Short review

RIFM fragrance ingredient safety assessment, isoamyl salicylate, CAS registry number 87-20-7

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A R T I C L E   I N F O

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Repeated dose, developmental and reproductive toxicity
Skin sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

A B S T R A C T

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined using to have the most conservative systemic exposure derived NOAEL of 47 mg/kg/day. A dietary 13-week subchronic toxicity study conducted in rats on a suitable read across analog resulted in a MOE of 2350 while considering 10.3% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

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**Abbreviation list**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AF</td>
<td>Assessment Factor</td>
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<tr>
<td>BCF</td>
<td>Bioconcentration factor</td>
</tr>
<tr>
<td>DEREK</td>
<td>Derek nexus is an in silico tool used to identify structural alerts</td>
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<tr>
<td>DST</td>
<td>Dermal Sensitization Threshold</td>
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<td>ECHA</td>
<td>European Chemicals Agency</td>
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<tr>
<td>EU</td>
<td>Europe/European Union</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>IFRA</td>
<td>The International Fragrance Association</td>
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<tr>
<td>LOEL</td>
<td>Lowest Observable Effect Level</td>
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<tr>
<td>MOE</td>
<td>Margin of Exposure</td>
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<tr>
<td>MPPD</td>
<td>Multiple-Path Particle Dosimetry. An in silico model for inhaled vapors used to simulate fragrance lung deposition</td>
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<tr>
<td>NA</td>
<td>North America</td>
</tr>
<tr>
<td>NESIL</td>
<td>No Expected Sensitization Induction Level</td>
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<tr>
<td>NOAEC</td>
<td>No Observed Adverse Effect Concentration</td>
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<td>NOAEL</td>
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<tr>
<td>NOEC</td>
<td>No Observed Effect Concentration</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
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<tr>
<td>OECD TC</td>
<td>Organisation for Economic Co-operation and Development Testing Guidelines</td>
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<tr>
<td>PBT</td>
<td>Persistent, Bioaccumulative, and Toxic</td>
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<tr>
<td>PEC/PNEC</td>
<td>Predicted Environmental Concentration/Predicted No Effect Concentration</td>
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<tr>
<td>QRA</td>
<td>quantitative risk assessment</td>
</tr>
<tr>
<td>REACH</td>
<td>Registration, Evaluation, Authorisation, and Restriction of Chemicals</td>
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<tr>
<td>RIFM</td>
<td>Research Institute for Fragrance Materials</td>
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<tr>
<td>RQ</td>
<td>Risk Quotient</td>
</tr>
<tr>
<td>TTC</td>
<td>Threshold of Toxicological Concern</td>
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<tr>
<td>UV/Vis.</td>
<td>Spectra Ultra Violet/Visible spectra</td>
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<tr>
<td>VCF</td>
<td>Volatile Compounds in Food</td>
</tr>
<tr>
<td>VoU</td>
<td>Volume of Use</td>
</tr>
<tr>
<td>vPvB</td>
<td>(very) Persistent, (very) Bioaccumulative</td>
</tr>
<tr>
<td>WOE</td>
<td>Weight of Evidence</td>
</tr>
</tbody>
</table>

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.

This safety assessment is based on RIFM's Criteria Document (Api et al., 2015) and 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).

Human health safety assessment

- **Genotoxicity**: Not Genotoxic (RIFM, 1999a)
- **Repeated dose toxicity**: NOAEL – 47 mg/kg/day (Belzito et al., 2007)
- **Developmental and reproductive toxicity**: NOAEL – 75 mg/kg/day (Collins et al., 1971)
- **Skin sensitization**: Not sensitizing (Ishihara et al., 1986; RIFM, 1970)
- **Phototoxicity/Photoallergenicity**: Not phototoxic/photoallergic (UV spectra, RIFM database)
- **Respiratory toxicity**: No NOAEC available. Exposure below TTC.

