Food and Chemical Toxicology 110 (2017) S421–S430

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short review

RIFM fragrance ingredient safety assessment, isoamyl alcohol CAS Registry Number 123-51-3

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ARTICLE INFO

Article history:
Received 22 May 2017
Received in revised form
28 July 2017
Accepted 12 August 2017
Available online 15 August 2017

1. Identification

1. **Chemical Name**: Isoamyl alcohol
2. **CAS Registry Number:** 123-51-3
3. **Synonyms:** 1-Butanol, 3-methyl-; Isoamyl alcohol; Isobutyl carbinol; Isopentyl alcohol; 3-Methyl-1-butanol; Isopentanol; 3-Methylbutan-1-ol; アルカノール(C = 5–38)
4. **Molecular Formula**: $C^5H^{12}O$
5. **Molecular Weight**: 88.15

2. Physical data

1. **Boiling Point:** 132 °C [Carpanini et al., 1973], 132 °C [FMA database], 123.17 °C [EPI Suite]
2. **Flash Point:** 109 °F; CC [FMA database]
3. **Log K_{OW}:** 1.28 [Abraham and Rafols, 1995], 1.16 [Patel et al., 2002], 1.26 [EPI Suite]
4. **Melting Point**: −117.2 °C [Carpanini et al., 1973], −61.49 °C [EPI Suite]
5. **Water Solubility:** 41580 mg/l [EPI Suite]
6. **Specific Gravity:** (20°C/20 °C) 0.809–0.815 [Carpanini et al., 1973], 0.812 [FMA database], 0.8149 [EOA, 1976 Sample 76–151]

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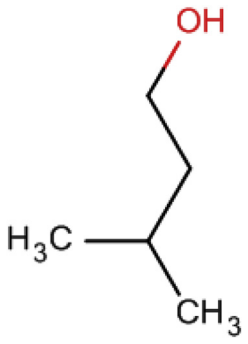
http://dx.doi.org/10.1016/j.fct.2017.08.015

Version: 050217. This version replaces any previous versions.
Name: Isoamyl alcohol
CAS Registry Number: 123-51-3



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; Safford et al., 2017) compared to a deterministic aggregate approach.
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA- European Chemicals Agency
EU- Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
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

The Expert Panel for Fragrance Safety* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.
Each endpoint discussed in this safety assessment 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 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 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, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data on the target material show that this material is not genotoxic, it does not have skin sensitization potential and provided a MOE >100 for the repeated dose and developmental toxicity endpoints. The reproductive toxicity endpoint was completed using data from the target material and from the read-across analog 3,7-dimethyl-1-octanol (CAS # 106-21-8), which provided a MOE > 100. 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 phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated and the material was not found to be PBT as per IFRA environmental standards and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(Kreja and Seidel, 2002; 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; RIFM, 2013b)
Skin Sensitization: Not sensitizing.	(Kern et al., 2010; RIFM, 1976)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available.	Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:

(*continued*)

Persistence: Critical Measured Value: 84% (OECD 301F)	(ECHA REACH Dossier: isoamyl alcohol)
Bioaccumulation: Screening Level: 2.706 l/kg	(EPI Suite ver 4.1)
Ecotoxicity: Screening Level: LC50: 523.6 mg/l	(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	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: LC50: 523.6 mg/l	(Salvito et al., 2002)
RIFM PNEC is: 0.5236 μg/l	
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: not applicable; cleared at screening level	

7. **Vapor Pressure:** 2.66 mmHg @ 20 °C [EPI Suite], 1.5 mm Hg 20C [FMA database], 3.84 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No absorbance in the region 290–700 nm; molar absorption coefficient is below the benchmark (1000 l mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** colorless liquid with a disagreeable alcohol odor and a pungent, repulsive taste (Merck Index (1976)); colorless to pale yellow clear liquid (est), Fusel, alcoholic, pungent, etherial, cognac, fruity, banana and molasses (Mosciano, Gerard P&F 22, No. 4, 75, (1997))*

