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Short review

# RIFM fragrance ingredient safety assessment, isoamyl acetate, CAS Registry Number 123-92-2

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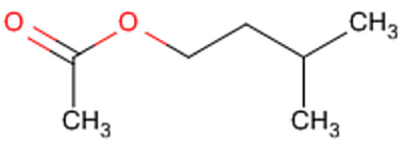

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**Abbreviation list:**

**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

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**NESIL**- No Expected Sensitization Induction Level
**NOAEC**- No Observed Adverse Effect Concentration
**NOAEL**- No Observed Adverse Effect Level
**NOEC**- No Observed Effect Concentration
**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 on the target material and suitable read across analogs isoamyl alcohol (CAS # 123-51-3) and acetic acid (CAS# 64-19-7) show that this material is not genotoxic. Data 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 acetic acid (CAS# 64-19-7) as suitable read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra along with data on the target material. 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; RIFM, 1986)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.

**Environmental Safety Assessments**

**Hazard Assessment:**
**Persistence:** Critical Measured Value: 90% (OECD 301F) (RIFM, 1999)
(EpiSuite ver 4.1)
**Bioaccumulation:** Screening Level: 14.18 L/kg (EpiSuite ver 4.1)
**Ecotoxicity:** Screening Level: 96 h Algae EC50: 10.06 mg/l
**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** (EpiSuite ver 4.1)
**Endpoint:** 96 h Algae EC50: 10.06 mg/l
**RIFM PNEC is:** 1.006 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe: <1

## 1. Identification

1 **Chemical Name**: Isoamyl acetate
2 **CAS Registry Number**: 123-92-2
3 **Synonyms**: Amyl acetate, common; 1-butanol, 3-methyl-, acetate; Isoamyl acetate; Isoamyl ethanoate; 3-methylbutyl acetate; β-methyl butyl acetate; 3-methyl-1-butanol acetate; Acetic acid 3-methylbutyl ester; Isopentyl acetate; Isopentyl ethanoate; 酢酸アミル; Isoamyl acetate (extra)
4 **Molecular Formula**: $C_7H_{14}O_2$
5 **Molecular Weight**: 130.19
6 **RIFM Number**: 454

## 2. Physical data

1 **Boiling Point**: 142 °C [FMA database], 134.87 °C [EPI Suite]
2 **Flash Point**: 33 °C [GHS], 77 °F; CC [FMA database]
3 **Log KOW**: 2.7 [RIFM, 2013], 2.7 at 35 °C [RIFM, 2004], 2.26 [EPI Suite]
4 **Melting Point**: −56.05 °C [EPI Suite]
5 **Water Solubility**: 1100 mg/L [EPI Suite]
6 **Specific Gravity**: 0.8728 [RIFM database], 0.873 [FMA database]
7 **Vapor Pressure**: 4.13 mmHg @ 20 °C [EPI Suite 4.0], 4.0 mm Hg @ 20 °C [FMA database], 5.67 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**: Colorless liquid with fruity pear- or banana-like odor

## 3. Exposure

1 **Volume of Use (worldwide band)**: 100–1000 metric tons per year (IFRA , 2011)
2 **Maximum Concentration in Toothpaste (no reported use in hydroalcoholics)**: 0.12% (RIFM, 2015)
3 **Inhalation Exposure***: 0.00047 mg/kg/day or 0.034 mg/day (RIFM, 2015)
4 **Total Systemic Exposure****: 0.0039 mg/kg/day (RIFM, 2015)

*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

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

2 **Analogs Selected**:
- a **Genotoxicity:** isoamyl alcohol (CAS# 123-51-3); acetic acid (CAS# 64-19-7)
- b **Repeated Dose Toxicity:** isoamyl alcohol (CAS# 123-51-3); acetic acid (CAS# 64-19-7)
- c **Developmental and Reproductive Toxicity:** isoamyl alcohol (CAS# 123-51-3); acetic acid (CAS# 64-19-7)
- 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

