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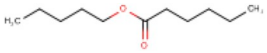
Short Review

RIFM fragrance ingredient safety assessment, amyl hexanoate, CAS Registry Number 540-07-8

A.M. Api[a], F. Belmonte[a], D. Belsito[b], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], A.D. Fryer[h], S. Gadhia[a], L. Jones[a], K. Joshi[a], S. La Cava[a], A. Lapczynski[a], M. Lavelle[a], D.C. Liebler[i], M. Na[a], D. O'Brien[a], T.M. Penning[j], G. Ritacco[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP, 05508-900, Brazil*
[g] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

Version: 091218. This version replaces any previous versions.



Name: Amyl hexanoate
CAS Registry Number: 540-07-8
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., 2015a, 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
NA - North America

* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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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
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 hexanoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog ethyl hexanoate (CAS # 123-66-0) show that amyl hexanoate is not expected to be genotoxic. Data from read-across analog ethyl hexanoate (CAS # 123-66-0) provide a calculated MOE > 100 for the repeated dose and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; amyl hexanoate 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 hexanoate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; amyl hexanoate 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 expected to be genotoxic.	(RIFM, 2015b; RIFM, 2016)
Repeated Dose Toxicity: NOAEL = 333 mg/kg/day.	RIFM (2017a)
Reproductive Toxicity: NOAEL = 1000 mg/kg/day.	RIFM (2017a)
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.	
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: 3.5 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012)
Bioaccumulation: Screening-level: 13.52 L/kg	(EPI Suite v4.11; US EPA, 2012)
Ecotoxicity: Screening-level: Fish LC50: 2.51 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 2.51 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00251 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Amyl hexanoate
2. **CAS Registry Number:** 540-07-8
3. **Synonyms:** Amyl caproate; Amyl capronate; Hexanoic acid, pentyl ester; Pentyl caproate; Pentyl hexanoate; ｱﾙｶﾝ酸(C = 6 ~ 10)ｱﾙｷﾙ(C = 1 ~ 10); n-Amyl caproate; Amyl hexanoate
4. **Molecular Formula:** $C_{11}H_{22}O_2$
5. **Molecular Weight:** 186.3
6. **RIFM Number:** 1100
7. **Stereochemistry:** No isomeric center present and no isomers possible.

2. Physical data

1. **Boiling Point:** 229.67 °C (EPI Suite)
2. **Flash Point:** 88 °C (GHS)
3. **Log K_{ow}:** 4.3 (EPI Suite)
4. **Melting Point**: 1.67 °C (EPI Suite)
5. **Water Solubility:** 10.87 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0636 mm Hg @ 20 °C (EPI Suite v4.0), 0.0972 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:** Colorless liquid with pungent fruity odor.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 0.1–1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0045% (RIFM, 2017b)
3. **Inhalation Exposure*:** 0.0000064 mg/kg/day or 0.00048 mg/day (RIFM, 2017b)
4. **Total Systemic Exposure**:** 0.00016 mg/kg/day (RIFM, 2017b)

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

4. Derivation of systemic absorption

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

5. 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:** Ethyl hexanoate (CAS # 123-66-0)
   b. **Repeated Dose Toxicity:** Ethyl hexanoate (CAS # 123-66-0)
   c. **Reproductive Toxicity:** Ethyl hexanoate (CAS # 123-66-0)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. **Read-across Justification**: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References: None.

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

Amyl hexanoate is reported to occur in the following foods by the VCF*:

Apple fresh (*Malus* species).
Apple processed (*Malus* species).
Apricot (*Prunus armeniaca* L.)
Beer.
Blue cheeses.
Capsicum species.
Chinese liquor (baijiu).
Chinese quince (*Pseudocydonia sinensis* Schneid).
Cider (apple wine).
Grape (*Vitis* species).
Melon.
Mushroom.
Passion fruit (*Passiflora* species).
Peach (*Prunus persica* L.)
Plum (*Prunus species*).
Soybean (*Glycine max*. L. Merr.)
Strawberry (*Fragaria* 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 containing information on published volatile compounds that 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 2010; no dossier available as of 09/12/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Amyl hexanoate 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, 2014). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects on the target material. There are no studies assessing the mutagenic activity of amyl hexanoate; however, read-across can be made to ethyl hexanoate (CAS # 123-66-0; see Section V).

