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RIFM fragrance ingredient safety assessment, phenethyl formate, CAS Registry Number 104-62-1

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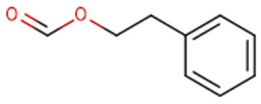

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Name: Phenethyl formate
CAS Registry Number: 104-62-1

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

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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, 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, 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.

Phenethyl formate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that phenethyl formate is not genotoxic. Data on read-across analogs phenethyl alcohol (CAS # 60-12-8) and formic acid (CAS # 64-18-6) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and local respiratory toxicity endpoints. The reproductive toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material; exposure is below the TTC (0.03 mg/kg/day). Data from read-across analog benzyl acetate (CAS # 140-11-4) show that there are no safety concerns for phenethyl formate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; phenethyl formate is not phototoxic/photoallergenic. The environmental endpoints were evaluated; phenethyl formate 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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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(RIFM, 1980; RIFM, 2015a)
Repeated Dose Toxicity: NOAEL = 385 mg/kg/day.	Owston (1981)
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.	
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(RIFM, 1985b; RIFM, 1986a; RIFM, 1987a; RIFM, 1988a)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: NOAEC = 5 mg/m^3 and 58.35 mg/m^3.	(RIFM, 2013b; NTP, 1992)

Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Screening-level: 2.95 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 10.07 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Critical Ecotoxicity Endpoint: Fish LC50: 194.6 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: 194.6 mg/L	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.1946 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Phenethyl formate
2. **CAS Registry Number:** 104-62-1
3. **Synonyms:** Benzylcarbinyl formate; Formic acid, phenylethyl ester; Phenylethyl formate; 2-Phenylethyl formate; 2-Phenylethyl methanoate; ｱﾙｶﾝ酸(C = 1 ~ 9)ﾌｪﾆﾙｱﾙｷﾙ; Phenethyl formate
4. **Molecular Formula:** $C_9H_{10}O_2$
5. **Molecular Weight:** 150.17 g/mol
6. **RIFM Number:** 371
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 226 °C (Fragrance Materials Association [FMA]), 217.34 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA)
3. **Log K_{OW}:** 2.02 (EPI Suite)
4. **Melting Point**: 8.2 °C (EPI Suite)
5. **Water Solubility:** 1413 mg/L (EPI Suite)
6. **Specific Gravity:** 1.06 (FMA)
7. **Vapor Pressure:** 0.04 mm Hg 20 °C (FMA), 0.0994 mm Hg at 20 °C (EPI Suite v4.0), 0.15 mm Hg at 25 °C (EPI Suite)

8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient (77 L mol^{-1} • cm^{-1} under neutral conditions) is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid, powerful green herbaceous rosy odor with some similarity to chrysanthemum, hyacinth, and watercress foliage. Moderate to poor tenacity (Arctander, 1969).

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM Aggregate exposure model v3.1)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0060% (RIFM, 2020b)
2. **Inhalation Exposure*:** 0.000072 mg/kg/day or 0.0052 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.00060 mg/kg/day (RIFM, 2020b)

*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 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, 2015, 2017; Safford, 2015, 2017).

5. Derivation of systemic absorption

1. **Dermal:** 77%

RIFM, 2013a (data also available in Ford, 1987; RIFM, 1986b; RIFM, 1987b; RIFM, 1988b; RIFM, 1988c; Ford, 1990; RIFM, 1990): Studies were conducted to compare the dermal absorption, plasma pharmacokinetics, and excretion of phenylethyl alcohol (PEA), a hydrolysis product of phenethyl formate, by pregnant and non-pregnant rats, non-pregnant rabbits, and non-pregnant humans. Following dermal (430, 700, or 1400 mg/kg [bw]), gavage (430 mg/kg), or dietary (430 mg/kg) administration of PEA to rats, plasma concentrations of PEA were found to be low regardless of the route of administration. The plasma concentrations of phenylacetic acid (PAA, the major metabolite of PEA) greatly exceeded the concentrations of PEA and were highest after gavage, followed by dermal, then dietary administration. The pharmacokinetic parameters were compared following topical application of [^{14}]C-labeled PEA to rats, rabbits, and humans (specific activities of dosing solutions: 58–580, 164, and 50 μCi/mL, respectively). In rabbits, the plasma concentration-time profile for PAA was markedly prolonged compared to rats or humans. In humans, only 7.6% of the applied dose of PEA was absorbed, versus 77% in rats and 50% in rabbits. Conservatively, the rat absorption data was selected for this safety assessment due to poor recovery of radioactivity due to evaporation from the human study (87.4% in rats compared to 10.8% in humans).