RIFM, 1974a: A study was conducted to determine the *in vitro* hydrolysis of aqueous solutions or emulsions of eight different carboxylic acid esters by intestinal enzymes isolated from pig jejunum. This was a follow-up to a study previously done with carboxylic acid esters that were split *in vitro* by pancreatin. The previous study determined that 20% of aqueous isoamyl acetate solution (100 μL) was hydrolyzed to isoamyl alcohol during the reaction (0, 60 and 120 min) which was confirmed by a gas chromatographic analysis (RIFM, 1974b). In this study, fresh pig small intestine was obtained and the jejunal part was separated. The jejunum was cut lengthwise and the separated mucosa was then pooled and homogenized and freeze dried for later storage in a freezer. The enzyme solution was prepared from the freeze dried intestinal powder which served as the enzyme for further studies. An aqueous solution of 500 μl/l of isoamyl acetate was mixed with equal volumes of enzyme solution and incubated at 37 °C in a glass stoppered test tube. GLC samples were collected at time 0, 30, 60 and 120 min. Isoamyl alcohol was rapidly split via hydrolysis by the intestinal mucosa preparation. Two alcohols were detected, the first one was identified as 2-methylbutanol and the second one as 3-methylbutanol. Hydrolysis was rapid with 90%, <1% and 0 parent ester compound detected at time 30, 60 and 120 min respectively.

### 6.1. Natural occurrence (discrete chemical) or composition (NCS)

Isoamyl acetate is reported to occur in the following foods* and in some natural complex substances (NCS):

Acerola (*Malpighia*).
Anise brandy.
Apple brandy (Calvados).
Apple fresh (*Malus* species).
Apple processed *(Malus* species).
Apricot (*Prunus armeniaca* L.)
Arrack.
*Artocarpus* species.
Banana (*Musa sapientum* L.)
Bantu beer.
Beans.
Beer.
Beli, bael (*Aegle marmelos* Correa).
Bilberry wine.
Black currants (*Ribes nigrum* L.)
Blue cheeses.
Camomile.
Cashew apple (*Anacardium occidentale*).
Cashew apple wine.
Ceriman, pinanona (*Monstera deliciosa* Liebm.)
Cheese, various types.
Cherimoya (*Annona cherimolia* Mill.)
Cherry.
Cherry brandy.
Cider (apple wine).
Citrus fruits.
Cocoa.
Coffee.
Custard apple, atemoya (*Annona atemoya*).
Date (*Phoenix dactylifera* L.)
Elderberry (*Sambucus nigra* L.)
Fig (*Ficus carica* L.)
Ginger (*Zingiber* species).
Grape (*Vitis* species).
Grape brandy.
Guava and feyoa.
Guava wine.
Honey.
Litchi (*Litchi chinensis* Sonn.)
Litchi wine.
Macadamia nut (*Macadamia integrifolia*).
Malt.
*Mangifera* species.
Melon.
Milk and milk products.
Mountain papaya (*C. candamarcensis, C. pubescens*).
Mulberry spirit (Mouro).
Mushroom.
Naranjilla fruit (*Solanum quitoense* Lam.)
Nectarine.
Olive (*Olea europaea*).
Papaya (*Carica papaya* L.)
Passion fruit *(passiflora* species).
Passion fruit wine.
Peach (*Prunus persica* L.)
Peanut (*Arachis hypogaea* L.)

Pear (*Pyrus communis* L.)
Pear brandy.
Pepino fruit (*Solanum muricatum*).
Pineapple (*Ananas comosus*).
Plum (*Prunus* species).
Plum brandy.
Plum wine.
Pomegranate juice (*Punica granatum* L.)
Pomegranate wine (*Punica granatum* L.)
Pork.
Quince, marmelo (*Cydonia oblonga* Mill.)
Rambutan (*Nephelium lappaceum* L.)
Raspberry brandy.
Raspberry, blackberry and boysenberry.
Rum.
Rye bread.
Sake.
Sauerkraut.
Sherry.
Shoyu (fermented soya hydrolysate).
Soybean (Glycine max. L. merr.)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species).
Strawberry wine.
Swiss cheeses.
Syzygium species.
Tapereba, caja fruit (*Spondias lutea* L.)
Tea.
Tequila (*Agave tequilana*).
Tomato (*Lycopersicon esculentum* Mill.)
Vinegar.
Wheaten bread.
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 compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

## 7. IFRA standard

None.

