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Short review

RIFM fragrance ingredient safety assessment phenethyl isovalerate, CAS Registry Number 140-26-1

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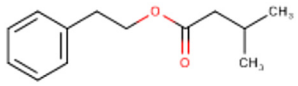
Version: 111617. This version replaces any previous versions.

Name: Phenethyl isovalerate

CAS Registry Number: 140-26-1



Abbreviation/Definition list:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
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

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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
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
Significant - Statistically significant difference in reported results as compared to controls with a $p < .05$ 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 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 (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.

Existing information supports the use of this material under current conditions.

Phenethyl isovalerate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog phenethyl isobutyrate (CAS# 103-48-0) show that phenethyl isovalerate is not expected to be genotoxic. Data from read-across analog 2-phenylethyl pivalate (CAS# 67662-96-8) show that phenethyl isovalerate is not a safety concern at the current, declared use levels for the skin sensitization endpoint. The reproductive toxicity endpoint was completed using the TTC for a Cramer Class I material; exposure to phenethyl isovalerate is below the TTC (0.03 mg/kg/day). The repeated dose and developmental toxicity endpoints were completed using phenethyl alcohol (CAS# 60-12-8) and isovaleric acid (CAS# 503-74-2) as read-across analogs; the calculated MOE > 100. The local respiratory toxicity endpoint was completed using benzyl acetate (CAS# 140-11-4) as a read-across analog; the calculated MOE > 100. Phenethyl isovalerate is not expected to be phototoxic/photoallergenic based on UV spectra. The environmental endpoints were evaluated and phenethyl isovalerate was found not to be PBT as per the IFRA Environmental Standards; its risk quotients, based on its current VoU in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic (RIFM, 2001d; RIFM, 2015a)
Repeated Dose Toxicity: NOAEL = 385 mg/kg/day (Owston et al., 1981)
Developmental and Reproductive Toxicity: Developmental toxicity NOAEL = 53.9 mg/kg/day. No Reproductive NOAEL. Exposure is below the TTC. (RIFM, 2010)
Skin Sensitization: Not sensitizing. (RIFM, 1981; RIFM, 1973; RIFM, 1977a; RIFM, 1980; RIFM, 1974b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: NOAEC = 61.4 mg/m^3 (RIFM, 2013c)

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 72% (OECD 301D) (RIFM, 2001b)
Bioaccumulation: Screening-Level: 193 L/kg (US EPA, 2012a)
Ecotoxicity: Screening-Level: 96-h Algae EC50: 1.02 mg/L (US EPA, 2012a)
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: 96-h Algae E50: 1.02 mg/L (US EPA, 2012a)
RIFM PNEC is: 0.102 μg/L
- **Revised PEC/PNECs (2011 IFRA Volume of Use)**: North America and Europe: < 1

1. Identification

1. **Chemical Name:** Phenethyl isovalerate
2. **CAS Registry Number:** 140-26-1
3. **Synonyms:** Benzylcarbinyl isovalerate; Benzylcarbinyl 3-methylbutanoate; Butanoic acid, 3-methyl-, 2-phenylethyl ester; Phenethyl 3-methylbutyrate; Phenylethyl isovalerate; 2-Phenylethyl isovalerate; 2-Phenylethyl 3-methylbutanoate; アルカン酸(C = 1–9)フェニルエチル; アルキル(C = 1–5)カルボン酸フェニルアルキル(C = 1–6); Phenyl ethyl isopentanoate; Phenethyl isovalerate
4. **Molecular Formula:** $C_{13}H_{18}O_2$
5. **Molecular Weight:** 206.29
6. **RIFM Number:** 513

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:** 0.973 (FMA Database]
7. **Vapor Pressure:** 0.00415 mmHg @ 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium, floral, fruity, sweet, rose, peach, apricot, ripe pineapple, tutti frutti, apple, blueberry odor. The taste is described as sweet, fruity, ripe pineapple, with honey, berry, and peachy nuances.*

*http://www.thegoodscentscompany.com/data/rw1010091.html#toorgano, retrieved 3/1/2017.

