Short review

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

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Local respiratory toxicity
Environmental safety

Abstract

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>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>Assessment Factor</td>
</tr>
<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>
</tr>
<tr>
<td>DST</td>
<td>Dermal Sensitization Threshold</td>
</tr>
<tr>
<td>ECHA</td>
<td>European Chemicals Agency</td>
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<tr>
<td>EU</td>
<td>Europe/European Union</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>IFRA</td>
<td>The International Fragrance Association</td>
</tr>
<tr>
<td>LOEL</td>
<td>Lowest Observable Effect Level</td>
</tr>
<tr>
<td>MOE</td>
<td>Margin of Exposure</td>
</tr>
<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>
</tr>
<tr>
<td>NOAEC</td>
<td>No Observed Adverse Effect Concentration</td>
</tr>
<tr>
<td>NOAEL</td>
<td>No Observed Adverse Effect Level</td>
</tr>
<tr>
<td>NOEC</td>
<td>No Observed Effect Concentration</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OECD TG</td>
<td>Organisation for Economic Co-operation and Development Testing Guidelines</td>
</tr>
<tr>
<td>PEC/PNEC</td>
<td>Predicted Environmental Concentration/Predicted No Effect Concentration</td>
</tr>
<tr>
<td>PBT</td>
<td>Persistent, Bioaccumulative, and Toxic</td>
</tr>
<tr>
<td>QRA</td>
<td>quantitative risk assessment</td>
</tr>
<tr>
<td>REACH</td>
<td>Registration, Evaluation, Authorisation, and Restriction of Chemicals</td>
</tr>
<tr>
<td>RIFM</td>
<td>Research Institute for Fragrance Materials</td>
</tr>
<tr>
<td>RQ</td>
<td>Risk Quotient</td>
</tr>
<tr>
<td>TTC</td>
<td>Threshold of Toxicological Concern</td>
</tr>
<tr>
<td>UV/Vis.</td>
<td>Spectra Ultra Violet/Visible spectra</td>
</tr>
<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 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 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.

Human health safety assessment

Genotoxicity: Not Genotoxic (RIFM, 1999a)
Repeated dose toxicity: NOAEL – 47 mg/kg/day (Belsoito 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

Hazard 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)
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, isooamyl salicylate, Isopentyl salicylate, 3-Methylbutyl salicylate, 3-Methylbutyl 0-hydroxybenzoate, トウロシ安息香酸アミル(ISO)酸 (C = 1 ~ 22)
4. **Molecular formula**: C₁₂H₁₆O₃
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% [IFRA, 2002]
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

4. Derivation of systemic absorption

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

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>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
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</table>

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

Isoamyl salicylate is reported to occur in the following foods¹: Grape (Vitis species), Tea.

7. IFRA standard

None.

8. REACH dossier

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

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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 in an Ames study conducted in accordance with OECD TG 471 (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 Griepentrog, 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; Williams, 1938; Davison et al., 1961; RIFM, 1984a; RIFM, 1979a; Yano et al., 1986; Scott Duncan et al., 2002; Riviere et al., 2001; Kleck, 1985; Martin et al., 2004; Pratzel et al., 1990; Loveday, 1961; Behrendt and Kampa-Frneyer, 1989; Siddiqi and Ritschel, 1972; Boehnlein et al., 1994; Davis et al., 1981; Danon et al., 1986; Watkinson et al., 1992; Riviere et al., 2000; Cross et al., 1998; Hanzlik and Wetzel, 1920; Robinson and Williams, 1956; Bohnlein et al., 1994; Williams, 1938; Davison et al., 1961; RIFM, 1984a; RIFM, 1979a; Yano et al., 1986; Scott Duncan et al., 2002; Riviere et al., 2001; Kleck, 1985; Martin et al., 2004; Pratzel et al., 1990; Loveday, 1961; Behrendt and Kampa-Frneyer, 1989; Siddiqi and Ritschel, 1972; Boehnlein et al., 1994; Davis et al., 1981; Danon et al., 1986; Watkinson et al., 1992; Riviere et al., 2000; Cross et al., 1997; Megwa et al., 1995; Belsito et al., 2007).

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

2 RIFM’s Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.
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, 1976).

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 hydroalcohols, the 97.5th percentile was reported to be 4.09%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and Reed diffusers/heat 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 Path 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.

2. Environmental endpoint summary

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, 1999a:** The acute toxicity in Daphnia magna was evaluated using a static system. The EC0 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 D. magna in accordance with OECD 203 guidelines. The LC50 was reported to be between 10 and 100 mg/l.

