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RIFM fragrance ingredient safety assessment, 3-phenylpropionaldehyde, CAS Registry Number 104-53-0

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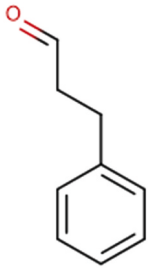


Name: 3-Phenylpropionaldehyde
CAS Registry Number: 104-53-0

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

(*continued on next column*)

(*continued*)

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-Phenylpropionaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog phenylacetaldehyde (CAS # 122-78-1) show that 3-phenylpropionaldehyde is not expected to be genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints and a No Expected Sensitization Induction Level (NESIL) of 590 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 3-phenylpropionaldehyde is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to 3-phenylpropionaldehyde is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 3-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, 2015; RIFM, 2016)
Repeated Dose Toxicity: NOAEL = 33.33 mg/kg/day.	RIFM (2017)
Reproductive Toxicity: Developmental and Fertility NOAEL = 100 mg/kg/day.	RIFM (2017)
Skin Sensitization: NESIL = 590 μg/cm^2.	(RIFM, 2003b; RIFM, 2004)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 87% (OECD 301F)	RIFM (2012)
Bioaccumulation: Screening-level: 10.19 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 403.3 mg/L	(RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 403.3 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.4033 μg/L

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

1. Identification

1. **Chemical Name:** 3-Phenylpropionaldehyde
2. **CAS Registry Number:** 104-53-0
3. **Synonyms:** Benzenepropanal; Benzylacetaldehyde; Hydrocinnamaldehyde; Phenylpropyl aldehyde; 3-Phenylpropanal; Phenyl propionic aldehyde; 3-Phenylpropionaldehyde
4. **Molecular Formula:** $C_9H_{10}O$
5. **Molecular Weight:** 134.17 g/mol
6. **RIFM Number:** 424
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 77 °C at 3 mm (Fragrance Materials Association [FMA]), 220.9 °C (EPI Suite)

2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA)
3. **Log K_{OW}:** 1.6 (RIFM, 2013), 2.03 (EPI Suite)
4. **Melting Point**: 0.89 °C (EPI Suite)
5. **Water Solubility:** 1624 mg/L (EPI Suite)
6. **Specific Gravity:** 1.010–1.020 (FMA), 1.012–1.022 (FMA)
7. **Vapor Pressure:** 0.0369 mm Hg at 20 °C (EPI Suite v4.0), 0.03 mm Hg 20 °C (FMA), 0.0628 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient (170 L mol^{-1} • cm^{-1}, condition not specified) is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A clear, colorless to pale yellow liquid with a floral odor reminiscent of hyacinth

3. Volume of use (worldwide band)

1 0.1–1 metric ton per year (IFRA, 2015)

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00038% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.000064 mg/kg/day or 0.0046 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00031 mg/kg/day (RIFM, 2018)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

6.2. Analogs Selected

a. **Genotoxicity:** Phenylacetaldehyde (CAS # 122-78-1)
b. **Repeated Dose Toxicity:** Phenylacetaldehyde (CAS # 122-78-1)
c. **Reproductive Toxicity:** Phenylacetaldehyde (CAS # 122-78-1)
d. **Skin Sensitization:** Phenylacetaldehyde (CAS # 122-78-1)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

3-Phenylpropionaldehyde is reported to occur in the following foods by the VCF*:

Artocarpus species	Origanum (Spanish) (*Coridothymus cap.* (L.) Rchb.)
Beer	Syzygium species
Cheese, various types	Tomato (*Lycopersicon esculentum* Mill.)
Cinnamomum species	Trassi (cooked)
Fig (*Ficus carica* L.)	

*VCF (Volatile Compounds in Food): Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

3-Phenylpropionaldehyde has been pre-registered for 2010; no dossier available as of 12/10/21.