* http://www.thegoodscentscompany.com/data/rw1014671.html, retrieved 03/28/2017.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.00048% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.0000042 mg/kg/day or 0.00030 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00021 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 and Safford et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015 and Safford 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. **Analogues Selected**:
   a. **Genotoxicity**: None
   b. **Repeated Dose Toxicity**: None
   c. **Developmental and Reproductive Toxicity**: 3,7-Dimethyl-1-octanol (CAS # 106-21-8)
   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

Kamil et al., 1953: The amount of glucuronide conjugated isoamyl alcohol excreted was studied after administering 25 mMoles/3 kg dose to large chinchilla rabbits. The animals were kept on a constant diet to obtain glucuronide levels 1 week prior to administration of isoamyl alcohol. Isoamyl alcohol was administered with water via gavage and the glucuronide acid output collected from urine for each alcohol was determined on 3 animals. An amount of 9% administered dose was found to be glucuronide conjugated-isoamyl alcohol at the end of 24 h. The urine did not contain aldehydes or ketones.

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

Isoamyl alcohol is reported to occur in the following foods* and as a component of some natural complex substances (NCS):

Acerola (*Malpighia*)
Allium species
Anise brandy
Apple brandy (*Calvados*)
Apple fresh (*Malus* species)
Apple processed (*Malus* species)
Apricot (*Prunus armeniaca* L.)
Arctic bramble (*Rubus arcticus* L.)
Arrack
Artichoke
Artocarpus species
Asparagus (*Asparagus officinalis* L.)
Avocado (*Persea americana* Mill.)
Babaco fruit (*Carica pentagona Heilborn*)
Banana (*Musa sapientum* L.)
Bantu beer
Beans
Beef
Beer

Beetroot (*Beta vulgaris* L.)
Beli, Bael (*Aegle marmelos Correa*)
Bilberry wine
Black currants (*Ribes nigrum* L.)
Blackberry brandy
Blue cheeses
Bread and bread preferment
Buckwheat
Bullock's heart (*Annona reticulata* L.)
Cabbage (*Brassica oleracea*)
Camomile
Capsicum species
Cardamom (*Ellettaria cardamomum Maton*.)
Cashew apple (*Anacardium occidentale*)
Cashew apple wine
Celery (*Apium graveolens* L.)
Ceriman, pinamona (*Monstera deliciosa* Liebm.)
Cheddar cheese
Cheese, various types
Cherimoya (*Annona cherimolia Mill*.)
Cherry
Cherry brandy
Chicken
Chinese quince (*Pseudocydonia sinensis Schneid*)
Cider (apple wine)
Citrus fruits
Cocoa category
Coffee
Crayfish
Crispbread
Crowberry (*Empetrum nigrum coll*.)
Cupuacu (*Theobroma grandiflorum Spreng*.)
Dalib, palmyra palm fruit (*Borassus aethiopum* L.)
Date (*Phoenix dactylifera* L.)
Durian (*Durio zibethinus*)
Dwarf quince (*Chaenomeles japonica*)
Elderberry (*Sambucus nigra* L.)
Filbert, hazelnut (*Corylus avellano*)
Fish
Gin
Ginger (*Zingiber* species)
Grape (*Vitis* species)
Grape brandy
Guava and feyoa
Guava wine
Honey
Hop (*Humulus lupulus*)
Katsuobushi (*dried bonito*)
Krill
Kumazasa (*Sasa albo-marginata*)
Laurel (*Laurus nobilis* L.)
Litchi (*Litchi chinensis Sonn*.)
Litchi wine
Loquat (*Eriobotrya japonica Lindl*.)
Maize (*Zea mays* L.)
Malt
Mangifera species
Marula (*Sclerocarya birrea* subsp. *caffra*)
Mate (*Ilex paraguayensis*)
Matsutake (*Tricholoma matsutake*)
Melon
Mentha oils
Mezcal (*Agave salmiana*)
Milk and milk products
Mountain papaya (*C. candamarcensis*, *C. pubescens*)
Mulberry spirit (*Mouro*)
Mushroom
Mussel
Mustard (*Brassica* species)
Naranjilla fruit (*Solanum quitoense Lam*.)
NectarineOats
(*Avena sativa* L.)
Olive (*Olea europaea*)
OystersPapaya
(*Carica papaya* L.)
Passion fruit (*passiflora* species)
Passion fruit wine
Peach (*Prunus persica* L.)
Pear (*Pyrus communis* L.)
Pear brandy
Peas (*Pisum sativum* L.)
Pecan (*Carya illinoensis Koch*)
Pineapple (*Ananas comosus*)
Plum (*Prunus* species)
Plum brandy
Plum wine
Pork
Potato (*Solanum tuberosum* L.)
Potato chips (American)
Prickly pear (*Opuntia ficus indica*)
Pulasan (*Nephelium ramboutan-ake* (Labill.) Leenh.)
Quince, marmelo (*Cydonia oblonga Mill*.)
Radish (*Raphanus sativus* L.)
Rambutan (*Nephelium lappaceum* L.)
Raspberry brandy
Raspberry, blackberry and boysenberry
Red currants (*Ribes rubrum* L.)
Rice (*Oryza sativa* L.)
Rooibos tea (*Aspalathus linearis*)
Rum
Rye bread
Sake
Salvia species
Sapodilla fruit (*Achras sapota* L.)
Sauerkraut
Scallop
Sherry
Shoyu (*fermented soya hydrolysate*)
Shrimps
Soursop (*Annona muricata* L.)
Southernpea (*Vinga unguiculata* L.)
Soybean (*Glycine max*. L. merr.)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species)
Strawberry wine
Sukiyaki
Swiss cheeses
Syzygium species
Tamarind (*Tamarindus indica* L.)
Tapereba, caja fruit (*Spondias lutea* L.)
Tea Tequila
(*Agave tequilana*)
Tomato (*Lycopersicon esculentum* Mill.)
Truffle
Vaccinium species
Vanilla
Vinegar
Walnut (*Juglans* species)
Wax gourd, winter melon (*Benincasa hispada Cogn*)
Wheaten bread

