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Short Review

RIFM fragrance ingredient safety assessment, isobutyl salicylate, CAS Registry Number 87-19-4

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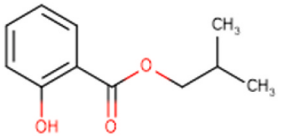
Name: Isobutyl salicylate CAS Registry Number: 87-19-4



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo)

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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, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
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
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment. This material has not been fully evaluated for photoallergenic potential.

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 includes 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 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment. This material has not been fully evaluated for photoallergenic potential.

Isobutyl salicylate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Target data and data from read-across analog ethyl hexyl salicylate (CAS # 118-60-5) show that isobutyl salicylate is not expected to be genotoxic. Data from read-across analog amyl salicylate (CAS # 2050-80-0) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints. Data from read-across analog hexyl salicylate (CAS # 6259-76-3) provide a No Expected Sensitization Induction Level (NESIL) of 35000 μg/cm^2 for the skin sensitization endpoint. The photoirritation endpoint was evaluated based on data; isobutyl salicylate does not present a concern for photoirritation. Isobutyl salicylate was not evaluated for photoallergenicity. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern for a Cramer Class I material, and the exposure to isobutyl salicylate is below the TTC (1.4 mg/day). Isobutyl salicylate was found not to be Persistent, Bioaccumulative, and Toxic as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration), are <1.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2017b; RIFM, 1989)
Repeated Dose Toxicity: NOAEL = 281 mg/kg/day. (RIFM, 2020a)
Reproductive Toxicity: Developmental toxicity and Fertility NOAEL = 333 mg/kg/day. (RIFM, 2020b)
Skin Sensitization: NESIL = 35000 μg/cm^2 (RIFM, 2004)
Photoirritation/Photoallergenicity: Not photoirritating/not evaluated for photoallergy. (RIFM, 2015a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Critical Measured Value: 80% (OECD 301F) (RIFM, 2012)
Bioaccumulation:
Screening-level: 203 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: *Daphnia Magna* 48-h LC50: 0.744 mg/L (ECOSAR v2.0; US EPA, 2012b)
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 Endpoint: *Daphnia Magna* 48-h LC50: 0.744 mg/L (ECOSAR v2.0; US EPA, 2012b)
RIFM PNEC is: 0.0744 μg/L
•**Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe <1

1. Identification

1. **Chemical Name:** Isobutyl salicylate
2. **CAS Registry Number:** 87-19-4
3. **Synonyms:** Benzoic acid, 2-hydroxy-, 2-methylpropyl ester; Isobutyl o-hydroxybenzoate; 2-Methylpropyl o-hydroxybenzoate; 2-Methyl-1-propyl salicylate; ヒドロキシ安息香酸アルキル(C 1–22); Isobutyl salicylate
4. **Molecular Formula:** $C_{11}H_{14}O_3$
5. **Molecular Weight:** 194.23 g/mol
6. **RIFM Number:** 167
7. **Stereochemistry:** No stereoisomer possible.

2. Physical data

1. **Boiling Point:** 262 °C (Fragrance Materials Association [FMA]), 291.25 °C (EPI Suite), 259.0 °C at atmospheric pressure (1010 hPa) (RIFM, 2016a)
2. **Flash Point:** >200 °F; closed cup (FMA), >93 °C (Globally Harmonized System), 124.0 °C (average corrected and rounded down to the nearest multiple of 0.5 °C) (RIFM, 2016b)
3. **Log K_{OW}:** 4 (EPI Suite), 4.09 at 21.9 °C (RIFM, 2017a)
4. **Melting Point**: 72.95 °C (EPI Suite), −31 °C at atmospheric pressure (1010 hPa) by differential scanning calorimetry (RIFM, 2016a)
5. **Water Solubility:** 67.83 mg/L (EPI Suite)
6. **Specific Gravity:** 1.064 (FMA)
7. **Vapor Pressure:** 0.00359 mm Hg at 20 °C (EPI Suite v4.0), 0.009 mm Hg at 20 °C (FMA), 0.00601 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with a peak at 306 nm and returning to baseline by 340 nm; molar absorption coefficient (3830 L mol^{-1} • cm^{-1}, condition not specified) is above the benchmark (1000 L mol^{-1} • cm^{-1})