## 8. REACH dossier

Available; accessed on 07/11/16.

## 9. Summary

### 9.1. Human health endpoint summaries

#### 9.1.1. Genotoxicity

Based on the current existing data, isoamyl acetate does not present a concern for genetic toxicity.

*9.1.1.1. Risk assessment.* The mutagenic activity of isoamyl acetate (CAS # 123-92-2) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA97,TA98, TA100 TA102 and TA104 were treated with isoamyl acetate at 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 (Zeiger et al., 1992). Under the conditions of the study, isoamyl acetate was not mutagenic in the Ames test. No increases in the mean number of revertant colonies of *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 were observed at any tested dose of isoamyl alcohol ranging from 0.1 to 10 mg/plate (McCarroll et al., 1985). The mutagenic activity of isoamyl acetate (CAS # 123-92-2) has been evaluated in a bacterial reverse mutation assay conducted using the preincubation method. *Salmonella typhimurium* strains TA1535, TA1537, TA92, TA98, TA94 and TA100 were treated with isoamyl acetate in DMSO (dimethyl sulfoxide) at maximum concentrations up to 5 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 acetate was not mutagenic in the Ames test.

The clastogenicity of isoamyl acetate was assessed in an *in vitro* chromosome aberration study. Chinese hamster lung cells were treated with isoamyl acetate 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 acetate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

Due to lack of additional clastogenicity data in presence of metabolic activation, read across can be made while considering isoamyl acetate will readily hydrolyze into isoamyl alcohol (CAS# 123-51-3; see section 5) and acetic acid (CAS# 64-19-7; 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). The clastogenicity of acetic acid was assessed in an *in vitro* chromosome aberration study conducted by following guideline equivalent to OECD TG 473. Chinese hamster ovary were treated with acetic acid in water at concentrations up to 20 mM in the presence and 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, either with or without S9 metabolic activation (ECHA REACH Dossier: acetic acid, 004 Key Experimental study; accessed 08/29/2016). Under the conditions of the study, acetic acid was considered to be non-clastogenic to mammalian cells. Under the conditions of the study, isoamyl alcohol and acetic acid were considered to be non-clastogenic in the *in vivo* micronucleus test and i*n vitro* chromosomal aberration study, respectively, which can be extended to isoamyl acetate based on metabolism.

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

**Additional References**: Yoo, 1986; RIFM, 1988; Kuroda et al., 1984; Zimmermann et al., 1985a, 1985b; Oda et al., 1978;

Foureman et al., 1994; ECHA REACH Dossier: Acetic acid.

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

*9.1.2. Repeated dose toxicity*

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

*9.1.2.1. Risk assessment.* There are no repeated dose toxicity data on isoamyl acetate. Isoamyl acetate will hydrolyze readily into isoamyl alcohol (CAS# 123-51-3; see section 5) and acetic acid (CAS# 64-19-7; 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 the 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 which were administered the 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 (Carpanini et al., 1973). There are insufficient repeated dose toxicity data on metabolite, acetic acid (CAS# 64-19-7). 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 repeated dose toxicity is equal to the isoamyl alcohol NOAEL divided by the total systemic exposure, 1250/0.0039 or 320513.

In addition, the total systemic exposure for isoamyl acetate (3.9 μg/kg bw/day) is below the TTC (30 μg/kg bw/day).

