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Short review

RIFM fragrance ingredient safety assessment, isoamyl hexanoate, CAS Registry Number 2198-61-0

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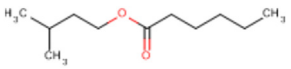

Name: Isoamyl hexanoate
CAS Registry Number: 2198-61-0

Abbreviation 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) compared to a deterministic aggregate approach.
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold

(*continued on next page*)

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(*continued*)

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
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
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* 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 reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

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

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

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analogues isoamyl butyrate (CAS # 106-27-4), isoamyl alcohol (CAS # 123-51-3) and hexanoic acid (CAS # 142-62-1) show that this material is not genotoxic. Data show that this material is below the non-reactive DST for the skin sensitization endpoint. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose, developmental and reproductive toxicity endpoint was completed using isoamyl alcohol (CAS# 123-51-3) and hexanoic acid (CAS# 142-62-1) as suitable read across analogues, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic (RIFM, 2015; Ishidate et al., 1984; RIFM, 2007)
Repeated Dose Toxicity: NOAEL = 1250 mg/kg/day (Schilling et al., 1997)
Developmental and Reproductive Toxicity: NOAEL = 300 mg/kg/day (ECHA REACH Dossier: 3-Methylbutan-1-ol)
Skin Sensitization: Not a sensitization concern. Exposure is below DST
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening Level: 3.2 (Biowin 3) (EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 284 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 2.884 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: 2.8884 mg/l (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.002884 μg/L

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

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1. Identification

1 **Chemical Name:** Isoamyl hexanoate
2 **CAS Registry Number:** 2198-61-0
3 .**Synonyms**: Hexanoic acid, 3-methylbutyl ester; Isoamyl caproate; Isoamyl hexanoate; Isopentyl caproate; Isopentyl hexanoate; 3-Methylbutyl hexanoate; アルカン酸(C = 6 ~ 10)アルキル(C = 1 ~ 10)
4 **Molecular Formula:** $C_{11}H_{22}O_2$
5 **Molecular Weight:** 186.3
6 **RIFM Number:** 805

2. Physical data

1 **Boiling Point**: 222 °C [FMA database], 218.34 °C [EPI Suite]
2 **Flash Point**: 190 °F; CC [FMA database], 88 °C [GHS]
3 **Log K_{OW}**: 4.23 [EPI Suite]
4 **Melting Point**: −9.14 °C [EPI Suite]
5 **Water Solubility:** 12.56 mg/L [EPI Suite]
6 **Specific Gravity**: 0.865 [FMA database], 0.8611 [RIFM database]
7 **Vapor Pressure**: 0.0646 mmHg @ 20 °C [EPI Suite 4.0], 0.06 mm Hg @ 20 °C [FMA database], 0.0987 mm Hg @ 25 °C [EPI Suite]
8 **UV Spectra:** No significant absorbance between 290 and 700 nm; molar extinction coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9 **Appearance/Organoleptic:** A colorless clear liquid with a medium fruity, banana, apple, pineapple, green odor. The odor is also described as pungent, sour and cheesy. The taste is described as fruity, green, pineapple and waxy.** http://www.thegoodscentscompany.com/data/rw1019751.html#toorgano, retrieved 4/8/2016

3. Exposure

1 Volume of Use (worldwide band): 1–10 metric tons per year (IFRA, 2011)
2 95th Percentile Concentration in Hydroalcoholics: 0.0177% (RIFM, 2016)
3 Inhalation Exposure*: 0.000091 mg/kg/day or 0.0070 mg/day (RIFM, 2016)
4 Total Systemic Exposure**: 0.00072 mg/kg/day (RIFM, 2016)

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

**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; and Safford et al., 2015).

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 Analogues Selected:
a **Genotoxicity:** isoamyl butyrate (CAS # 106-27-4); isoamyl alcohol (CAS# 123-51-3); hexanoic acid (CAS# 142-62-1)
b **Repeated Dose Toxicity:** isoamyl alcohol (CAS# 123-51-3); hexanoic acid (CAS# 142-62-1)
c **Developmental and Reproductive Toxicity:** isoamyl alcohol (CAS# 123-51-3); hexanoic acid (CAS# 142-62-1)
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

See Appendix below.

