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Short Review

RIFM fragrance ingredient safety assessment, isoamyl benzoate, CAS registry number 94-46-2

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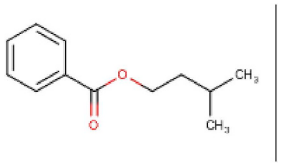
Version: 121918. This version replaces any previous versions.
Name: Isoamyl benzoate
CAS Registry Number: 94-46-2



Abbreviation/Definition List:

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2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 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
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 Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
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
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.

Isoamyl benzoate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog hexyl benzoate (CAS # 6789-88-4) show that isoamyl benzoate is not expected to be genotoxic. Data on read-across analogs benzoic acid (CAS # 65-85-0) and isoamyl alcohol (CAS # 123-51-3) provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog methyl benzoate (CAS # 93-58-3) show that there are no safety concerns for isoamyl benzoate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; isoamyl benzoate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to isoamyl benzoate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; isoamyl benzoate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2014a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 2.16 mg/kg/day.	(ECHA REACH Dossier: Benzoic Acid; ECHA, 2011a)
Reproductive Toxicity: NOAEL = 300 mg/kg/day.	(ECHA REACH Dossier: 3-Methylbutan-1-ol; ECHA, 2011b)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(ECHA REACH Dossier: Methyl Benzoate; ECHA, 2013)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Screening-level: 2.9 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 254.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 1.428 mg/L	(ECOSAR; 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 96-h Algae EC50: 1.428 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.1428 μg/L	

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1

1. Identification

1. **Chemical Name:** Isoamyl benzoate
2. **CAS Registry Number:** 94-46-2
3. **Synonyms:** Amyl (iso) benzoate; 1-Butanol, 3-methyl-, benzoate; Isopentyl benzoate; 3-Methylbutyl benzoate; 安息香酸アルキル（C = 1 ~ 8 ）; Isoamyl benzoate
4. **Molecular Formula:** $C_{12}H_{16}O_2$
5. **Molecular Weight:** 192.25
6. **RIFM Number:** 241
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 261 °C (FMA Database), 258.98 °C (EPI Suite)
2. **Flash Point**: > 93 °C (GHS), > 200 °F; CC (FMA Database)
3. **Log K_{OW}**: 3.72 (EPI Suite)
4. **Melting Point**: 21.57 °C (EPI Suite)
5. **Water Solubility:** 13.68 mg/L (EPI Suite)
6. **Specific Gravity:** 0.988 (FMA Database)
7. **Vapor Pressure:** 0.00938 mm Hg @ 20 °C (EPI Suite v4.0), 0.01 mm Hg 20 °C (FMA Database), 0.0151 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not available

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0045% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0078 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00050 mg/kg/day (RIFM, 2017)

*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; and Comiskey et al., 2017).

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. **Analogs Selected:**
   a. **Genotoxicity:** Hexyl benzoate (CAS # 6789-88-4)
   b. **Repeated Dose Toxicity:** Benzoic acid (CAS # 65-85-0) and isoamyl alcohol (CAS # 123-51-3)
   c. **Reproductive Toxicity:** Benzoic acid (CAS # 65-85-0) and isoamyl alcohol (CAS # 123-51-3)
   d. **Skin Sensitization:** Methyl benzoate (CAS # 93-58-3)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

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

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

Isoamyl benzoate is reported to occur in the following foods by the VCF*:

Beer	Litchi (*Litchi chinensis* Sonn.)
Capers (*Capparis spinoza*)	Mastic (*Pistacia lentiscus*)
Cherimoya (Annona cherimolia Mill.)	Papaya (*Carica papaya* L.)
Cherry (*Prunus avium* [sweet], *Pr. cerasus* [sour])	Sea buckthorn (*Hippophaë rhamnoides* L.)
Cocoa	Vinegar

*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. This is a partial list.

8. IFRA standard

None.

9. REACH dossier

Available; accessed 12/19/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, isoamyl benzoate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. Isoamyl benzoate was assessed in the BlueScreen assay and found positive for cytotoxicity without metabolic activation (positive: < 80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic and clastogenic activity of isoamyl benzoate; however, read-across can be made to hexyl benzoate (CAS # 6789-88-4; see Section V).

The mutagenic activity of hexyl benzoate 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with hexyl benzoate 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, 2014a). Under the conditions of the study, hexyl benzoate was not mutagenic in the Ames test, and this can be extended to isoamyl benzoate.