10. Conclusion

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

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.045
2	Products applied to the axillae	0.014
3	Products applied to the face/body using fingertips	0.27
4	Products related to fine fragrances	0.20
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.064
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.064
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.064
5D	Baby cream, oil, talc	0.021
6	Products with oral and lip exposure	0.15
7	Products applied to the hair with some hand contact	0.041
8	Products with significant ano-genital exposure (tampon)	0.021
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.49
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.8
10B	Aerosol air freshener	1.8
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.021
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted

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-phenylpropionaldehyde, the basis was the subchronic reference dose of 0.33 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 590 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).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.4.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. There were limited genotoxicity data for 3-phenylpropionaldehyde. 3-Phenylprioprionaldehyde, with or without S9 metabolic activation, is reported as not mutagenic in the *Salmonella* assay; however, there are limited details available for this study, and it was a qualitative evaluation of mutagenicity (spot test). This compound is also reported to not impact Mitomycin C-induced sister chromatid exchange formation in cultured Chinese hamster ovary cells. There are no additional data assessing the mutagenic activity of 3-phenylpropionaldehyde (Florin et al., 1980).

The genotoxic potential of the read-across material phenylacetaldehyde (CAS # 122-78-1; see Section VI) was evaluated. The mutagenic activity of phenylacetaldehyde 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/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with phenylacetaldehyde in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2015). Under the conditions of the study, phenylacetaldehyde was not mutagenic in the Ames test, and this can be extended to 3-phenylpropionaldehyde.

There are no studies assessing the clastogenicity of 3-phenylpropionaldehyde. The clastogenic activity of read-across material phenylacetaldehyde (CAS # 122-78-1; see Section VI) was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with phenylacetaldehyde in DMSO at concentrations up to 1202 μg/mL in the presence and absence of S9 for 4 and 20 h. Phenylacetaldehyde did not induce binucleated cells with micronuclei when tested up to the maximum dose in either non-activated or S9-activated test systems (RIFM, 2016). Under the conditions of the study, phenylacetaldehyde was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 3-phenylpropionaldehyde.

Based on the available data, 3-phenylpropionaldehyde acid does not present a concern for genotoxic potential, and this can be extended to 3-phenylproprionic acid.

Additional References: Sasaki et al., 1989.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

The MOE for 3-phenylpropionaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3-phenylpropionaldehyde. Read-across material phenylacetaldehyde (CAS # 122-78-1; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In an OECD 422 (combined repeated dose and reproductive toxicity) and GLP-compliant study, 12 Sprague Dawley (Crl: CD[SD]) SPF rats/sex/dose were orally administered phenylacetaldehyde through gavage at doses of 0, 25, 100, and 400 mg/kg/day. Recovery groups consisting of 6 animals/sex from the control and high doses were maintained for a 2-week post-exposure period. During the main study, 1 female was found to be moribund (day 14), and 2 males (day 40) and 1 female (day 39) were found dead in the 400 mg/kg/day group. Mortality was not reported in other dose groups. Increased salivation was reported in the 400 mg/kg/day treatment group (5 males and 7 females) from day 5 onwards; this was also observed in the 400 mg/kg/day recovery group (5 males, 3 females). Although no change in male body weight was reported during treatment, female body weights were significantly decreased in the 100 and 400 mg/kg/day groups on postpartum day 0 and gestation day 7, respectively. In contrast, in the recovery groups, only male body weights were significantly decreased on treatment days 8 and 14, but the differences were reversed during the recovery period. Since no information on bodyweight gain was reported in the study report, it does not allow for determining if the bodyweight changes were treatment-related adverse events. During the study (including the recovery period), no alterations were reported in male food consumption in any treatment group. However, among females, food consumption was significantly lower in the 100 and 400 mg/kg/day groups. This effect was observed on gestation days 1 and 7 and postpartum day 4 at 100 mg/kg/day dose and on gestation day 7 only in the 400 mg/kg/day group. Moreover, significantly lower food consumption was reported only at the end of the recovery period (study day 63) in the recovery group females receiving the highest dose. Due to a lack of consistent change, these effects were not considered to be treatment-related adverse effects. No treatment-related effects for hematology, clinical chemistry, auditory reflex, pinna reflex, pupillary reflex, the corneal reflex test, and grip strength were reported in animals of both sexes at any dose level. At the highest dose, erythrophagocytosis and diffuse lymphoid hyperplasia of mesenteric lymph nodes and centrilobular hepatocellular hypertrophy were reported in both sexes. Additionally, thymus atrophy was also reported in females of the high-dose group. In the absence of other histopathological alterations, the centrilobular hepatocellular hypertrophy was regarded as a treatment-related adaptive response. Hence, based on the treatment-related erythrophagocytosis and diffuse lymphoid hyperplasia of mesenteric lymph nodes in both sexes as well as thymus atrophy in females at the highest dose, 100 mg/kg/day was considered to be the NOAEL for repeated dose toxicity endpoint (RIFM, 2017).