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

Isoamyl hexanoate is reported to occur in the following foods*:
Apple brandy (Calvados).
Apple fresh (Malus species).
Apricot (Prunus armeniaca L.)
Artocarpus species.
Banana (Musa sapientum L.)
Beer.
Bilberry wine.
Blue cheeses.
Cheese, various types.
Cherimoya (Annona cherimolia Mill.)
Cider (apple wine).
Citrus fruits.
Grape (Vitis species).
Grape brandy.
Guava and Feyoa
Litchi wine.
Mangifera species.
Mastic (Pistacia lentiscus).
Passion fruit (passiflora species).
Pear brandy.
Pineapple (Ananas comosus).
Plum (Prunus species).
Plum brandy.
Pomegranate wine (Punica granatum L.)
Rum.
Sea buckthorn (Hippophaë rhamnoides L.)
Sherry.
Strawberry (Fragaria species).
Strawberry wine.
Whisky.
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, contains information on published volatile

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compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010, no dossier available as of 1/30/2017

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, isoamyl hexanoate does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Isoamyl hexanoate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013). There are no studies assessing the mutagenic/clastogenic activity of isoamyl hexanoate however, read across can be made to isoamyl butyrate (CAS # 106-27-4; see Section 5). The mutagenic activity of isoamyl butyrate (CAS # 106-27-4) 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/pre-incubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and *Escherichia coli* strain WP2uvrA were treated with isoamyl butyrate in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2015). Under the conditions of the study, isoamyl butyrate was not mutagenic in the Ames test.

The clastogenicity of isoamyl butyrate was assessed in an *in vitro* chromosome aberration study. Chinese hamster lung cells were treated with isoamyl butyrate in DMSO at concentrations up to 2 mg/mL in the absence of exogenous metabolic activation. No significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, without S9 metabolic activation (Ishidate et al., 1984). Under the conditions of the study, isoamyl butyrate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Due to lack of additional clastogenicity data in the presence of metabolic activation, read across can be made while considering isoamyl hexanoate will readily hydrolyze into isoamyl alcohol (CAS# 123-51-3; see section 5) and hexanoic acid (CAS# 142-62-1; see section 5). Metabolite, isoamyl alcohol (CAS# 123-51-3; see section 5) has sufficient genotoxicity data. The clastogenic activity of isoamyl alcohol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral gavage, to groups of male and female NMRI mice (5/sex/dose). Doses of 500, 1000, and 2000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2007). Hexanoic acid (CAS# 142-62-1) also gave a negative result in Unscheduled DNA synthesis (UDS) assay (Heck et al., 1989). Under the conditions of the study, isoamyl alcohol and hexanoic acid were considered to be non-clastogenic in the *in vivo* micronucleus test, which can be extended to isoamyl hexanoate based on metabolism.

Based on the data available, isoamyl butyrate, isoamyl alcohol and hexanoic acid do not present a concern for genotoxic potential and this can be extended to isoamyl hexanoate.

Additional References: Kuroda et al., 1984.

Literature Search and Risk Assessment Completed on: 06/24/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for isoamyl hexanoate 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 isoamyl hexanoate. Isoamyl hexanoate will hydrolyze readily into isoamyl alcohol (CAS# 123-51-3; see section 5) and hexanoic acid (CAS# 142-62-1; see section 5). Metabolite, isoamyl alcohol (CAS# 123-51-3; see section 5) has sufficient repeated dose toxicity data. An OECD 422 combined repeated dose reproduction/developmental toxicity screening test was conducted on groups of 12 male and female Sprague-Dawley rats/group administered test material, isoamyl alcohol, via gavage at doses of 0, 30, 100 and 300 mg/kg/day; an additional satellite recovery group of 5 animals/sex/group was administered test material at doses of 0 and 300 mg/kg/day. The NOAEL was determined to be 100 mg/kg/day, based on reduced body weight gain in males (ECHA REACH Dossier: 3-methylbutan-1-ol, accessed 07/09/14). In another study, an OECD/GLP 408 study (90 day treatment) was conducted on a group of 10 SPF-Wistar, Chbb:THOM rats/sex/group administered test material, isoamyl alcohol, via drinking water at concentrations of 0, 1000 ppm (about 80 mg/kg/day), 4000 ppm (about 340 mg/kg/day) & 16,000 ppm (about 1250 mg/kg/day). Although there were slight alterations in the hematological parameters, the NOAEL was determined to be 1600 ppm or 1250 mg/kg/day, the highest dose tested, since the effects were not considered to be treatment related (Schilling et al., 1997; data available in RIFM, 1991). In another study, a group of 15 rats/sex/group were gavaged with test material, isoamyl alcohol, at doses of 0, 150, 500 and 1000 mg/kg/day for 17 weeks. There were no adverse effects reported due to the test material administration up to the highest dose tested. Thus the NOAEL was determined to be 1000 mg/kg/day (Carpanini et al., 1973). There is limited repeated dose toxicity data on hexanoic acid to support the repeated dose toxicity endpoint for isoamyl hexanoate. Since no adverse effects were reported among the animals during the 13 and 17 week studies, the NOAEL was determined to be 1250 mg/kg/day. **Therefore, the MOE is equal to the isoamyl alcohol NOAEL divided by the total systemic exposure, 1250/0.00072 or 1736111.**

