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RIFM fragrance ingredient safety assessment, 3-phenylpropyl acetate, CAS Registry Number 122-72-5

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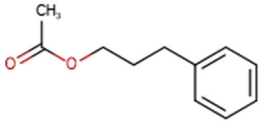

Name: 3-Phenylpropyl acetate
CAS Registry Number: 122-72-5

Abbreviation/Definition List:

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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

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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 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-Phenylpropyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs phenethyl acetate (CAS # 103-45-7) and phenethyl propionate (CAS # 122-70-3) show that 3-phenylpropyl acetate is not genotoxic. Data on read-across analogs phenylpropyl alcohol (CAS # 122-97-4) and acetic acid (CAS # 64-19-7) provide a calculated MOE >100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog benzyl acetate (CAS # 140-11-4) show that there are no safety concerns for 3-phenylpropyl acetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; 3-phenylpropyl acetate is not phototoxic/photoallergenic. The local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material; the exposure to 3-phenylpropyl acetate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 3-phenylpropyl acetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2002; RIFM, 2015)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	RIFM (2016)
Reproductive Toxicity: Developmental NOAEL = 300 mg/kg/day. Fertility NOAEL = 1000 mg/kg/day.	RIFM (2016)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(RIFM, 1985b; RIFM, 1986; RIFM, 1987; RIFM, 1988a)
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: Screening-level: 2.8 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 48.76 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 72.3 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: 72.3 mg/L	(RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.0723 μg/L

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

1. Identification

1. **Chemical Name:** 3-Phenylpropyl acetate
2. **CAS Registry Number:** 122-72-5
3. **Synonyms:** Benzenepropanol, acetate; Hydrocinnamyl acetate; β-Phenylpropyl acetate; Phenylpropyl acetate; アルキル (C = 1–4) カルボン酸フェニルプロピル; アルキル(C = 1–5)カルボン酸フェニルアルキル(C = 1–6); 3-Phenylpropyl acetate
4. **Molecular Formula:** $C_{11}H_{14}O_2$
5. **Molecular Weight:** 178.23 g/mol
6. **RIFM Number:** 423
7. **Stereochemistry:** No stereocenter possible.

2. Physical data

1. **Boiling Point:** 172 °C (Fragrance Materials Association [FMA]), 252.15 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System), >200 °F; CC (FMA)
3. **Log K_{OW}:** 2.6 (RIFM, 2013b), 3.06 (EPI Suite)
4. **Melting Point:** 21.44 °C (EPI Suite)
5. **Water Solubility:** 136 mg/L (EPI Suite)
6. **Specific Gravity:** 1.01 (FMA), 1.012–1.015 (Givaudan Index, 1961)

7. **Vapor Pressure:** 0.0153 mm Hg at 20 °C (EPI Suite v4.0), 0.02 mm Hg 20 °C (FMA), 0.0243 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid with a spicy and floral character (Givaudan Index, 1961)

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 v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0035% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.000078 mg/kg/day or 0.0054 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.00062 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; 2017; and Comiskey et al., 2017).

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** Phenethyl acetate (CAS # 103-45-7) and phenethyl propionate (CAS # 122-70-3)
   b. **Repeated Dose Toxicity:** Phenylpropyl alcohol (CAS # 122-97-4) and acetic acid (CAS # 64-19-7)
   c. **Reproductive Toxicity:** Phenylpropyl alcohol (CAS # 122-97-4) and acetic acid (CAS # 64-19-7)
   d. **Skin Sensitization:** Benzyl acetate (CAS # 140-11-4)
   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.

7.1. Additional References

None.

8. Natural occurrence

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

Artocarpus species	Melon
Cinnamomum species	Passion fruit (*Passiflora* species)
Cocoa	Tapereba, caja fruit (*Spondias lutea* L.)
Guava and feyoa	

*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

Available; accessed on 02/11/22.

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 existing data, 3-phenylpropyl acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. 3-phenylpropyl acetate 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, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an equi-reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of 3-phenylpropyl acetate; however, read-across can be made to phenethyl acetate (CAS # 103-45-7; see Section VI).

The mutagenic activity of phenethyl acetate 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 and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with phenethyl acetate 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 concentration in the presence or absence of

S9 (RIFM, 2002). Under the conditions of the study, phenethyl acetate was not mutagenic in the Ames test, and this can be extended to 3-phenylpropyl acetate.