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

Thus, the derived NOAEL for the repeated dose toxicity data is 100/3 or 33.33 mg/kg/day.

Therefore, the 3-phenylpropionaldehyde MOE for the repeated dose toxicity endpoint can be calculated by dividing the phenylacetaldehyde NOAEL in mg/kg/day by the total systemic exposure to 3-phenylpropionaldehyde, 33.33/0.00031 or 107516.

In addition, the total systemic exposure to 3-phenylpropionaldehyde (0.31 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose endpoint of a Cramer Class I material at the current level of use.

Derivation of subchronic reference dose (RfD):

Section X 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, 2020b) and a subchronic reference dose of 0.33 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic reference dose for 3-phenylpropionaldehyde was calculated by dividing

the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 33.33 mg/kg/day by the uncertainty factor, 100 = 0.33 mg/kg/day.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/14/21.

11.1.3. Reproductive toxicity

The MOE for 3-phenylpropionaldehyde is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 3-phenylpropionaldehyde. Read-across material phenylacetaldehyde (CAS # 122-78-1; see Section VI) has sufficient data to support the developmental and reproductive toxicity endpoint. There are sufficient developmental and reproductive toxicity data on phenylacetaldehyde that can be used to support the developmental and reproductive toxicity endpoints. An OECD 422/GLP study was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered via oral gavage test material phenylacetaldehyde at doses of 0, 25, 100, or 400 mg/kg/day. Males were dosed for a total of 49 days (2 weeks prior to mating, during the 2-week mating period, and up to 21 days post-mating), while females were dosed 2 weeks prior to mating, throughout gestation, and for 13 days after delivery. Additional groups of 6 rats/sex/dose were assigned to the control and high-dose groups to serve as the 14-day treatment-free recovery groups and were not mated. Males and females of the recovery groups were dosed for 49 days. In addition to systemic toxicity parameters, reproductive toxicity parameters were also assessed. At 400 mg/kg/day, 1 dam was found moribund, and 2 males and 1 dam were found dead. The females showed irregular respiration before their moribund state or death. The dead animals exhibited thickening of the forestomach and centrilobular hepatocellular hypertrophy of the liver. Furthermore, they showed poor condition/stress-related gross observations (i.e., adrenal enlargement, black area/red discoloration of the glandular stomach, and small thymus or spleen). Thymic atrophy was found in 2 high-dose group dams whose pups were all dead. A statistically significant increase in post-implantation loss and a statistically significant decrease in the live birth index were observed among the 400 mg/kg/day group dams. The viability index on the postnatal day (PND) PND 4 for the control, low-, mid-, and high-dose groups were 97.4%, 96.1%, 98.8%, and 68.9%, respectively. Although the viability on PND 4 was not statistically significant at 400 mg/kg/day, this finding was considered to be toxicologically significant since the differences were substantial as compared to the controls. Thus, the NOAEL for reproductive toxicity was considered to be 400 mg/kg/day for males and 100 mg/kg/day for females, based on increased post-implantation loss and decreased live birth index among high-dose group dams. The NOAEL for developmental toxicity was considered to be 100 mg/kg/day, based on decreased viability on PND 4 among high-dose group pups (RIFM, 2017).

