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Short review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT phenylethyl 2-methylbutyrate, CAS Registry Number 24817-51-4

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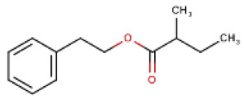

Abbreviation/Definition List:

2-Box Model- a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF- Assessment Factor
BCF- Bioconcentration Factor
Creme RIFM model- The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA- European Chemicals Agency
EU- Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD- Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

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NA- North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
NOEL- No Observed Effect Level
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- Quantitative Risk Assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/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 under the limits 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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

The material (phenylethyl 2-methylbutyrate) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the read across analog phenethyl isobutyrate (CAS # 103-48-0) show that phenylethyl 2-methylbutyrate is not genotoxic. Data from the read across analog 2-phenylethyl pivalate (CAS # 67662-96-8) show that phenylethyl 2-methylbutyrate does not have skin sensitization potential. The repeated dose toxicity and developmental toxicity endpoints were completed using phenethyl alcohol (CAS # 60-12-8) and 2-methylbutyric acid (CAS # 116-53-0) as read across analogs, which provided a MOE > 100. The fertility endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day). The local respiratory toxicity endpoint was completed using benzyl acetate (CAS # 140-11-4) as a read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, phenylethyl 2-methylbutyrate 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.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2001a; RIFM, 2015a)
Repeated Dose Toxicity: NOAEL = 385 mg/kg/day.	(Owston et al., 1981)
Reproductive Toxicity: Developmental toxicity NOAEL = 53.9 mg/kg/day. No fertility toxicity NOAEL. Exposure is below the TTC.	(RIFM, 2010)
Skin Sensitization: Not a concern for skin sensitization.	(RIFM, 1981; RIFM, 1973; RIFM, 1980)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: NOAEC = 61.4 mg/m^3.	(RIFM, 2013a)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 86% (OECD 301F)	(RIFM, 2012)
Bioaccumulation: Screening-Level: 193.4 L/kg	(US EPA, 2012a)
Ecotoxicity: Screening-Level: Fish LC50: 5.37 mg/L	(RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 5.37 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.00537 μg/L

- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Phenylethyl 2-methylbutyrate
2. **CAS Registry Number:** 24817-51-4
3. **Synonyms:** Benzylcarbinyl 2-methylbutyrate; Butanoic acid, 2-methyl-, 2-phenylethyl ester; Phenethyl 2-methylbutyrate; β-Phenylethyl α-methylbutanoate; 2-Phenylethyl 2-methylbutanoate; ｱﾙｶﾝ酸(C = 1–9)ﾌｪﾆﾙｱﾙｷﾙ; Phenylethyl 2-methylbutyrate
4. Molecular Formula: $C_{13}H_{18}O_2$
5. Molecular Weight: 206.29
6. RIFM Number: 1187

2. Physical data

1. **Boiling Point:** 263 °C [FMA database], 275.55 °C [US EPA, 2012a]
2. **Flash Point:** > 93 °C [GHS database], > 200 °F; CC [FMA database]
3. **Log K_{OW}:** 3.97 [US EPA, 2012a]
4. **Melting Point**: 24.45 °C [US EPA, 2012a]
5. **Water Solubility:** 16.47 mg/L [US EPA, 2012a]
6. **Specific Gravity:** 0.975 [FMA database]
7. **Vapor Pressure:** 0.00415 mm Hg @ 20 °C [US EPA, 2012a], 0.005 mm Hg 20 °C [FMA database], 0.0068 mm Hg @ 25 °C [US EPA, 2012a]
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** A colorless to pale yellow clear liquid with a medium floral, green, sweet, tropical, waxy, rose odor. The taste is described as fruity, floral, green, sweet and waxy.*

*http://www.thegoodscentscompany.com/data/rw1029302.html#toorgano, **retrieved 9/20/2017**.

3. Exposure

1. **Volume of Use (Worldwide Band):** 0.1–1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0088% (RIFM, 2015b)
3. **Inhalation Exposure*:** 0.000063 mg/kg/day or 0.0045 mg/day (RIFM, 2015b)
4. **Total Systemic Exposure**:** 0.00088 mg/kg/day (RIFM, 2015b)

*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; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015, 2017; Comiskey et al., 2017).

4. Derivation of systemic absorption

1. **Dermal:** 77%, read across from phenethyl alcohol (CAS # 60-12-8)

Politano et al., 2013b (data also available in RIFM, 1986a; RIFM, 1987; RIFM, 1988a; RIFM, 1988b; RIFM, 1990; Ford et al., 1987a, 1990): Studies were conducted to compare the dermal absorption, plasma pharmacokinetics, and excretion of phenylethyl alcohol (PEA) by pregnant and non-pregnant rats, non-pregnant rabbits, and non-pregnant humans. Following dermal (430, 700, or 1400 mg/kg body weight [bw]), gavage (430 mg/kg bw), or dietary (430 mg/kg bw) 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%