There are no studies assessing the clastogenicity of 3-phenylpropyl acetate; however, read-across can be made to phenethyl propionate (CAS # 122-70-3; see Section VI).

The clastogenic activity of phenethyl propionate 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 propionate in dimethyl sulfoxide (DMSO) at concentrations up to 1783 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 1783 μg/mL in the presence and absence of metabolic activation. Phenethyl propionate 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, 2015). Under the conditions of the study, phenethyl propionate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 3-phenylpropyl acetate.

Based on the data available, phenethyl acetate and phenethyl propionate do not present a concern for genotoxic potential, and this can be extended to 3-phenylpropyl acetate.

Additional References: RIFM, 1980; RIFM, 2000; Florin et al., 1980; Mortelmans et al., 1986; Yoo (1986); Caspary et al., 1988; Galloway et al., 1987; Rudd et al., 1983; Rogan et al., 1986; McGregor et al., 1988; Schunk et al., 1986; Longnecker et al., 1990; Tennant et al., 1987; Elmore and Fitzgerald, 1990; Mirsalis et al., 1989; Mirsalis et al., 1983; Foureman et al., 1994; Yoshikawa (1996); Matsuoka et al., 1996; Miyagawa et al., 1995; Mitchell and Caspary, 1987; Zimmermann et al., 1989; Honma et al., 1999; Kevekordes et al., 1999; Rossman et al., 1991; Witt et al., 2000; Sasaki et al., 2000; Brewer and Colditz, 1999; Kevekordes et al., 2001; Sekihashi et al., 2002; Yasunaga et al., 2004; Oda et al., 1978; Scott et al., 2007; Demir et al., 2010.

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

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for 3-phenylpropyl acetate 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-phenylpropyl acetate. 3-Phenylpropyl acetate is expected to hydrolyze to phenylpropyl alcohol (CAS # 122-97-4; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI).

In a GLP and OECD 422-compliant study, 12 Sprague Dawley rats/sex/dose were administered phenylpropyl alcohol via gavage at doses of 0, 100, 300, and 1000 mg/kg/day. Males were treated for 2-weeks pre-mating through until sacrifice (at least 50 days); females were treated for 2 weeks pre-mating through to lactation day (LD) 13. An additional 12 Sprague Dawley rats/sex/dose at 0 and 1000 mg/kg/day were maintained as recovery groups for 2-weeks after treatment. No mortality occurred throughout the study period. No treatment-related effects were observed on body weight, food consumption, functional behavior, motor activity, macroscopic, or microscopic findings. Total red blood cell (RBC) count was decreased in males at the high dose. Blood urea nitrogen (BUN) was decreased in males at the high dose. Glucose in serum was increased in females at the mid and high doses. Total bilirubin, calcium, and inorganic phosphorus in serum were increased in females at the high dose. Changes in clinical chemistry were not considered adverse because the values remained within historical control ranges and there were no correlated histopathological effects. Absolute and relative liver weights were increased in females at the high dose. Although the organ weight changes were statistically significant, they were not considered adverse due to the lack of correlated microscopic findings. Based on no toxicologically relevant adverse effects seen up to the highest dose, the NOAEL for this study was considered to be 1000 mg/kg/day (RIFM, 2016).

Acetic acid has been reviewed by several agencies. The US Food and Drug Administration (US FDA) has granted acetic acid a generally recognized as safe (GRAS) status (US FDA, 2020). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) also evaluated acetic acid and stated that for acetic acid, it is not necessary to indicate acceptable daily intakes for humans (WHO, 2006). The European Food Safety Authority (EFSA) reviewed the data on acetic acid (EFSA, 2012). They stated that there is now an application for the reauthorization of acetic acid and these salts as preservatives in feed and for the new use of acetic acid as a preservative in water for drinking. They may be used alone or in combination with other organic acids, typically in a concentration of 200–2500 mg acetate/kg complete feedstuffs. The Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) provides a comprehensive review of the toxicity data on acetic acid as a part of their human health Tier II assessment for acetic acid (NICNAS, 2013). They state that acetates are normal components in human and animal diets. They are produced in small (molar) quantities daily in the gastrointestinal tract, where they are rapidly and completely metabolized. Based on the limited data available, acetic acid is not likely to be a carcinogen. Thus, acetic acid does not pose systemic toxicity to human health when used in fragrances.