Environmental safety assessment

- **Persistence**: Critical measured value: 86% based on read-across to Amyl Salicylate (RIFM, 1996a, b)
- **Bioaccumulation**: Screening level: 429 L/Kg (EPISUITE ver 4.1)
Ecotoxicity: Critical ecotoxicity endpoint: based on read across to cis-E-hexenyl salicylate (CAS# 65405-77-8) (RIFM, 2010)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1

Critical Ecotoxicity Endpoint: Based on read across to cis-E-hexenyl salicylate (CAS# 65405-77-8). Daphnia magna 48 h EC50: 0.28 mg/l (Salvo et al., 2002)

RIFM PNEC is 0.28 µg/L

Revised PEC/PNECs (2011 IFRA VolU): North America and Europe <1

1. Identification

1. Chemical Name: Isoamyl salicylate
2. CAS Registry Number: 87-20-7
3. Synonyms: Amyl(iso) salicylate, Benzoic acid, 2-hydroxy-, 3-methylbutyl ester, Isoamyl o-hydroxybenzoate, isoamyl salicylate, Isopentyl salicylate, 3-Methylbutyl salicylate, 3-Methylbutyl o-hydroxybenzoate, イソアミル亜硝酸スルホキシド, 3-メチルブタニルホルマリン酸, イソアミルオルソク酸, イソアミルオルソク酸(1)
4. Molecular formula: C_{12}H_{16}O_{3}
5. Molecular weight: 208.26
6. RIFM number: 102

2. Physical data

1. Boiling point: >200 °C [FMA database], (calculated) 306.01 °C [EPI Suite]
2. Flash point: >200 °F; CC [FMA database]
3. Log Kow: 4.49 [EPI Suite]
4. Melting point: 82.45 °C [EPI Suite]
5. Water solubility: 21.89 mg/L [EPI Suite]
6. Specific gravity: 1.049 [FMA database]
7. Vapor pressure: 0.000338 mm Hg @ 20 °C [EPI Suite 4.0], 0.000651 mm Hg @ 25 °C [EPI Suite]
8. UV Spectra: Minor absorbance between 290 and 200 nm; molar absorption coefficient below the benchmark (1000 L/mol cm\(^{-1}\))

3. Exposure

1. Volume of Use (worldwide band): 100–1000 metric tons per year [IFRA, 2011]
2. Average Maximum Concentration in Hydroalcohols: 2.19%
3. 97.5th Percentile: 4.09% [IFRA, 2002]
4. Dermal Exposure: 0.1042 mg/kg/day [IFRA, 2002]
5. Oral Exposure: Not available
6. Inhalation Exposures: 0.009 mg/kg/day [IFRA, 2002]
7. Total Systemic Exposure (Dermal + Inhalation): (0.1042 mg/kg/day X 10.3%) + 0.009 mg/kg/day = 0.20 mg/kg/day

Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

“Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heat oil plug-ins) result calculated using RIFM’s 2-Box/MPPD in silico models, based on the IFRA survey results for the 97.5th percentile use in hydroalcohols for a 60 kg individual.

4. Derivation of systemic absorption

1. Dermal: 10.3% (Read-across from amyl salicylate (CAS # 2050-08-0))

RIFM (1984a, b, c, d): The penetration of radiolabeled isomer amyl salicylate (CAS # 2050-08-0) through intact pig skin under in vitro conditions using a glass penetration chamber was evaluated at 1, 6, and 16 h after application. It was concluded that 10.3% of amyl salicylate was absorbed.

2. Oral: Data not available — not considered.
3. Inhalation: Assumed 100%
4. Total: Assume Dermal (10.3%) + Inhalation (100%) absorbed = (0.1042 mg/kg/day X 10.3%) + 0.009 mg/kg/day = 0.20 mg/kg/day

5. Computational toxicology evaluation

<table>
<thead>
<tr>
<th>Expert judgment</th>
<th>Toxtree (v 2.6.0)</th>
<th>OECD QSAR Toolbox (v. 3.2)</th>
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1. Cramer classification: Class I, low

2. Analogues Selected:
   a. Genotoxicity: Ethyl hexyl salicylate (CAS # 118-60-5)
   b. Repeated dose toxicity: Amyl salicylate (CAS # 2050-08-0)
   c. Developmental and reproductive toxicity: Amyl salicylate (CAS # 2050-08-0); methyl salicylate (CAS # 119-36-8)
   d. Skin sensitization: None
   e. Phototoxicity/Photoallergenicity: None
   f. Local respiratory toxicity: None
   g. Environmental toxicity: Salicylates SAG

3. Read across justification: See Appendix below

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

Isoamyl salicylate is reported to occur in the following foods:
1. Grape (Vitis species).
2. Tea.