**Additional References**: None.

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

*9.1.3. Developmental and reproductive toxicity*

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

*9.1.3.1. Risk assessment.* There are no developmental toxicity data on isoamyl acetate. Isoamyl acetate will hydrolyze readily into isoamyl alcohol (CAS# 123-51-3; see section 5) and acetic acid (CAS# 64-19-7; 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 in ECHA REACH dossier on 3-methylbutan-1-ol, accessed on 6/20/2016). In another study, an OECD 414 developmental toxicity study was conducted on a group of 25 female pregnant Wistar rats/group administered the 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 in ECHA REACH dossier on 3-methylbutan-1-ol, accessed on 6/20/2016). 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 the 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. In addition, metabolite acetic acid (CAS# 64-19-7; see section 5) had developmental toxicity studies conducted in rats, mice and rabbits. In all three species, the NOAEL was 1600 mg/kg/day, the highest dose tested (ECHA REACH Dossier: acetic acid, accessed 06/28/16). The most conservative NOAEL of 300 mg/kg/day was selected for the developmental toxicity endpoint.

There is no reproductive toxicity data on isoamyl acetate. 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). The NOAEL for reproductive toxicity was determined to be 300 mg/kg/day the highest dose tested.

Therefore, the MOE for developmental and reproductive toxicity is equal to the isoamyl alcohol NOAEL divided by the total systemic exposure, 300/0.0039 or 76923.

In addition, the total systemic exposure for isoamyl acetate (3.9 μg/kg bw/day) is below the TTC (30 μg/kg bw/day).

**Additional References**: None.

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

*9.1.4. Skin sensitization*

Based on the existing data, Isoamyl acetate does not present a concern for skin sensitization.

*9.1.4.1. Risk assessment.* Based on the existing data, isoamyl acetate 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 guinea pig maximization test, a mixture of primary amyl acetates did not result in reactions indicative of sensitization (Ballantyne et al., 1986). Similarly, isoamyl acetate was found to be negative in a guinea pig Open

Epicutaneous Test (OET) (Klecak, 1979, 1985). In a human maximization test, no skin sensitization reactions were observed with 8% or 5520 μg/cm<sup>2</sup> isoamyl acetate (RIFM, 1973). Additionally, in a confirmatory human repeated insult patch test (HRIPT) with 20% or 23622 μg/cm<sup>2</sup> of 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 animal and human data isoamyl acetate does not present a concern for skin sensitization.

**Additional References**: None.

**Literature Search and Risk Assessment Completed on**: 07/08/16.

*9.1.5. Phototoxicity/photoallergenicity*

Based on the available UV/Vis spectra along with existing data, isoamyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

*9.1.5.1. Risk assessment.* UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L $mol^{-1}$ $cm^{-1}$ (Henry et al., 2009). When 20% isoamyl acetate was applied dermally to 25 volunteers, there was no evidence of phototoxicity or photoallergenicity (RIFM, 1986). Based on lack of absorbance and clinical data, isoamyl acetate does not present a concern for phototoxicity or photoallergenicity.

**Additional References**: None.

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

*9.1.6. Local respiratory toxicity*

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

*9.1.6.1. Risk assessment.* There are limited inhalation data available on isoamyl acetate. Based on the Creme RIFM model, the inhalation exposure is 0.034 mg/day. This exposure is 41.2 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 and Smyth, 1928; Cattarelli et al., 1977; Roth and Tansy, 1972; Schwartz et al., 1994; Leclerc et al., 2002; Bensafi et al., 2002; Cain et al., 2010.

**Literature Search and Risk Assessment Completed on**: 07/08/2016.

*9.2. Environmental endpoint summary*

*9.2.1. Screening-level assessment*

A screening level risk assessment of isoamyl acetate 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 acetate was identified as a fragrance material with the 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 acetate 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 I.

*9.2.2. Risk assessment*

Based on current VoU (2011), isoamyl acetate presents a risk to the aquatic compartment in the screening level assessment.

*9.2.2.1. Biodegradation.* RIFM, 1999: The Ready Biodegradability of the test material was evaluated by the Manometric Respirometry Test according to OECD 301F guideline. Isoamyl acetate (100 mg/l) was added to flasks containing mineral salts medium inoculated with activated sludge. The incubation was conducted for 37 days. The biodegradation rate was 74% at the 10-day window, 88% after 28 days and 90% after 37 days.