The NOAEL of 1000 mg/kg/day was taken from the OECD 422 study on phenylpropyl alcohol. A default safety factor of 3 was used when deriving a NOAEL from an 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 1000/3, or 333 mg/kg/day.

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, 333/0.00062 or 537096.

When correcting for skin absorption, the total systemic exposure to phenethyl formate (0.62 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

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

Additional References: None.

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

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no developmental or fertility data on 3-phenylpropyl acetate. 3-Phenylpropyl acetate is expected to hydrolyze to phenylpropyl alcohol (CAS # 122-97-4; see Section VI) and acetic acid (CAS # 64-19-7; see Section VI).

In a GLP and OECD 422-compliant study, 12 Sprague Dawley rats/sex/dose were administered phenylpropyl alcohol via gavage at doses of 0, 100, 300, and 1000 mg/kg/day. Males were treated for 2-weeks pre-mating through until sacrifice (at least 50 days); females were treated for 2 weeks pre-mating through to lactation day (LD) 13. An additional 12 Sprague Dawley rats/sex/dose at 0 and 1000 mg/kg/day were

maintained as recovery groups for 2-weeks after treatment. No treatment-related effects were observed on the estrous cycle, pre-coital time, or fertility parameters. No treatment-related effects were observed on pup clinical signs, external examination, anogenital distance, nipple retention, or thyroid hormone (T4) analysis. The number of pups found dead or cannibalized was significantly increased at the high dose. Viability index was significantly decreased at the high dose. This was mainly affected by the loss of one whole litter, consisting of 20 pups. Pup body weights were significantly decreased at the high dose. Based on no fertility effects seen up to the highest dose, the fertility NOAEL for this study was 1000 mg/kg/day. Based on decreased viability index and pup weights at 1000 mg/kg/day, the developmental NOAEL for this study was 300 mg/kg/day (RIFM, 2016).

Acetic acid has been reviewed by EFSA (EFSA, 2012), NICNAS (NICNAS, 2013), and JECFA (WHO, 2006) for its use as a food additive and by CIR (CIR, 2010) for its use in cosmetics. It was concluded that acetic acid does not show specific fertility or developmental toxicity effects.

The phenethyl formate MOE for the developmental toxicity endpoint can be calculated by dividing the phenethyl alcohol NOAEL in mg/kg/day by the total systemic exposure to phenethyl formate, 300/0.00062 or 483870.

When correcting for skin absorption, the total systemic exposure to phenethyl formate (0.62 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

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

11.1.4. Skin sensitization

Based on the available material-specific data and read-across to benzyl acetate (CAS # 140-11-4), 3-phenylpropyl acetate 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 available for 3-phenylpropyl acetate. Based on the available material-specific data and read-across to benzyl acetate (CAS # 140-11-4; see Section VI), 3-phenylpropyl acetate does not present a concern for skin sensitization. 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 et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine Local Lymph Node Assay (LLNA), 3-phenylpropyl acetate was not found to be sensitizing up to 50% (12500 μg/cm^2) in 4:1 acetone:olive oil (Kern et al., 2010). 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, 1986). Additionally, 3-phenylpropyl acetate did not result in reactions indicative of skin sensitization in guinea pig tests (Klecak, 1985). In human maximization tests, no reactions indicative of sensitization were observed with 3-phenylpropyl acetate and read-across material benzyl acetate (RIFM, 1973; Greif, 1967). In Confirmation of No Induction in Humans tests (CNIHs) up to 8% (9449 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, 1987; RIFM, 1988a; RIFM, 1988b; RIFM, 1988c; RIFM, 1988d; 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, 3-phenylpropyl acetate 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: 05/21/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra, 3-phenylpropyl acetate 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-phenylpropyl acetate in experimental models. UV/Vis absorption spectra indicate no absorption 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 absorbance, 3-phenylpropyl acetate does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009).

Additional References: None.

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

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3-phenylpropyl acetate 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-phenylpropyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.0054 mg/day. This exposure is 259.3 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-phenylpropyl acetate 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-phenylpropyl acetate 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-phenylpropyl acetate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

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

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

3-Phenylpropyl acetate has been registered for REACH with no additional data at this time.

