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Short Review

RIFM fragrance ingredient safety assessment, isopropoxy ethyl salicylate, CAS Registry Number 79915-74-5

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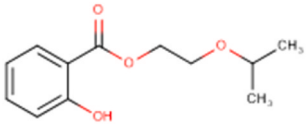

Name: Isopropoxy ethyl salicylate
CAS Registry Number: 79915-74-5

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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

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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) 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 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.

Isopropoxy ethyl salicylate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that isopropoxy ethyl salicylate is not genotoxic. Target data provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints.

Data from read-across analog hexyl salicylate (CAS # 6259-76-3) provided a No Expected Sensitization Induction Level (NESIL) of 35000 μg/cm^2 for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; isopropoxy ethyl salicylate is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to isopropoxy ethyl salicylate was below the TTC (1.4 mg/day). The environmental endpoints were evaluated; isopropoxy ethyl salicylate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) 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 [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.	(RIFM, 2013; ECHA REACH Dossier: 2-Isopropoxyethyl salicylate; ECHA, 2018)
Repeated Dose Toxicity: NOAEL = 33.33 mg/kg/day.	RIFM (2017a)
Reproductive Toxicity: Developmental Toxicity and Fertility NOAEL = 100 mg/kg/day.	(RIFM, 2017a; RIFM, 2020)
Skin Sensitization: NESIL = 35000 μg/cm^2.	RIFM (2004)
Photoirritation/ Photoallergenicity: Not photoirritating/not expected to be photoallergenic.	(UV/Vis Spectra, RIFM Database; RIFM, 1984b; RIFM, 2017b)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 100% Ministry of International Trade and Industry, Japan [MITI])	RIFM (2015e)
Bioaccumulation: Screening-level: 63 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 2.332 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)	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 2.332 mg/L	(ECOSAR v2.0; US EPA, 2012b)

RIFM PNEC is: 0.2332 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: <1

1. Identification

1. **Chemical Name:** Isopropoxy ethyl salicylate
2. **CAS Registry Number:** 79915-74-5
3. **Synonyms:** Benzoic acid, 2-hydroxy-, 2-(1methylethoxy)ethyl ester; Sakura salicylate; Isopropoxy ethyl salicylate
4. **Molecular Formula:** $C_{12}H_{16}O_4$
5. **Molecular Weight:** 224.25 g/mol
6. **RIFM Number:** 6660
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 320.39 °C (EPI Suite v4.11)
2. **Flash Point:** 154 °C (Globally Harmonized System)
3. **Log K_{OW}:** 3.24 (EPI Suite v4.11)
4. **Melting Point**: 95.46 °C (EPI Suite v4.11)
5. **Water Solubility:** 213.3 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available

(*continued on next column*)

7. **Vapor Pressure:** 4.17e-005 mm Hg at 25 °C (EPI Suite), 0.0000204 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** Some absorbance between 290 and 700 nm with peak at approximately 300 nm and returning to baseline by about 330 nm. Under neutral and acidic conditions, molar absorption coefficients (243 and 342 L mol^{-1} • cm^{-1}, respectively) are below the benchmark (1000 L mol^{-1} • cm^{-1}). Under basic conditions, molar absorption (2126 L mol^{-1} • cm^{-1}) is above the benchmark of concern.
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.3)

1. **95**th **Percentile Concentration in Fine Fragrance:** 2.4% (RIFM, 2019)
2. **Inhalation Exposure*:** 0.0027 mg/kg/day or 0.22 mg/day (RIFM, 2019)
3. **Total Systemic Exposure**:** 0.016 mg/kg/day (RIFM, 2019)

*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:** 40% RIFM Skin Absorption Model (SAM)
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	III

*See the Appendix below for details.

2. **Analogs Selected**:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   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

Isopropoxy ethyl 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 04/25/23.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for isopropoxy ethyl 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)	0.0042
2	Products applied to the axillae	0.80
3	Products applied to the face/body using fingertips	0.13
4	Products related to fine fragrances	9.9
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.3
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.14
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.21
5D	Baby cream, oil, talc	0.046
6	Products with oral and lip exposure	0.0042
7	Products applied to the hair with some hand contact	0.21
8	Products with significant ano-genital exposure (tampon)	0.046
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.67
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.038
10B	Aerosol air freshener	3.4
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.046
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	21

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 isopropoxy ethyl salicylate, the basis was the subchronic reference dose of 0.33 mg/kg/day, a predicted skin absorption value of 40%, 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, isopropoxy ethyl salicylate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of isopropoxy ethyl 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 preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with isopropoxy ethyl 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, 2013). Under the conditions of the study, isopropoxy ethyl salicylate was not mutagenic in the Ames test.