3. Exposure

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0039% (RIFM, 2015b)
3. **Inhalation Exposure*:** 0.000090 mg/kg/day or 0.0062 mg/day (RIFM, 2015b)
4. **Total Systemic Exposure**:** 0.00054 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)

RIFM, 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 owing to poor recovery of radioactivity due to evaporation in 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 Judgment	Toxtree v2.6	OECD QSAR Toolbox v3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Phenethyl isobutyrate (CAS # 103-48-0)
   b. **Repeated Dose Toxicity:** Phenethyl alcohol (CAS # 60-12-8); isovaleric acid (CAS # 503-74-2)
   c. **Developmental and Reproductive Toxicity:** Phenethyl alcohol (CAS # 60-12-8); isovaleric acid (CAS # 503-74-2)
   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)

Phenethyl isovalerate is reported to occur in the following foods*:
Artocarpus species.
Banana (*Musa sapientum* L.)
Beer.
Cider (apple wine)
Eucalyptus oil (*Eucalyptus globulus Labille*)
Grape brandy.
Lamb's lettuce (*Valerianella locusta*)
Mangifera species.
Mentha oils.
Syzygium species.
Wine.

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. [eds]. – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database 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

Available, accessed 03/01/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, phenethyl isovalerate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Phenethyl isovalerate was tested in the BlueScreen assay and found to be negative for both cytotoxicity and genotoxicity, indicating a lack for genotoxic concern (RIFM, 2013d). The mutagenic activity of phenethyl isovalerate 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 50–5000 μg/plate in the presence of metabolic activation and 1.5–5000 μg/plate in the absence of metabolic activation. No increases in revertant colonies were observed in any of the tester strains at any concentration (RIFM, 2001d). Under the conditions of the study, phenethyl isovalerate was considered not mutagenic in the Ames test.

There are no clastogenicity data on phenethyl isovalerate. The clastogenic activity of read-across material phenethyl isobutyrate (CAS # 103-48-0; see Section V) 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 the vehicle control at any dose level (RIFM, 2015a). 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, and this can be extended to phenethyl isovalerate.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 2/11/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for phenethyl isovalerate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on phenethyl isovalerate. Phenethyl isovalerate will hydrolyze readily into phenethyl alcohol (CAS # 60-12-8; see Section 5) and isovaleric acid (CAS # 503-74-22; see Section 5). Metabolite phenethyl alcohol has a dermal 90-day repeated dose toxicity study. Groups of 15 Sprague Dawley rats/sex/dose were administered test material phenethyl alcohol in an open application to shaved dorsa 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. 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 (RIFM, 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 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 isovalerate acid. Although phenethyl isovalerate is expected to hydrolyze to phenethyl alcohol and isovalerate acid, the toxicity is expected to result from phenethyl alcohol. Hydrolysis product isovalerate acid is expected to be directly excreted and thus not contribute towards the toxicity of phenethyl isovalerate (RIFM, 2012). The NOAEL for phenethyl isovalerate was considered to be 385 mg/kg/day from the study conducted on phenethyl alcohol. **Therefore, the phenethyl isovalerate 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 isovalerate, 385/0.00054 or 712963.**

When correcting for skin absorption, the total systemic exposure to phenethyl isovalerate (0.54 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.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for phenethyl isovalerate is adequate for the developmental toxicity endpoint at the current level of use.

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

10.1.3.1. Risk assessment. There are no developmental toxicity data on phenethyl isovalerate. Phenethyl isovalerate will hydrolyze readily into phenethyl alcohol (CAS # 60-12-8; see Section 5) and isovaleric acid (CAS # 503-74-22; see Section 5). Metabolite phenethyl alcohol has several developmental toxicity studies in rats. In a dietary developmental toxicity study, 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 the 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 (RIFM, 2013a). In a dermal developmental toxicity study, 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. A dose-related increase in skeletal abnormalities was reported among mid- and high-dose group animals. Thus, the NOAEL for developmental toxicity was determined to be 140 mg/kg/day (RIFM, 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 (RIFM, 2013a). A study was also conducted to determine the reversibility of skeletal alterations (e.g., rudimentary cervical ribs and vertebral irregularities) and delays in skeletal ossification following test material exposure to

pregnant rats 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 20 rats per dosage group were allowed to deliver naturally; the dams and pups were euthanized on postpartum day (PPD) 21. 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). Metabolite isovaleric acid has an OECD 414 gavage developmental toxicity conducted in rats, which determined the NOAEL for developmental toxicity to be 600 mg/kg/day, the only dosage tested (ECHA REACH Dossier: Isovaleric acid, accessed 02/20/14).