5. Computational toxicology evaluation

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

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

2. **Analogs Selected:**
   a. **Genotoxicity:** Phenthyl isobutyrate (CAS # 103-48-0)
   b. **Repeated Dose Toxicity:** Phenethyl alcohol (CAS # 60-12-8); 2-methylbutyric acid (CAS # 116-53-0)
   c. **Reproductive Toxicity:** Phenethyl alcohol (CAS # 60-12-8); 2-methylbutyric acid (CAS # 116-53-0)
   d. **Skin Sensitization:** 2-Phenylethyl pivalate (CAS # 67662-96-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Benzyl acetate (CAS # 140-11-4)
   g. **Environmental Toxicity:** None
3. **Read across Justification:** See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Phenylethyl 2-methylbutyrate is reported to occur in the following foods by the VCF*:

Alpina species
Cider (apple wine)
Mentha oils.

*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 that contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

pre-registered for 11/30/2010; no dossier available as of 8/31/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.2. Risk assessment

Phenylethyl 2-methylbutyrate was tested in using the BlueScreen assay and found to be negative for both cytotoxicity and genotoxicity (RIFM, 2013b). There are no studies assessing the mutagenicity of phenylethyl 2-methylbutyrate. The mutagenic activity of read across material, phenethyl isobutyrate (CAS # 103-48-0; see Section 5) has been assessed in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were exposed to phenethyl isobutyrate in DMSO (dimethyl sulfoxide) at concentrations of 5, 15, 50, 150, 500, 1500 and 5000 μg/plate in the presence and absence of metabolic activation. No increases in revertant colonies were observed in any of the tester strains at the concentrations tested (RIFM, 2001a). Under the conditions of the study, phenethyl isobutyrate was considered not mutagenic in the Ames test.

There are no studies assessing the clastogenicity of phenylethyl 2-methylbutyrate. The clastogenic activity of phenethyl isobutyrate was assessed 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 isobutyrate in DMSO at concentrations ranging from 0.192 to 1920 μg/plate with and without metabolic activation. The percentage of cells with micronucleated binucleated cells in the test substance-treated groups was not statistically significantly increased relative to vehicle control at any dose level. Based on the findings of the study, phenylethyl isobutyrate was concluded to be negative for the induction of micronuclei in the *in vitro* mammalian cell micronucleus test using human peripheral blood lymphocytes.

Based on the available data, phenethyl isobutyrate does not present a concern for genotoxic potential, and this can be extended to phenylethyl 2-methylbutyrate.

Additional References: None.

Literature Search and Risk Assessment Completed on: 2/12/2017.

10.1.3. Repeated dose toxicity

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

10.1.4. Risk assessment

There are no repeated dose toxicity data on phenylethyl 2-methylbutyrate. Phenylethyl 2-methylbutyrate will hydrolyze readily into phenethyl alcohol (CAS # 60-12-8; see Section 5) and 2-methylbutyric acid (CAS # 116-53-0; see Section 5). Metabolite phenethyl alcohol has a dermal 90-day repeated dose toxicity study. Groups of 15 rats/sex/dose were administered test material, phenethyl alcohol, at doses of 0.25, 0.5, 1.0 and 2.0 ml/kg/day (250, 500, 1000 and 2000 mg/kg/day) for 90 days in an open application to shaved dorsa of Sprague Dawley rats. The NOAEL was determined to be 0.5 ml/kg/day (500 mg/kg/day), based on reduced body weight and body weight gains among the higher dose group animals (Owston et al., 1981). To account for bioavailability following dermal application of phenethyl alcohol, data from a rat *in vivo* study (Politano et al., 2013b; see Section 4) were 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.

There are no repeated dose toxicity data on 2-methylbutyric acid. Although phenylethyl 2-methylbutyrate is expected to hydrolyze to phenethyl alcohol and 2-methylbutyric acid, the toxicity is expected to result from phenethyl alcohol. Hydrolysis product, 2-methylbutyric acid, is expected to be directly excreted thus, it would not contribute towards the toxicity of phenylethyl 2-methylbutyrate (Belsito et al., 2012). Thus, the NOAEL for phenylethyl 2-methylbutyrate was considered to be 385 mg/kg/day from the study conducted on phenethyl alcohol. Therefore, the phenylethyl 2-methylbutyrate 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 phenylethyl 2-methylbutyrate, 385/0.00088 or 437500.

When correcting for skin absorption, the total systemic exposure to phenylethyl 2-methylbutyrate (0.88 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Zaitsev and Rakhmanina, 1974.

Literature Search and Risk Assessment Completed on: 02/17/2017.

10.1.5. Reproductive toxicity

The margin of exposure for phenylethyl 2-methylbutyrate is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient fertility data on phenylethyl 2-methylbutyrate or any read across materials. The total systemic exposure to phenylethyl 2-methylbutyrate is below the TTC for fertility endpoint of a Cramer Class I material at the current level of use.