In addition, the total systemic exposure for isoamyl hexanoate (0.72 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

Additional References: ECHA REACH Dossier: 3-methylbutan-1-ol; RIFM, 1992

Literature Search and Risk Assessment Completed on: 6/23/2016.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for isoamyl hexanoate is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on isoamyl hexanoate. Isoamyl hexanoate will hydrolyze readily into isoamyl alcohol (CAS# 123-51-3; see section 5) and hexanoic acid (CAS# 142-62-1; see section 5). Metabolite, isoamyl alcohol

(CAS# 123-51-3; see section 5) has sufficient developmental toxicity data. There is an OECD 414 developmental toxicity study conducted on 15 female pregnant Himalayan rabbits/dose group administered test material, isoamyl alcohol via inhalation at doses of 0, 0.5, 2.5 and 10 mg/l equivalent to 0, 68, 341 and 1365 mg/kg/day, respectively according to standard minute volume and body weight parameters of New Zealand rabbits. The NOAEL for developmental toxicity was determined to be 10 mg/l or 1365 mg/kg/day, the highest dose tested (RIFM, 1990a; data also available on available in ECHA REACH dossier on 3-methylbutan-1-ol). In another study, an OECD 414 developmental toxicity study was conducted on a group of 25 female pregnant Wistar rats/group administered test material, isoamyl alcohol, at doses of 0, 0.5, 2.5 and 10 mg/l, equivalent to 0, 135, 674 and 2695 mg/kg/day according to standard minute volume and body weight parameters of Wistar rats. The NOAEL for developmental toxicity was determined to be 10 mg/l or 2695 mg/kg/day the highest dose tested (RIFM, 1990b; data also available on available in ECHA REACH dossier on 3-methylbutan-1-ol). Subsequently an OECD 422 gavage combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test was conducted on a group of 12 Sprague-Dawley rats/sex/group administered test material, isoamyl alcohol at doses of 0, 30, 100 and 300 mg/kg/day. There were no signs of toxicity towards the development of the fetus up to the highest dose tested (ECHA REACH Dossier: 3-methylbutan-1-ol). Thus the NOAEL was determined to be 300 mg/kg/day the highest dose tested. There is limited developmental toxicity data on metabolite hexanoic acid to support the developmental toxicity endpoint for isoamyl hexanoate. The most conservative NOAEL of 300 mg/kg/day was selected for the developmental toxicity endpoint.

There are no reproductive toxicity data on isoamyl hexanoate. Isoamyl hexanoate will hydrolyze readily into isoamyl alcohol (CAS# 123-51-3; see section 5) and hexanoic acid (CAS# 142-62-1; see section 5). Metabolite, isoamyl alcohol (CAS# 123-51-3; see section 5) has sufficient reproductive toxicity data. An OECD 422 gavage combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test was conducted on a group of 12 Sprague-Dawley rats/sex/group administered test material, isoamyl alcohol at doses of 0, 30, 100 and 300 mg/kg/day. There were no signs of toxicity towards the reproductive performance of the parental generation animals up to the highest dose tested (ECHA REACH Dossier: 3-methylbutan-1-ol). There is limited reproductive toxicity data on metabolite hexanoic acid to support the reproductive toxicity endpoint for isoamyl hexanoate. The NOAEL for reproductive toxicity was determined to be 300 mg/kg/day the highest dose tested.

Therefore, the MOE for the developmental and reproductive toxicity endpoint is equal to the isoamyl alcohol NOAEL divided by the total systemic exposure, 300/0.00072 or 416667.

In addition, the total systemic exposure for isoamyl hexanoate (0.72 μg/kg bw/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the developmental and reproductive toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed on: 6/23/2016.