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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.6	2.6
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 additional assessment is necessary.

The RIFM PNEC is 0.0723 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: 06/03/21.

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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	72.3			1000000	0.0723	

*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 02/11/22.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113055.

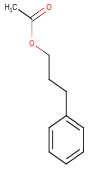
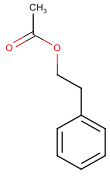
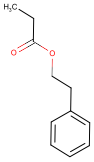
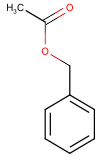
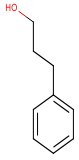
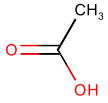
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020). These criteria are in compliance with 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 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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	Read-across Material	Read-across Material
Principal Name	3-Phenylpropyl acetate	Phenethyl acetate	Phenethyl propionate	Benzyl acetate	3-phenyl-1-propanol	Acetic acid
CAS No.	122-72-5	103-45-7	122-70-3	140-11-4	122-97-4	64-19-7
Structure						
Similarity (Tanimoto Score)		0.58	0.55	0.39	0.64	0.14
SMILES	CC(=O)OCCCc1ccc cc1	CC(=O)OCCc1 ccccc1	CCC(=O)OCCc1 ccccc1	CC(=O)Occ 1ccccc1	OCCCc1ccccc1	CC(O) = O
Endpoint		• Genotoxicity	• Genotoxicity	• Skin sensitization	• Repeated dose toxicity • Reproductive toxicity	• Repeated dose toxicity • Reproductive toxicity
Molecular Formula	$C_{11}H_{14}O_2$	$C_{10}H_{12}O_2$	$C_{11}H_{14}O_2$	$C_9H_{10}O_2$	$C_9H_{12}O$	$C_2H_4O_2$
Molecular Weight (g/mol)	178.231	164.204	178.231	150.177	136.194	60.052
Melting Point (°C, EPI Suite)	21.44	−31.10	21.44	−51.30	16.79	16.64
Boiling Point (°C, EPI Suite)	252.15	232.60	238.00	213.00	235.00	117.90
	3.24E+00	4.19E+00	6.85E+00	2.36E+01	2.65E+00	2.09E+03

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(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Vapor Pressure (Pa @ 25 °C, EPI Suite)						
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	1.36E+02	7.11E+02	1.36E+02	3.10E+03	5.68E+03	1.00E+06
Log KOW	3.06	2.3	3.06	1.96	1.88	−0.17
J_{max} (μg/cm^2/h, SAM)	7.22	17.66	7.22	64.04	146.17	6282.71
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.52E+00	1.90E+00	2.52E+00	1.14E+00	2.06E-02	1.45E-02
Genotoxicity						
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters	AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters	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	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	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			
Carcinogenicity (ISS)	No alert found	No alert found	No alert found			
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found			
In Vitro Mutagenicity (Ames, ISS)	No alert found	No alert found	No alert found			
In Vivo Mutagenicity (Micronucleus, ISS)	No alert found	No alert found	No alert found			
Oncologic Classification	Not classified	Not classified	Not classified			
Repeated Dose Toxicity						
Repeated Dose (HESS)	Toluene (Renal toxicity) Alert				Styrene (Renal Toxicity) Alert|Toluene (Renal toxicity) Alert	Acetamide (Renal Toxicity) Alert|Carboxylic acids (Hepatotoxicity) No rank
Reproductive Toxicity						
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, without OH or NH2 group				Non-binder, without OH or NH2 group	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)				Toxicant (good reliability)	Toxicant (low reliability)
Skin Sensitization						
Protein Binding (OASIS v1.1)	No alert found			SN2|SN2 ≫ SN2 Reaction at a sp3		

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(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
				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.		
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	See Supplemental Data 4	See Supplemental Data 5	N/A

Summary

There are insufficient toxicity data on 3-phenylpropyl acetate (CAS # 122-72-5). 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, phenethyl acetate (CAS # 103-45-7), phenethyl propionate (CAS # 122-70-3), benzyl acetate (CAS # 140-11-4), phenylpropyl alcohol (CAS # 122-97-4), and acetic acid (CAS # 64-19-7) were identified as read-across materials with data for their respective toxicity endpoints.

