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Short review

RIFM fragrance ingredient safety assessment, isoamyl propionate, CAS Registry Number 105-68-0

A.M. Api [a, *], D. Belsito [b], D. Botelho [a], D. Browne [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], P. Calow [f], M.L. Dagli [g], M. Date [a], W. Dekant [h], C. Deodhar [a], A.D. Fryer [i], K. Joshi [a], S. La Cava [a], A. Lapczynski [a], D.C. Liebler [j], D. O'Brien [a], R. Parakhia [a], A. Patel [a], T.M. Penning [k], G. Ritacco [a], J. Romine [a], D. Salvito [a], T.W. Schultz [l], I.G. Sipes [m], Y. Thakkar [a], S. Tsang [a], J. Wahler [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, Humphrey School of Public Affairs, University of Minnesota, 301 19th Avenue South, Minneapolis, MN 55455, USA
[g] 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
[h] Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany
[i] Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA
[j] 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
[k] 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
[l] Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996-4500, USA
[m] 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

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1. Identification

1. **Chemical Name:** Isoamyl propionate
2. **CAS Registry Number:** 105-68-0
3. **Synonyms:** Amyl(iso) propionate; 1-Butanol, 3-methyl-, propanoate; Isoamyl propanoate; Isoamyl propionate; Isopentyl propanoate; Isopentyl propionate; 3-Methylbutyl propionate; 3-Methylbutyl propanoate; 7βロヒβオン酸アルキル(C = 1 ~ 12)
4. **Molecular Formula:** $C_8H_{16}O_2$
5. **Molecular Weight:** 144.21
6. **RIFM Number:** 631

2. Physical data

1. **Boiling Point:** 157.09 °C [EPI Suite]
2. **Flash Point:** 40 °C [GHS], 104 °F; CC [FMA database]
3. **Log K_{OW}:** log Pow = 2.9 [RIFM, 2013], 2.76 [EPI Suite]
4. **Melting Point**: −43.92 °C [EPI Suite]
5. **Water Solubility:** 356.7 mg/L [EPI Suite]
6. **Specific Gravity:** 0.868 [FMA database]
7. **Vapor Pressure:** 1.77 mmHg @ 20 °C [EPI Suite 4.0], 2.3 mm Hg 20C [FMA database], 2.49 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L · mol^{-1} · cm^{-1})

* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

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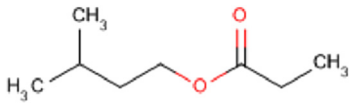
Version: 011817. This version replaces any previous versions.
Name: Isoamyl propionate
CAS Registry Number: 105-68-0



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
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 target material and suitable read across analog isoamyl alcohol (CAS# 123-51-3) show that this material is not genotoxic. Data from the suitable read across analog isoamyl acetate (CAS# 123-92-2) show that this material does not have skin sensitization potential. 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 endpoints were completed using isoamyl alcohol (CAS# 123-51-3) and propionic acid (CAS# 79-09-4) as suitable read across analogs, 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. (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 (RIFM, 1987)
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: Critical Measured Value: 74% (OECD 301F) (RIFM, 2012)
Bioaccumulation: Screening Level: 30.54 (Biowin 3) (EpiSuite ver4.1)
Ecotoxicity: Screening Level: Fish LC50: 32.06 mg/l (RIFM Framework; RIFM, 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

(*continued on next page*)

(*continued*)

Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 32.06 mg/l	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.03206 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; Cleared at Screening level	

9. **Appearance/Organoleptic:** Colorless mobile liquid, with a very sweet-fruity, Apricot-Pineapple type odor. Has a sweet-fruity taste.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0029% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00029 mg/kg/day or 0.022 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0031 mg/kg/day (RIFM, 2016)

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

2. **Analogues Selected:**
   a. **Genotoxicity:** isoamyl alcohol (CAS# 123-51-3)
   b. **Repeated Dose Toxicity:** isoamyl alcohol (CAS# 123-51-3) and propionic acid (CAS# 79-09-4)
   c. **Developmental and Reproductive Toxicity:** isoamyl alcohol (CAS# 123-51-3) and propionic acid (CAS# 79-09-4)
   d. **Skin Sensitization:** Isoamyl acetate (CAS# 123-92-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None

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

3. **Read-across Justification:** See Appendix below

6. Metabolism

See Appendix below.