10.1.4. Skin sensitization

Based on the existing data and application of DST, isoamyl hexanoate does not present a concern for skin sensitization.

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 2.6.6; OECD toolbox v3.3). No predictive skin sensitization studies are available for isoamyl hexanoate. However, in a confirmatory human maximization test on 33 subjects, no skin sensitization reactions were observed with 2% isoamyl hexanoate (1380 μg/cm^2; RIFM, 1976). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2. The current dermal exposure from hydroalcoholic products, 0.0177%, is below the DST for non-reactive materials when evaluated in QRA categories 3 and 4 (DST levels of 0.14% and 0.41%, respectively). Isoamyl hexanoate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/11/16.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, isoamyl 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 isoamyl hexanoate in experimental models. UV/Vis absorption spectra indicate no significant absorbance 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, isoamyl hexanoate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 06/30/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, isoamyl hexanoate, exposure level 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 isoamyl hexanoate. Based on the Creme RIFM model, the inhalation exposure is 0.0070 mg/day. This exposure is 200.0 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: 07/12/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of isoamyl hexanoate was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety

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Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, isoamyl 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 EPISUITE ver 4.1 did not identify isoamyl hexanoate as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

10.2.2. Risk assessment

Based on current Volume of Use (2011), isoamyl hexanoate does not present a 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. Isoamyl 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)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	2.884 mg/L			1,000,000	0.002884 μg/L	

Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002; #40315).

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	4.23	4.23
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

The RIFM PNEC is 0.002884 μg/L. The revised PEC/PNECs for EU and NA: Not Applicable; cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 6/20/2016.

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://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid%3d0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS**http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary**http://cfpub.epa.gov/hpv-s/
- **Japanese NITE**http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base**http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google**https://www.google.com/webhp?tab%3dww%26ei%3dKMSoUpiQK-arsQS324GwBg%26ved%3d0CBQQ1S4

*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.2017.03.040.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.03.040.

Appendix

Methods

- The identified read-across analogues were confirmed by using expert judgment.

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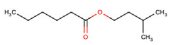
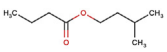
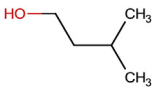
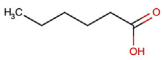
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of target and analogues were calculated using EPI SuiteTM v4.11 developed by US EPA (USEPA, 2012).
- Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogues were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

	Target material	Read across material		
Principal Name	Isoamyl hexanoate	Isoamyl butyrate	Isoamyl alcohol	Hexanoic acid
CAS No.	2198-61-0	106-27-4	123-51-3	142-62-1
Structure				
Similarity (Tanimoto score)		0.84	N/A[a]	N/A[a]
Read across endpoint		• Genotoxicity	• Genotoxicity, • Repeated dose, • Developmental and reproductive	• Genotoxicity, • Repeated dose, Developmental and reproductive
Molecular Formula	$C_{11}H_{22}O_2$	$C_9H_{18}O_2$	$C_5H_{12}O$	$C_6H_{12}O_2$
Molecular Weight	186.30	158.24	88.15	116.16
Melting Point (°C, EPISUITE)	−9.14	−32.06	−61.49	26.23
Boiling Point (°C, EPISUITE)	218.34	178.41	123.17	207.76
Vapor Pressure (Pa @ 25 °C, EPISUITE)	13.2	135	512	37.1
Log Kow (KOWWIN v1.68 in EPI SUITE)	4.23	3.25	1.16	1.92
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	12.56	117.8	4.158e+004	5898
J_{max} (mg/cm^2/h, SAM)	1.684432	11.16992	1142.301	259.3577
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.71E+002	9.73E+001	1.34E+000	1.72E-001
Genotoxicity				
DNA binding (OASIS v 1.1 QSAR Toolbox 3.4)	• No alert found	• No alert found	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found	• No alert found	• No alert found
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found	• No alert found	• No alert found
In-vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found	• No alert found	• No alert found
In-vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified	• Not classified	• Not classified
Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	• Carboxylic acids (Hepatotoxicity) No rank
Reproductive and developmental toxicity				
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, non cyclic structure		• Non-binder, non cyclic structure	• Non-binder, non cyclic structure
Developmental Toxicity Model by CAESAR v2.1.6	• Non-Toxicant (low reliability)		• Toxicant (good reliability)	• Non-Toxicant (low reliability)
Metabolism				
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1 • 10 metabolites from Rat S9 simulator. • Aldehydes, anionic surfactants, esters, Schiff base formation	See Supplemental Data 2 • 8 metabolites from Rat S9 simulator. • Aldehydes, anionic surfactants, esters, Schiff base formation.	See Supplemental Data 3 • 8 metabolites from Rat S9 simulator. • Aldehydes, Schiff base formation.	See Supplemental Data 4 • 6 metabolites from Rat S9 simulator. Aldehydes, anionic surfactants, Schiff base formation.