10.1.5.1. Risk assessment. There are no developmental toxicity data on phenylethyl 2-methylbutyrate. Phenylethyl 2-methylbutyrate will hydrolyze readily into phenethyl alcohol (CAS # 60-12-8; see Section 5) and 2-methylbutyric acid (CAS # 116-53-0; see Section 5). Metabolite phenethyl alcohol has several developmental toxicity studies in rats. A dietary developmental toxicity study conducted on groups of 28 pregnant rats, were fed diets containing test material, phenethyl alcohol at doses of 0, 1000, 3000 or 10000 ppm, equivalent to 0, 83, 266 or 799 mg/kg/day according to calculated food intake from Gestation Days (GDs) 6–15. There were no maternal or fetal developmental toxicity effects reported among treated animals. Thus, the NOAEL for maternal and developmental toxicity was determined to be 10000 ppm or 799 mg/kg/day, the highest dose tested (Politano et al., 2013a). In another study, a dermal developmental toxicity study conducted on groups of 25–35 pregnant female rats were administered test material, phenethyl alcohol at doses of 0, 140, 430 or 1400 mg/kg/day from GDs 6–15. There was significant maternal toxicity reported among the high dose animals. Thus, the maternal toxicity NOAEL was determined to be 430 mg/kg/day. Dose related increase in skeletal abnormalities was reported among the animals of the mid- and high-dose group animals. Thus, the NOAEL for developmental toxicity was determined to be 140 mg/kg/day (Politano et al., 2013a). In another dermal developmental toxicity study, phenethyl alcohol was administered at doses of 0, 70, 140, 280, 430 and 700 mg/kg/day to groups of 10 rats/sex/group from GDs 6–15. Fetal effects included a dose-dependent decrease in fetal body weights for litters of the 140 mg/kg/day and higher dose groups. Dosages as high as 700 mg/kg/day did not adversely affect average litter sizes, numbers of implantations, live fetuses, or post-implantation loss. Thus, the NOAEL for developmental toxicity was determined to be 70 mg/kg/day, based on a decrease in body weights of litters among the higher dose groups (Politano et al., 2013a). Another study was conducted to determine the reversibility of skeletal alterations (e.g., rudimentary cervical ribs and vertebral

irregularities) and delays in skeletal ossification following exposure of pregnant rats to the test material during the gestation period, and to evaluate any safety concerns relating to human health. Dosages of 0 (water), 140, 430 or 1400 mg/kg/day phenylethyl alcohol were percutaneously administered once daily on GDs 7–20. Twenty rats per dosage group were cesarean-sectioned on GD 21. The remaining twenty rats per dosage group were allowed to deliver naturally; the dams and pups were euthanized on Postpartum Day (PPD) 21. Thus, the maternal toxicity NOAEL was determined to be 430 mg/kg/day, based on increased incidences of altered clinical observations and mortality among the high dose group animals. The NOAEL for developmental toxicity was determined to be 140 mg/kg/day, based on increased incidences of fetal skeletal ossifications among the mid- and high-dose group animals, and gross, soft tissue and skeletal alterations among the high dose group animals (RIFM, 2010). The most conservative NOAEL was determined to be 70 mg/kg/day, based on a decrease in body weight of litters among the higher dose groups (Politano et al., 2013a). To account for bioavailability following dermal application, data from a rat *in vivo* study (Politano et al., 2013b; see Section 4) was used to revise the NOAEL of 70 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 53.9 mg/kg/day.

There are no developmental toxicity data on 2-methylbutyric acid. Although phenylethyl 2-methylbutyrate is expected to hydrolyze to phenethyl alcohol and 2-methylbutyric acid, the toxicity is expected to result from phenethyl alcohol. Hydrolysis product, 2-methylbutyric acid is expected to be directly excreted thus, it would not contribute towards the toxicity of phenylethyl 2-methylbutyrate (Belsito et al., 2012). Thus, the developmental toxicity NOAEL for phenylethyl 2-methylbutyrate was considered to be 53.9 mg/kg/day from the study conducted on phenethyl alcohol. Therefore, the phenylethyl 2-methylbutyrate 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 phenylethyl 2-methylbutyrate, 53.9/0.00088 or 61250.

When correcting for skin absorption, the total systemic exposure to phenylethyl 2-methylbutyrate (0.88 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no fertility data on phenylethyl 2-methylbutyrate or any read across materials or metabolites that can be used to support the fertility endpoint. When correcting for skin absorption, the total systemic exposure to phenylethyl 2-methylbutyrate (0.88 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 1985; Burdock et al., 1987; RIFM, 1988c; Ford et al., 1987b; Maganova and Saitsev, 1973; Mankes et al., 1983, 1984, 1985, RIFM, 1986b, Politano et al., 2011.

Literature Search and Risk Assessment Completed on: 02/17/2017.

10.1.6. Skin sensitization

Based on available data on read across material 2-phenylethyl pivalate (CAS # 67662-96-8), phenylethyl 2-methylbutyrate does not present a concern for skin sensitization.