Therefore, the 3-phenylpropionaldehyde MOE for the reproductive toxicity endpoint can be calculated by dividing the phenylacetaldehyde NOAEL in mg/kg/day by the total systemic exposure to 3-phenylpropionaldehyde, 100/0.00031, or 322580.

In addition, the total systemic exposure to 3-phenylpropionaldehyde (0.31 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/14/21.

11.1.4. Skin sensitization

Based on the existing data and read-across to phenylacetaldehyde (CAS # 122-78-1), 3-phenylpropionaldehyde is considered a skin sensitizer with a defined NESIL of 590 μg/cm^2.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 3-phenylpropionaldehyde. Based on the existing data and read-across to phenylacetaldehyde (CAS # 122-78-1; see Section VI), 3-phenylpropionaldehyde is considered a moderate skin sensitizer. The chemical structure of these materials indicates that they would be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Read-across phenylacetaldehyde was found to be positive in *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens, and human cell line activation test (h-CLAT), but both positive and negative in U-SENS (Natsch et al., 2013; Urbisch et al., 2015; Piroird et al., 2015). In guinea pig studies, both positive and negative results were observed with 3-phenylpropionaldehyde (Klecak et al., 1977; Sharp, 1978). In a murine local lymph node assay (LLNA), read-across material phenylacetaldehyde was found to be sensitizing with a weighted mean EC3 value of 5.5% (1375 μg/cm^2) (Basketter et al., 2001; Gerberick et al., 2004; Basketter et al., 2003; Basketter et al., 2002). In a human maximization test, no sensitization reactions were observed with 8% (5520 μg/cm^2) 3-phenylpropionaldehyde in petrolatum (RIFM, 1973). Nevertheless, in a CNIH with 1% or 1181 μg/cm^2 read-across phenylacetaldehyde stabilized with 0.5% tocopherol in 3:1 ethanol: diethyl phthalate (EtOH:DEP), reactions indicative of sensitization were observed in 7/27 volunteers (RIFM, 2003b). However, in another CNIH with 1% or 1181 μg/cm^2 phenylacetaldehyde stabilized with 0.5% tocopherol in 1:3 EtOH:DEP, no reactions indicative of sensitization was observed in any of the 26 volunteers (RIFM, 2003a). Similarly, in a separate CNIH with 0.5% or 591 μg/cm^2 phenylacetaldehyde stabilized with 0.5% tocopherol in 1:3 EtOH:DEP conducted according to the method of Politano and Api (Politano and Api, 2008), no reactions indicative of sensitization were observed in any of the 110 volunteers (RIFM, 2004).

Based on the available data and read-across to phenylacetaldehyde, 3-phenylpropionaldehyde is considered a moderate skin sensitizer with a defined NESIL of 590 μg/cm^2 (see Table 1). Section X 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, 2020b) and a subchronic reference dose of 0.33 mg/kg/day.

Additional References: Klecak (1979); Klecak (1985); RIFM, 1972; RIFM, 1974a; RIFM, 1976; RIFM, 1974b; Roberts et al., 2007.

Literature Search and Risk Assessment Completed On: 06/01/21.

11.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis absorption spectra, 3-phenylpropionaldehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 3-phenylpropionaldehyde in experimental models. The available UV/Vis spectra for 3-phenylpropionaldehyde 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, 3-phenylpropionaldehyde does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. The available UV/Vis spectra for 3-phenylpropionaldehyde indicate minor absorbance between 290 and 700 nm. The molar absorption coefficient (170 L mol^{-1} • cm^{-1}, condition not specified) is below the benchmark of concern for phototoxic effects,

Table 1
Data summary for read-across material phenylacetaldehyde.