Metabolism

There are no metabolism data on 3-phenylpropyl acetate (CAS # 122-72-5). Metabolism of the target material was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is metabolized via ester hydrolysis to phenylpropyl alcohol (CAS # 122-97-4) and acetic acid (CAS # 64-19-7) in the first step with 0.95 intrinsic probability. Hence, phenylpropyl alcohol (CAS # 122-97-4) and acetic acid (CAS # 64-19-7) can be used as read-across analogs for the target material. Linalool was out of domain for the *in vivo* 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 is provided.

Conclusions

- Phenethyl acetate (CAS # 103-45-7) was used as a read-across analog for the target material 3-phenylpropyl acetate (CAS # 122-72-5) for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of esters.
  - o The target material and the read-across analog have a phenyl fragment common among them.
  - o The key difference is that the target material has an acetate part, while the analog has an isovalerate part.
  - o The target material and the read-across analog have the Tanimoto score, as mentioned in the above table. The Tanimoto score is mainly driven by the phenylethyl fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevant from a toxicology endpoint perspective.
  - 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 QSAR OECD model for DNA binding shows a Michael addition alert for the target material and the read-across analog. The target material and the read-across analog do not have other DNA binding alerts for genotoxicity. The data described in the genotoxicity endpoint section shows that the read-across analog does not pose a concern. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the alert will be superseded by the availability of the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the genotoxicity endpoint between the metabolites of the read-across analog and the target material are consistent.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically significant.

- Phenethyl propionate (CAS # 122-70-3) was used as a read-across analog for the target material 3-phenylpropyl acetate (CAS # 122-72-5) for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of esters.
  - o The target material and the read-across analog have a phenyl fragment common among them.
  - o The key difference is that the target has a propionate, while the analog has an isovalerate part. 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 QSAR OECD model for DNA binding shows Michael addition alert for the target material and the read-across analog. The target material and the read-across analog do not have other DNA binding alerts for genotoxicity. The data described in the genotoxicity endpoint section shows that the read-across analog does not pose a concern. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the alert will be superseded by the availability of the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the clastogenicity endpoint between the metabolites of the read-across analog and the target material are consistent.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically significant.
- Benzyl acetate (CAS # 140-11-4) was used as a read-across analog for the target material 3-phenylpropyl acetate (CAS # 122-72-5) for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to a class of esters.
  - o The target material and the read-across analog have a phenylethyl fragment common among them.
  - o The key difference is that the target is propionate, while the analog is a dimethylpropanoiate. 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 There are several SN2 reaction *in silico* alerts by different models for skin sensitization endpoint. The data on the read-across analog confirms it does not pose a concern for skin sensitization under current levels of use. Therefore, the alert will be superseded by the availability of the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the skin sensitization endpoint between the metabolites of the read-across analog and the target material are consistent.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically significant.
- Phenylpropyl alcohol (CAS # 122-97-4) and acetic acid (CAS # 64-19-7) are used as read-across analogs for 3-phenylpropyl acetate (CAS # 122-72-5) for the repeated dose toxicity and reproductive 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 repeated dose, reproductive, and respiratory toxicity endpoints are consistent between the target material and the read-across analog.
  - o The CAESAR model for developmental toxicity predicts the read-across analogs phenylpropyl alcohol (CAS # 122-97-4) and acetic acid (CAS # 64-19-7) to be toxicant with good reliability while the target material is predicted to be non-toxicant. According to these predictions, the read-across analogs are expected to be more reactive compared to the target material. The MOE for the target material is adequate for the endpoints at the current level of use. The availability of data for the read-across superseded this prediction.
  - o The structural differences between the target material and the read-across analog are deemed to be toxicologically insignificant for the repeated dose, reproductive, and local respiratory toxicity endpoints.

References

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

Brewer, T., Colditz, G.A., 1999. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. JAMA 281 (9), 824–829.

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

Caspary, W.J., Langerbach, R., Penman, B.W., Crespi, C., Myhr, B.C., Mitchell, A.D., 1988. The mutagenic activity of selected compounds at the TK locus: rodent vs. human cells. Mutat. Res. Rev. Genet. Toxicol. 196 (1), 61–81.

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

CIR, 2010. Cosmetic Ingredient Review. Blue Book 1: Methyl Acetate. Retrieved from. https://www.cir-safety.org/sites/default/files/116_final_methyl.pdf.

