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Short Review

RIFM fragrance ingredient safety assessment, amyl valerate, CAS Registry Number 2173-56-0

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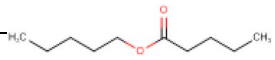

Name: Amyl valerate
CAS Registry Number: 2173-56-0

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association

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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
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
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

Amyl valerate was evaluated for genotoxicity, repeated dose, reproductive, and local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that amyl valerate is not genotoxic. Data on read-across analog butyl propionate (CAS # 590-01-2) provide a calculated MOE > 100 for the repeated dose toxicity endpoint. Data on read-across analogs butyl propionate (CAS # 590-01-2) and butyl acetate (CAS # 123-86-4) provide a calculated MOE > 100 for the reproductive toxicity endpoint. Data show that there are no safety concerns for amyl valerate for skin sensitization under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; amyl valerate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to amyl valerate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; amyl valerate 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.	(ECHA REACH Dossier: Pentyl valerate; ECHA, 2018)
Repeated Dose Toxicity: NOAEL = 2071 mg/kg/day.	(Banton et al., 2000)
Reproductive Toxicity: Developmental toxicity: NOAEL = 5638 mg/kg/day. Fertility: NOAEL = 2222 mg/kg/day.	(EPA HPVIS: Propanoic acid butyl ester; ECHA REACH Dossier: Butyl acetate; ECHA, 2011)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(ECHA Dossier: Pentyl valerate; ECHA, 2018)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence:	
Screening-level: 3.55 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a, 2012b)
Bioaccumulation:	
Screening-level: 151.8 L/kg	(EPI Suite v4.11; US EPA, 2012a, 2012b)
Ecotoxicity:	
Screening-level: Fish LC50: 6.19 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: 6.19 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.00619 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Amyl valerate
2. **CAS Registry Number:** 2173-56-0
3. **Synonyms:** Pentanoic acid, pentyl ester; Pentyl pentanoate; Pentyl valerate; ﾍﾟﾝﾀﾝ酸ｱﾙｷﾙ(C = 1 ~ 5); Amyl valerate
4. **Molecular Formula:** $C_{10}H_{20}O_2$
5. **Molecular Weight:** 172.26
6. **RIFM Number:** 6188
7. **Stereochemistry:** No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 210.7 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 3.81 (EPI Suite)
4. **Melting Point:** −9.5 °C (EPI Suite)
5. **Water Solubility:** 33.39 mg/L (EPI Suite)

6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.162 mm Hg @ 20 °C (EPI Suite v4.0), 0.241 mm Hg @ 25 °C (EPI Suite)
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:** Not Available

3. Volume of use (Worldwide band)

1. **Volume of Use (Worldwide Band):** 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 6.06% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.0022 mg/kg/day or 0.16 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.032 mg/kg/day (RIFM, 2017)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Butyl propionate (CAS # 590-01-2)
   c. **Reproductive Toxicity:** Butyl propionate (CAS # 590-01-2); butyl acetate (CAS # 123-86-4)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence (discrete chemical) or composition (NCS)

Amyl valerate is reported to occur in nature in the following foods by the VCF*:
Banana (*Musa sapientum* L.)
Capsicum species.
Cider (apple wine).
Mentha oils.
Wine.
*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 04/19/19 (ECHA, 2018).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, amyl valerate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Amyl valerate was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen HC is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of amyl valerate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with amyl valerate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2018). Under the conditions of the study, amyl valerate was not mutagenic in the Ames test.

The clastogenicity of amyl valerate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with amyl valerate in ethanol at concentrations up to 1720 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test item, either with or without S9 metabolic activation (ECHA, 2018). Under the conditions of the study, amyl valerate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Based on the data available, amyl valerate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/11/19.

11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for amyl valerate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on amyl valerate. Read-across material butyl propionate (CAS # 590-01-2; see Section VI) has sufficient repeated dose toxicity data. In a GLP-compliant subchronic study, 15 Sprague Dawley rats/sex/dose were administered butyl propionate by inhalation at targeted concentrations of 0, 250, 750 and 1500 ppm (equivalent to 345, 1036, and 2071 mg/kg/day) for 13 weeks for 6 h/day, 5 days/week. In addition, 5 animals/sex/dose were maintained as recovery groups for 8 weeks after the end of the treatment period. Although several local microscopic effects were observed in the nasal cavity of animals in mid- and high-dose groups, no treatment-related mortality or systemic toxicity was reported during the study. In high-dose group males, body weight, bodyweight gains, and feed consumption were significantly lower than the control group, but these changes were reversed at the end of the recovery period. Hence, these alterations were not considered to be treatment-related adverse effects. The NOAEL for repeated dose toxicity endpoint was considered to be 2071 mg/kg/day (1500 ppm) based on the absence of systemic toxicity at the highest tested dose (Banton et al., 2000).

