
Structure			
Similarity (Tanimoto score)		0.88	0.67
Read-across endpoint		• Genotoxicity	• Genotoxicity
Molecular Formula	$C_9H_{10}O$	$C_{10}H_{12}O_2$	$C_{13}H_{18}O$
Molecular Weight	134.18	148.21	190.29
Melting Point (°C, EPI Suite)	−10.00	1.20	09.10
Boiling Point (°C, EPI Suite)	209.32	228.35	270.29
Vapor Pressure (Pa @ 25°C, EPI Suite)	40.4	11.4	1.14
Log Kow (KOWWIN v1.68 in EPI Suite)	1.96	2.45	3.8[2]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1877	20,00[1]	100[3]
J_{max} (μg/cm^2/h, SAM)	116.887	71.605	9.506
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.37E-001	9.78E-001	1.90E+000
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• Schiff base formers • Michael addition	• Schiff base formers • Michael addition	• Schiff base formers • Michael addition
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Carcinogen (moderate reliability)	• Carcinogen (moderate reliability)	• Carcinogen (low reliability)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	• No alert found
***In vitro* Mutagenicity (Ames test) alerts by ISS**	• Simple Aldehyde	• Simple Aldehyde	• Simple Aldehyde
***In vivo* mutagenicity (Micronucleus) alerts by ISS**	• Simple Aldehyde	• Simple Aldehyde	• Simple Aldehyde
Oncologic Classification	• Aldehyde type compound	• Aldehyde type compound	• Aldehyde type compound
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	• See Supplementary Data 1	• See Supplementary Data 2	• See Supplementary Data 3

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

Summary

There are insufficient toxicity data on the 2-phenylpropionaldehyde (CAS # 93-53-8). 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, analogs 3-phenylbutanal (CAS # 16,251-77-7) and isopropylphenylbutanal (CAS # 125,109-85-5) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 3-Phenylbutanal (CAS # 16,251-77-7) was used as a read-across analog for target material 2-phenylpropionaldehyde (CAS # 93-53-8) for the genotoxicity endpoint. The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The target material and the read-across analog share a common aromatic aldehyde fragment.
  - o The key difference between the target material and the read-across analog is that the read-across analog is a butanal, whereas the target is a propanal. This structural difference between the target material and the read-across analog does not affect consideration of the toxicity endpoint.
  - o The similarity between the target material 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 material 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 genotoxicity endpoint are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have a carcinogenicity alert by the ISS model. Both materials also have an *in vivo* and *in vitro* mutagenicity alert and DNA binding alerts by OECD. Further, the target material and read-across analog are also classified as simple aldehyde type compounds. This shows that the read-across analog is predicted to have comparable reactivity to the target material. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genotoxicity. Therefore, the alert will be superseded by the availability of the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the 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.
- Isopropylphenylbutanal (CAS # 125,109-85-5) was used as a read-across analog for the target material 2-phenylpropionaldehyde (CAS # 93-53-8) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - o The target material and the read-across analog share a phenylbutanal fragment.
  - o The key difference between the target material 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 material and the read-across analog does not affect consideration of the toxicity endpoint.
  - o The similarity between the target material 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 material 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 material and the read-across analog.
  - o The target material and the read-across analog have a carcinogenicity alert by the ISS model. Both materials also have an *in vivo* and an *in vitro* mutagenicity alert and DNA binding alerts by OECD. Further, the target material and read-across analog are also classified as simple aldehyde-type compounds. This shows that the read-across analog is predicted to have comparable reactivity to the target material. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genotoxicity. In addition, the target material and the read-across analog are structurally very similar except that the read-across analog has an isopropyl substitution on the meta position of the 3-phenylbutanal structure. The reactivity is driven by the aldehyde group as confirmed by the alerts. The aromatic ring and any substitution on the ring do not play an important part (any part for that matter) in the reactivity towards proteins and nucleic acids. Therefore, the structural difference between the target material and the read-across analog can be deemed toxicologically insignificant for genotoxicity endpoint. Therefore, the alert will be superseded by the availability of the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the 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.

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