Whisky
Win
*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

Available; accessed on 08/25/14.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, isoamyl alcohol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment

Isoamyl alcohol was tested in the BlueScreen assay and was found negative for genotoxicity in the presence and absence of metabolic activation indicating a lack for genotoxic concern (RIFM, 2013a). The mutagenic activity of isoamyl alcohol was assessed in an *in vitro* mammalian cell gene mutation test conducted equivalent to OECD TG 476. Chinese hamster lung fibroblast cells (V79) were treated with isoamyl alcohol in DMSO (dimethyl sulfoxide) at concentrations up to 51.5 mM in the presence and absence of an exogenous, metabolically active microsomal mix (S-9 mix). No increase in the number of spontaneous MN (micronuclei) frequencies was observed at the concentrations tested (Kreja and Seidel, 2002). Under the conditions of the study, isoamyl alcohol was considered not mutagenic in the mammalian gene mutation test.

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 route, to groups of male and female NMRI mice (5/sex/dose). Doses of 500, 1000, and 2000 mg/kg bodyweight 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). Under the conditions of the study, isoamyl alcohol was considered to be not clastogenic in the *in vivo* micronucleus test.

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

Additional References: Chen et al., 1984; Kreja and Seidel, 2001; Seidel and Plappert, 1999; Nakajima et al., 2006.