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:** None
b. **Repeated Dose Toxicity:** Phenethyl alcohol (CAS # 60-12-8) and formic acid (CAS # 64-18-6)
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Benzyl acetate (CAS # 140-11-4)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** Phenethyl alcohol (CAS # 60-12-8) and formic acid (CAS # 64-18-6)
g. **Environmental Toxicity:** None

6.3. Read-across Justification

See Appendix below

7. Metabolism

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

8. Natural occurrence

Phenethyl formate is reported to occur in the following foods by the VCF*:

Cherry (*Prunus avium* [sweet], *Pr.cerasus* [sour])	Rum
Cider (apple wine)	Sherry
Cloudberry (*Rubus chamaemorus* L.)	Syzygium species
Cocoa category	Tea
Coffee	Tequila (*Agave tequilana*)
Crispbread	Tomato (*Lycopersicon esculentum* Mill.)
Grape brandy	*Vaccinium* species
Litchi (*Litchi chinensis* Sonn.)	Vinegar
Raspberry, blackberry, and boysenberry	Wheaten bread
Rooibos tea (*Aspalathus linearis*)	Whisky
	Wine

*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

No dossier available as of 02/14/22.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current exposure and usage data, phenethyl formate does not present a concern for genotoxic potential.

11.1.1.1. Risk assessment. Phenethyl formate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2015b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of phenethyl formate 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 TA1538 were treated with phenethyl formate in dimethyl sulfoxide (DMSO) at concentrations up to 5 μL/plate (5290 μg/plate). A small increase in the mean number of revertant colonies was observed at 0.05 μL/plate (52.9 μg/plate) in strain TA1537 in the presence of S9 (RIFM, 1980). However, in a repeat assay, no increases were observed, so the result was considered not biologically relevant. Under the conditions of the study, phenethyl formate was not mutagenic in the Ames test.

The clastogenic activity of phenethyl formate 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 phenethyl formate in DMSO at concentrations up to 1500 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1500 μg/mL in the presence and absence of metabolic activation. Phenethyl formate did not induce binucleated cells with micronuclei when tested up to the cytotoxic or maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2015a). Under the conditions of the study, phenethyl formate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, phenethyl formate does not present a concern for genotoxic potential.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for phenethyl formate 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 phenethyl formate. Phenethyl formate is expected to hydrolyze to phenethyl alcohol (CAS # 60-12-8; see Section VI) and formic acid (CAS # 64-18-6; see Section VI).

Phenethyl alcohol was administered at 0.25, 0.5, 1.0, and 2.0 mL/kg/day (250, 500, 1000, and 2000 mg/kg/day) for 90 days in open application to shaved dorsa of Sprague Dawley rats, 15 rats per sex per dose. The NOAEL was determined to be 0.5 mL/kg/day (500 mg/kg/day) based on a reduction in body weight and bodyweight gains among the higher dose group animals (Owston, 1981). The metabolite formic acid has an OECD 413 inhalation subchronic 13-week toxicity study conducted on groups of 10 F344/N rats/sex/group. Formic acid was administered via whole-body inhalation at concentrations of 0, 8, 32, 64, and 128 ppm, equivalent to 0, 4, 17, 34, and 68 mg/kg/day according to standard minute volume and body weight parameters for F344/N rats. The NOAEL was determined to be 128 ppm or 68 mg/kg/day, the highest dose tested (NTP, 1992). The NOAEL of 500 mg/kg/day for phenethyl alcohol was considered for the repeated dose toxicity endpoint. To account for bioavailability following dermal application, data from a rat *in vivo* study (RIFM, 2013a; see Section V) was used to revise the NOAEL of 500 mg/kg/day to reflect the systemic dose. At a dermal penetration of 77% of the applied dose, the revised phenethyl alcohol toxicity NOAEL from the dermal study is 385 mg/kg/day.