The clastogenicity of isopropoxy ethyl salicylate was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovary cells were treated with isopropoxy ethyl salicylate in DMSO. The main study was conducted at concentrations up to 188 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2018). Under the conditions of the study, isopropoxy ethyl salicylate was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

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

Additional References: RIFM, 1987; RIFM, 2016b.

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

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated toxicity data on isopropoxy ethyl salicylate. An OECD 422- and GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 10 rats/sex/dose were administered the test material, isopropoxy ethyl salicylate, at doses of 0, 50, 100, or 200 mg/kg/day via oral gavage in corn oil. Males were treated for 28 days, up to and including the day before the scheduled necropsy (this included 2 weeks prior to mating and during the mating period). Females were treated for 42–52 days (14 days prior to mating, post-coitum, and postpartum periods until day 3 of postpartum, up to and including the day before the scheduled necropsy). A male dosed at 50 mg/kg/day was found dead on day 6 of the premating phase (due to malignant leukemia), while 1 female dosed at 200 mg/kg/day was euthanized for humane reasons (on day 22 of gestation phase), and another female at 200 mg/kg/day was found dead (day 0 postpartum). The factor contributing to the death of the early decedent animal could be attributed mainly to hepatic, renal, and pancreatic injuries and as a consequence of thymus atrophy (the histopathological evaluation revealed cortical tubular necrosis and glomerular proteinaceous material in kidneys, hepatocytic necrosis of the liver, atrophy of the thymus, and acinar atrophy of the pancreas), while the poor health conditions of the second female (humanely euthanized) could be stress-related and may be associated with the difficulty in parturition. The observed deaths at the highest dose were considered to be treatment related. No treatment-related effects were seen in body weight and food consumption at any dose groups. No changes of toxicological significance were recorded for hematological and clinical chemistry in males. In females, macrocytic anemia and reticulocytosis were seen at 200 mg/kg/day. An increase in the absolute and relative weight of the spleen and a decrease in the absolute and relative weight of the adrenals were seen in the females at the highest dose. Furthermore, 3 females of the high-dose group were found not pregnant. One female from the control group did not mate. No treatment-related changes were detected at postmortem examination (terminal body weight, organ weights, macroscopic and microscopic examinations) in treated males when compared with controls. Thus, the NOAEL for repeated dose was considered to be 100 mg/kg/day, based on mortality and changes in spleen and adrenal gland weights at 200 mg/kg/day (RIFM, 2017a).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 100/3 or 33.33 mg/kg/day.

Therefore, the isopropoxy ethyl salicylate MOE for the repeated dose toxicity endpoint can be calculated by dividing the isopropoxy ethyl salicylate NOAEL in mg/kg/day by the total systemic exposure to isopropoxy ethyl salicylate, 33.33/0.016 or 2083.

In addition, the total systemic exposure to isopropoxy ethyl salicylate (16 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material 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 0.33 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 isopropoxy ethyl salicylate was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 33 mg/kg/day by the uncertainty factor, 100 = 0.33 mg/kg/day.

Additional References: None.

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

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on isopropoxy ethyl salicylate. An OECD 422- and GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 10 rats/sex/dose were administered the test material isopropoxy ethyl salicylate at doses of 0, 50, 100, or 200 mg/kg/day via oral gavage in corn oil. Males were treated for 28 days, up to and including the day before the scheduled necropsy (this included 2 weeks prior to mating and during the mating period). Females were treated for 42–52 days (14 days prior to mating, post-coitum, and postpartum periods until day 3 of postpartum, up to and including the day before the scheduled necropsy). A male dosed at 50 mg/kg/day was found dead on day 6 of the premating phase (due to malignant leukemia), while 1 female dosed at 200 mg/kg/day was euthanized for humane reasons (on day 22 of gestation phase), and another female at 200 mg/kg/day was found dead (day 0 postpartum). The factor contributing to the death of the early decedent animal could be attributed mainly to hepatic, renal, and pancreatic injuries and as a consequence of thymus atrophy, while the poor health conditions of the second female (humanely euthanized)

could be stress-related and may be associated with the difficulty in parturition. Three females of the high-dose group were found not pregnant. One female from the control group did not mate. No treatment-related anomalies were noted in the estrous cycle. The fertility indices were 90%, 100%, 100%, and 70% for control, low, mid, and high doses, respectively. Reduction in total litter size at birth, a severe increase in pre-birth loss, and a reduction in the number of females with live pups on day 4 postpartum were observed at the highest dose. No treatment-related changes were detected in treated males at any dose groups. Thus, the NOAEL for reproductive toxicity was considered to be 100 mg/kg/day, based on the reduced number of pregnant females, smaller litter size, mean total litter weights, and increased pup loss at 200 mg/kg/day (RIFM, 2017a).