The most conservative NOAEL for developmental toxicity was determined to be 70 mg/kg/day, based on a decrease in body weight of litters among the higher-dose groups (RIFM, 2013a). To account for bioavailability following dermal application, data from a rat *in vivo* study (RIFM, 2013b; see Section 4) was used to revise the NOAEL from 70 mg/kg/day to reflect the systemic dose. At a dermal penetration of 77% of applied dose, the revised phenethyl alcohol toxicity NOAEL is 53.9 mg/kg/day. **Therefore, the phenethyl isovalerate 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 isovalerate, 53.9/0.00054 or 99815.**

When correcting for skin absorption, the total systemic exposure to phenethyl isovalerate (0.54 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 phenethyl isovalerate, nor 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 phenethyl isovalerate (0.54 μg/kg/day) is below the TTC (30 μg/kg bw/day) 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.

10.1.4. Skin sensitization

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

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for phenethyl isovalerate. Based on the existing data and read-across material 2-phenylethyl pivalate (CAS # 67662-96-8; see Section 5), phenethyl isovalerate does not present a concern for skin sensitization. The chemical structures 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 WOE 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 (HRIPT), phenethyl isovalerate did not induce sensitization reactions at 4% or 3101 μg/cm < sup > 2 < / sup > (RIFM, 1971). In a human maximization test conducted on 31 subjects, no reactions indicative of sensitization were observed with 4% phenethyl isovalerate (2760 μg/cm < sup > 2 < /sup >) (RIFM, 1974a). Additionally, in a human confirmatory study, no sensitization reactions were observed to read-across material 2-phenylethyl pivalate (RIFM, 1981). Based on WOE from structural analysis, human data, and read-across to 2-phenylethyl pivalate, phenethyl isovalerate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 2/24/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, phenethyl isovalerate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for phenethyl isovalerate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. 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, phenethyl isovalerate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

10.1.6. Local respiratory toxicity

There are no inhalation data available on phenethyl isovalerate; 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, 2013c.

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 2-week study conducted in rats with nose-only inhalation exposure, a NOAEC of 614 mg/m^3 was reported for benzyl acetate (RIFM, 2013c). 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^3/1000 L) = 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 0.0062 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). 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 0.0095 mg/kg lung weight/day resulting in a MOE of 247368 (i.e., [2350 mg/kg lung weight/day]/[0.0095 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 0.0062 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York,

NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: RIFM, 1977b; 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 phenethyl isovalerate was performed following the RIFM Environmental Framework (Salvito et al., 2002; #40315), which provides 3 tiers of screening level for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{ow} and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, phenethyl isovalerate was identified as a fragrance material with the 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 phenethly isovalerate as possibly being either 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; #68218). 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., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on current Volume of Use (2011), phenethyl isovalerate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.1.1.1. Biodegradation. RIFM, 2001b: Ready biodegradability of the test material was evaluated according to the OECD 301D method. Under the conditions of the study, biodegradation of 72% was observed after 28 days.

10.2.1.1.2. Ecotoxicity. RIFM, 2001a: *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be 6.2 mg/L.

10.2.1.1.3. Other available data. Phenethyl isovalerate has been registered under REACH with no additional data at this time.

10.2.1.1.4. Risk assessment refinement. Since phenethyl isovalerate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>5.357 mg/L</u>			1,000,000	0.005374 µg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.946 mg/L	3.275 mg/L	<u>1.020 mg/L</u>	10,000	0.102 µg/L	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.872 mg/L	1.956 mg/L	3.093 mg/L			Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.97	3.97
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	1–10
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 0.102 µg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore, phenethyl isovalerate 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.

11. 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://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

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

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2018.01.006.

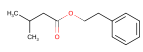
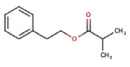
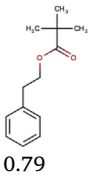
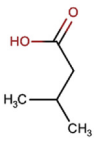
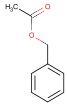
Appendix

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 were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite™ v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, 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 isovalerate	Phenethyl isobutyrate	2-Phenylethyl pivalate	Isovaleric acid	Benzyl acetate	Phenethyl alcohol
CAS No.	140-26-1	103-48-0	67662-96-8	503-74-2	140-11-4	60-12-8
Structure						
Similarity (Tanimoto score)		0.89	0.79	NA[a]	0.64	NA[a]
Read-across endpoint		• Genotoxicity	• Skin sensitization	• Repeated dose • Developmental	• Respiratory	• Repeated dose • Developmental
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, EPI Suite)	24.45	21.57	38.87	3.61	−0.50	5.81
Boiling Point (°C, EPI Suite)	275.55	258.98	269.09	175.25	215.57	224.85
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.907	3.63	0.99	152	25	0.0243
Log Kow						