In an OECD 413 study, 10 F344N rats/sex/group were exposed to formic acid via whole-body inhalation at concentrations of 0, 8, 16, 32, 64, and 128 ppm (equivalent to 0, 4, 17, 34, and 68 mg/kg/day) for 6 h/day, 5 days/week for 13 weeks. The NOAEL was determined to be 128 ppm or 68 mg/kg/day, the highest dose tested (NTP, 1992). No exposure-related clinical signs were noted during the study. Absolute liver weights were greater in the male rats in all exposure groups, whereas relative liver weights increased only in male rats exposed to 32, 64, and 128 ppm formic acid. Absolute and relative lung weights were decreased in females from all treatment groups. In male rats, relative lung weights were decreased in all exposure groups, and absolute weights were only decreased in the 64 and 128 ppm groups. Microscopic changes attributed to formic acid exposure occurred in the respiratory and olfactory epithelium of the nose and generally were limited to the 128 ppm exposure groups. Several local respiratory effects were reported during the study duration, but no systemic adverse effects were observed. Based on the absence of any systemic toxicity at the highest tested dose, a NOAEC of 128 ppm (68 mg/kg/day) was determined for the repeated dose toxicity endpoint. In addition, a similar NOAEC was determined from a mice study (see Table 1 below; NTP, 1992).

Based on no effects seen up to the highest dose in the OECD 413 study on formic acid, the NOAEL of 385 mg/kg/day was taken from the 90-day study on phenethyl alcohol.

Therefore, the phenethyl formate MOE for the repeated dose toxicity endpoint can be calculated by dividing the phenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to phenethyl formate, 385/0.00060 or 641667.

When correcting for skin absorption, the total systemic exposure to phenethyl formate (0.60 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/23/21.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on phenethyl formate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to phenethyl formate (0.60 μg/kg/day) is below the TTC (30 μg/kg/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: 05/23/21.

11.1.4. Skin sensitization

Based on the available data and read-across to benzyl acetate (CAS # 140-11-4), phenethyl formate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization studies are

Table 1
Summary of other available studies.

Duration in Detail	GLP/ Guideline	No. of Animals/ Dose (Species, Strain, Sex)	Route (Vehicle)	Doses (in mg/kg/day; Purity)	NOAEC	Justification of NOAEL/LOAEL/ NOEL	References
13-weeks (6 h a day, 5 days per week)	GLP	10 mice/sex/ dose (mice, B6C3F1, male and female)	Inhalation (whole-body)	0, 8, 16, 32, 64, 128 ppm (95% with 5% water as contaminant; equivalent to 0, 6, 13, 26, 51, 102 mg/kg/day according to standard minute volume and body weight parameters for B6C3F1 mice)	128 ppm	No treatment-related alterations in evaluated parameters for systemic toxicity were reported among treated animals up to the highest dose tested.	NTP (1992)