Literature Search and Risk Assessment Completed on: 09/26/2016.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on isoamyl alcohol. A gavage OECD 422 combined repeated dose toxicity study was conducted on groups of 12 male and female Sprague-Dawley rats/group and they were 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 test material 3-methylbutan-1-ol (isoamyl alcohol) in 1 w/v% CMC solution containing 1% Tween 80 in water was administered to male and female Sprague-Dawley rats daily by oral gavage for 42 days for the males (14 days before mating, 14 days during the mating period and 14 days after the end of the mating period), 41–53 days for the females (14 days before mating, throughout the mating and gestation periods up to day 4 of lactation) and for 42 days in the satellite recovery group. The NOAEL was determined to be 100 mg/kg/day, based on reduced bodyweight gain in the high dose group males (ECHA REACH Dossier: 3-methylbutan-1-ol). In another study, an OECD/GLP 408, 13-week study was conducted on groups of 10 SPF-Wistar, Chbb:THOM rats/sex/group and they were 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) and 16,000 ppm (about 1250 mg/kg/day). Although there were slight alterations in the hematological parameters at the high dose (a marginal increase in the red blood cell count as well as a slight decrease in the mean corpuscular volume and the mean corpuscular hemoglobin content was observed in the males only. The toxicological significance of these findings is unclear), the NOAEL was determined to be 16000 ppm or 1250 mg/kg/day, the highest dose tested, since the effects were not considered to be treatment-related (Schilling et al., 1997). In another study, groups of 15 Ash/CSE strain 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, 1973). The only effects reported among treated animals during the OECD 422 gavage study were reduced body weight gains among males. Since no adverse effects were reported among the animals during the longer duration 13 (drinking water) and 17 (gavage) week studies, the NOAEL was determined to be 1250 mg/kg/day, the highest dose tested. Therefore, the isoamyl alcohol MOE for the repeated dose toxicity endpoint can be calculated by dividing the isoamyl alcohol NOAEL in mg/kg/day by the total systemic exposure to isoamyl alcohol, 1250/0.00021 or 5952381.

In addition, the total systemic exposure to isoamyl alcohol (0.21 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 1988c; RIFM, 1991; Gibel et al., 1975; RIFM, 1992; RIFM, 1988b; Klimisch and Hellwig, 1995; RIFM, 1990b; RIFM, 1988a; RIFM, 1990c; RIFM, 2010b; RIFM, 2010a; Meyer, 1965; McLaughlin et al., 1964.

Literature Search and Risk Assessment Completed on: 10/21/2016.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are sufficient developmental toxicity data on isoamyl alcohol. There is an OECD 414 developmental toxicity study conducted on 15 pregnant female Himalayan rabbits/group. The animals were 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 bodyweight 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, 1990c). In another study, an OECD 414 developmental toxicity study conducted on groups of 25 pregnant female Wistar rats/group were 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, respectively, according to standard minute volume and bodyweight 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 conducted on groups of 12 Sprague-Dawley rats/sex/group were administered test material isoamyl alcohol at doses of 0, 30, 100 and 300 mg/kg/day. The test material 3-methylbutan-1-ol (isoamyl alcohol) in 1 w/v% CMC solution containing 1% Tween 80 in water was administered to male and female Sprague-Dawley rats daily by oral gavage for 42 days for the males (14 days before mating, 14 days during the mating period and 14 days after the end of the mating period), 41–53 days for the females (14 days before mating, throughout the mating and gestation periods up to day 4 of lactation) and 42 days in the satellite recovery group. 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. Due to uncertainty involved in the dose conversion from inhalation studies, the most conservative NOAEL of 300 mg/kg/day from the OECD 422 gavage study was selected for the developmental toxicity endpoint.

There are sufficient reproductive toxicity data on isoamyl alcohol. An OECD 422 gavage study (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test) was conducted on groups of 12 Sprague-Dawley rats/sex/group which were administered the test material isoamyl alcohol at doses of 0, 30, 100 and 300 mg/kg/day. The test material 3-methylbutan-1-ol (isoamyl alcohol) in 1 w/v% CMC solution containing 1% Tween 80 in water was administered to male and female Sprague-Dawley rats daily by oral gavage for 42 days for the males (14 days before mating, 14 days during the mating period and 14 days after the end of the mating period), 41–53 days for the females (14 days before mating, throughout the mating and gestation periods up to day 4 of lactation) and 42 days in the satellite recovery group. 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). A 14-day screening study for reproductive toxicity in the male rats was done on read-across material 3,7-dimethyl-1-octanol (CAS # 106-21-8; See Section 5). There were no adverse effects on the male reproductive organs or sperm parameters at 1000 mg/kg/day, the only dose tested (RIFM, 2013b). The NOAEL of 1000 mg/kg/day supports the NOAEL for reproductive toxicity which was determined to be 300 mg/kg/day based on the OECD 422 study on isoamyl alcohol.