**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).

<table>
<thead>
<tr>
<th>RIFM Framework</th>
<th>LC50 (Fish)</th>
<th>EC50 (Daphnia)</th>
<th>EC50 (Algae)</th>
<th>AF</th>
<th>PNEC</th>
<th>Chemical Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Level (Tier 1)</td>
<td>1.91 mg/l</td>
<td>1,000,000</td>
<td></td>
<td>0.00191 μg/l</td>
<td>Esters</td>
<td></td>
</tr>
<tr>
<td>ECOSAR Acute Endpoints (Tier 2) Ver 1.11</td>
<td>0.9787 mg/l</td>
<td>1.558 mg/l</td>
<td>0.447 mg/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOSAR Acute Endpoints (Tier 2) Ver 1.11</td>
<td>0.463 mg/l</td>
<td>0.423 mg/l</td>
<td>1.526 mg/l</td>
<td>10,000</td>
<td>0.0423 μg/l</td>
<td>Phenols</td>
</tr>
<tr>
<td>ECOSAR Acute Endpoints (Tier 2) Ver 1.11</td>
<td>0.993 mg/l</td>
<td>0.710 mg/l</td>
<td>1.367 mg/l</td>
<td></td>
<td></td>
<td>Neutral Organics</td>
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</table>

Tier 3: Measured Data including Read-across

<table>
<thead>
<tr>
<th>Exposure</th>
<th>LC50</th>
<th>EC50</th>
<th>NOEC</th>
<th>AF</th>
<th>PNEC</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish</td>
<td>10-100 mg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daphnia</td>
<td>2.8 mg/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Algae</td>
<td>0.28 mg/l</td>
<td></td>
<td></td>
<td>1,000</td>
<td>0.28 μg/l</td>
<td></td>
</tr>
</tbody>
</table>

Exposure Europe (EU) North America (NA)

| Log Kow used | 4.49 | 4.49 |
| Biodegradation Factor Used | 1 | 1 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | 100-1000 | 10-100 |

Risk Characterization: PEC/PNEC <1 <1

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 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=0EF5C212B7906229F477472A9A4D0587

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

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.

### Principal name

<table>
<thead>
<tr>
<th>Target material</th>
<th>Read across materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoamyl salicylate</td>
<td>Ethyl hexyl salicylate</td>
</tr>
<tr>
<td>CAS No. Structure</td>
<td>87-20-7</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C$<em>{12}$H$</em>{16}$O$_3$</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>208.26</td>
</tr>
<tr>
<td>Melting point (°C, EPISUITE)</td>
<td>82.45</td>
</tr>
<tr>
<td>Boiling point (°C, EPISUITE)</td>
<td>306.01</td>
</tr>
<tr>
<td>Log Kow (KOWWIN v1.68 in EPISUITE)</td>
<td>4.49</td>
</tr>
<tr>
<td>Water solubility (mg/L @ 25°C, WSKOW v1.42 in EPISUITE)</td>
<td>21.89</td>
</tr>
<tr>
<td>J$_{max}$ (mg/cm$^2$/h, SAM)</td>
<td>41.58888349</td>
</tr>
<tr>
<td>Henry’s Law (Pa·m$^3$/mol, Bond method, EPISUITE)</td>
<td>1.430709</td>
</tr>
<tr>
<td>Similarity (Tanimoto score)$^1$</td>
<td>71%</td>
</tr>
</tbody>
</table>

**Skin absorption**

| Skin absorption percentage (SAM) | 80% | 80% |

**Genotoxicity**

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

**DNA alerts for Ames, MN (OASIS v1.1)**

<p>| In vitro mutagenicity (Ames test) alerts (ISS) | H-acceptor-path3-H-acceptor | H-acceptor-path3-H-acceptor |
| In vivo mutagenicity (Micronucleus) alerts (ISS) | No alert found | No alert found |</p>
<table>
<thead>
<tr>
<th>Principal name</th>
<th>Target material</th>
<th>Read across materials</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncologic classification (OECD)</td>
<td>Isoamyl salicylate</td>
<td>Ethyl hexyl salicylate</td>
<td>See Supplemental data 1</td>
</tr>
<tr>
<td>Repeated dose toxicity</td>
<td>Not categorized</td>
<td>Strong binder, OH group</td>
<td>See Supplemental data 2</td>
</tr>
<tr>
<td>Developmental and reproductive toxicity</td>
<td>Toxicant (moderate reliability)</td>
<td>NON-Toxicant (moderate reliability)</td>
<td>See Supplemental data 3</td>
</tr>
<tr>
<td>Rat liver S9 metabolism simulator (OECD)</td>
<td>Phenol Type Compounds</td>
<td>Phenol Type Compounds</td>
<td>See Supplemental data 4</td>
</tr>
</tbody>
</table>

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 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 materials are expected to be metabolized similarly. As per the OECD Toolbox both the materials are predicted to have similar metabolites.
- Methyl salicylate (analog) was used as a read-across for isoamyl salicylate (target) based on:
  - The target and analog belong to the generic class of aromatic esters, specifically salicylates.
  - The only difference between the target and methyl salicylate is 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.
  - Both materials are expected to be metabolized similarly. As per the OECD Toolbox both the materials are predicted to have similar metabolites.
- Amyl 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.

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 between 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 Study</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 96 h Fish LC50: 1.34 mg/l (LC0/LC100) (RIFM, 1993) 96 h Danio rerio OECD 203: LC50: 10–100 mg/l (RIFM, 2000c, <a href="http://rifmdatabase.rifm.org/RifmDatabase/Studies/42556">http://rifmdatabase.rifm.org/RifmDatabase/Studies/42556</a>)</td>
<td>48 h acute Daphnia Magna: EC0: 0.39 mg/l (RIFM, 1995c) 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>
<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)/ 21.39 mg/l</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>4.08/ 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/ N/A</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/ I</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: EC0/EC100: 0.39 mg/l (RIFM, 1995c) 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>
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2015.09.014.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.09.014.

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