available for phenethyl formate. Based on the available data and read-across to benzyl acetate (CAS # 140-11-4; see Section VI), phenethyl formate is not considered a skin sensitizer. The chemical structure of the target material indicates that it would not be expected to react with skin proteins directly, while the read-across would be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In several guinea pig test methods no reactions indicative of sensitization were observed with read-across material benzyl acetate (RIFM, 1985a; RIFM, 1985b; RIFM, 1985c; RIFM, 1986a). Additionally, in human maximization tests, no reactions indicative of sensitization were observed to phenethyl formate and read-across material benzyl acetate (RIFM, 1972; Greif, 1967). In Confirmation of No Induction in Humans tests (CNIHs) up to 8% (9448 μg/cm^2) of read-across material, benzyl acetate in 3:1 ethanol:diethylphthalate (EtOH:DEP), no reactions indicative of skin sensitization were observed (RIFM, 1987a; RIFM, 1988a; RIFM, 1988d; RIFM, 1988e; RIFM, 1988f; RIFM, 1975a; RIFM, 1975b; RIFM, 1975c; RIFM, 1975d; RIFM, 1975e).

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/20/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, phenethyl formate 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 phenethyl formate 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, 2009). Based on the lack of significant absorbance in the critical range, phenethyl formate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient (77 L mol^{-1} • cm^{-1} under neutral conditions) 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: 05/26/21.

11.1.6. Local respiratory toxicity

There are no inhalation data available on phenethyl formate. However, the target material can undergo ester hydrolysis to generate phenethyl alcohol and formic acid. In a 2-week inhalation study for the read-across analogs phenethyl alcohol (CAS # 60-12-8; see Section VI) and formic acid (CAS # 64-18-6; see Section VI), NOAECs of 5 mg/m^3 (RIFM, 2013b) and 58.35 mg/m^3 were reported (NTP, 1992), respectively.

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery.

In a 2-week inhalation study conducted in rats, a NOAEC of 5 mg/m^3 was reported for phenethyl alcohol (RIFM, 2013b). In this study, 5 male and 5 female Sprague Dawley rats were exposed to aerosolized phenethyl alcohol by nose-only inhalation at 0.5, 5, and 50 mg/m^3 (equivalent to 0.1, 1, and 10 ppm), for 2 weeks (6 h/day, 5 days/week) and a total of 10 exposures. Histopathology revealed effects limited to mucous secretions in the nasal cavity. Nasal levels II through VI in the 50 mg/m3 group males, level VI in the 0.5 mg/m^3 group males, levels IV and V in all test material-exposed female groups, and level VI in the 5 and 50 mg/m^3 group females exhibited luminal secretions consistent with mucous. The changes were more commonly observed in the caudal nasal sections (V and VI) of the nasal cavity and were also observed in the control groups. Mild histiocytic (mononuclear) infiltrates in the lungs were noted in the 50 mg/m^3 group females but not in the control animals. As such, the NOAEC for local respiratory effects was observed at 5 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (5.0 mg/m^3) × (1 m^3/1000 L) = 0.0050 mg/L
- Minute ventilation of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.0050 mg/L) × (61.2 L/d) = 0.306 mg/day
- (0.306 mg/day)/(0.0016 kg lung weight of rat*) = 191.3 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0052 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey, 2015; Safford, 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.0077 mg/kg lung weight/day resulting in a MOE of 24844 (i.e., [191.3 mg/kg lung weight/day]/[0.0077 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.005 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

In a 2-week study, 5 F344/N rats per sex per group were exposed to formic acid vapors at concentrations 0, 58.35, 117.64, 235.28, 470.55, and 941.1 mg/m^3 (NTP, 1992). The exposures were carried out for 12 days for 6 h/day + T90/day (30 min), 5 days/week. At the end of the exposures, samples were collected for biochemistry and clinical pathology. Necropsy examinations were carried out on all animals, and tissues (larynx, lungs, and tracheobronchial lymph nodes, nasal cavity, and trachea) were represented for histopathology. The highest exposure concentration showed mortality with 1 female and 3 male rats. In male and female rats, the upper respiratory tract associated histopathologic