Therefore, the isopropoxy ethyl salicylate MOE for the reproductive toxicity endpoint can be calculated by dividing the isopropoxy ethyl salicylate NOAEL in mg/kg/day by the total systemic exposure to isopropoxy ethyl salicylate, 100/0.016 or 6250.

In addition, the total systemic exposure to isopropoxy ethyl salicylate (16 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, isopropoxy ethyl 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 isopropoxy ethyl salicylate. Therefore, read-across material hexyl salicylate (CAS # 6259-76-3; see Section VI) was used for the risk assessment of isopropoxy ethyl salicylate. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, isopropoxy ethyl 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). Read-across material hexyl salicylate was predicted not to be sensitizing based on OECD Guideline No.

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

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm²	NOEL-HMT (induction) μg/cm²	LOEL[2] (induction) μg/cm²	WoE NESIL[3] μg/cm²	LLNA Weighted Mean EC3 Value μg/cm²	GPMT[4]	Buehler[4]
Very weak	35433	2070	NA	35000	45	Negative	NA
	In vitro Data[5]				*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.
[1]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)..
[2]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Studies conducted according to the OECD TG 406 are included in the table..
[5]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table..

497: Defined Approaches on Skin Sensitization (OECD, 2021a). Hexyl salicylate was negative in the direct peptide reactivity assay (DPRA) and KeratinoSens, inconclusive in the human cell line activation test (h-CLAT), and positive in the U-SENS test (RIFM, 2014; Urbisch et al., 2015; RIFM, 2015a; RIFM, 2015b; Piroird et al., 2015). In a murine local lymph node assay: BrdU-ELISA (LLNA:BrdU-ELISA), isopropoxy ethyl salicylate was found to be sensitizing with an EC1.6 value < 25% (6250 μg/cm^2) (RIFM, 2016c). Additionally, in a standard LLNA, read-across material 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 read-across material hexyl salicylate was tested at 2070 μg/cm^2 (RIFM, 1975; 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 weight of evidence (WoE) from structural analysis and *in vitro*, animal, and human studies on the read-across material and the target material, isopropoxy ethyl 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 0.33 mg/kg/day.

Additional References: RIFM, 1984a; RIFM, 1968; Sharp (1978); RIFM, 2003; RIFM, 1967.

Literature Search and Risk Assessment Completed On: 03/31/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra and *in vitro* and *in vivo* study data, isopropoxy ethyl salicylate would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, isopropoxy ethyl salicylate would not be expected to present a concern for photoallergy.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm under both the biologically relevant neutral condition and the acidic condition. The corresponding molar absorption coefficients are below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Absorbance under the basic condition between 290 and 700 nm was demonstrated, and the corresponding molar absorption coefficient was above the benchmark of concern. However, the basic condition in this assay is defined as pH 10 or greater and may not be biologically relevant for our purposes, where the route of exposure is topical. In an *in vitro* 3T3 Neutral Red uptake photoirritation assay, isopropoxy ethyl salicylate was not predicted to be photoirritating (RIFM, 2017b). In an *in vivo* photoirritation test conducted on guinea pigs, isopropyl ethyl salicylate was not found to be photoirritating at concentrations between 5% and 50% in acetone (RIFM, 1984b). Based on the available UV/Vis absorption spectra and *in vitro* and *in vivo* study data, isopropoxy ethyl salicylate would not be expected to present a concern for photoirritation. Based on the available UV/Vis absorption spectra, isopropoxy ethyl salicylate would not be expected to present a concern for photoallergy.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate minor absorbance in the range of 290–700 nm under neutral and acidic conditions and significant absorbance under basic conditions. Under neutral and acidic conditions, molar absorption coefficients (243 and 342 L mol^{-1} • cm^{-1}, respectively) are below the benchmark of concern for photoirritating effects, 1000 L mol^{-1} • cm^{-1} (Henry et al., 2009). Under basic conditions, molar absorption (2126 L mol^{-1} • cm^{-1}) is above the benchmark 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 isopropoxy ethyl salicylate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on isopropoxy ethyl salicylate. Based on the Creme RIFM Model, the inhalation exposure is 0.22 mg/day. This exposure is 6.4 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: 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 isopropoxy ethyl 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, isopropoxy ethyl 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 isopropoxy ethyl 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.

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

11.2.1.2. Key studies. ***Biodegradation***:

RIFM, 2015e: The ready biodegradability of the test material was determined using the modified MITI Test. Mean biodegradation on day 28 via biological oxygen demand, dissolved organic carbon, and compound-specific analysis was 63%, 60%, and 100%, respectively.