[a] Metabolites of the target.

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Summary

There are insufficient toxicity data on isoamyl hexanoate (CAS # 2198-61-0). Hence *in-silico* evaluation was conducted to determine suitable read across analogues for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogues isoamyl butyrate (CAS # 106-27-4), isoamyl alcohol (CAS # 123-51-3) and hexanoic acid (CAS # 142-62-1) were identified as read across materials with data for their respective toxicity endpoints.

Conclusion/Rationale

- Metabolism
  The target substance isoamyl hexanoate (CAS # 2198-61-0) metabolically hydrolyzes to isoamyl alcohol (CAS # 123-51-3) and hexanoic acid (CAS # 142-62-1) as described under the repeated dose toxicity section. In addition, metabolism of the read across materials isoamyl alcohol and hexanoic acid were predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4; See metabolism section in the table above). Isoamyl hexanoate is predicted to be metabolized to isoamyl alcohol and hexanoic acid in the first step with 0.950 pre-calculated probability. Hence isoamyl alcohol and hexanoic acid can be use as read across for isoamyl hexanoate. Isoamyl alcohol and hexanoic acid were out of domain for the *in vivo* rat S9 simulator and out of domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgement, the model's domain exclusion was overridden and a justification is provided.
- Isoamyl butyrate (CAS # 106-27-4) could be used as structurally similar read across analogue for the target material isoamyl hexanoate (CAS # 2198-61-0) for the genotoxicity toxicological endpoint.
  - The target substance and the read across analogue are structurally similar and belong to the structural class of esters.
  - The key difference between the target substance and the read across analogue is that the target has a longer straight chain alkane on the acid portion (hexanoate) while the read across has shorter straight chain alkane on acid portion (butyrate). The differences in structure between the target substance and the read across analogue do not raise additional structural alerts so the structural differences are not relevant from a toxicological endpoint perspective.
  - The target substance and the read across analogue have a Tanimoto scores as mentioned in the above table. The Tanimoto score is mainly driven by the alkane chain fragment on the acid portion. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicological endpoint perspective.
  - The target substance and the read across analogue have similar physical chemical properties. Any differences in some of the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for the genotoxicity endpoint.
  - According to the QSAR OECD Toolbox (V3.4), structural alerts for the genotoxicity endpoint are consistent between the target substance and the read across analogue (as seen in the table above).
  - The target substance and the read across analogue are expected to be metabolized similarly as shown by the metabolism simulator.
  - The structural alerts for the genotoxicity toxicological endpoint are consistent between the metabolites of the read across analogue and the target substance.
  - The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.
- Isoamyl alcohol (CAS # 123-51-3) and hexanoic acid (CAS # 142-62-1) are used as a structurally similar read across analogues for isoamyl hexanoate (CAS # 2198-61-0) for the genetoxicity, repeated dose, developmental and reproductive toxicological endpoints.
  - The read across materials (alcohol and acid) are major metabolites of the target substance which is an ester.
  - The structural difference in the target substance and the read across analogues can be mitigated by the fact that the target could be metabolically hydrolyzed to the read across analogues. Therefore the toxicity profile of the target is expected to be that of the metabolites.
  - The target substance and the read across analogue have different physical chemical properties. The physical chemical properties mainly affect the absorption of the target substance through skin or cell membrane. The read across analogues used here are metabolites of the target substance and will only be produced post absorption of the target substance. So any differences in the physical chemical properties of the target substance and the read across analogues are deemed to be toxicologically insignificant for the genetoxicity, repeated dose, developmental, and reproductive toxicological endpoints.
  - OECD Toolbox (V3.4) shows a repeated dose (HESS) categorization alert for hexanoic acid and CAESAR model (V2.1.6) shows a developmental toxicity toxicant alert for isoamyl alcohol, the alert not seen for the target. This alerts shows that read across may have increased *in vivo* reactivity and so could be utilized as read across for the target.

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