Therefore, the MOE can be calculated by dividing the butyl propionate NOAEL by the total systemic exposure for amyl valerate, 2071/0.032 or 64719.

Additional References:

None.

Literature Search and Risk Assessment Completed On: 06/03/19.

11.1.3. Reproductive toxicity

The MOE for amyl valerate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no developmental toxicity data on amyl valerate. Read-across material butyl propionate (CAS # 590-01-2; see Section VI) has sufficient developmental toxicity data that can be used to support the developmental toxicity endpoint.

A GLP and EPA OTS 798.4900 guideline prenatal developmental toxicity study was conducted in pregnant female Sprague Dawley rats. Groups of 24 rats were exposed to butyl propionate via whole-body inhalation at concentrations of 0, 500, 1000, or 2000 ppm (mean analytical concentrations were 0, 495, 1011, and 2000 ppm, equivalent to 0, 698, 1425, and 2819 mg/kg/day using standard minute volume and body weights for female Sprague Dawley rats) for 6 h/day on gestation days (GDs) 6–15. Dams were euthanized on GD 20. Clinical signs of toxicity included slightly drooping eyelids and salivation among the mid- and high-dose group dams, in a dose-dependent manner. Body weights were significantly reduced in all treatment groups when compared to controls during GDs 7–20. The mean gravid uterine weight was not affected by the treatment. No treatment-related abnormalities were reported in any of the gestational and developmental parameters. There were statistically significant increases in the incidence of reduced ossification of the thirteenth ribs in all treatment groups and unossified sternebrae number 5 and/or 6 in the 1000 ppm litters; however, these skeletal variations were within the historical control data and were not considered biologically relevant. No teratogenic or embryotoxic effects were observed at any dose level. The NOAEL for maternal toxicity could not be established due to treatment-related effects on body weight and feed consumption in all dose groups. Therefore, the LOAEL for maternal toxicity was considered to be 495 ppm or 698 mg/kg/day. The NOAEL for developmental toxicity was considered to be 2000 ppm or 2819 mg/kg/day, the highest dose tested (Banton et al., 2000; Ulrich et al., 2000; data also available in ECHA, 2018).

In another GLP-compliant developmental toxicity study conducted in pregnant female Sprague Dawley rats, groups of 12 rats were exposed to butyl propionate via whole-body inhalation at concentrations of 0, 250, 500, 2500, or 4000 ppm (equivalent to 0, 352, 705, 3523, and 5638 mg/kg/day, using standard minute volume and body weights for female Sprague Dawley rats) for 6 h/day on GDs 6–15. All animals were euthanized on GD 20, and necropsy was performed. There was no treatment-related mortality reported throughout the study. Treatment-related clinical signs of toxicity reported in the 2500 and 4000 ppm groups included drooping eyelids and salivation during exposure and red or brown material or staining around the nose and/or mouth 1 h following exposure. There were decreases in gravid uterine weights, body weights, and bodyweight gains in the 2500 and 4000 ppm dose groups (statistical significance not reported). No treatment-related changes were reported in any of the developmental parameters evaluated. The NOAEL for maternal toxicity was considered to be 500 ppm or 705 mg/kg/day, based on observed clinical signs of toxicity and decreased body weight and feed consumption at ≥ 2500 ppm. There was a decrease in the gravid uterine weights among the 2500 and 4000 ppm dose groups; however, intrauterine survival was not affected by exposure to n-butyl propionate in any of the treatment groups, and gestational and litters parameters (post-implantation loss, live litter size, numbers of corpora lutea, and implantation sites) were comparable to the control values. Therefore, the NOAEL for developmental toxicity was considered to be 2500 ppm or 5638 mg/kg/day, the highest dose tested (EPA HPVIS: Propanoic acid butyl ester).