10.1.6.1. Risk assessment. Limited skin sensitization studies are available for phenylethyl 2-methylbutyrate. Based on available data and read across material 2-phenylethyl pivalate (CAS # 67662-96-8; see Section 5), phenylethyl 2-methylbutyrate does not present a concern for skin sensitization. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). Based on a weight of evidence in guinea pig test methods, taking into account the relevant dermal studies both with and without adjuvant, read across material 2-phenylethyl pivalate is not considered to be a skin sensitizer (RIFM, 1973; RIFM, 1980). In a human repeat insult patch test of 2.5% of 1938 μg/cm^2 phenylethyl 2-methylbutyrate in alcohol, SDA39C did not result in sensitization reactions in any of the subjects tested (RIFM, 1971). In a human maximization test, no reaction, were observed with 4% phenylethyl 2-methylbutyrate (2760 μg/cm^2) in petrolatum (RIFM, 1982). Additionally, in a human confirmatory study, no sensitization reactions were observed to 2-phenylethyl pivalate (RIFM, 1981; Stokes and Aueron, 1980). Based on weight of evidence from structural analysis human data and read across to 2-phenylethyl pivalate, phenylethyl 2-methylbutyrate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/24/17.

10.1.7. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, phenylethyl 2-methylbutyrate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.7.1. Risk assessment. There are no phototoxicity studies available for phenylethyl 2-methylbutyrate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of absorbance, phenylethyl 2-methylbutyrate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/09/17.

10.1.8. Local respiratory toxicity

There are no inhalation data available on phenylethyl 2-methylbutyrate; however, in a 2-week inhalation study for the analog benzyl acetate (CAS # 140-11-4; see Section 5), a NOAEC of 61.4 mg/m^3 is reported by RIFM (2013a).

10.1.8.1. 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 study conducted in rats with nose-only inhalation exposure, a NOAEC of 614 mg/m^3 was reported for benzyl acetate (RIFM, 2013a). Test substance-related higher levels of lactate dehydrogenase were noted in the bronchoalveolar lavage fluid. Although the authors did not consider these effects as adverse, for the purpose of estimating local respiratory toxicity MOE, a NOAEC of 61.4 mg/m^3 (the mid-dose given) was considered.

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

- (61.4 mg/m^3)/(1m^3/1000L) = 0.0614 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat X duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.0614 mg/L) (61.2 L/day) = 3.76 mg/day
- (3.76 mg/day)/(0.0016 kg lung weight of rat*) = 2350 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0045 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015, 2017; Comiskey et al., 2017). 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 et al., 2009) to give 0.0069 mg/kg lung weight/day resulting in a MOE of 340580 (i.e., [2350 mg/kg lung weight/day]/[0.0069 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 0.0045 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2nd 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: RIFM, 1977; RIFM, 1997b; Silver, 1992; RIFM, 1997a; Isola et al., 2003b; RIFM, 2003a; Rogers et al., 2003; RIFM, 2003b; Isola et al., 2003a; Isola et al., 2004b; Smith et al., 2004; RIFM, 2004; Isola et al., 2004a; Rogers et al., 2005; Randazzo et al., 2014; Vethanayagam et al., 2013.

Literature Search and Risk Assessment Completed on: 07/24/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of phenylethyl 2-methylbutyrate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates; US EPA, 2012b) is used, and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, phenylethyl 2-methylbutyrate 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 phenylethyl 2-methylbutyrate as either being possibly persistent nor bioaccumulative based on its structure and physical chemical properties. This screening-level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental safety assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current Volume of Use (2011), phenylethyl 2-methylbutyrate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 2012: The ready biodegradability of the test material was evaluated using the Manometric Respirometry Test according to the OECD 301F method. Under the conditions of the study, biodegradation of 86% was observed.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Phenylethyl 2-methylbutyrate has been pre-registered for REACH with no additional data at this time.

11. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	5.37 mg/L			1,000,000	0.00537 µg/L	

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.97	3.97
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.00537 µg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at screening-level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 02/09/2017.

12. Literature Search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**

- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2018.01.038.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2018.01.038.

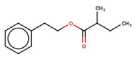
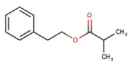
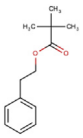
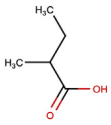
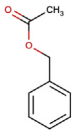
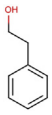
Appendix

Read across justification

Methods

The read across analogs were identified following the strategy for structuring and reporting a read across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was 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 and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target material	Read across material				
Principal Name	Phenethyl 2-methylbutyrate	Phenethyl isobutyrate	2-Phenylethyl pivalate	2-Methylbutyric acid	Benzyl acetate	Phenethyl alcohol
CAS No.	24817-51-4	103-48-0	67662-96-8	116-53-0	140-11-4	60-12-8
Structure						
Similarity (Tanimoto score)		0.89	0.81	NA[a]	0.68	NA[a]
Read across endpoint		• Genotoxicity	• Skin sensitization	• Repeated dose • Reproductive	• Local respiratory	• Repeated dose • Reproductive
Molecular Formula	$C_{13}H_{18}O_2$	$C_{12}H_{16}O_2$	$C_{13}H_{18}O_2$	$C_5H_{10}O_2$	$C_9H_{10}O_2$	$C_8H_{10}O$
Molecular Weight	206.29	192.26	206.29	102.13	150.18	122.17
Melting Point (°C, EPISUITE)	24.45	21.57	38.87	3.61	−0.50	5.81
Boiling Point (°C, EPISUITE)	275.55	258.98	269.09	175.25	215.57	224.85
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.907	3.63	0.99	149	25	0.0243
Log Kow (KOWWIN v1.68 in EPISUITE)	3.97	3.5[1]	3.93	1.18	1.96	1.36
	16.47	160[2]	17.74	45000	3100	22200

Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)						
J_{max} (mg/cm^2/h, SAM)	1.431	10.939	22.329	896.78	64.03	355.140
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	4.45E+000	3.31E-005	4.40E-005	1.30E-001	1.43E+000	2.89E-007
Genotoxicity						
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found				
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition	• Michael addition				
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Carcinogen (low reliability)	• Non-carcinogen (moderate reliability)				
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found				
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found				
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found				
Oncologic Classification	• Not classified	• Not classified				
Repeated dose toxicity						
Repeated Dose (HESS)	• Not categorized			• Carboxylic acids (Hepatotoxicity) No ranks		• Not categorized
Reproductive and developmental toxicity						
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, without OH or NH_2 group			• Non-binder, non-cyclic structure		• Non-binder without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)			• Toxicant (good reliability)		• Toxicant (good reliability)
Skin Sensitization						
Protein binding by OASIS v1.4	• No alert found		• No alert found			
Protein binding by OECD	• No alert found		• No alert found			
Protein binding potency	• Not possible to classify		• Not possible to classify			
Protein binding alerts for skin sensitization by OASIS v1.4	• No alert found		• No alert found			
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (moderate reliability)		• Sensitizer (moderate reliability)			
Respiratory						
Respiratory sensitization OECD QSAR Toolbox (3.4)	• No alert found				• No alert found	• No alert found
Metabolism						
OECD QSAR Toolbox (3.4) Rat liver S9 Metabolism Simulator and structural alerts for metabolites	See supplemental data 1	See supplemental data 2	See supplemental data 3	See supplemental data 4	See supplemental data 5, 6 & 7	See supplemental data 8

NA[a] - Major metabolites or analog of major metabolites of the target substance.

1. RIFM, 1999.
2. RIFM, 2001b.
3. Chidgey et al., 1987.
4. McMahon et al., 1989.

Summary

There are insufficient toxicity data on the target material phenethyl 2-methylbutyrate (CAS # 24817-51-4). Hence, *in silico* evaluation was conducted to determine read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgement, analogs phenethyl isobutyrate (CAS # 103-48-0), 2-phenylethyl pivalate (CAS # 67662-96-8), benzyl acetate (CAS # 140-11-4), phenethyl alcohol (CAS # 60-12-8) and 2-methylbutyric acid (CAS # 116-53-0) were identified as read across materials with data for their respective toxicological endpoints.