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

Isoamyl propionate is reported to occur in the following foods*:

Apple brandy (Calvados)Apple fresh (Malus species)BeerCheese, various typesCherimoya (*Annona cherimolia Mill.*)Cider (apple wine)CocoaCustard apple, atemoya (*Annona atemoya*)Durian (*Durio zibethinus*)Grape brandyHop (*Humulus lupulus*)MelonRumTomato (*Lycopersicon esculentum Mill.*)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 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 1/18/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.2. Risk assessment

The mutagenic activity of isoamyl propionate (CAS # 105-68-0) has been evaluated in a bacterial reverse mutation assay conducted using the pre-incubation method. Salmonella typhimurium strains TA1535, TA1537, TA92, TA98, TA94 and TA100 were treated with isoamyl propionate in DMSO (dimethyl sulfoxide) at maximum concentrations up to 10 mg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (Ishidate et al., 1984). Under the conditions of the study, isoamyl propionate was not mutagenic in the Ames test.

The clastogenicity of isoamyl propionate was assessed in an in vitro chromosome aberration study. Chinese hamster lung cells were treated with isoamyl propionate 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 propionate was considered to be non-clastogenic to 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 propionate will readily hydrolyze into isoamyl alcohol (CAS# 123-51-3; see section 5) and propionic acid (CAS# 79-09-4; 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, 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). The clastogenic activity of propionic acid was evaluated in an in vivo micronucleus test conducted in accordance with OECD TG 474. The test material was administered in physiological saline via intraperitoneal injection, to groups of male and female Chinese hamster mice (6/sex/dose). A dose of 125 mg/kg was administered. Mice from each dose level were euthanized at 12, 24 or 48 h, 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 (Basler et al., 1987). Under the conditions of the study, propionic acid was considered to be not clastogenic in the in vivo micronucleus test. Under the conditions of the study, isoamyl alcohol and propionic acid was considered to be non clastogenic in the in vivo micronucleus test, which can be extended to isoamyl propionate based on metabolism.

Based on the data available, isoamyl propionate does not present a concern for genotoxic potential.

Additional References: Kuroda et al., 1984;

Literature Search and Risk Assessment Completed on: 06/23/2016.

10.1.3. Repeated dose toxicity

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

10.1.4. Risk assessment

There are no repeated dose toxicity data on isoamyl propionate. Isoamyl propionate will hydrolyze readily into isoamyl alcohol (CAS# 123-51-3; see section 5) and propionic acid (CAS# 79-09-4; see Section 5). Metabolite, isoamyl alcohol (CAS# 123-51-3; see section 5) has sufficient repeated dose toxicity data. A gavage OECD 422 combined repeated dose toxicity study was conducted on a group 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 were 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 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 also 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 (Carpaninini et al., 1973). In another study, metabolite, propionic acid (CAS# 79-09-4; see section 5) had a 90 day diet study in rats and OECD 409 diet study in dogs conducted. There were local effects in both species. The NOAEL for systemic effects for rats and dogs was 2500 mg/kg/day and 1832 mg/kg/day, respectively, the highest dose tested (SIDS Initial Assessment Report for SIAM 25). 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 for isoamyl propionate for the repeated dose toxicity endpoint is equal to the isoamyl alcohol NOAEL divided by the total systemic exposure for isoamyl propionate, 1250/0.0031 or 403226.

In addition, the total systemic exposure for isoamyl propionate (3.1 μg/kg/day) is below the TTC (30 μg/kg bw/day).

Additional References: ECHA REACH Dossier: 3-methylbutan-1-ol.

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

10.1.5. Developmental and reproductive toxicity

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

10.1.6. Risk assessment

There are no developmental toxicity data on isoamyl propionate. Isoamyl propionate will hydrolyze readily into isoamyl alcohol (CAS# 123-51-3; see section 5) and propionic acid (CAS# 79-09-4; 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). 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). 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. The most conservative NOAEL of 300 mg/kg/day was selected for the developmental toxicity endpoint.

There are no reproductive toxicity data on isoamyl propionate. Isoamyl propionate will hydrolyze readily into isoamyl alcohol

(CAS# 123-51-3; see section 5) and propionic acid (CAS# 79-09-4; 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). In addition, metabolite, propionic acid (CAS# 79-09-4; see section 5) has a 90 day diet study in rats and OECD 409 diet study in dogs conducted. There were no adverse effects on reproductive organs. The NOAEL for fertility effects for rats and dogs was 2500 mg/kg/day and 1832 mg/kg/day, respectively, the highest dose tested (SIDS Initial Assessment Report for SIAM 25). The NOAEL for reproductive toxicity was determined to be 300 mg/kg/day the highest dose tested in the isoamyl alcohol study.