*9.2.2.2. Ecotoxicity.* RIFM, 1993: A 96 h fish (Zebra fish) acute toxicity study was conducted according to the OECD 203 method under static conditions. The LCC50 was reported to be greater than 21.5 mg/l but less than 46.40 mg/l.

RIFM, 1990c: Daphnia magna immobilization study was conducted according to the DIN 38412 L11 method, and the 48 h EC50 was reported to be 42 mg/l.

RIFM, 1989: An Algae growth inhibition study was conducted according to the DIN 38412 L9 method. The 48 h ErC50 was reported to be > 100 mg/l.

*9.2.2.3. Other available data.* Isoamyl acetate has been registered and the following additional information is available:

An Algae growth inhibition study was conducted according to the OECD 201 method. The 48 h ErC50 was reported to be > 100 mg/l.

*9.2.3. Risk assessment refinement*

Since isoamyl acetate has passed the screening criteria, measured values are included for completeness only and have 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)** | 43.21 mg/L | | | 1,000,000 | 0.04321 µg/L | |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 12.2 mg/L | 24.66 mg/L | 10.06 mg/L | 10,000 | 1.006 µg/L | Esters |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 61.95 mg/L | 36.04 mg/L | 29.69 mg/L | | | Neutral Organic SAR (Baseline toxicity) |

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ used | 2.7 | 2.7 |
| Biodegradation Factor Used | 1 | 1 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | 10–100 | 10–100 |
| **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 1.006 µg/L. The revised PEC/PNECs for EU and NA are <1 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.

## 10. Literature search*

- RIFM database: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHAhttp://echa.europa.eu/
- NTPhttp://tools.niehs.nih.gov/ntp_tox/index.cfm
- OECD Toolbox
- SciFinderhttps://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- PUBMEDhttp://www.ncbi.nlm.nih.gov/pubmed
- TOXNEThttp://toxnet.nlm.nih.gov/
- IARC (http://monographs.iarc.fr)
- OECD SIDShttp://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- EPA Actorhttp://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid%3d0EF5C212B7906229F477472A9A4D05B7
- US EPA HPVIShttp://www.epa.gov/hpv/hpvis/index.html
- US EPA Robust Summaryhttp://cfpub.epa.gov/hpv-s/
- Japanese NITEhttp://www.safe.nite.go.jp/english/db.html
- Japan Existing Chemical Data Basehttp://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- Googlehttps://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.2017.03.046.

## Transparency document

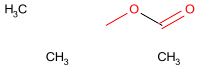
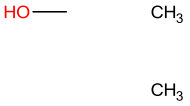
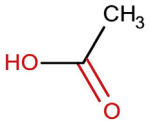
Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.03.046.