Conclusion/Rationale

- For the target material phenethyl 2-methylbutyrate (CAS # 24817-51-4), phenethyl isobutyrate (CAS # 103-48-0) was used as a read across analog for the genotoxicity endpoint, 2-phenylethyl pivalate (CAS # 67662-96-8) was used as a read across analog for the skin sensitization endpoint and benzyl acetate (CAS # 140-11-4) was used as a read across analog for the local respiratory endpoint.
  - The target substance and the read across analogs are structurally similar and belong to the structural class of esters with a primary aryl alkyl alcohol.
  - The target substance and the read across analogs share a primary aryl alkyl alcohol component.
  - The key difference between the target substance and the read across analogs are in the aliphatic acid component.
  - This structural difference between the target substance and the read across analogs does not affect consideration of the toxicological endpoints.
  - Similarity between the target substance and the read across analogs is indicated by the Tanimoto score in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoint.
  - The physical-chemical properties of the target substance and the read across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicological endpoints are consistent between the target substance and the read across analogs.
  - The target substance and the read across analog, 2-phenylethyl pivalate, are predicted to be sensitizers by the CAESAR model for skin sensitization. Other protein binding alerts are negative for both of the substances. The data described in the skin sensitization section above show that the read across analog does not pose a concern for the skin sensitization endpoint. Therefore, the alert is superseded by the available data.
  - The target substance and the read across analog are given alert of Michael addition. This alert is due to presence of aryl moiety on both of them which can undergo P450 mediated epoxidation followed by conversion to reactive quinone. Since the read across analog as well as the target substance is given this alert, they are expected to have comparable reactivity or toxicity.
  - The target substance is alerted as carcinogen while the while the read across analog is not alerted as carcinogen by ISS model. This alert is due to the fact that the target substance has methyl butyric acid portion. The substances belonging this chemical class are potentially reactive as peroxisome proliferators (PPs). These chemicals are considered nongenotoxic agents, given generally negative results in genotoxicity assays. Even if the mechanism by which these chemicals cause tumors is not fully understood, peroxisome proliferator-activated receptor alpha (PPAR a) is thought to mediate most of the PP effects in the rodent liver (Gonzalez et al., 1998). Two hypotheses have been proposed to account for PP induced hepatocarcinogenesis in rodents: (i) increase in DNA damage through induction of oxidative stress (Reddy and Rao, 1989) and (ii) alteration of hepatocyte growth control by enhanced cell proliferation or decreased apoptosis (Corton et al., 2000). The data shown for the read across analog confirms that the read across analog does not pose a concern for genetic toxicity at current level of use. Therefore based on structural similarity between the read across analog and the target substance, and data described for the read across analog, the alert for the target substance will be superseded.
  - The target substance and the read across analog are given alert of Michael addition. This alert is due to presence of aryl moiety on both of them which can undergo P450 mediated epoxidation followed by conversion to reactive quinone. Since the read across analog as well as the target substance is given this alert, they are expected to have comparable reactivity or toxicity.
  - The target substance is alerted as carcinogen while the while the read across analog is not alerted as carcinogen by ISS model. This alert is due to the fact that the target substance has methyl butyric acid portion. The substances belonging this chemical class are potentially reactive as peroxisome proliferators (PPs). These chemicals are considered nongenotoxic agents, given generally negative results in genotoxicity assays. Even if the mechanism by which these chemicals cause tumors is not fully understood, peroxisome proliferator-activated receptor alpha (PPAR a) is thought to mediate most of the PP effects in the rodent liver (Gonzalez et al., 1998). Two hypotheses have been proposed to account for PP induced hepatocarcinogenesis in rodents: (i) increase in DNA damage through induction of oxidative stress (Reddy and Rao, 1989) and (ii) alteration of hepatocyte growth control by enhanced cell proliferation or decreased apoptosis (Corton et al., 2000). The data shown for the read across analog confirms that the read across analog does not pose a concern for genetic toxicity at current level of use. Therefore based on structural similarity between the read across analog and the target substance, and data described for the read across analog, the alert for the target substance will be superseded.
  - The target substance and the read across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the toxicological endpoints are consistent between the metabolites of the read across analogs and the target material.
- Metabolism

Metabolism of the target substance 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 2-methylbutyrate (CAS # 24817-51-4) was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). The target material is predicted to be metabolized to phenethyl alcohol (CAS # 60-12-8) and 2-methylbutyric acid (CAS # 116-53-0) in the first step with 0.95 pre-calculated probability. Benzyl alcohol was out of domain for the *in vivo* and *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgement, the model's domain exclusion was overridden, and a justification is provided.

- Phenethyl alcohol (CAS # 60-12-8) and 2-methylbutyric acid (CAS # 116-53-0) are used as read across analogs for the repeated dose and reproductive toxicity endpoints.
  - The read across materials are major metabolites or analogs of the major metabolites of the target.
  - The target substance is an ester formed from the read across analog alcohol and the read across analog acid.
  - Structural differences between the target substance and the read across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read across analog. Therefore, the toxicological profile of the target is expected to be that of metabolites.
  - The target substance and the read across analogs have similar physical-chemical properties. Any differences in the physical-chemical properties of the target substance and the read across analogs do not affect consideration of the toxicological endpoints.
  - According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicological endpoints are consistent between the target substance and the read across analogs.

- The read across analog, 2-methylbutyric acid, is categorized as a carboxylic acid with a hepatotoxicity alert by HESS categorization. Data described above in the repeated dose toxicity section show that 2-methylbutyric acid is excreted out from the system and does not contribute towards toxicity. The margin of exposure for the read across analog is adequate at the current level of use. Therefore, the alert is superseded by the available data.
- The target substance and the read across analogs, phenethyl alcohol and 2-methylbutyric acid, are predicted to be toxicants by the CAESAR model for developmental (reproductive) toxicity. The ER binding alert is negative for both of the substances. The data described in the developmental toxicity section shows that the margin of exposure is adequate at the current level of use. Therefore, the alert is superseded by the available data.

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., Renkers, 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.

Belsito, D., Bickers, D., Bruze, M., Calow, P., Dagli, M.L., Fryer, A.D., Greim, H., Miyachi, Y., Saurat, J.H., Sipes, I.G.R.I.F.M., 2012. A toxicological and dermatological assessment of aryl alkyl alcohol simple acid ester derivatives when used as fragrance ingredients. Food Chem. Toxicol. 50 (Suppl. 2), S269–S313.

Burdock, G.A., Ford, R.A., Bottomley, A.M., John, D.M., 1987. An evaluation of the teratogenic potential of orally administered phenylethyl alcohol (PEA). Toxicologist 7 (1), 176.

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

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

Chidgey, M., Kennedy, J., Caldwell, J., 1987. Studies on benzyl acetate. III. The percutaneous absorption and disposition of [Methylene{14}C]benzyl acetate in the rat. Food Chem. Toxicol. 25, 521–525 (in vivo).