The mutagenic activity of ethyl hexanoate 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 *Escherichia coli* WP2uvrA were treated with ethyl hexanoate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2015b). Under the conditions of the

study, ethyl hexanoate was not mutagenic in the Ames test.

The clastogenic activity of ethyl hexanoate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with ethyl hexanoate in DMSO at concentrations up to 824 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 20 h. Ethyl hexanoate did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2016). Under the conditions of the study, ethyl hexanoate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, ethyl hexanoate does not present a concern for genotoxic potential, and this can be extended to amyl hexanoate.

Additional References: RIFM, 2015a.

Literature Search and Risk Assessment Completed On: 05/17/18.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on amyl hexanoate. Read-across material ethyl hexanoate (CAS # 123-66-0; see Section V) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. An OECD 422/GLP combined repeated dose toxicity with reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered test material ethyl hexanoate (ethyl caproate) at doses of 0, 100, 300, or 1000 mg/kg/day via oral gavage. Males were dosed for at least 50 days (2 weeks prior to mating and continued through the day before euthanasia), while females were dosed for 2 weeks prior to mating and continued through lactation day (LD) 13. Additional animals (6 rats/sex/group) in the control and high-dose recovery groups received ethyl caproate but were not mated; they were assigned to a 2-week period of recovery. One female in the control group was euthanized on LD 3 because all pups were found expired. This was considered to be incidental since it was observed in the control group and there were no clinical signs of toxicity. At 1000 mg/kg/day, statistically significant increased prothrombin time in both sexes and statistically significant increased kidney weights in females were observed. Furthermore, statistically significant decreases in gamma glutamyl transpeptidase was observed in all treatment group males. A statistically significant increase in thyroid hormone (T4) was observed in adult males and pups of the highest dose group. Since there were no correlated microscopic findings associated with any of the alterations observed in the highest dose group, these findings were not considered to be toxicologically relevant. Reversibility was also observed in the high-dose animals after the recovery period. Thus, the NOAEL for systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2017a; ECHA, 2017).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the amyl hexanoate MOE for the repeated dose toxicity endpoint can be calculated by dividing the ethyl hexanoate NOAEL in mg/kg/day by the total systemic exposure to amyl hexanoate, 333/0.00016 or 2081250.

In addition, the total systemic exposure to amyl hexanoate (0.16 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.

The RIFM Criteria Document (Api et al., 2015) calls for a default margin of exposure of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The RfD for amyl hexanoate was calculated by dividing the NOAEL of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 mg/kg/day.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/13/18.

10.1.3. Reproductive toxicity

The margin of exposure for amyl hexanoate is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on amyl hexanoate. Read-across material ethyl hexanoate (CAS # 123-66-0; see Section V) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. An OECD 422/GLP combined repeated dose toxicity with reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered test material ethyl hexanoate (ethyl caproate) at doses of 0, 100, 300, or 1000 mg/kg/day via oral gavage. Males were dosed for at least 50 days (2 weeks prior to mating and continued through the day before euthanasia), while females were dosed for 2 weeks prior to mating and continued through LD 13. Additional animals (6 rats/sex/group) in the control and high-dose recovery groups received ethyl caproate but were not mated; they were assigned to a 2-week recovery period. In addition to systemic toxicity parameters, the reproductive toxicity parameters were also assessed. One female in the control group was euthanized on LD 3 because all pups were found expired. This was considered to be incidental since it was observed in the control group and there were no clinical signs of toxicity. Non-parturition was also observed in 1 female in each group of the 100, 300, and 1000 mg/kg/day dose groups, respectively; these dams were euthanized on GD 28. This was considered incidental since there were no treatment-related macroscopic or microscopic findings. A statistically significant increase in thyroid hormone (T4) was observed in adult males (1.14-fold of control) and pups (1.20-fold of control) of the highest dose group. Since there were no correlated changes in other parameters including microscopic findings in thyroids (with parathyroids), this was not considered to be toxicologically relevant. No treatment-related adverse effects were observed in estrus cycle, pre-coital time, fertility data, reproductive and littering findings, clinical signs, body weight, anogenital distance, nipple retention, or external examination of pups. The NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (RIFM, 2017a; ECHA, 2017). Therefore, the amyl hexanoate MOE for the reproductive toxicity endpoint can be calculated by dividing the ethyl hexanoate NOAEL in mg/kg/day by the total systemic exposure to amyl hexanoate, 1000/0.00016 or 6250000.