The clastogenic activity of hexyl benzoate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with hexyl benzoate in DMSO at concentrations up to 2064 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and in the absence of metabolic activation for 24 h. Hexyl benzoate did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2014b). Under the conditions of the study, hexyl benzoate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to isoamyl benzoate.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/17/19.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data for the target material, isoamyl benzoate. However, the target ester is expected to hydrolyze into the metabolites isoamyl alcohol (CAS # 123-51-3; see Section V) and benzoic acid (CAS # 65-85-0; see Section V). Both metabolites have sufficient repeated dose toxicity data. A gavage OECD 422 combined repeated dose toxicity study was conducted on groups of 12 male and female Sprague Dawley rats/group. Test animals were administered isoamyl alcohol via gavage at doses of 0, 30, 100, and 300 mg/kg/day, and an additional satellite recovery group of 5 animals/sex/group were administered the test material at doses of 0 and 300 mg/kg/day. The test material 3-methylbutan-1-ol (isoamyl alcohol) in a 1% w/v CMC solution containing 1% Tween 80 in water was administered to male and female Sprague Dawley rats daily by oral gavage for 42 days for the males (14 days before mating, 14 days during the mating period, and 14 days after the end of the mating period), 41–53 days for the females (14 days before mating, throughout the mating and gestation periods, and up to day 4 of lactation), and for 42 days in the satellite recovery group. The NOAEL was determined to be 100 mg/kg/day, based on reduced bodyweight gain in the high-dose group males (ECHA, 2011b). In another study, a 13-week OECD 408/GLP study was conducted on groups of 10 SPF-Wistar, Chbb:THOM rats/sex/group. Animals were administered isoamyl alcohol via the drinking water at concentrations of 0, 1000 ppm (about 80 mg/kg/day), 4000 ppm (about 340 mg/kg/day), and 16000 ppm (about 1250 mg/kg/day). Slight alterations in hematological parameters were observed in males at the high dose. These included a marginal increase in the red blood cell count and a slight decrease in the mean corpuscular volume. The toxicological significance of these findings is unclear. The NOAEL was determined to be 16000 ppm or 1250 mg/kg/day, the highest dose tested, since the effects were not considered to be treatment-related (Schilling et al., 1997). In another study, groups of 15 Ash/CSE strain rats/sex/group were gavaged with isoamyl alcohol at doses of 0, 150, 500, and 1000 mg/kg/day for 17 weeks. There were no adverse effects reported due to test material administration up to the highest dose tested. Thus, the NOAEL was determined to be 1000 mg/kg/day (Carpanini et al., 1973).

The only effects reported among treated animals during the OECD 422 gavage study were reduced bodyweight gains among males. Since no adverse effects were reported among the animals during the longer duration 13- (drinking water) and 17-week (gavage) studies, **the NOAEL was determined to be 1250 mg/kg/day, the highest dose tested.**

There are sufficient repeated dose toxicity data on benzoic acid. In addition to the key study used to determine a conservative NOAEL (below), additional studies on benzoic acid involving other routes of administration and varying lengths are summarized in Table 1. In a GLP-compliant study equivalent or similar to an OECD 412 subacute inhalation toxicity 28-day study, Sprague Dawley CD rats (10/sex/dose) were exposed to benzoic acid (purity not reported) at concentrations of 0, 25, 250, or 1200 mg/m^3 (equivalent to 0, 6.48, 64.83, or 311.19 mg/kg/day, respectively) for 6 h/day, 5 days/week, through whole-body exposure over 4 weeks. Parameters evaluated included clinical signs (twice daily), body weight (prior to exposure and thereafter weekly), serum biochemistry, hematology, organ weights, and histopathology. At the 1200 mg/m^3 dose, mortality in 2 rats, decreased body weight, statistically significantly decreased platelets, decreased absolute/relative liver weights, and decreased relative weight of trachea with lungs (females only) were reported. At the highest dose, absolute kidney weight and body weight were reported to be slightly decreased (though not significantly) in females compared to controls. No treatment-related gross lesions were reported in any of the tested doses for the following organs: adrenal, nasal turbinate, brain, pancreas, colon, pituitary, esophagus, prostate/uterus, eye with optic nerve, submaxillary salivary gland, testis (both), ovary, jejunum, Harderian glands, spleen, heart, sternum (bone marrow), kidney, stomach, liver, thymus, lungs (5 lobes), thyroid/parathyroid, bronchial lymph node, urinary bladder, and mammary gland. Treatment-related but not dose-dependent microscopic lesions were reported, which included increased inflammatory cell infiltrate and increased incidence, intensity, and extent of interstitial fibrosis in the lungs of animals from the low-, mid-, and high-dose groups. The interstitial fibrosis in the lungs was due to a local corrosive property of benzoic acid through the inhalational route. In both mid- and high-dose groups, reddish discharge around the nares was reported. At the 250 mg/m^3 dose, upper respiratory tract irritation was observed, which was confirmed by inflammatory exudate around the nares. Based on the presence of systemic effects observed at 1200 (the highest tested dose) and 250 mg/m^3, the no observed adverse effect concentration (NOAEC) was considered to be 25 mg/m^3; local effects observed at the low dose were predominantly due to the local corrosive property of benzoic acid (ECHA, 2011a).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day studies. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus the derived NOAEL for the repeated dose toxicity data is 6.48/3 or 2.16 mg/kg/day.