9. **Appearance/Organoleptic:** A colorless liquid having an orchid odor

3. Volume of use (Worldwide band)

1. 10–100 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.2.10)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.050% (RIFM, 2022)
2. **Inhalation Exposure*:** 0.00087 mg/kg/day or 0.064 mg/day (RIFM, 2022)
3. **Total Systemic Exposure**:** 0.0053 mg/kg/day (RIFM, 2022)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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; Safford et al., 2017; Comiskey et al., 2017).

5. Derivation of systemic absorption

1. **Dermal:** 58.6%

Yano et al., 1986: The dermal absorption of read-across material ethyl salicylate (CAS # 118-61-6; see Section VI) was determined in 28 healthy male volunteers between the ages of 18 and 36 years. A 0.5-mg aliquot of ethyl salicylate in 10 μL of acetone was applied to 2 1.4-cm^2 areas of intact skin on the ventral forearm of each subject. The test sites were demarcated with petrolatum prior to ethyl salicylate application. The foil was removed from one site immediately after application and from the 2nd site after 4 h. Ethyl salicylate was recovered from the foil and the skin surface. The percentage absorption from 0 to 4 h was reported to be 58.6% ± 6.6% (mean ± S.E.).

2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. Computational toxicology evaluation

1. **Cramer Classification**: Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.5
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Ethyl hexyl salicylate (CAS # 118-60-5)
   b. **Repeated Dose Toxicity:** Amyl salicylate (CAS # 2050-08-0)
   c. **Reproductive Toxicity:** Amyl salicylate (CAS # 2050-08-0)
   d. **Skin Sensitization** Hexyl salicylate (CAS # 6259-76-3)
   e. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment. **Additional References:** None.

8. Natural occurrence

Isobutyl salicylate is not reported to occur in foods by the VCF*.

*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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. Reach Dossier

Available (ECHA, 2018); accessed on 04/13/22.

10. Conclusion: the maximum acceptable concentrations[a] in finished products for isobutyl salicylate are detailed below

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	2.3
2	Products applied to the axillae	0.80
3	Products applied to the face/body using fingertips	1.2
4	Products related to fine fragrances	4.7
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	3.5
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.58
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	1.2
5D	Baby cream, oil, talc	0.19
6	Products with oral and lip exposure	5.8
7	Products applied to the hair with some hand contact	1.2
8	Products with significant ano-genital exposure (tampon)	0.19
9	Products with body and hand exposure, primarily rinse-off (bar soap)	2.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	2.3
10B	Aerosol air freshener	8.2
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.19
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For isobutyl salicylate, the basis was the subchronic reference dose of 2.81 mg/kg/day, a skin absorption value of 58.60%, and a skin sensitization NESIL of 35000 μg/cm^2.

[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.2.10.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, isobutyl salicylate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Isobutyl salicylate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of isobutyl salicylate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with isobutyl salicylate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2017b). Under the conditions of the study, isobutyl salicylate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of isobutyl salicylate; however, read-across can be made to ethyl hexyl salicylate (CAS # 118-60-5; see Section VI).

The clastogenic activity of ethyl hexyl salicylate 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 Arachis oil via oral gavage to groups of male and female NMRI mice. Doses of 2000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24, 48, and 72 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 1989). Under the conditions of the study, ethyl hexyl salicylate was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to isobutyl salicylate.

Based on the data available, ethyl hexyl salicylate does not present a concern for genotoxic potential, and this can be extended to isobutyl salicylate.

Additional References: RIFM, 1988; RIFM, 2013b.

Literature Search and Risk Assessment Completed On: 04/01/22.