Therefore, the isoamyl alcohol MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the isoamyl alcohol NOAEL in mg/kg/day by the total systemic exposure to isoamyl alcohol, 300/0.00021 or 1428571.

In addition, the total systemic exposure to isoamyl alcohol (0.21 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: RIFM, 1988c; Carpanini et al., 1973; Schilling et al., 1997; RIFM, 1991; Gibel et al., 1975; RIFM, 1992; RIFM, 1988b; Klimisch and Hellwig, 1995; RIFM, 1988a; RIFM, 2010b; RIFM, 2010a; Meyer, 1965; McLaughlin et al., 1964.

Literature Search and Risk Assessment Completed on: 10/21/2016.

10.1.4. Skin sensitization

Based on the available data, isoamyl alcohol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Based on the existing data, isoamyl alcohol 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 a murine local lymph node assay (LLNA), isoamyl alcohol was found to be non-sensitizing up to 50% (12500 μg/cm^2) (Kern et al., 2010). In a confirmatory human maximization test, no skin sensitization reactions were observed with 8% isoamyl alcohol (5520 μg/cm^2) (RIFM, 1976). Based on weight of evidence from structural analysis, animal and human studies isoamyl alcohol does not present a concern for skin sensitization.

Additional References: Enoch et al., 2008; Patlewicz et al., 2007.

Literature Search and Risk Assessment Completed on: 10/28/2016.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, isoamyl alcohol 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 alcohol experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009). Based on lack of absorbance, isoamyl alcohol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/13/16.

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There are limited inhalation data available on isoamyl alcohol. Based on the Creme RIFM model, the inhalation exposure is 0.00030 mg/day. This exposure is 4667 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: Smyth et al., 1969; Kane et al., 1980; Frantik et al., 1994; Klimisch and Hellwig, 1995; Kumagai et al., 1999; Korpi et al., 1999; RIFM, 1979; RIFM, 1990b; RIFM, 1990c; RIFM, 1988a; RIFM, 1988b.

Literature Search and Risk Assessment Completed on: 10/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of isoamyl alcohol 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 alcohol 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 alcohol 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 alcohol does not present a risk to the aquatic compartment in the screening level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. **RIFM, 1989**: An algae growth inhibition test was conducted according to the DIN 38412 part 9 method. The EbC50 values were 493 and 180 mg/l at 72 and 96 h, respectively. The ErC50 values were 573 mg/l and 273 mg/l at 72 and 96 h, respectively.

RIFM, 1990a: A *Daphnia magna* acute toxicity study was conducted according to the DIN 38412 L11 method. The 48 h EC50 was reported to be 255 mg/l.

10.2.3.3. Other available data. Isoamyl alcohol has been registered under REACH and the following data is available:

Ready biodegradability test was conducted with isoamyl alcohol following the OECD 301F guidelines. Biodegradation of 84% was observed after 28 days.

A fish (*oncorhynchus mykiss*) acute toxicity test was conducted according to the OECD 203 method. The 96-hour LC50 was reported to be 700 mg/l.

10.3. Risk assessment refinement

Since isoamyl alcohol passed the screening criteria (LEVEL I) measured data, including REACH data is reported in this document for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	523.6 mg/l			1,000,000	0.5236 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	1.26	1.26
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.5236 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: 8/13/14.

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

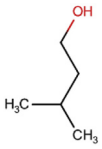
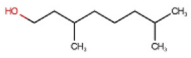
*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

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.2017.08.015.

- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (EPI Suite v4.1).
- The 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 estimated 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 (v2.1.6) (Cassano et al., 2010).
- Protein binding were 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).