Since both developmental toxicity studies considered the NOAEL to be the highest dose tested, the NOAEL of 5638 mg/kg/day was selected for the developmental toxicity endpoint. **Therefore, the amyl valerate MOE for the developmental toxicity endpoint can be calculated by dividing the butyl propionate NOAEL in mg/kg/day by the total systemic exposure to amyl valerate, 5638/0.032, or 176188.**

There are no fertility data on amyl valerate. Read-across material butyl acetate (CAS # 123-86-4; see Section VI) has sufficient data that can be used to support the fertility endpoint. An OECD 416/GLP 2-generation reproduction toxicity study was conducted in Sprague Dawley rats. Groups of 30 rats/sex/dose were exposed via whole-body inhalation to butyl acetate at concentrations of 0, 750, 1500, or 2000 ppm (equivalent to 0, 833, 1667, or 2222 mg/kg/day, respectively, using standard minute volume and body weight of Sprague Dawley rats for chronic exposure) for 6 h/day, 7 days/week. All F0 and F1 animals were exposed for at least 70 days prior to mating. Exposure of F0 and F1 males continued throughout mating and up to the day prior to euthanasia. F0 and F1 females were exposed throughout gestation until day 20 and from lactation day (LD) 5 to the day prior to euthanasia. From gestation day (GD) 21 through LD 4, F0 and F1 females were treated via oral gavage at doses of 0 (control: deionized water), 1125, 2250, or 3000 mg/kg/day. Inhalation exposure for F1 and F2 rats was initiated on postnatal day (PND) 22 and continued up to 2–3 weeks. No treatment-related mortalities or clinical signs of toxicity were reported in F0, F1, or F2 generations at any dose level. A significant decrease in bodyweight gain was reported in the mid- and high-dose groups in all generations throughout treatment in males except F2 males. A significant decrease in bodyweight gain was reported in females in the mid- and high-dose groups in all generations throughout treatment except F0 females during gestation. The decreased body weights were accompanied by significant decreases in feed consumption in the mid- and high-dose groups for all generations in both sexes throughout treatment, except for F0 females and F1 males, which showed an occasional significant decrease in feed consumption during lactation (F0 females) and throughout treatment (F1 males). No treatment-related changes were reported in the reproductive parameters (estrous cycle evaluation, sperm analysis, gestation length, the process of parturition, and necropsy) in both males and females of the F0 and F1 generations at any dose level. No treatment-related changes were reported in litter parameters (number of pups born, live litter size, sex ratio, and postnatal survival) for both F1 and F2 generations at any

Table 1
13-week toxicity study in Sprague Dawley rats.

Duration in detail	GLP/Guideline	No. of animals/dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
13 weeks, (6 h/day)	Non-GLP and non-guideline	Male Sprague Dawley rats (15/group)	Inhalation	0, 500, 1500, or 3000 ppm (equivalent to 616, 1848, and 3696 mg/kg/day, as per standard minute volume and bodyweight parameters for Sprague Dawley rats; US EPA, 1998)	Male fertility NOAEL = 3696 mg/kg/day	No reproductive effects (weight of testis, sperm count, number and concentration of testicular spermatids and epididymal spermatozoa) observed up to the highest tested dose	David et al., 2001

dose level. No treatment-related mortalities or clinical signs of toxicity were reported in F1 and F2 pups at any dose level. A significant decrease in pup body weight was reported in the mid- and high-dose groups of both F1 and F2 litters, except F2 male litters, which reflected decreased pup body weight only at 2000 ppm. No treatment-related changes in the sexual maturation were reported in F1 and F2 generations in both sexes at any dose level. However, the average age of attainment of balanopreputial separation in F1 and F2 high-dose males was slightly higher than the controls. The average age of attainment of vaginal patency was slightly higher in the F2 high-dose females; this was attributed to the secondary effects of decreased body weights of their respective high-dose dams. No treatment-related changes were reported in the necropsy and developmental landmarks in both F1 and F2 generations at any dose level. Thus, the NOAEL for fertility effects was considered to be 2000 ppm or 2222 mg/kg/day, the highest dose tested (ECHA, 2011).

Butyl acetate did not induce any male or female fertility effects up to the highest tested dose of 2222 mg/kg/day in the 2-generation reproductive toxicity study (ECHA, 2011) and up to 3696 mg/kg/day in a 13-week toxicity study for males (David et al., 2001; see Table 1 for details). The most conservative NOAEL for fertility was considered to be 2222 mg/kg/day. **Therefore, the amyl valerate MOE for the fertility endpoint can be calculated by dividing the butyl acetate NOAEL in mg/kg/day by the total systemic exposure to amyl valerate, 2222/0.032, or 69438.**

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/12/19.

11.1.4. Skin sensitization

Based on the existing data, amyl valerate does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, amyl valerate is not considered a skin sensitizer under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), amyl valerate was found to be not sensitizing when tested up to 100% (ECHA, 2018).

Based on the weight of evidence (WoE) from structural analysis and animal and human studies, amyl valerate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References:

None.

Literature Search and Risk Assessment Completed On:

06/13/19.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for amyl valerate 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 (Henry et al., 2009). Based on the lack of absorbance, amyl valerate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References:

None.