11.1.2. Repeated dose toxicity

The MOE for isobutyl salicylate is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on isobutyl salicylate. Read-across material amyl salicylate (CAS # 2050-80-0; see Section VI) has sufficient data to support the repeated dose toxicity endpoint. In a GLP- and OECD 408-compliant study, 10 Wistar Han rats/sex/dose were administered amyl salicylate via diet at concentrations of 0, 750, 3750, and 7500 ppm (equivalent to doses of 0, 55, 281, and 569 mg/kg/day in males, and 0, 67, 329, and 607 mg/kg/day in females, according to the study report) for 90 days. No mortality was observed throughout the study. No treatment-related adverse effects were observed in clinical signs, hematology, clinical chemistry, gross necropsy, organ weights, or histopathology. Reduced body weights and bodyweight gains, reflective of undernutrition, were observed in both sexes at the high dose. Based on reduced body weights and bodyweight gains observed in both sexes at 7500 ppm, the repeated dose toxicity NOAEL for this study was determined to be 3750 ppm (equivalent to 281 mg/kg/day in males and 329 mg/kg/day in females) (RIFM, 2020a).

In a GLP and OECD 421-compliant study, 10 Wistar Han rats/sex/dose were administered amyl salicylate via diet at concentrations of 0, 500, 1500, and 5000 ppm (equivalent to doses of 0, 33, 100, and 333 mg/kg/day, according to the study report) for a minimum of 28 days. No mortality was observed throughout the study. No treatment-related adverse effects were observed in clinical signs, macroscopic examination, organ weights, or macroscopic examination. Reduced body weights and bodyweight gains were observed in females at 5000 ppm during premating but recovered during the remainder of the study period and thus were not considered adverse. Based on no treatment-related adverse effects up to the highest dose, the repeated dose toxicity NOAEL for this study was determined to be 5000 ppm (equivalent to 333 mg/kg/day) (RIFM, 2020b).

The more conservative NOAEL was derived from the OECD 408 study at 281 mg/kg/day.

Therefore, the isobutyl salicylate MOE is equal to the amyl salicylate NOAEL (mg/kg/day) divided by the total systemic exposure (mg/kg/day) to isobutyl salicylate, 281/0.0053, or 53018.

In addition, the total systemic exposure to isobutyl salicylate (5.3 μg/kg/day) is below the TTC of a Cramer Class I material (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1.1. Derivation of subchronic reference dose (RfD). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 2.81 mg/kg/day.

The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for isobutyl salicylate was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 281 mg/kg/day by the uncertainty factor, 100 = 2.81 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/29/22.

11.1.3. Reproductive toxicity

The MOE for isobutyl salicylate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on isobutyl salicylate. Read-across material amyl salicylate (CAS # 2050-08-0; see Section VI) has sufficient data to support the reproductive toxicity endpoint. In a GLP- and OECD 421-compliant study, 10 Wistar Han rats/sex/dose were administered amyl salicylate via diet at concentrations of 0, 500, 1500, and 5000 ppm (equivalent to doses of 0, 33, 100, and 333 mg/kg/day, according to the study report) for a minimum of 28 days. Males were exposed for 29 days (from 14 days prior to mating and during the mating period), and females were exposed from 51 to 61 days (which includes 14 days prior to mating, variable time to conception, the duration of pregnancy and at least 13 days after delivery, up to and including the day of scheduled necropsy). No treatment-related adverse effects were observed on mating and fertility indices, precoital time, number of implantations, estrous cycle, or histopathology of reproductive organs. No treatment-related adverse effects were observed on gestation, viability, and lactation indices, gestation duration, parturition, maternal care, litter size, sex ratio, pup mortality, pup clinical signs, pup body weights, pup anogenital distance, pup areola/nipple retention, T4 thyroid hormone levels, or macroscopic examination. Based on no treatment-related adverse effects up to the highest dose, the reproductive toxicity NOAEL for this study was

determined to be 5000 ppm (equivalent to 333 mg/kg/day) (RIFM, 2020b).

Therefore, the isobutyl salicylate MOE for the reproductive toxicity endpoints can be calculated by dividing the amyl salicylate NOAEL in mg/kg/day by the total systemic exposure to isobutyl salicylate, 333/0.0053, or 62830.