	Target material	Read-across material
Principal Name	Isoamyl alcohol	3,7-Dimethyl-1-octanol
CAS No.	123-51-3	106-21-8
Structure		
Similarity (Tanimoto score)		0.58
Read-across endpoint		• Developmental and reproductive toxicity
Molecular Formula	$C_5H_{12}O$	$C_{10}H_{22}O$
Molecular Weight	88.15	158.29
Melting Point (°C, EPI Suite)	−61.49	−13.66
Boiling Point (°C, EPI Suite)	123.17	216.17
Vapor Pressure (Pa @ 25°C, EPI Suite)	512	4.74
Log Kow (KOWWIN v1.68 in EPI Suite)	1.16[1]	3.9[2]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	26700	175.4
J_{max} (mg/cm²/h, SAM)	733.512	65.909
Henry's Law (Pa·m³/mol, Bond Method, EPI Suite)	1.33E-005	5.47E-005
Developmental and reproductive toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	• Non binder, non-cyclic structure	• Non binder, non-cyclic structure
Developmental Toxicity Model by CAESAR v2.1.6	• toxicant (good reliability)	• Non-toxicant (low reliability)
Metabolism		
OECD QSAR Toolbox (3.4)	See supplemental data 1	See supplemental data 2
Rat liver S9 metabolism simulator		

1. Patel et al., 2002
2. RIFM, 1999.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.08.015.

Appendix

Read-across justification

Methods

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

Summary

There are insufficient toxicity data on isoamyl alcohol (CAS # 123-51-3). Hence, *in silico* evaluation was conducted by determining read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, 3,7-dimethyl-1-octanol (CAS # 106-21-8) was identified as a proper read-across material with data for the developmental and reproductive toxicity endpoint.

Conclusion/Rationale

- For the target material isoamyl alcohol (CAS # 123-51-3), the following material, 3,7-dimethyl-1-octanol (CAS # 106-21-8),

could be used as a structurally similar read-across analog for the reproductive endpoint.

- o The target substance and the read-across analog are structurally similar and belong to a class of saturated branched chain aliphatic alcohols.
- o The key difference between the target substance and the read-across is that they have different aliphatic carbon chain lengths. The target substance has a shorter carbon chain length compared to the read-across analog. This structural difference between the target and read-across analogs is not relevant from a toxicity endpoint perspective.
- o The target substance and the read-across analog have a Tanimoto score as mentioned in the table above. The Tanimoto score is mainly driven by the four carbon long branched aliphatic chain (isoamyl portion) fragment. The differences in the structure which are responsible for a Tanimoto score <1 are not relevant from a toxicity endpoint perspective.
- o The target substance and the read-across analog have similar physical-chemical properties. The J_{max} value of the target and the read-across analog appear to be different, however with the calculated J_{max}, the read-across analog substance and the target are predicted to have skin absorption up to 80%. Other differences in some of the physical-chemical properties of the target substance and the read-across analog are estimated to be toxicologically insignificant for the development and reproductive endpoint.
- o According to the QSAR OECD Toolbox (v3.4), structural alerts for the reproductive toxicity endpoint are consistent between the target substance and the read-across analog. The CAESAR model for developmental and reproductive toxicity predicts the target substance to be a toxicant while the read-across analog 3,7-dimethyl-1-octanol is predicted to be non-toxic. All other developmental and reproductive alerts for the target substance and the read-across analog are negative. The data described above in the developmental and reproductive toxicity section show that the margin of exposure for the read-across substance is adequate at the current level of use. Based on comparison of structure similarity, physical-chemical properties and reactivity predictions between the read-across analog and the target substance, the alert for the target will be superseded by availability of data for the read-across analog.
- o The target substance and the read-across analog are expected to be metabolized similarly as shown by the metabolism simulator in the table above.
- o The structural alerts for the developmental and reproductive toxicity endpoint are consistent between the metabolites of the read-across analog and the target substance.
- o The structural differences between the target substance and the read-across analog are deemed to be toxicologically insignificant for the developmental and reproductive toxicity endpoint.

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