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

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

Demir, E., Kocaoglu, S., Kaya, B., 2010. Assessment of genotoxic effects of benzyl derivatives by the comet assay. Food Chem. Toxicol. 48 (5), 1239–1242.

ECHA, 2012. Guidance on information requirements and chemical safety assessment. November 2012 v2.1. http://echa.europa.eu/.

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

EFSA, 2012. Scientific Opinion on the safety and efficacy of acetic acid, sodium diacetate and calcium acetate as preservatives for feed for all animal species. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). EFSA J. 10 (2), 2571, 2012, Retrieved from. https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2012.2571.

Elmore, E., Fitzgerald, M.P., 1990. Evaluation of the bioluminescence assays as screens for genotoxic chemicals. Prog. Clin. Biol. Res. 340 (Part D), 379–387. Mutation & Environment.

Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames Test. Toxicology 18 (3), 219–232.

Foureman, P., Mason, J.M., Valencia, R., Zimmering, S., 1994. Chemical mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. Environ. Mol. Mutagen. 23 (3), 208–227.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., Zeiger, E., 1987. Chromosome aberration and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environ. Mol. Mutagen. 10 (10), 1–175.

Greif, N., 1967. Cutaneous safety of fragrance material as measured by the maximization test. Am. Perfum. Cosmet. 82, 54–57.

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

Honma, M., Hayashi, M., Shimada, H., Tanaka, N., Wakuri, S., Awogi, T., Yamamoto, K. I., Kodani, N.-U., Nishi, Y., Nakadate, M., Sofuni, T., 1999. Evaluation of the mouse lymphoma tk assay (microwell method) as an alternative to the in vitro chromosomal aberration test. Mutagenesis 14 (1), 5–22.

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

Kern, P.S., Gerberick, G.F., Ryan, C.A., Kimber, I., Aptula, A., Basketter, D.A., 2010. Local lymph node data for the evaluation of skin sensitization alternatives: a second compilation. Dermatitis 21 (1), 8–32.

Kevekordes, S., Mersch-Sundermann, V., Burghaus, C.M., Spielberger, J., Schmeiser, H. H., Arlt, V.M., Dunkelberg, H., 1999. SOS induction of selected naturally occurring substances in Escherichia coli (SOS chromotest). Mutat. Res. Genet. Toxicol. Environ. Mutagen 445 (1), 81–91.

Kevekordes, S., Spielberger, J., Burghaus, C.M., Birkenkamp, P., Zietz, B., Paufler, P., Diez, M., Bolten, C., Dunkelberg, H., 2001. Micronucleus formation in human lymphocytes and in the metabolically competent human hepatoma cell line Hep G2: results with 15 naturally occurring substances. Anticancer Res. 21 (1A), 461–470.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. Curr. Probl. Dermatol. 14, 152–171.

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

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

Longnecker, D.S., Roebuck, B.D., Curphey, T.J., MacMillan, D.L., 1990. Evaluation of promotion of pancreatic carcinogenesis in rats by benzyl acetate. Food Chem. Toxicol. 28 (10), 665–668.

Matsuoka, A., Yamakage, K., Kusakabe, H., Wakuri, S., Asakura, M., Noguchi, T., Sugiyama, T., Shimada, H., Nakayama, S., Kasahara, Y., Takahashi, Y., Miura, K.F., Hatanaka, M., Ishidate Jr., M., Morita, T., Watanabe, K., Hara, M., Odawara, K., Tanaka, N., Hayashi, M., Sofuni, T., 1996. Re-evaluation of chromosomal aberration induction on nine mouse lymphoma assay 'unique positive' NTP carcinogens. Mutat. Res. Genet. Toxicol. 369 (3–4), 243–252.

McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D., Riach, C., Caspary, W.J., 1988. Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay: III. 72 Coded chemicals. Environ. Mol. Mutagen. 12 (2), 85–153.

Mirsalis, J., Tyson, K., Beck, J., Loh, E., Steinmetz, K., Contreras, C., Austere, L., Martin, S., Spalding, J., 1983. Induction of unscheduled DNA synthesis (UDS) in hepatocytes following in vitro and in vivo treatment. Environ. Mutagen. 5 (3), 482.