Therefore, the MOE for isoamyl propionate for the developmental and reproductive toxicity is equal to the isoamyl alcohol NOAEL divided by the total systemic exposure for isoamyl propionate, 300/0.0031 or 96774.

In addition, the total systemic exposure for isoamyl propionate (3.1 μg/kg/day) is below the TTC (30 μg/kg bw/day).

Additional References: None.

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

10.1.7. Skin sensitization

Based on the existing data and read across to isoamyl acetate (CAS# 123-92-2), isoamyl propionate does not present a concern for skin sensitization.

10.1.8. Risk assessment

Based on the existing data and read across to isoamyl acetate (CAS# 123-92-2; see section 5), isoamyl propionate does not present a concern for skin sensitization. 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). In guinea pig maximization test, a mixture of primary amyl acetates did not result in reactions indicative of sensitization (Ballantyne et al., 1986). Similarly, isoamyl propionate and read across material isoamyl acetate were found to be negative in a guinea pig Open Epicutaneous Test (OET) (Klecak, 1979, 1985). In human maximization tests, no skin sensitization reactions were observed with 4% isoamyl propionate (2760 μg/cm^2) or 8% (5520 μg/cm^2) isoamyl acetate (RIFM, 1975; RIFM, 1973). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 20% or 23622 μg/cm^2; isoamyl acetate in 75:25 Ethanol:DEP, no reactions indicative of sensitization was observed in any of the 197 volunteers (RIFM, 1987). Based on the available data and read across to isoamyl acetate, isoamyl propionate does not present a concern for skin sensitization.

Additional References: None.

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

10.1.9. Phototoxicity/photoallergenicity

Based on available UV spectra, isoamyl propionate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for isoamyl propionate in experimental models. UV absorption spectra indicate no absorption between 290 and 400 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 propionate does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

10.1.11. Local Respiratory Toxicity

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

10.1.12. Risk assessment

There are no inhalation data available on isoamyl propionate. Based on the Creme RIFM model, the inhalation exposure is 0.022 mg/day. This exposure is 63.6 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: 07/08/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of isoamyl propionate 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 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 propionate 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 propionate 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). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current VoU (2011), isoamyl propionate does not present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Biodegradation

RIFM, 2012: The ready biodegradability of the test material was evaluated using the Manometric Respirometry Test according to the OECD 301F method. Under the conditions of the study, biodegradation of 74% was reached after 28 days.

Ecotoxicity: No data available.

10.2.4. Other available data

Isoamyl propionate has been pre-registered for REACH with no additional information at this time.

10.2.5. 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)**	32.06 mg/L			1,000,000	0.03206 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.9	2.9
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.03206 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=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

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

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.03.021.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.03.021.

Appendix

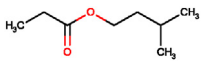
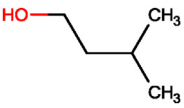
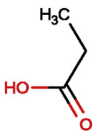
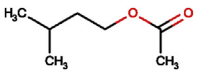
Methods:

- The identified read-across analogs were confirmed by using expert judgment.
- Tanimoto structure similarity scores were calculated using ECFC 6 fingerprints (Rogers and Hahn, 2010).
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- J_{max} 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 analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012).

Summary:

There are insufficient toxicity data on isoamyl propionate (CAS # 105-68-0). Hence *in-silico* evaluation was conducted to determine suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogs isoamyl alcohol (CAS # 123-51-3), propionic acid (CAS #79-09-4), and isoamyl acetate (CAS #123-92-2) were identified read across materials with data for