## 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).

| | Target material | Read across material | |
|---|---|---|---|
| Principal Name | Isoamyl acetate | Isoamyl alcohol | Acetic acid |
| CAS No. | 123-92-2 | 123-51-3 | 64-19-7 |
| Structure |  |  |  |
| Similarity (Tanimoto score) | 1 | 0.59 | 0.4462 |
| Read across endpoint | | • Genotoxicity,<br>• Repeated dose,<br>• Developmental and reproductive toxicity | • Genotoxicity,<br>• Repeated dose,<br>• Developmental and reproductive toxicity |
| Molecular Formula | $C_7H_{14}O_2$ | $C_5H_{12}O$ | $C_2H_4O_2$ |
| Molecular Weight | 130.19 | 88.15 | 60.05 |
| Melting Point (°C, EPISUITE) | −56.05 | −61.49 | −21.26 |
| Boiling Point (°C, EPISUITE) | 134.87 | 123.17 | 122.30 |
| Vapor Pressure (Pa @ 25 °C, EPISUITE) | 756 | 512 | 2.29E+003 |
| Log Kow (KOWWIN v1.68 in EPISUITE) | 2.25 | 1.16 | −0.17 |
| Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE) | 1100 | 4.158e+004 | 4.759e+005 |
| $J_{max}$ (mg/cm$^2$/h, SAM) | 55.89014 | 1142.301 | 2990.101 |
| Henry's Law (Pa·m$^3$/mol, Bond Method, EPISUITE) | 5.52E+001 | 1.34E+000 | 5.55E-002 |
| *Genotoxicity* | | | |
| DNA binding (OASIS v 1.1 QSAR Toolbox 3.1) | • AN2, SN1, SN2 | • No alert found | • No alert found |
| DNA binding by OECD QSAR Toolbox (3.1) | • 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 |
| DNA alerts for Ames, MN, CA by OASIS v 1.1 | • 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 |
| In-vivo mutagenicity (Micronucleus) alerts by ISS | • No alert found | • No alert found | • No alert found |
| Oncologic Classification | • 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 (3.1) | • Non binder, non cyclic structure | • Non binder, non cyclic structure | • Non binder, non cyclic structure |
| Developmental Toxicity Model by CAESAR v2.1.6 | • Toxicant (good reliability) | • Toxicant (good reliability) | • Toxicant (low reliability) |
| *Sensitization* | | | |
| Protein binding by OASIS v1.1 | • No alert found | • No alert found | • No alert found |
| Protein binding by OECD | • No alert found | • 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) | • 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 | • No alert found |
| Skin Sensitization model (CAESAR) (version 2.1.6) | • Sensitizer (good reliability) | • Non-Sensitizer (good reliability) | • Non-Sensitizer (good reliability) |
| *Metabolism* | | | |
| OECD QSAR Toolbox (3.1) | See supplemental data 1 | See supplemental data 2 | • No metabolism. |
| Rat liver S9 metabolism simulator | • 5 metabolites from Rat S9 simulator.<br>• Aldehydes, esters, AN2, SN1, SN2, Schiff base formation. | • 8 metabolites from Rat S9 simulator.<br>• Aldehydes, Schiff base formation. | |

*Summary*

There are insufficient toxicity data on isoamyl acetate (CAS # 123-92-2). 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) and acetic acid (CAS # 64-19-7) were identified as read across materials with data for their respective toxicity end points.

*Conclusion/Rationale*

- Metabolism
  As mentioned above in metabolism section, isoamyl acetate metabolizes into isoamyl alcohol (CAS # 123-51-3) and acetic acid (CAS # 64-19-7). In addition, metabolism of the material was also predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4; See Appendix). Isoamyl acetate is metabolized to isoamyl alcohol and acetic acid in the first step both with 0.950 probability. Hence isoamyl alcohol and acetic acid can be use as read across for isoamyl acetate. Isoamyl alcohol and acetic acid was out of domain for *in vivo* rat and out of domain for *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 provided.
- Isoamyl alcohol (CAS # 123-51-3) is used as a structurally similar read across analog for isoamyl acetate (CAS # 123-92-2) for clastogenicity, repeated dose, developmental and reproductive toxicological end points.
  - The target belongs to a class of esters, while the analog belongs to a class of alcohols.
  - The read across is a direct metabolite of target.
  - The target and read across analog have a Tanimoto score of 0.59.
  - The physical chemical properties of the target and the read across analog are very similar.
  - The structural alerts for the toxicological end points are consistent between the target as well as the read across material.
  - The structural alerts show that the read across material is similarly reactive for the toxicological end points as compared to the target material.
  - The structural differences between target and the read across analog appear to be toxicologically insignificant.
- Acetic acid (CAS # 64-19-7) is used as a structurally similar read across analog for isoamyl acetate (CAS # 123-92-2) for clastogenicity, repeated dose, developmental and reproductive toxicological end points.
  - The target belongs to a class of esters while the analog is an organic acid.
  - The analog is a direct metabolite of target.
  - The target and read across analog have a Tanimoto score of 0.44262.
  - The physical chemical properties of the target and the read across analog are very similar.
  - The structural alerts for the toxicological end points are consistent between the target as well as the read across material.
  - The structural alerts show that the read across material is more reactive for the particular end points as compared to the target material.
  - The target and analog are expected to be metabolized similarly as shown by the metabolism simulator. All of the read across metabolites show no structural alerts for reproductive and skin sensitization toxicity
  - The structural differences between target and the read across analog appear to be toxicologically insignificant.

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