7. IFRA standard

None.

8. REACH dossier

Pre-registered for 2010; No dossier available as of 7/16/2015.

9. Summary

1. Human Health Endpoint Summaries:

9.1. Genotoxicity

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

9.2. Risk assessment

Isoamyl salicylate was determined not to be genotoxic with or without metabolic activation in the BlueScreen assay (RIFM, 2013). The mutagenic activity of isoamyl salicylate was assessed in an Ames study conducted in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* TA1535, TA1537, TA98, TA100, and TA102 were treated with isoamyl salicylate in DMSO (dimethyl sulfoxide) at the concentrations 0.5, 15, 50, 150, 500 and 1500 μg/plate in the absence of exogenous metabolic activation and 0, 5, 15, 50, 150, 500, 1500 and 5000 μg/plate presence and absence of metabolic activation. No increase in the number of revertant colonies was observed in any of the tester strains at any concentration (RIFM, 1999a, b, c). Under the conditions of the study, isoamyl salicylate was considered not mutagenic in the Ames test.

There are no studies assessing the clastogenicity of isoamyl salicylate. The clastogenic activity of read across material, ethyl hexyl salicylate (CAS # 118-60-5; see Section V), was assessed in an in vivo micronucleus study conducted in compliance with GLP regulations and in accordance with OECD TG 474. Groups of male and female NMRI mice were administered a single dose of ethyl hexyl salicylate in 10 ml/kg b.w. arachis oil via oral gavage at the concentration of 2000 mg/kg b.w. Animals were euthanized at 24, 48 and 72 ours post administration and bone marrow smears prepared. There were no increases in the number of micronucleated polychromatic erythrocytes in treated samples compared to negative controls (RIFM, 1989). Under the conditions of the study, ethyl hexyl salicylate was considered unable to induce chromosomal damage or damage to the mitotic apparatus in the bone marrow cells of mice and this can be extended to the target material, isobutyl salicylate.

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

Additional references: RIFM, 2013.

Literature search and risk assessment completed on: 07/12/13.

9.3. Repeated dose toxicity

The margin of exposure for the repeated dose toxicity endpoint is 2350.

9.4. Risk assessment

A dietary 13-week subchronic toxicity study was conducted with isoamyl salicylate (Drake et al., 1975). RIFM’s Expert Panel reviewed the study and concluded the NOAEL to be 47 mg/kg/day since the only finding at this dose was increased relative kidney weights in females that had no histopathological correlates (Belsito et al., 2007). Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 47/0.020 or 2350.