	Target material	Read across material		
Principal Name	Isoamyl propionate	Isoamyl alcohol	Propionic acid	Isoamyl acetate
CAS No.	105-68-0	123-51-3	79-09-4	123-92-2
Structure				
Similarity (Tanimoto score)	1.0	N/A[a]	N/A[a]	0.8
Read across endpoint		• Genotoxicity, • Repeated dose, • Developmental and reproductive	• Repeated dose, • Developmental and reproductive	•Skin sensitization
Molecular Formula	$C_8H_{16}O_2$	$C_5H_{12}O$	$C_3H_6O_2$	$C_7H_{14}O_2$
Molecular Weight	114.22	88.15	74.08	130.19
Melting Point (°C, EPISUITE)	−43.92	−61.49	−8.99	−56.05
Boiling Point (°C, EPISUITE)	157.09	123.17	145.02	134.87
Vapor Pressure(Pa @ 25 °C, EPISUITE)	332	512	806	756
Log Kow (KOWWIN v1.68 in EPISUITE)	2.76	1.16	0.33	2.25
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	356.7	4.158e+004	1.736e+005	1100
J_{max} (mg/cm^2/h, SAM)	43.63543	1142.301	1758.189	55.89014
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	7.33E+001	1.34E+000	7.37E-002	5.52E+001
Genotoxicity				
DNA binding (OASIS v 1.1 QSAR Toolbox 3.4)	• No alert found	• No alert found		
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found		
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found		
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found		
In-vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found		
In-vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found		
Oncologic Classification	• Not classified	• Not classified		
Repeated dose toxicity				
Repeated Dose (HESS)	• Not categorized	• 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)	• Toxicant (low reliability)	
Sensitization				
Protein binding by OASIS v1.1	• No alert found			• No alert found
Protein binding by OECD	• No alert found			• No alert found
Protein binding potency	• Not possible to classify according to these rules (GSH)			• Not possible to classify according to these rules (GSH)
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found			• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)			• Sensitizer (good reliability)
Metabolism				
OECD QSAR Toolbox (3.4)	105-68-0 pdf	123-51-3 pdf	• No metabolites	123-92-2 pdf
Rat liver S9 metabolism simulator	• 5 metabolites from Rat S9 simulator. • Aldehydes, anionic surfactants, esters, Schiff base formation.	• 8 metabolites from Rat S9 simulator. • Aldehydes, Schiff base formation.		• 5 metabolites from Rat S9 simulator. • Aldehydes, esters, AN2, SN1, SN2, Schiff base formation.

[a] metabolites of the target.

their respective toxicity endpoints.

Conclusion/rationale

- Metabolism
  The target substance isoamyl formate (CAS # 110-45-2) metabolically hydrolyzes to isoamyl alcohol (CAS # 123-51-3) and propionic acid (CAS #79-09-4) as described in the repeated dose toxicity section. In addition, metabolism of the target substance was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4) (see metabolism section in the table above). Isoamyl propionate is predicted to metabolized to isoamyl alcohol and propionic acid in the first step with 0.950 precalculated probability. Hence isoamyl alcohol and propionic acid can be use as read across for isoamyl propionate. Isoamyl propionate was out of domain for the in vivo and in vitro rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgement, the model's domain exclusion was overridden and a justification is provided.
- Isoamyl alcohol (CAS # 123-51-3) and propionic acid (CAS # 79-09-4) are used as structurally similar read across analogues for isoamyl formate (CAS # 110-45-2) for genetoxicity, repeated dose, developmental, and reproductive toxicological endpoints.
  - The read across materials (alcohol and acid) are major metabolite 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 read across analogues used here. Therefore the toxicity profile of the target is expected to be that of 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 the target substance. So any differences in the physical chemical properties of the target substance and the read across analogue are deemed to be toxicologically insignificant for genetoxicity, repeated dose, developmental, and reproductive toxicological endpoints.
  - OECD Toolbox (V3.4) shows a repeated dose (HESS) categorization alert for propionic acid, the alert is 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 said target.
- Isoamyl acetate (CAS # 123-92-2) could be used as a structurally similar read across analogue for the target material Isononyl propionate (CAS # 65155-45-5) for skin sensitization 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 longer straight chain alkane on acid portion (propionate) while the read across has shorter straight chain alkane on acid portion (acetate). This structure difference between the target substance and the read across analogue do not raise additional structural alerts so the structure differences are not relevant from a toxic endpoint perspective.
  - The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the alkane chain fragment on 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 skin sensitization endpoint.
  - According to the QSAR OECD Toolbox (V3.4), structural alerts for the skin sensitization endpoint are consistent between the target substance and the read across analogue.
  - The target substance and the read across analogue are expected to be metabolized similarly as shown by metabolism simulator.
  - The structural alerts for skin sensitization 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.

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