Mirsalis, J.C., Tyson, C.K., Steinmetz, K.L., Loh, E.K., Hamilton, C.M., Bakke, J.P., Spalding, J.W., 1989. Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following in vivo treatment: testing of 24 compounds. Environ. Mol. Mutagen. 14 (3), 155–164.

Mitchell, A.D., Caspary, W.J., 1987. Concordance of results between in-vitro mammalian cell mutagenesis and clastogenesis assays. Environ. Mutagen. 9 (Suppl. 8), 74.

Miyagawa, M., Takasawa, H., Sugiyama, A., Inoue, Y., Murata, T., Uno, Y., Yoshikawa, K., 1995. The in vivo-in vitro replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F1 mice as an early prediction assay for putative nongenotoxic (Ames-negative) mouse hepatocarcinogens. Mutat. Res. Genet. Toxicol. 343 (1), 157–183.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeiger, E., 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ. Mutagen. 8 (7), 1–119.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352, 2021 Sep-Oct 01.

NICNAS, 2013. Acetic acid: human health tier II assessment. Retrieved from. https://www.industrialchemicals.gov.au/sites/default/files/Acetic%20acid_Human%20health%20tier%20II%20assessment.pdf.

Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978. Mutagenicity of food flavours in bacteria (1st Report). Osaka-furitsu Koshu Eisei Kenkyu Hokoku Shokuhin Eisei Hen. 9, 177–181.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

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

RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1802. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975a. Repeated Insult Patch Test of Benzyl Acetate in Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 24175.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975b. Repeated Insult Patch Test of Benzyl Acetate in Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 24176.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975c. Repeated Insult Patch Test of Benzyl Acetate on Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 24177.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975d. Repeated Insult Patch Test of Benzyl Acetate in Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 24178.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975e. Repeated Insult Patch Test of Benzyl Acetate in Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from International Flavors and Fragrances. RIFM report number 24179.

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of Phenethyl Acetate. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Quest International. RIFM report number 46691.

RIFM (Research Institute for Fragrance Materials, Inc.), 1985a. Closed Epicutaneous Test of Methyl-2-Octynoate, Methyl-2-Nonynoate, Benzyl Acetate, Trans,trans-2,4-Hexadienal, 2-hexylidene Cyclopentanone, Hexen-2-Al, Trans-2-hexenal Diethyl Acetal and Isoeugenol in guinea Pigs. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 4474.

RIFM (Research Institute for Fragrance Materials, Inc.), 1985b. Guinea Pig Maximization Test. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 4899.

RIFM (Research Institute for Fragrance Materials, Inc.), 1985c. Open and Closed Epicutaneous and Maximization Tests of Fragrance Materials in guinea Pigs. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan Corporation. RIFM report number 6068.

RIFM (Research Institute for Fragrance Materials, Inc.), 1986. Delayed Contact Hypersensitivity Study of Benzyl Acetate in guinea Pigs. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 4513.

RIFM (Research Institute for Fragrance Materials, Inc.), 1987. Report on Human Repeated Insult Patch Test. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 7973.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988a. Repeated Insult Patch Test in Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 8881.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988b. Repeated Insult Patch Test in Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 27673.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988c. Repeated Insult Patch Test in Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 27674.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988d. Repeated Insult Patch Test in Human Subjects. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 27675.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000. Mutagenicity Study of Phenethyl Acetate in the Salmonella typhimurium/mammalian Microsome Reverse Mutation Assay (Ames-test). RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise GmbH & Co. KG. RIFM report number 57617.

RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Evaluation of the Mutagenic Activity of Phenethyl Acetate in the Salmonella typhimurium Reverse Mutation Assay. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Givaudan. RIFM report number 43053.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. Report on the Testing of 3-phenylpropyl Acetate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 65506.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Partition Coefficient N-Octanol/water of 3-phenylpropyl Acetate. RIFM, Woodcliff Lake, NJ, USA (phenylpropyl acetate). Unpublished report from Givaudan. RIFM report number 66641.

RIFM (Research Institute for Fragrance Materials, Inc.), 2015. Phenethyl Propionate: in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69706.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016. 3-Phenyl-1-propanol (Phenylpropyl Alcohol): Combined Repeated Oral Gavage Toxicity Study with the Reproduction/developmental Toxicity Screening in Sprague-Dawley Rats. (RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 74658.