Ecotoxicity:

RIFM, 2016a: A 96-h fish (*Oncorhynchus mykiss*) acute toxicity test was conducted according to the OECD 203 method under semi-static conditions. Based on the geometric mean measured concentrations, the 96 h LC50 was reported to be 3.7 mg/L.

RIFM, 2015d: An algae growth inhibition test was conducted according to the OECD 201 method. Based on the geometric mean measured test concentration, the 72-h EC50 was reported to be 95 mg/L and 3.5 mg/L for growth rate and yield, respectively. The 72-h NOEC was reported to be 2.5 mg/L for the growth rate and 0.76 mg/L for yield.

RIFM, 2015c: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under static conditions. Under the conditions of this study, the 48-h EC50 based on mean measured test concentrations was 24 mg/L (95% confidence limits of 21–27).

11.2.1.3. Other available data. Isopropoxy ethyl salicylate has been registered under REACH, with no additional data at this time.

11.2.2. Risk assessment refinement

Since isopropoxy ethyl salicylate has passed the screening criteria, measured data are included for completeness only and have not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe	North America
Log K_{ow} Used	3.2	3.2
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional VoU Tonnage Band	1–10	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.2332 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: 03/30/22.

12. 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 Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>25.20</u>			1000000	0.0252	
ECOSAR v2.0 Acute Endpoints **(Tier 2)**	5.674	10.33	3.614			Esters
ECOSAR v2.0 Acute Endpoints **(Tier 2)**	4.463	<u>2.332</u>	9.510	10000	0.2332	Phenols
ECOSAR v2.0 Acute Endpoints **(Tier 2)**	14.24	9.066	10.83			Neutral Organic SAR

- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

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 05/01/23.

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.2023.114267.

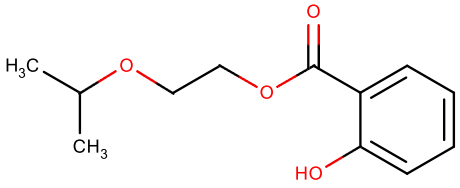
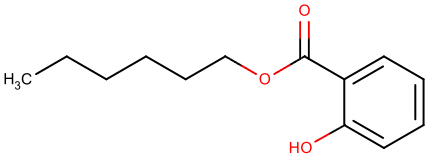
Appendix

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 Chemical 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
Principal Name	Isopropoxy ethyl salicylate	Hexyl salicylate
CAS No.	79915-74-5	6259-76-3
Structure		
Similarity (Tanimoto Score)		0.65
SMILES	CC(C)OCCOC(=O)c1ccccc1O	CCCCCCOC(=O)c1ccccc1O
Endpoint		Skin sensitization
Molecular Formula	$C_{12}H_{16}O_4$	$C_{13}H_{18}O_3$
Molecular Weight (g/mol)	224.256	222.284
Melting Point (°C, EPI Suite)	95.46	99.68
Boiling Point (°C, EPI Suite)	320.39	327.79
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.56E-03	3.25E-03
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.13E+02	6.08E+00

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
Log K_{OW}	3.24	5.06
J_{max} (μg/cm^2/h, SAM)	5.24	0.86
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.27E-02	1.89E+00
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

Summary

There are insufficient toxicity data on isopropoxy ethyl salicylate (CAS # 79915-74-5). Hence, *in silico* evaluation was conducted to determine read-across materials. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, hexyl salicylate (CAS # 6259-76-3) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusion

- Hexyl salicylate (CAS # 6259-76-3) was used as a read-across analog for the target material, isopropoxy ethyl salicylate (CAS # 79915-74-5), for the skin sensitization endpoint.
  - o The target material and the read-across analog belong to the generic class of salicylate esters.
  - o The key difference between the target material and read-across analog is that the target material has an isopropyl alcohol fragment, while the read-across analog has a hexyl alcohol fragment. 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.
  - o 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification:

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1	A normal constituent of the body? No.
Q2	Contains functional groups associated with enhanced toxicity? No.
Q3	Contains elements other than C, H, O, N, and divalent S? No.
Q5	Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6	Benzene derivative with certain substituents? No.
Q7	Heterocyclic? No.
Q16	Common terpene? (see Cramer et al., 1978 for detailed explanation). No.
Q17	Readily hydrolyzed to a common terpene? No.
Q19	Open chain? No.
Q23	Aromatic? Yes.
Q27	Rings with substituents? Yes.
Q28	More than one aromatic ring? No.
Q30	Aromatic ring with complex substituents? No.
Q18	One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories). No. Class Low (Class I).

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