In addition, the total systemic exposure to isobutyl salicylate (5.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/29/22.

11.1.4. Skin sensitization

Based on the existing data on the read-across material hexyl salicylate, isobutyl salicylate is a skin sensitizer with a defined NESIL of 35000 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for isobutyl salicylate. Therefore, read-across material hexyl salicylate (CAS # 6259-76-3; see Section VI) was used for the risk assessment of isobutyl salicylate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, isobutyl salicylate is a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Isobutyl salicylate was predicted not to be sensitizing based on OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a). Isobutyl salicylate was negative in the direct peptide reactivity assay (DPRA) and KeratinoSens, but positive in the human cell line activation test (h-CLAT) (RIFM, 2018b; RIFM, 2018a; RIFM, 2018c). Read-across hexyl salicylate was predicted not to be sensitizing based on OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a). Hexyl salicylate was negative in the DPRA and KeratinoSens, inconclusive in the human cell line activation test (h-CLAT), but positive in the U-SENS test (RIFM, 2014; Urbisch et al., 2015; RIFM, 2015b; RIFM, 2015c; Piroird et al., 2015). In a murine local lymph node assay (LLNA), read-across hexyl salicylate was found to be sensitizing with an EC3 value of 0.18% (45 μg/cm^2) (RIFM, 2006). In a guinea pig maximization test, read-across hexyl salicylate did not lead to skin sensitization reactions (RIFM, 1981). In human maximization tests, no skin sensitization reactions were observed when isobutyl salicylate and read-across material hexyl salicylate were tested at 6900 μg/cm^2 and 2070 μg/cm^2, respectively (RIFM, 1973; RIFM, 1976). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 35433 μg/cm^2 of read-across material hexyl salicylate in 3:1 diethyl phthalate: ethanol, no reactions indicative of sensitization were observed in any of the 103 volunteers (RIFM, 2004).

Based on the weight of evidence (WoE) from structural analysis and *in vitro*, animal, and human studies on the read-across material and the target material, isobutyl salicylate is a sensitizer with a WoE NESIL of 35000 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 2.81 mg/kg/day.

Additional References: RIFM, 1970; Klecak (1985); Ishihara et al., 1986; RIFM, 1968; Sharp (1978); RIFM, 2003; RIFM, 1967.

Literature Search and Risk Assessment Completed On: 04/04/22.

11.1.5. Photoirritation/Photoallergenicity

Based on *in vitro* study data, isobutyl salicylate does not present a concern for photoirritation. Isobutyl salicylate was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of isobutyl salicylate.

11.1.5.1. Risk assessment. UV spectra indicate significant absorbance in the critical range of 290–700 nm. The molar absorption coefficient is above the benchmark of concern for photoirritation (Henry et al., 2009). In an *in vitro* 3T3-Neutral Red Uptake photoirritation assay, isobutyl salicylate was not found to be photoirritating (RIFM, 2015a). Based on *in vitro* study data, isobutyl salicylate does not present a concern for photoirritation. Isobutyl salicylate was not evaluated for photoallergy; however, RIFM is sponsoring an *in vitro* photoallergy research program to evaluate the photoallergy potential of isobutyl salicylate.

11.1.5.2. UV spectra analysis. The available spectrum indicates significant absorbance between 290 and 700 nm, with a peak at 306 nm and returning to baseline by 340 nm. The molar absorption coefficient (3830 L mol^{-1} • cm^{-1}, condition not specified) is above the benchmark (1000 L mol^{-1} • cm^{-1}) and is, therefore, considered to be of concern for photoirritating effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/24/22.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for isobutyl salicylate is below the Cramer Class I TTC value for inhalation exposure local effects.

Table 1
Summary of existing data on hexyl salicylate as a read-across for isobutyl salicylate.