Additional references: Lapczynski et al., 2007a; Jimbo, 1983; Novikov et al., 1992; Webb and Hansen, 1963; Cross et al., 1998; Lapczynski et al., 2007b; Webb and Hansen, 1962; Giroux et al., 1954; RIFM, 1978; Hruban et al., 1966; Gage, 1970; Stoner et al., 1973; NTP, 1984; Harrisson et al., 1963; Packman et al., 1961; Bar and Griedentrog, 1967; Burdette and Strong, 1941; RIFM, 1984d; Morrissey et al., 1989; Chapin and Sloane, 1997; Pyun, 1970; Warkany and Takacs, 1959; Infurna et al., 1990; Overman and White, 1978, 1983; Kavlock et al., 1982; Daston et al., 1988; Bertone and Monie, 1965; Overman, 1979; Woo and Hoar, 1972; Lamb et al., 1997a, 1997b; Gross et al., 1970; Miller et al., 2001; Fang et al., 2003; Hanzlik and Wetzel, 1920; Robinson and Williams, 1956; Bohnlein et al., 1994, 1938; Davison et al., 1961; RIFM, 1984a; RIFM, 1979a; Yano et al., 1986; Scott Duncan et al., 2002; Riviere et al., 2001; Klecak, 1985; Martin et al., 2004; Pratzzel et al., 1990; Loveday, 1961; Behrendt and Kompffmeyer, 1989; Siddiqui and Ritschel, 1972; Boehnlein et al., 1989; Davis et al., 1981; Danon et al., 1986; Watkinson et al., 1992; Rivierr et al., 2000; Cross et al., 1998; Bertone and Monie, 1965; Overman, 1979; Woo and Hoar, 1972; Lamb et al., 1997a, 1997b; Gross et al., 1970; Miller et al., 2001; Fang et al., 2003; Hanzlik and Wetzel, 1920; Robinson and Williams, 1956; Bohnlein et al., 1994, 1938; Davison et al., 1961; RIFM, 1984a; RIFM, 1979a; Yano et al., 1986; Scott Duncan et al., 2002; Riviere et al., 2001; Klecak, 1985; Martin et al., 2004; Pratzzel et al., 1990; Loveday, 1961; Behrendt and Kompffmeyer, 1989; Siddiqui and Ritschel, 1972; Boehnlein et al., 1989; Davis et al., 1981; Danon et al., 1986; Watkinson et al., 1992; Rivierr et al., 2000; Cross et al., 1998; Bertone and Monie, 1965; Overman, 1979; Woo and Hoar, 1972; Lamb et al., 1997a, 1997b; Gross et al., 1970; Miller et al., 2001; Fang et al., 2003; Hanzlik and Wetzel, 1920; Robinson and Williams, 1956; Bohnlein et al., 1994, 1938; Davison et al., 1961; RIFM, 1984a; RIFM, 1979a; Yano et al., 1986; Scott Duncan et al., 2002; Riviere et al., 2001; Klecak, 1985; Martin et al., 2004; Pratzzel et al., 1990; Loveday, 1961; Behrendt and Kompffmeyer, 1989; Siddiqui and Ritschel, 1972; Boehnlein et al., 1989; Davis et al., 1981; Danon et al., 1986; Watkinson et al., 1992; Rivierr et al., 2000; Cross et al., 1998; Bertone and Monie, 1965; Overman, 1979; Woo and Hoar, 1972; Lamb et al., 1997a, 1997b; Gross et al., 1970; Miller et al., 2001; Fang et al., 2003; Hanzlik and Wetzel, 1920; Robinson and Williams, 1956; Bohnlein et al., 1994, 1938; Davison et al., 1961; RIFM, 1984a; RIFM, 1979a; Yano et al., 1986; Scott Duncan et al., 2002; Riviere et al., 2001; Klecak, 1985; Martin et al., 2004; Pratzzel et al., 1990; Loveday, 1961; Behrendt and Kompffmeyer, 1989; Siddiqui and Ritschel, 1972; Boehnlein et al., 1989; Davis et al., 1981; Danon et al., 1986; Watkinson et al., 1992; Rivierr et al., 2000; Cross et al., 1998; Bertone and Monie, 1965; Overman, 1979; Woo and Hoar, 1972; Lamb et al., 1997a, 1997b; Gross et al., 1970; Miller et al., 2001; Fang et al., 2003; Hanzlik and Wetzel, 1920; Robinson and Williams, 1956; Bohnlein et al., 1994, 1938; Davison et al., 1961; RIFM, 1984a; RIFM, 1979a; Yano et al., 1986; Scott Duncan et al., 2002; Riviere et al., 2001; Klecak, 1985; Martin et al., 2004; Pratzzel et al., 1990; Loveday, 1961; Behrendt and Kompffmeyer, 1989; Siddiqui and Ritschel, 1972; Boehnlein et al., 1989; Davis et al., 1981; Danon et al., 1986; Watkinson et al., 1992; Riviere et al., 2000; Cross et al., 1997; Megwa et al., 1995;
Higo et al., 1995; Kasting et al., 1987; Brown and Scott, 1934a, 1934b; Bliss, 1935; Meyer, 1965; Beutner et al., 1943; Lapczynski et al., 2007c; RIFM, 1979b; RIFM, 1984b; RIFM, 1995a; RIFM, 1996a, b; RIFM, 1995b; Treffel and Gabard, 1996; RIFM, 2002a; Lapczynski et al., 2007d; Morohoshi et al., 2005; RIFM, 2002b; RIFM, 2002c, RIFM, 1995c.