LLNA Weighted Mean EC3 Value [No. Studies] μg/cm^2	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
1375 [3]	moderae	591	NA	1181	590

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans 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 CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/26/21.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3-phenylpropionaldehyde is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 3-phenylpropionaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.0046 mg/day. This exposure is 304.3 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: 06/03/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3-phenylpropionaldehyde was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 3-phenylpropionaldehyde was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 3-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 v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 3-phenylpropionaldehyde does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 2012:** The ready biodegradability of the test material was evaluated in a manometric respirometry test according to the OECD 301F method. Under the conditions of the study, biodegradation of 87% was observed after 28 days.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. 3-Phenylpropionaldehyde has been pre-registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.6	1.6
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.4033 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 06/01/21.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	403.3			1000000	0.4033	

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **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 12/10/21.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.112903.

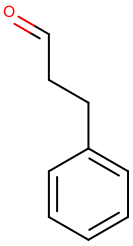
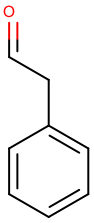
Appendix

Read-across justification

Methods

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

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

	Target Material	Read-across Material
Principal Name	3-Phenylpropionaldehyde	Phenylacetaldehyde
CAS No.	104-53-0	122-78-1
Structure		
Similarity (Tanimoto Score)		0.68
SMILES	O=CCCc1ccccc1	O=CCc1ccccc1
Endpoint		Genotoxicity Skin sensitization Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_9H_{10}O$	C_8H_8O
Molecular Weight (g/mol)	134.178	120.151
Melting Point (°C, EPI Suite)	47.00	33.50
Boiling Point (°C, EPI Suite)	224.00	195.00
Vapor Pressure (Pa @ 25 °C, EPI Suite)	8.37E+00	5.23E+01
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	1.62E+03	3.03E+03
Log K_{OW}	2.03	1.78
J_{max} (μg/cm^2/h, SAM)	55.07	98.61
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.37E-01	5.55E-01
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes|Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes|Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes
Carcinogenicity (ISS)	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
In Vitro Mutagenicity (Ames, ISS)	Simple aldehyde	Simple aldehyde
In Vivo Mutagenicity (Micronucleus, ISS)	Simple aldehyde	Simple aldehyde
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds
Repeated Dose Toxicity		
Repeated Dose (HESS)	Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert	Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH_2 group	Non-binder, without OH or NH_2 group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (moderate reliability)	Toxicant (low reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Protein Binding (OECD)	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.	Alert for Schiff base formation identified.
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on the target material, 3-phenylpropionaldehyde (CAS # 104-53-0). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, phenylacetaldehyde (CAS # 122-78-1) was identified as a read-across material with data for the respective toxicity endpoints.

Conclusions

- Phenylacetaldehyde (CAS # 122-78-1) was used as a read-across analog for the target material, 3-phenylpropionaldehyde (CAS # 104-53-0), for the genotoxicity, repeated dose toxicity, reproductive toxicity, and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aromatic aldehydes.
  - o The target material and the read-across analog share an aldehyde functional group with an aromatic ring.
  - o The key difference between the target material and the read-across analog is that the target material is propionaldehyde, but the read analog is acetaldehyde. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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 aldehyde functional group with an aromatic ring fragment. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoints.
  - 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 OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have carcinogenicity alert by the ISS model. Both substances also have *in vitro* and *in vivo* mutagenicity alerts and are classified as aldehyde-type compounds. This shows that the read-across analog is predicted to have comparable reactivity with the target material. The data described in the genotoxicity section shows that the read-across analog does not pose a concern for genotoxicity.
  - o The target material and the read-across analog have Schiff base formation alert by skin sensitization reactivity domains in Toxtree. The target and the read-across analog also have several protein-binding alerts. This shows that the read-across analog is predicted to have comparable reactivity with the target material. The data described in the skin sensitization section shows that the read-across analog is considered to be a moderate sensitizer. Data and the *in silico* alerts together denote the read-across analog to be a skin sensitizer.
  - o The target material and the read-across analog have been alerted for Styrene type or Toluene-related toxicity and toxicant with moderate reliability. The data on the read-across analog confirms that the MOE of the material is adequate under current declared levels of use. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the prediction is superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural differences between the target material and the read-across analog do not affect consideration of the toxicity endpoints.

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