WoE Skin Sensitization Potency Category[a]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2	LLNA Weighted Mean EC3 Value μg/cm^2	GPMT[d]	Buehler[d]
Very weak	35433	2070	NA	35000	45	Negative	NA
	In vitro Data[e]				***In silico* protein binding alerts (OECD Toolbox v4.5)**		
	KE 1	**KE 2**	**KE 3**		**Target Material**	**Autoxidation simulator**	**Metabolism simulator**
	Negative	Negative	Inconclusive		No alert found	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; GPMT = Guinea Pig Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Studies conducted according to the OECD TG 406 are included in the table.

[e] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

11.1.6.1. Risk assessment. There are no inhalation data available on isobutyl salicylate. Based on the Creme RIFM Model, the inhalation exposure is 0.064 mg/day. This exposure is 21.9 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on a human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/23/22.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of isobutyl salicylate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, isobutyl 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 EPI Suite v4.11 (US EPA, 2012a) did not identify isobutyl salicylate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current VoU (2019), isobutyl salicylate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 2012**: The ready biodegradability of the test material was evaluated using a manometric respirometry test following the OECD 301F method. Under the conditions of this study, the test material underwent 80% biodegradation after 28 days.

11.2.2.1.2. Ecotoxicity. **RIFM, 2017c:** An algae growth inhibition test was conducted according to the OECD 201 method. Based on geometric mean measured test material concentrations, the 72-h EC50-values with 95% confidence intervals for inhibition of growth rate (ErC50) and yield (EyC50) were 0.745 (0.542–1.51) mg/L and 0.690 (0.547–1.55) mg/L, respectively. The EC10-values with 95% confidence intervals for inhibition of growth rate (ErC10) and yield (EyC10) after 72 h were 0.578 (0.528–1.41) mg/L and 0.393 (<0.0557–0.519) mg/L, respectively. The NOEC values for both inhibitions of growth rate and yield after 72 h were 0.163 mg/L, respectively.

RIFM, 2017d: An acute immobilization test using *Daphnia magna* was conducted according to the OECD 202 method under semi-static conditions. Under the conditions of the study and based on the geometric mean measured concentrations, the 48-h EC50 was 3.96 mg/L (95% confidence limits: 3.22 - >4.34 mg/L).

11.2.2.1.3. Other available data. Isobutyl salicylate has been pre-registered under REACH, with no additional data at this time.

11.2.3. 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 Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.0	4.0
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.0744 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 03/29/22.

Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
  - **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
  - **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
  - **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
  - **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
  - **IARC:** https://monographs.iarc.fr
  - **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
  - **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
  - **US EPA ChemView:** https://chemview.epa.gov/chemview/
  - **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	4.767			1000000	0.004767	
ECOSAR Acute Endpoints **(Tier 2)** ***v2.0***	1.756	2.945	0.913			Esters
ECOSAR Acute Endpoints **(Tier 2)**	1.012	0.744	2.816	10000	0.0744	Phenols

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 04/24/23.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2023.113909.