Literature search and risk assessment completed on: 07/12/13.

9.7. Skin sensitization

Based on the existing data, isoamyl salicylate does not present a concern for skin sensitization.

9.8. Risk assessment

Based on the existing data, isoamyl salicylate does not present a concern for skin sensitization. It is predicted to be non-reactive to skin proteins and therefore would not be expected to act as a skin sensitizer (Roberts et al., 2007; Toxtree 2.5.0; OECD Toolbox v3.1). Also, based on available guinea pig test data, isoamyl salicylate is not a skin sensitizer (Ishihara et al., 1986; RIFM, 1970).

RIFM’s Expert Panel reviewed the available data and concluded that isoamyl salicylate does not present a concern for skin sensitization (Belzito et al., 2007).

Additional references: None.

Literature search and risk assessment completed on: 07/12/13.

9.9. Phototoxicity/Photoallergenicity

Based on UV/Vis absorption spectra, isoamyl salicylate would not be expected to present a concern for phototoxicity or photoallergenicity.

9.10. Risk assessment

There are no phototoxicity studies available for isoamyl salicylate in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The molar absorption coefficient is below the benchmark (1000 L/mol · cm⁻¹) of concern for phototoxic effects (Henry et al., 2009). Based on lack of significant absorbance in the critical range, isoamyl salicylate does not present a concern for phototoxicity or photoallergenicity.

Additional references: None.

Literature search and risk assessment completed on: 07/12/13.

9.11. Local respiratory toxicity

The isoamyl salicylate exposure level is below the inhalation TTC Cramer Class I limit for local effects.

9.12. Risk assessment

There are no inhalation data available in the database. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 4.09%. Assuming the same amount is used in all product types (e.g., fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heatable oil plug-ins) the inhalation aggregate exposure would be 0.54 mg/day, as calculated by RIFM’s 2-Box Model and further refined using the Multiple Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value. This value is below the Cramer Class I TTC level of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009) and is deemed safe for use at the reported use level.

Additional references: None.

Literature search and risk assessment completed on: 07/12/13.

9.13. Screening-level assessment

A screening level risk assessment of isoamyl salicylate 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 Kow 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). Following the RIFM Environmental Framework, isoamyl salicylate 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 salicylate 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., US EPA’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.


Based on current VoU (as of 2011) isoamyl salicylate presents a risk to the aquatic compartment.

9.15. Key studies

**Biodegradation:** No data available. Please see “other available data” section for read across data

9.15.1. Ecotoxicity

RIFM, 1999b: The acute toxicity in Daphnia magna was evaluated using a static system. The ECO at 48 h was 2 mg/l; the EC100 was 4 mg/l. The geometric mean determined at 48 h was 2.8 mg/l.

RIFM, 1983: A 24 h acute toxicity test with D. magna was conducted with test material. The EC50 at 24 h was 4.5 mg/l.

RIFM, 2000a, b, c: An acute toxicity study was conducted for REACH with no additional data. For the summary of read-across data, see Appendix below.

Other available data: Isoamyl salicylate has been pre-registered for REACH with no additional data. For the summary of read-across data, see Appendix below.

9.16. 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.
Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito et al., 2002).

The RIFM PNEC is 0.28 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature search and risk assessment Completed on: 07/12/13.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Europe (EU)</th>
<th>North America (NA)</th>
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<tbody>
<tr>
<td>Log $K_{ow}$ used</td>
<td>4.49</td>
<td>4.49</td>
</tr>
<tr>
<td>Biodegradation Factor Used</td>
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<td>1</td>
</tr>
<tr>
<td>Dilution Factor</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Regional Volume of Use Tonnage Band</td>
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<td>10–100</td>
</tr>
<tr>
<td>Risk Characterization: PEC/PNEC</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Based on read across, the RQs for these materials are <1. No further assessment is necessary.