RIFM (Research Institute for Fragrance Materials, Inc.), 2018. Exposure Survey 22, November 2018.

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

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

Rogan, E.G., Cavalieri, E.L., Walker, B.A., Balasubramanian, R., Wislocki, P.G., Roth, R. W., Saugier, R.K., 1986. Mutagenicity of benzylic acetates, sulfates and bromides of polycyclic aromatic hydrocarbons. Chem. Biol. Int. Rep. 58 (3), 253–275.

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

Rossman, T.G., Molina, M., Meyer, L., Boone, P., Klein, C.B., Wang, Z., Li, F., Lin, W.C., Kinney, P.L., 1991. Performance of 133 compounds in the lambda prophage induction endpoint of the Microscreen assay and a comparison with S. typhimurium mutagenicity and rodent carcinogenicity assays. Mutat. Res. Genet. Toxicol. 260 (4), 349–367.

Rudd, C.J., Mitchell, A.D., Spalding, J., 1983. L5178Y Mouse lymphoma cell mutagenesis assay of coded chemicals incorporating analyses of the colony size distributions. Environ. Mutagen. 5 (3), 419.

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

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

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

Sasaki, Y.F., Sekihashi, K., Izumiyama, F., Nishidate, E., Saga, A., Ishida, K., Tsuda, S., 2000. The Comet Assay with multiple mouse organs: comparison of comet assay results and carcinogenicity with 208 chemicals selected from the IARC monographs and U.S. NTP carcinogenicity database. Crit. Rev. Toxicol. 30 (6), 629–799.

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

Schunk, H.H., Shibamoto, T., Tan, H.K., Wei, C.-I., 1986. Biological and chemical studies on photochemical products obtained from eugenol, benzyl acetate and benzyl benzoate. In: Flavors and Fragrances: A World Perspective, vol. 18, pp. 1045–1068.

Scott, A., Malcomber, S., Maskell, S., M, C., Windebank, S., Diaz, D., Carmichael, P., 2007. An assessment of the performance of an automated scoring system (Cellomics) for the in vitro micronucleus assay in CHPO-K1 cells. Toxicology 231 (2–3), 104–119.

Sekihashi, K., Yamamoto, A., Matsumura, Y., Ueno, S., Watanabe-Akanuma, M., Kassie, F., Knasmuller, S., Tsuda, S., Sasaki, Y.F., 2002. Comparative investigation of multiple organs of mice and rats in the comet assay. Mutat. Res. Genet. Toxicol. Environ. Mutagen 517 (1–2), 53–75.

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

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., Minor, R., 1987. Prediction of chemical carinogenicity in rodents from in vitro genetic toxicity assays. Science 236, 933–941.

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

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

US FDA, 2020. Code of Federal Regulations Title 21, vol. 3, 21CFR184.1005. Retrieved from. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=184.1005.

WHO, 2006. Safety evaluation of certain food additives. WHO Food Additives Series: 54. Retrieved from. https://inchem.org/documents/jecfa/jecmono/v54je01.pdf.

Witt, K.L., Knapton, A., Wehr, C.M., Hook, G.J., Mirsalis, J., Shelby, M.D., MacGregor, J. T., 2000. Micronucleated erythrocyte frequency in peripheral blood of B6C3F1 mice from short-term, prechronic, and chronic studies of the NTP carcinogenesis bioassay program. Environ. Mol. Mutagen. 36 (3), 163–194.

Yasunaga, K., Kiyonari, A., Oikawa, T., Abe, N., Yoshikawa, K., 2004. Evaluation of the Salmonella umu test with 83 NTP chemicals. Environ. Mol. Mutagen. 44 (4), 329–345.

Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. J. Osaka City Med. Cent. 34 (3–4), 267–288 ([Osaka-shi Igakkai Zasshi]).

Yoshikawa, K., 1996. Anomalous nonidentity between Salmonella genotoxicants and rodent carcinogens: nongenotoxic carcinogens and genotoxic noncarcinogens. Environ. Health Perspect. 104 (1), 40–46.

Zimmermann, F.K., Scheel, I., Resnick, M.A., 1989. Induction of chromosome loss by mixtures of organic solvents. Mutat. Res. Genet. Toxicol. 224 (2), 287–303.