lesions related to formic acid exposures were similar in nature and dose-related in incidence and severity at concentrations of 117.64 mg/m^3 and above. Minimal to mild squamous metaplasia of the respiratory epithelium was observed in the most anterior nasal section (Level I). Rats exposed to 235.28 mg/m^3 formic acid had a decreased severity and incidence of nasal lesions when compared to those in the higher exposure groups; histopathologic lesions generally consisted of a minimal to mild squamous metaplasia of the respiratory epithelium on the nasal septum, lateral walls, and tips of the nasoturbinates. Microscopic lesions in rats exposed to 470.55 mg/m^3 were slightly less severe than in the 941.1 mg/m^3 group; inflammation and squamous metaplasia of the larynx was not present at this exposure concentration. All the rats, male and female, showed severe necrosis in the nose and olfactory epithelium and squamous metaplasia and inflammation of the respiratory epithelium in the nose at the highest exposure concentration. Squamous metaplasia of the larynx occurred in 1 male and 1 female rat at 941.1 mg/m^3. There were no treatment-related lesions in rats at 58.35 mg/m^3 exposure. No lesions in the lower respiratory tract were considered related to formic acid exposure at any exposure concentration. Therefore, considering the local respiratory effects observed in rats in the 2-week studies of formic acid exposure, the NOAEC was identified at 58.35 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (58.35 mg/m^3) × (1m^3/1000L) = 0.0584 mg/L
- Minute ventilation of 0.12 L/min for an F344/N rat × duration of exposure of 390 min per day (min/day) (according to GLP study guidelines) = 46.8 L/day
- (0.0584 mg/L) × (46.8 L/d) = 2.73 mg/day
- (2.73 mg/day)/(0.0016 kg lung weight of rat*) = 1706.25 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.005 mg/day—this value was derived from the concentration survey data in the Creme RIFM Exposure Model (Comiskey, 2015; Safford, 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew, 2009) to give 0.0077 mg/kg lung weight/day resulting in a MOE of 221591 (i.e., [1706.25 mg/kg lung weight/day]/[0.0077 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.005 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: Troy (1977); (The Union of German Candle Manufacturers, 1997); Silver (1992); RIFM, 1997; RIFM, 2003b; RIFM, 2003c; Rogers (2003a); RIFM, 2003d; RIFM, 2003a; RIFM, 2004a; RIFM, 2004b; RIFM, 2004c; Isola (2004a); Rogers (2005); RIFM, 2014; Vethanayagam (2013).

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 phenethyl formate was performed following the RIFM Environmental Framework (Salvito, 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, phenethyl formate 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 phenethyl formate as possibly being 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), phenethyl formate 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. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Phenethyl formate 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 Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.02	2.02
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 additional assessment is necessary.

The RIFM PNEC is 0.1946 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: 06/03/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	194.6			1000000	0.1946	

21.

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 02/14/22.

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.2022.112955.

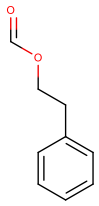
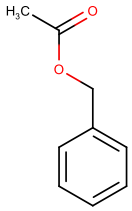
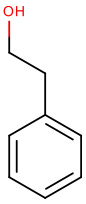
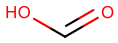
Appendix