The RIFM PNEC is 0.28 μg/L. The revised PEC/PNECs for EU and NA are <1 and therefore, do not present a risk to the aquatic environment at the current reported volumes of use.

Literature search and risk assessment Completed on: 07/12/13.

10. Literature search

- RIFM database: Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHA: http://echa.europa.eu/
- OECD toolbox
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- 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

3 Information sources outside of RIFM’s database are noted as appropriate in the safety assessment.
Summary

There are insufficient toxicity data on isoamyl salicylate (RIFM #102, CAS # 87-20-7). Hence, in silico evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Appendix

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<tr>
<th>Principal name</th>
<th>Target material</th>
<th>Read across materials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isoamyl salicylate</td>
<td>Ethyl hexyl salicylate</td>
</tr>
<tr>
<td>CAS No. Structure</td>
<td>87-20-7</td>
<td>118-60-5</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C12H16O3</td>
<td>C15H22O3</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>208.26</td>
<td>250.34</td>
</tr>
<tr>
<td>Melting point</td>
<td>82.45</td>
<td>108.87</td>
</tr>
<tr>
<td>Boiling point</td>
<td>306.01</td>
<td>344.94</td>
</tr>
<tr>
<td>Log Kow</td>
<td>4.49</td>
<td>5.97</td>
</tr>
<tr>
<td>Water solubility</td>
<td>21.89</td>
<td>0.7171</td>
</tr>
<tr>
<td>Henry's Law</td>
<td>41.58888349</td>
<td>5.518241291</td>
</tr>
<tr>
<td>Jmax (mg/cm²/h, SAM)</td>
<td>1.430709</td>
<td>3.347778</td>
</tr>
<tr>
<td>Similarity (Tanimoto score)</td>
<td>71%</td>
<td>79%</td>
</tr>
<tr>
<td>Skin absorption percentage (SAM)</td>
<td>80%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Genotoxicity

DNA binding (OASIS v1.1) • No alert found
DNA binding (OECD) • No alert found
Carcinogenicity (genotoxic and non-genotoxic) alerts (ISS) • Structural alert for nongenotoxic carcinogenicity
Substituted n-alkylcarboxylic acids (Nongenotoxic) • No alert found

DNA alerts for Ames, MN, CA (OASIS v1.1)
In vitro mutagenicity (Ames test) alerts (ISS) • H-acceptor-path3-H-acceptor
In vivo mutagenicity (Microsomal) alerts (ISS) • No alert found

This is not an exhaustive list.
Methods

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- The Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010), the parameters were calculated using consensus model (CAESAR v2.1.6).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012).

Conclusion/Rationale

- Ethyl hexyl salicylate (analog) was used as a read-across for isoamyl salicylate (target) based on:
  - The target and analog both belong to the generic class of aromatic esters, specifically salicylates.
  - The key differences are that the target has an isopentyl chain, while the analog has a 2-ethyl hexyl chain. These differences do not materially change the physicochemical properties nor raise any additional structural alerts and therefore, the genotoxicity profiles are expected to be similar.
  - Both the target and the analog show similar alerts for DNA binding and mutagenicity. The analog shows additional alerts that they have different alcohol parts. These differences do not materially change the physicochemical properties nor raise any additional structural alerts and therefore, the reproductive and developmental toxicity profiles are expected to be similar.
  - As per the OECD Toolbox both the materials are predicted to have similar metabolites.
  - Both are structural isomers. The key differences are that the target has an isopentyl chain, while the analog has a 2 ethyl hexyl chain. These differences do not materially change the physicochemical properties nor raise any additional structural alerts and therefore, the repeated dose toxicity profiles are expected to be similar.

Environmental toxicity justification

Within the RIFM Database there are a number of salicylate materials that are structurally related. Some of these materials have measured data available which can be useful in assessing the safety of other “data poor” materials. For details see below.