(KOWWIN v1.68 in EPI Suite)	3.97	3.5[1]	3.93	1.16	1.96	1.36
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	16.47	160[2]	17.74	40700	3100	22200
J_{max} (mg/cm^2/h, SAM)	14.027	10.939	22.329	785.313	64.032	355.140
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	4.40E-005	3.31E-005	4.40E-005	1.28E-006	1.42E-005	2.89E-007
Genotoxicity						
DNA binding (OASIS v1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found				
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition	• Michael addition				
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• Non-carcinogen (good reliability)	• Non-carcinogen (moderate reliability)				
DNA alerts for Ames, MN, CA by OASIS v1.1	• 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 acid (hepatotoxicity) alert		• 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	
Observed Mammalian metabolism: See supplemental data 6[3]						

Observed Rat *In vivo* metabolism: See supplemental data 7[4]	See supplemental data 8

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

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

Summary:

There are insufficient toxicity data on the target material phenethyl isovalerate (CAS # 140-26-1). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, analogs phenethyl isobutyrate (CAS # 103-48-0), 2-phenylethyl pivalate (CAS # 67662-96-8), benzyl acetate (CAS # 140-11-4), isovaleric acid (CAS # 503-74-2), and phenethyl alcohol (CAS # 60-12-8) were identified as read-across materials with data for their respective toxicological endpoints.

Conclusion/Rationale:

- For the target substance phenethyl isovalerate (CAS # 140-26-1), the following mentioned materials are used as read-across analogs for the toxicological endpoints specified: phenethyl isobutyrate (CAS # 103-48-0) for genotoxicity, 2-phenylethyl pivalate (CAS # 67662-96-8) for skin sensitization, and benzyl acetate (CAS # 140-11-4) for the respiratory endpoint.
  - o The target substance and the read-across analogs are structurally similar and belong to the structural class of esters or are hydrolysis products primary aryl alcohol and/or carboxylic acids.
  - o The target substance and the read-across analog have a primary aryl alcohol portion in common.
  - o The key differences between the target substance and two of the read-across analogs are that the read-across analogs are isobutyrate or pivalate esters of phenethyl alcohol, whereas the target is an isovalerate ester. The other difference is with benzyl acetate, which has one less carbon in the aralkyl alcohol fragment. These structural differences between the target substance and the read-across analogs do not affect consideration of the toxicological endpoints.
  - o 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.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for the toxicological endpoints are consistent between the target substance and the read-across analogs.
  - o According to the CAESAR model for skin sensitization, the read-across analog and the target substance are predicted to be sensitizers. Other protein binding alerts for skin sensitization are negative. The data described in the skin sensitization section above shows that the read-across analog does not pose a concern for the skin sensitization endpoint. Therefore, the alert will be superseded by the available data.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- **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 isovalerate (CAS # 140-26-1) was predicted using the rat liver S9 metabolism simulator (OECD QSAR Toolbox v3.4). The target material is predicted to metabolize to phenethyl alcohol (CAS # 60-12-8) and isovaleric acid (CAS # 503-74-2) in the first step with 0.95 pre-calculated probability. Phenethyl alcohol was out of domain for the *in vivo* rat and out of domain for *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden, and a justification is provided.

- Phenethyl alcohol (CAS # 60-12-8) and isovaleric acid (CAS # 503-74-2) are used as read-across analogs for developmental and repeated dose toxicity endpoints.
  - o The read-across materials are major metabolites or are analogs of the major metabolites of the target.
  - o The target substance is an ester formed from the read-across analog alcohol and the read-across analog acid.
  - o 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 analogs. Therefore, the toxicity profile of the target is expected to be that of metabolites.
  - o The target substance and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the read-across ester analogs do not affect consideration of the toxicological endpoints.
  - o 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.
  - o The read-across analog isovaleric acid (CAS # 503-74-2) is categorized by HESS as a carboxylic acid with a hepatotoxicity alert. Data described above in the repeated dose toxicity section show that isovaleric acid is execrated 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 will be superseded by the available data.
  - o The read-across analogs are predicted to be toxicants by the CAESAR model for developmental toxicity. The target substance does not have such alert. ER binding alert is negative for both of the substances. These alerts show higher reactivity of the read-across analog compared the

target substance. Data described in the developmental toxicity section above show that the margin of exposure for the read-across analog is adequate at the current level of use. Therefore, the alert will be superseded by the available data.

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