Therefore, most conservative NOAEL was chosen as the point of departure for isoamyl benzoate. The isoamyl benzoate MOE for the repeated dose toxicity endpoint can be calculated by dividing the benzoic acid NOAEL by the total systemic exposure for isoamyl benzoate, 2.16/0.0005 or 4320.

In addition, the total systemic exposure to isoamyl benzoate (0.5 μg/kg bw/day) is below the TTC (30 μg/kg bw/day); (Kroes et al., 2007) **for the repeated dose endpoint for a Cramer Class I material at the current level of use.**

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: RIFM, 1988c; RIFM, 1991; Gibel et al., 1975; Dow (1992); RIFM, 1988b; Klimisch and Hellwig, 1995; RIFM,

Table 1
Additional animal studies conducted on benzoic acid.

Duration in Detail	GLP/Guideline	No. of Animals/Dose (Species, Strain, Sex)	Route (Vehicle)	Doses (in mg/kg/day; Purity)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	References
90-day	Not reported; non-GLP and non-guideline study	50 mice/dose/sex (cross-bred white)	Oral (gavage)	80 mg/kg/day. Note: 14 surviving mice were subjected to a restricted dietary intake (90% restriction) for up to 5 days	LOAEL: 80 mg/kg/day	✓ Highest mortality rate 85.7% (56.3% in controls) after 5 days on restricted diet	Shtenberg and Ignat'ev, 1970
504-day	Not reported; non-GLP and non-guideline study	Wistar Rats; 20 males and 30 females; control group 13 males and 12 females	Oral (diet)	1.5% in diet (~1125 mg/kg/day)	LOAEL: 1125 mg/kg/day	✓ Reduced feed intake, growth retardation, increased mortality rate (15/50 vs. 3/25 in the control)	OECD (2001)
7-, 14-, or 35-day	Not reported; non-GLP and non-guideline study	No of animals not reported/ Rat/Wistar	Oral	1.1% (~550 mg/kg/day)	LOAEL: 550 mg/kg/day	✓ Significantly poor weight gain	HSDB (2018)
28-day	Not reported; non-GLP and non-guideline study	Rats (strain not reported) 10 males/dose	Oral (Diet)	0, 760, 3800 or 7600 ppm via diet (approx. 0, 65, 324, or 647 mg/kg/day)	NOAEL: 647 mg/kg/day	✓ No adverse effects reported up to highest dose tested	ECHA (2011a)
Not reported	Not reported	Rat (no. of animals, strain, sex not reported)	Exposure	up to ~500 mg/kg/day	Not reported	✓ No neurotoxicity observed	NICNAS (2013)
250 days	Not reported; non-GLP and non-guideline study	Dogs (strain and sex not reported) 17/dose	Oral (Diet)	1000 mg/kg/day	LOAEL: 1000 mg/kg/day	✓ At higher doses ataxia, epileptic convulsions, and mortality reported	IPCS (2018)
52 weeks	Not reported; non-GLP and non-guideline study	Sprague Dawley rats, 20/ sex/dose	Oral (Diet)	0.5% or 2% (~250 or 1000 mg/kg/day)	NOAEL: 1000 mg/kg/day	✓ No effects up to highest teste dose	Nair (2001)
4-week 6 h/day; 5 days/week	GLP/OECD 412	10/dose/Crl:CD (SD) rats/ sex	Inhalation (nose-only)	0 (Control group, filtered air) 2.5 and 12.5 mg/m^3 (0.65 and 3.24 mg/kg/day)	NOAEL: 12.6 mg/m^3 (3.24 mg/kg/day)	✓ No effects up to highest teste dose	RIFM (2009)
Lifelong	Not reported; non-GLP and non-guideline study	Swiss albino mice (50 mice/sex/group)	Oral (drinking water)	2% benzoic acid (equivalent to 5960–6200 mg/kg/day)	NOAEL (for carcinogenicity): 6200 mg/ kg/day	✓ No carcinogenic effect (such as on survival or incidence of tumors)	NICNAS (2013)
21 days	GLP (EPA OPP 82–2), 21-day (5 days/week) repeated dose dermal toxicity study	New Zealand White rabbits (4 rabbits/sex/dose)	Dermal	100, 500, 2500 mg/kg/day	NOAEL: 2500 mg/kg/day	✓ No systemic adverse effects observed up to highest tested dose	ECHA (2011a)
35 days	Not reported; non-GLP and non-guideline study	Male Wistar rats (5–10 rats/dose)	Oral (diet)	0%, 1.1%, and 3.0% (~0, 825, and 2250 mg/kg/day, respectively)	NOAEL: 1.1% (~825 mg/ kg/day)	✓ At higher doses, adverse effects reported for mortality, bodyweight gain, metabolic changes, and histopathology	ECHA (2011a)
8 weeks	Not reported; non-GLP and non-guideline study	Strain not reported); 40 rats/group (20/sex/group)	Oral (diet)	0%, 0.5%, 1%, and 5% (equivalent to 0, 250, 500, and 2500 mg/kg/day, respectively)	NOAEL: 1% (~500 mg/kg/ day)	✓ Diet intolerance of rats to benzoate and mortality of all of the rats at the highest dose tested	OECD (2001)