Read-across Justification

Methods

The read-across analogs were 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 substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, 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	Read-across Material	Read-across Material
Principal Name	Phenethyl formate	Benzyl acetate	Phenethyl alcohol	Formic acid
CAS No.	104-62-1	140-11-4	60-12-8	64-18-6
Structure				
Similarity (Tanimoto Score)		0.37	0.70	0.10
Endpoint		• Skin sensitization	• Repeated dose toxicity • Local respiratory toxicity	• Repeated dose toxicity • Local respiratory toxicity
Molecular Formula	$C_9H_{10}O_2$	$C_9H_{10}O_2$	$C_8H_{10}O$	CH_2O_2
Molecular Weight (g/mol)	150.177	150.177	122.167	46.025
Melting Point (°C, EPI Suite)	8.20	−51.30	−27.00	8.30
Boiling Point (°C, EPI Suite)	217.34	213.00	218.20	101.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.00E+01	2.36E+01	1.16E+01	5.68E+03
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.41E+03	3.10E+03	2.22E+04	1.00E+06
Log K_{OW}	2.02	1.96	1.36	−0.54
J_{max} (μg/cm^2/h, SAM)	32.07	64.04	355.17	4847.49
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.60E+00	1.14E+00	2.59E-02	1.69E-02
Repeated Dose Toxicity				
Repeated Dose (HESS)	Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert		Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert	Carboxylic acids (Hepatotoxicity) No rank
Skin Sensitization				
Protein Binding (OASIS v1.1)	No alert found	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom| SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		
Protein Binding (OECD)	No alert found	SN2|SN2 ≫ SN2 reaction at sp3 carbon atom| SN2 ≫ SN2 reaction at sp3 carbon atom ≫ Allyl acetates and related chemicals		
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)		
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	SN2|SN2 ≫ SN2 Reaction at a sp3 carbon atom| SN2 ≫ SN2 Reaction at a sp3 carbon atom ≫ Activated alkyl esters and thioesters		
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified.	Alert for Acyl Transfer agent identified.		
Local Respiratory Toxicity				
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	No alert found	No alert found	No alert found	No alert found
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	N/A*

*Formic acid does not create metabolites via the simulator. It is a natural constituent of the human body and is cleared by conversion to carbon dioxide and water.

Summary

There is insufficient toxicity data on phenethyl formate (CAS # 104-62-1). 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, benzyl acetate (CAS # 140-11-4), formic acid (CAS # 64-18-6), and phenethyl alcohol (CAS # 60-12-8) were identified as read-across materials with data for their respective toxicity endpoints.

Metabolism

Metabolism of the target material was not considered for the risk assessment, and therefore metabolism, data were not reviewed, except where it may pertain in specific endpoint sections above. Metabolism of the target material phenethyl formate (CAS # 104-62-1) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2) (See Appendix). The target material is predicted to metabolize to formic acid (CAS # 64-18-6) and phenethyl alcohol (CAS # 60-12-8) in the first step with a 0.95 pre-calculated probability. Hence, phenethyl alcohol is the driver of toxicity for local respiratory toxicity. Hence, phenethyl alcohol and formic acid can be used as read-across for the target material. Read-across analogs were out of domain for the *in vivo* rat and *in vitro* rat S9 simulators (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion

was overridden, and a justification was provided.

Conclusions

- Benzyl acetate (CAS # 140-11-4) was used as a read-across analog for the target material phenethyl formate (CAS # 104-62-1) for skin sensitization.
  - o The target material and the read-across analog are structurally similar and belong to a class of benzylic esters.
  - o The key difference between the target material and the read-across analog is that the target material is an ester of phenethyl alcohol while the read-across analog is an ester of benzyl alcohol. 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. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a 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 an alert SN2 reaction. This is due to the presence of a benzene ring in the structure, which can undergo epoxidation and quinone formation. The data for the read-across analog confirms that the analog does not pose a concern for genotoxicity. Therefore, based on the structural similarity between the target material and the read-across analog and data on the read-across analog, the alerts are 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 alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Phenethyl alcohol (CAS # 60-12-8) and formic acid (CAS # 64-18-6) are used as structurally similar read-across analogs for phenethyl formate (CAS # 104-62-1) for the repeated dose toxicity and local respiratory toxicity endpoints.
  - o The read-across materials are analogs of the major metabolites of the target.
  - o The structural difference in the target material and the read-across analog can be mitigated by the fact that the target could be metabolically hydrolyzed to analogs of read-across analog substances used here. Therefore, the toxicity profile of the target is expected to be that of metabolites.
  - 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 (v4.2), structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant for repeated dose, reproductive, and local respiratory toxicity endpoints.

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