In addition, the total systemic exposure to amyl hexanoate (0.16 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/13/18.

10.1.4. Skin sensitization

Based on existing data and the application of DST, amyl hexanoate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for amyl hexanoate. However, in a human maximization test, no skin sensitization reactions

Table 1
Maximum acceptable concentration for Amyl hexanoate that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.07%	0.00%[b]
2	Products applied to the axillae	0.02%	0.00%[b]
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.00%[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%[b]
6	Products with oral and lip exposure	0.23%	0.00%[b]
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.01%
10	Household care products with mostly hand contact	2.70%	0.00%[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.04%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

were observed (RIFM, 1980). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Safford et al., 2015b; Roberts et al., 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for amyl hexanoate that present no appreciable risk for skin sensitization based on the non-reactive DST. These concentrations are not limits; they represent acceptable concentrations based on the DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/22/18.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, amyl hexanoate 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 amyl hexanoate 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 lack of absorbance, amyl hexanoate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. 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} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/11/18.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on ethyl decanoate. Based on the Creme RIFM Model, the inhalation exposure is 0.00048 mg/day. This exposure is 2917 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: 08/03/18.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of amyl hexanoate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{ow}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (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. 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 hexanoate 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 did not identify amyl hexanoate 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). 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).

10.2.2. Risk assessment

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

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data

Amyl hexanoate has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.51			1,000,000	0.00251	

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.3	4.3
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.

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

The RIFM PNEC is 0.00251 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the 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: 4/12/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- 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. The links listed above were active as of 08/27/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110621.

Appendix

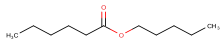
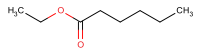
Read-across Justification

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 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, 2012).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Amyl hexanoate	Ethyl hexanoate
CAS No.	540-07-8	123-66-0
Structure		
Similarity (Tanimoto Score)		0.82
Read-across Endpoint		• Genotoxicity • Repeated dose • Reproductive
Molecular Formula	$C_{11}H_{11}O_2$	$C_8H_{16}O_2$
Molecular Weight	186.3	144.21
Melting Point (°C, EPI Suite)	1.67	−32.64
Boiling Point (°C, EPI Suite)	229.67	170.05
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.06	240
Log Kow (KOWWIN v1.68 in EPI Suite)	4.3	2.83
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	8.8	629
J_{max} (μg/cm^2/h, SAM)	1.2	36.394
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.7E-003	7.33E+001
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found
Carcinogenicity (ISS)	Non-carcinogen (low reliability)	Non-carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
In Vitro Mutagenicity (Ames, ISS)	No alert found	No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	No alert found	No alert found
Oncologic Classification	Not classified	Not classified
Repeated dose (HESS)	Not categorized	Urethane (Renal toxicity) Alert
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Toxicant (good reliability)
Protein Binding (OASIS v1.1)	No alert found	
Protein binding (OECD)	No alert found	
Protein Binding Potency	Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No alert found	
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on amyl hexanoate (CAS # 540-07-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, ethyl hexanoate (CAS # 123-66-0) was identified as a read-across material with sufficient data for toxicological evaluation.

14. Conclusions

- Ethyl hexanoate (CAS # 123-66-0) was used as a read-across analog for the target material amyl hexanoate (CAS # 540-07-8) for the genotoxicity, repeated dose, and reproductive toxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to a class of saturated aliphatic esters.
  - o The key difference between the target substance and the read-across analog is that the target is a hexonate amyl ester while the read-across analog is a hexanoate ethyl ester. This structural difference is toxicologically insignificant.

- o 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.
- 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 OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- o The target substance and the read-across analog do not have alerts for toxicity. Data are consistent with *in silico* alerts.
- o The read-across material presents an alert because of its structural similarity with urethanes. However, the read-across material does not have a urethane group. Data superseded predictions in this case.
- o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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