Literature Search and Risk Assessment Completed On:
05/10/19.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on amyl valerate. Based on the Creme RIFM Model, the inhalation exposure is 0.16 mg/day. This exposure is 8.75 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References:

None.

Literature Search and Risk Assessment Completed On:
05/15/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of amyl valerate was performed following the RIFM Environmental Framework (Salvito et al., 2002), 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 (EPI Suite v4.11), 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 (Table 2). 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, amyl valerate 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) (see Table 3).

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

Table 3
Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{OW} used	3.81	3.81
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	Not reported
Risk Characterization: PEC/PNEC	**< 1**	**NA**

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

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), amyl valerate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.2. Other available data

Amyl valerate has been registered for REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

The RIFM PNEC is 0.00619 μg/L. The revised PEC/PNECs for EU and NA (No VoU) are: not applicable. The material was 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:
06/14/19.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS

Table 2
Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L); endpoints used to calculate PNEC are underlined.

	(mg/L)	(*Daphnia*) (mg/L)	(Algae) (mg/L)			
RIFM Framework Screening-level **(Tier 1)**	<u>6.19</u>			1,000,000	0.00619	

- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/22/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111335.

Appendix

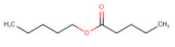
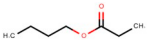
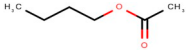
Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as 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 Chemicals 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, 2012b).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

Table 4
Physical-chemical properties of the target material and read-across analogs

	Target Material	Read-across Material	Read-across Material
Principal Name	Amyl valerate	Butyl propionate	Butyl acetate
CAS No.	2173-56-0	590-01-2	123-86-4
Structure			
Similarity (Tanimoto Score)		0.82	0.71
Endpoint		• Reproductive toxicity • Repeated dose toxicity	• Reproductive toxicity
Molecular Formula	$C_8H_{16}O_2$	$C_7H_{14}O_2$	$C_6H_{12}O_2$
Molecular Weight	144.214	130.187	116.16
Melting Point (°C, EPI Suite)	−70.70	−89.00	−78.00
Boiling Point (°C, EPI Suite)	167.50	146.80	126.10
Vapor Pressure (Pa @ 25 °C, EPI Suite)	2.41E+02	5.89E+02	1.53E+03
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	5.00E+02	1.50E+03	8.40E+03
Log KOW	2.83	2.34	1.78
J_{max} (mg/cm^2/h, SAM)	39.24	85.94	301.12
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	6.96E+01	5.12E+01	2.85E+01
Repeated Dose Toxicity			
Repeated Dose (HESS)	Valproic acid (Hepatotoxicity) Alert	Not categorized	
Reproductive and Developmental Toxicity			

(*continued on next page*)

Table 4 (*continued*)

	Target Material	Read-across Material	Read-across Material
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)	Non-toxicant (low reliability)
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on amyl valerate (CAS # 2173-56-0). Hence, the *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, butyl acetate (CAS # 123-86-4) and butyl propionate (CAS # 590-01-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

- Butyl propionate (CAS # 590-01-2) was used as a read-across analog for the target material amyl valerate (CAS # 2173-56-0) for the repeated dose toxicity and the reproductive toxicity endpoints.
  - The target substance and the read-across analog are structurally similar and belong to a class of aliphatic esters.
  - The target substance and the read-across analog are ethyl esters.
  - The key difference between the target substance and the read-across analog is that the target is a valerate ester of amyl alcohol while the read-across analog is a propionate ester of Butenol. This structural difference is toxicologically insignificant.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance has a repeated dose toxicity alert of Sodium Valproate and Valproic acid renal toxicity. This alert is due to more than 50% structural similarity via the Dice score. The reactive moieties of C2 to C4 branched alkyl chain in Valproic acid is not present in the target substance. Therefore, the target substance is out of the structural domain of the model. The data described in the repeated dose section confirm that the margin of exposure for the read-across analog is adequate at the current level of use. Therefore, the alert is superseded by the data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Butyl acetate (CAS # 123-86-4) was used as a read-across analog for the target material amyl valerate (CAS # 2173-56-0) for the reproductive toxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to a class of aliphatic esters.
  - The target substance and the read-across analog share an ester functionality.
  - The key difference between the target substance and the read-across analog is that the target is a valerate ester of amyl alcohol, whereas the read-across analog acetate ester of butenol. This structural difference is toxicologically insignificant.
  - The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - There are no toxicological alerts for the read-across analog or the target substance. Data are consistent with *in silico* alerts.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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