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

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

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

Ford, R.A., Api, A.M., Hawkins, D.R., 1987a. Absorption distribution and excretion of topical doses of 14C-phenylethyl alcohol (PEA). Toxicologist 7 (1), 237.

Ford, R.A., Api, A.M., Palmer, A.K., 1987b. The effect of phenylethyl alcohol applied dermally to pregnant rats. Toxicologist 7 (1), 175.

Ford, R.A., 1990. Metabolic and kinetic criteria for the assessment of reproductive hazard. In Basic Science In Toxicology 59–68.

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

IFRA (International Fragrance Association), 2011. Volume of Use Survey, February 2011.

Isola, D.A., Smith, L.W., Rogers, R.E., Black, M.S., 2003a. Exposure characterization of fragranced air fresheners. Allergy Clin. Immunol. Int. Supplement 1, 132.

Isola, D., Smith, L.W., Ansari, R., Black, M.S., 2003b. Exposure characterization from a fragranced plug-in air freshener. Toxicologist 72 (S-1), 291.

Isola, D.A., Rogers, R., Black, M.S., Smith, L.W., 2004a. Exposure characterizations of three fragranced products. Int. J. Toxicol. 23 (6), 397.

Isola, D.A., Rogers, R.E., Myshaniuk, A., Jeng, C.-J., Ansari, R., Smith, L.W., 2004b. Exposure characterization from a surrogate fine fragrance. Toxicologist 78 (S-1), 107.

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.

Maganova, N.B., Saitsev, A.N., 1973. Study of the embryotoxic action of some synthetic food flavorings. Vopr. Pitan. 32 (4), 50–54.

Mankes, R., LeFevre, R., Bates, H., Abraham, R., 1983. Effects of various exposure levels of 2-phenylethanol on the fetal development and survival in long-evans rats. J. Toxicol. Environ. Health 12, 235–244.

Mankes, R.F., LeFevre, R., Abraham, R., 1984. Reproductive effects of some solvent alcohols: evaluations of structure-activity relationships in 2-substituted ethanols. J. Am. Coll. Toxicol. 3 (2), 166.

Mankes, R.F., LeFevre, R., Renak, V., Fiesher, J., Abraham, R., 1985. Reproductive effects of some solvent alcohols with differing partition coefficients. Teratology 31 (3), 67A.

McMahon, T., Diliberto, J., Birnbaum, L., 1989. Age-related changes in the disposition of benzyl acetate: a model compound for glycine conjugation. Drug Metabol. Dispos. 17 (5), 506–512 (in vivo).

OECD, 2012. The OECD QSAR Toolbox, v. 3.4. Retrieved from. http://www.qsartoolbox.org/.

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/.

Owston, E., Lough, R., Opdyke, D.L., 1981. A 90-day study of phenylethyl alcohol in the rat. Food Chem. Toxicol. 19 (6), 713–715.

Politano, V.T., Lewis, E.M., Hoberman, A.M., Diener, R.M., Api, A., 2011. Evaluation of a combined dermal developmental and perinatal/postnatal reproduction toxicity study of PEA (phenethyl alcohol) in rats - including an examination of skeletal variants postnatally. Toxicologist 120 (Suppl. 2), 221.

Politano, V.T., Diener, R.M., Christian, M.S., Hoberman, A.M., Palmer, A., Ritacco, G., Adams, T.B., Api, A.M., 2013a. Oral and dermal developmental toxicity studies of phenylethyl alcohol in rats. International Journal of Toxicology. (formerly Journal of the American College of Toxicology) 32 (1), 32–38.

Politano, V.T., Diener, R.M., Christian, M.S., Hawkins, D.R., Ritacco, G., Api, A.M., 2013b. The pharmacokinetics of phenylethyl alcohol (PEA): safety evaluation comparisons in rats, rabbits, and humans. Int. J. Toxicol. 32 (1), 39–47.

Randazzo, J., Kirkpatrick, D.T., Vitale, D., Singal, M., 2014. Evaluation of nose-only inhalation exposure to aerosolized benzyl acetate in Sprague-Dawley rats. Toxicologist 138 (1), 416.