Ecotoxicity

There are a number of studies that were conducted for multiple salicylates; unfortunately most of these studies did not follow generally acceptable guidelines (ex. OECD) or the reported results were not supported by appropriate analytical analyses. Therefore, to support the most conservative approach for safety for this class of materials, a 72 h EC50 of 0.28 mg/l for an Algae Inhibition Study conducted with cis-E-hexenyl salicylate was selected as the key
study/endpoint in deriving the PNEC for this class of chemicals. This value was derived based on standard methodology (OECD 201 guidelines) following GLP requirements. The shorter chain length salicylates would be less toxic; therefore using the higher chain length measured value with an assessment factor of 1000 provides a conservatively derived PNEC for this class of materials.

**Biodegradation**

There are a number of biodegradation studies, using different OECD guidelines that demonstrate similar degradation rates across the class, which indicates that a read — across these materials is appropriate.

For details on Ecotoxicity and biodegradation studies available in RIFM Database see table below.

In addition, 1 hexyl salicylate (CAS# 6259-76-3) has been registered under REACH and the following additional data is available:

Hexyl salicylate: OECD 202: Daphnia magna: 48 h EC50: 0.357 mg/l.

<table>
<thead>
<tr>
<th>Name</th>
<th>CAS</th>
<th>Structure</th>
<th>Kow/Water solubility</th>
<th>Biodegradation (all useful for safety and hazard assessment)</th>
<th>Ecotoxicity</th>
<th>Usefulness/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyl salicylate</td>
<td>2050-08-0</td>
<td><img src="image" alt="Structure" /></td>
<td>4.4 and 4.5 (measured)</td>
<td>301B: 81.3% - RIFM, 1994b; 301F: 86% - RIFM, 1996a; 92/69/EEC C.4: 84% - RIFM, 2001a; 79/831/EVG V.C: 29% - RIFM, 2001b</td>
<td>96 h Fish LC50: 1.34 mg/l (LC0/LC100) (RIFM, 1993); 96 h Danio rerio OECD 203: LC50: 10–100 mg/l (RIFM, 2000b, <a href="http://rifmdatabase.rifm.org/RifmDatabase/Studies/42556">http://rifmdatabase.rifm.org/RifmDatabase/Studies/42556</a>)</td>
<td>Useful with limitations</td>
</tr>
<tr>
<td>Benzoic acid, 2-hydroxy-, 2-methylbutyl ester</td>
<td>51115-63-0</td>
<td><img src="image" alt="Structure" /></td>
<td>4.4 and 4.5 (measured)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Butyl salicylate</td>
<td>2052-14-4</td>
<td><img src="image" alt="Structure" /></td>
<td>0.08/19.78 mg/l</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>1,3-Dimethyl-3-butenyl salicylate</td>
<td>80118-10-1</td>
<td><img src="image" alt="Structure" /></td>
<td>4.91/8.43 mg/l</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ethyl hexyl salicylate</td>
<td>118-60-5</td>
<td><img src="image" alt="Structure" /></td>
<td>5.97/0.71 mg/l</td>
<td>84/449 EEC: 89% (RIFM, 1992)</td>
<td>48 h Daphnia magna 67/548/EEC C.2: EC50: between 10 and 31 mg/l (RIFM, 1992); 96 h Brachydanio rerio acute: LC50: 613 mg/l (RIFM, 1992)</td>
<td>Useful with limitations</td>
</tr>
<tr>
<td>Hexyl salicylate</td>
<td>6259-76-3</td>
<td><img src="image" alt="Structure" /></td>
<td>5.5 (measured)/6.084 mg/l</td>
<td>OECD 301F: 91% (RIFM, 1995a); OECD 301B: 89.9% (RIFM, 1994a)</td>
<td>48 h acute Daphnia Magna: ECO/EC100: 0.39 mg/l (RIFM, 1996c); 24 h Acute Daphnia magna EC50: 1.5 mg/l (RIFM, 1983); 96 h Danio rerio Acute OECD 203; LC50: &gt;100 mg/l (RIFM, 2000b)</td>
<td>Useful with limitations</td>
</tr>
</tbody>
</table>
### References


Essential Estimation Programs Interface (EPI) SuiteTM (version 4.1) [Software].