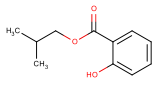
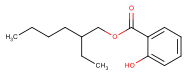
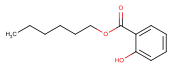
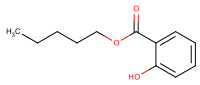
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.5 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Isobutyl salicylate	Ethyl hexyl salicylate	Hexyl salicylate	Amyl salicylate
CAS No.	87-19-4	118-60-5	6259-76-3	2050-08-0
Structure				
Similarity (Tanimoto Score)		0.84	0.83	0.85
Endpoint		•Genotoxicity	•Skin sensitization	•Repeated dose toxicity •Reproductive toxicity
Molecular Formula	$C_{11}H_{14}O_3$	$C_{15}H_{22}O_3$	$C_{13}H_{18}O_3$	$C_{12}H_{16}O_3$
Molecular Weight (g/mol)	194.23	250.34	222.28	208.26
Melting Point (°C, EPI Suite)	5.90	108.87	99.68	90.74
Boiling Point (°C, EPI Suite)	261.00	344.94	327.79	270
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.80	0.00	0.00	0.11
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	67.83	0.72	6.08	18.94
Log K_{OW}	4.00	5.97	5.06	4.57
J_{max} (μg/cm^2/h, SAM)	7.18	0.11	0.86	2.44
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.07	3.34	1.89	1.43
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found		
DNA Binding (OECD QSAR Toolbox v4.5)	No alert found	No alert found		
Carcinogenicity (ISS)	No alert found	Structural alert for nongenotoxic carcinogenicity|Substituted n-alkylcarboxylic acids (Nongenotox)		
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No skin sensitization reactivity domain alerts identified	No skin sensitization reactivity domain alerts identified		
Oncologic Classification	Phenol-type Compounds	Phenol-type Compounds		
Repeated Dose Toxicity				
Repeated Dose (HESS)	Propanolol (Renal toxicity) Alert			Not categorized
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.5)	Moderate binder, OH group			Strong binder, OH group
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)			Non-toxicant (moderate reliability)
Skin Sensitization				
Protein Binding (OASIS v1.1)	No alert found		No alert found	
Protein Binding (OECD)	No alert found		No alert found	
Protein Binding Potency	Not possible to classify according to these rules (GSH)		Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found		No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified		No skin sensitization reactivity domain alerts identified	
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on isobutyl salicylate (CAS # 87-19-4). Hence, *in silico* evaluation was conducted to determine a read-across material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, ethyl hexyl salicylate (CAS # 118-60-5), hexyl salicylate (CAS # 6259-76-3), and amyl salicylate (CAS # 2050-08-0) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusion

- Ethyl hexyl salicylate (CAS # 118-60-5) was used as a read-across analog for the target material, isobutyl salicylate (CAS # 87-19-4), for the genotoxicity endpoint.

- The target material and the read-across analog belong to the generic class of aromatic esters, specifically salicylates.
- The target material and read-across analog have the same carboxylic acid part (salicylic acid) and similar alcohol parts.
- The key difference between the target material and read-across analog is that the target material has an isobutyl alcohol, while the read-across analog has an ethyl hexyl alcohol, respectively. The differences between structures do not essentially change the physical–chemical properties nor raise any additional structural alerts, and therefore, the toxicity profiles are expected to be similar.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- Hexyl salicylate (CAS # 6259-76-3) was used as a read-across analog for the target material, isobutyl salicylate (CAS # 87-19-4), for the skin sensitization endpoint.
  - The target material and the read-across analog belong to the generic class of aromatic esters, specifically salicylates.
  - The target material and read-across analog have the same carboxylic acid part (salicylic acid) and similar alcohol parts.
  - The key difference between the target material and read-across analog is that the target material has an isobutyl alcohol, while the read-across analog has a hexyl alcohol, respectively. The differences between structures do not essentially change the physical–chemical properties nor raise any additional structural alerts, and therefore, the toxicity profiles are expected to be similar.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator. The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Amyl salicylate (CAS # 2050-08-0) was used as a read-across analog for the target material, isobutyl salicylate (CAS # 87-19-4), for the repeated dose toxicity and reproductive toxicity endpoints.
  - The target material and the read-across analog belong to the generic class of aromatic esters, specifically salicylates.
  - The target material and read-across analog have the same carboxylic acid part (salicylic acid) and similar alcohol parts.
  - The key difference between the target material and read-across analog is that the target material has an isobutyl alcohol, while the read-across analog has a pentyl alcohol, respectively. The differences between structures do not essentially change the physical–chemical properties nor raise any additional structural alerts, and therefore, the toxicity profiles are expected to be similar.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material shows renal toxicity alert for Repeated Dose (HESS) Categorization. The target material and the read-across analog show similar alerts for ER Binding. ER Binding is a molecular initiating event analogous to protein binding. ER Binding is not necessarily predictive of endocrine disruption, given the complex pre- and post-receptor events that determine activity. The data described in the developmental and reproductive toxicity and repeated dose toxicity sections confirm that the MOE for isobutyl salicylate is adequate under the current usage. Therefore, the alert is superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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