RIFM (Research Institute for Fragrance Materials, Inc.), 1971. Repeated Insult Patch Study with Phenylethyl 2-methylbutyrate in Humans. Unpublished report from International Flavors and Fragrances. RIFM report number 54730. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Skin Irritation and Capacity of Allergenic Sensitization Determined by the Open Epicutaneous Test (OET) of 2-phenylethyl Pivalate (Centifolyl) on guinea Pigs. Unpublished report from Givaudan-Roure Corporation. RIFM report number 19870. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Doctoral Dissertation: the Comparative Respiratory Irritation Potential of Fourteen Fragrance Raw Materials. Report to RIFM. RIFM report number 9011. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Maximization Test with 2-phenylethyl Pivalate in guinea Pigs. Unpublished Report from Quest International. RIFM report number 17628. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1981. Repeated Insult Patch Test/photosensitization Study of 2-phenylethyl Pivalate in Humans Subjects. Unpublished report from Firmenich Incorporated. RIFM report number 17946. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1643. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1985. Effect of dietary administration of micro-encapsulated phenylethyl alcohol on pregnancy of the rat. Report to FEMA. Unpublished report by Bottomley et al. RIFM report number 2960. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1986a. Dermal Absorption and Disposition of (14)C-2-phenylethanol in Rats. Report to RIFM. RIFM report number 14274. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1986b. Effect of Phenylethyl Alcohol (PEA) on Pregnancy of the Rat. Report to RIFM. RIFM report number 14279. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1987. The Dermal Absorption of (14)C-2-phenylethanol in Man Following a Single Topical Application. Report to RIFM. RIFM report number 14275. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988a. The Percutaneous Absorption and Disposition of (14)C-2-phenylethanol in Rabbits. Report to RIFM. RIFM report number 14276. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988b. Plasma Concentrations and Pharmacokinetics of Phenylacetic Acid and Phenylethanol in Rats Following Single Dermal Applications of Phenylethanol. Report to RIFM. RIFM report number 14277. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988c. Dosage-range Developmental Toxicity (Embryo/fetal Toxicity and Teratogenicity) Study of 2-phenylethylalcohol (PEA) Administered Dermally to Presumed Pregnant Mice. Unpublished RIFM report number 14280. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1990. Plasma and Urine Concentrations and Pharmacokinetics of Phenylacetic Acid and Phenylethanol in the Rat Following Single Doses of Phenylethanol Administered via Different Routes. Report to RIFM. RIFM report number 14278. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1997a. Benzyl Acetate - Acute

Inhalation Toxicity in Rats 4-hour Exposure. Unpublished report from Haarmann & Reimer GmbH. RIFM report number 35546. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1997b. Investigation of Oxidation Gases from Paraffin Aromatic Candles in Toxicological Relevance to Classes of Damaging Materials. Unpublished report from the Union of German Candle Manufacturers. RIFM report number 18011. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1999. Partition Coefficient N-octanol/water of Phenethyl Isobutyrate. Unpublished report from Givaudan. RIFM report number 51491. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. Mutagenicity Study of Phenethyl Isobutyrate in the Salmonella typhimurium/mammalian Microsome Reverse Mutation Assay (Ames-Test). Unpublished report from Symrise. RIFM report number 57723. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. Phenethyl Isobutyrate: Water Solubility. Unpublished Report from Symrise. RIFM report number 60290. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2003a. Airborne Levels of Selected Fragrance Materials in a Simulated Bathroom. RIFM report number 41708. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2003b. Indoor Air Quality Evaluation of a Plug-in Air Freshener. RIFM report number 43292. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Airborne Levels of Selected Fragrance Materials Following a Controlled Exposure to a Surrogate Fine Fragrance. RIFM report number 47425. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2010. Combined Dermal Developmental and Perinatal/postnatal Reproduction Toxicity Study of PEA (Phenethyl Alcohol) in Rats [Amendment Attached]. RIFM report number 58462. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2012. Ready Biodegradability of Phenylethyl 2-methylbutyrate (Anatolyl). Unpublished Report from Givaudan. RIFM report number 63208. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. A 2-week Inhalation Toxicity Study of Aerosolized Benzyl Acetate in the Sprague-Dawley Rat. RIFM report number 65459. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Report on the Testing of Phenylethyl 2-methylbutyrate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 66142. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015a. Phenethyl Isobutyrate: in vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM report number 68616. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2015b. Use Level Survey, October 2015.
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.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Rogers, R.E., Isola, D.A., Smith, L.W., Jeng, C.J., Dews, P., Myshaniuk, A., 2003. Characterization of potential human exposure to fragrances during residential consumer product use. J. Allergy Clin. Immunol. 111 (2), S239.
Rogers, R.E., Isola, D.A., Jeng, C.-J., Smith, L.W., Lefebvre, A., 2005. Simulated inhalation levels of fragrance materials in a surrogate air freshener formulation. Environmental Science and Technology. Environmental Science & Technology 39 (20), 7810–7816.
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., Smith, B., Thomas, R., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T.D., 2015. A strategy for structuring and reporting a read across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.
Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.
Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. Ann. N. Y. Acad. Sci. 641, 152–163.
Smith, L.W., Rogers, R.E., Black, M.S., Isola, D.A., 2004. Exposure characterizations of three fragranced products. Toxicol. Appl. Pharmacol. 197 (3), 189.
Stokes, J.B., Aueron, F., 1980. Prevention of organ damage in massive ethylene glycol ingestion. J. Am. Med. Assoc. 243 (20), 2065–2066.
US EPA, 2012a. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.0-v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft® Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
Vethanayagam, D., Vilagoftis, H., Mah, D., Beach, J., Smith, L., Moqbel, R., 2013. Fragrance materials in asthma: a pilot study using a surrogate aerosol product. J. Asthma 50 (9), 975–982.
Zaitsev, A.N., Rakhmanina, N.L., 1974. Some data on the toxic properties of phenylethanol and cinnamic alcohols. Vopr. Pitan. 6, 48–53.