1990a; RIFM, 1988a; RIFM, 1990b; RIFM, 2010b; RIFM, 2010a; Meyer (1965); McLaughlin et al., 1964.

Literature Search and Risk Assessment Completed On: 08/18/18.

10.1.3. Reproductive toxicity

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

10.1.3.1. Risk assessment. There are no reproductive toxicity data on isoamyl benzoate. Isoamyl benzoate is expected to hydrolyze to benzoic acid (CAS # 65-85-0; see Section V) and isoamyl alcohol (CAS # 123-51-3; see Section V).

There are sufficient reproductive toxicity data on read-across material benzoic acid (CAS # 65-85-0; see Section V). In a non-GLP, 4-generation oral reproductive toxicity study, groups of 20 rats/sex/dose/generation were fed diets containing benzoic acid at doses of 0%, 0.5% and 1% (equivalent to 0, 450, and 900 mg/kg/day for males and 0, 600, and 1176 mg/kg/day for females, as per ECHA Dossier). The first generation was exposed for 8 weeks and then allowed to mate (1:1 for a period of 14 days). Mating was repeated in week 48 to raise a second litter. The first and second generations were treated for a lifetime; the third generation was treated for 16 weeks, and the fourth generation was treated up to breeding. No treatment-related adverse effects on fertility or the development of pups were reported in all 4 generations. The NOAEL for fertility effects and maternal and developmental toxicity was considered to be 1%, the highest dose tested (Kieckebusch and Lang, 1960; also available at ECHA, 2011a).

Read-across material isoamyl alcohol (CAS # 123-51-3; see Section V) has sufficient developmental toxicity data. An OECD 414/GLP prenatal developmental toxicity study was conducted in pregnant female Wistar rats. Groups of 25 rats/dose were exposed to test material 3-methylbutan-1-ol (isoamyl alcohol) via inhalation, 6 h per day, at concentrations of 0, 0.5, 2.5, or 10 mg/L from days 6–15 post-coitum (p.c.). All dams were euthanized, and their fetuses were removed and examined on day 20 p. c. The NOAEL for developmental toxicity was considered to be 10 mg/L or 2769 mg/kg/day (using standard minute volume and bodyweight values for female Wistar rats), the highest dose tested (RIFM, 1990a). In another study, an OECD 414/GLP prenatal developmental toxicity study was conducted in pregnant female Himalayan rabbits. Groups of 15 rabbits/dose were exposed to test material 3-methylbutan-1-ol (isoamyl alcohol) via inhalation, 6 h per day, at concentrations of 0, 0.5, 2.5, or 10 mg/L from days 7–19 post insemination. All dams were euthanized, and their fetuses were removed and examined on day 29 post insemination. The NOAEL for developmental toxicity was considered to be 10 mg/L or 1359 mg/kg/day (using standard minute volume and body weight values for female New Zealand rabbits), the highest dose tested (RIFM, 1990b).

In another study using read-across material isoamyl alcohol (CAS # 123-51-3; see Section V), an OECD 422/GLP combined repeated dose toxicity with a reproduction/development toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered isoamyl alcohol via oral gavage at doses of 0, 30, 100, or 300 mg/kg/day in 1% w/v CMC solution containing 1% Tween 80 in water. Additional satellite groups of 5 rats/sex/dose were administered isoamyl alcohol at doses of 0 or 300 mg/kg/day to serve as the 14-day treatment-free recovery groups. Males were treated for 42 days (14 days before mating, 14 days during the mating period, and 14 days after the end of the mating period), while females were treated for 41–53 days (14 days before mating, throughout mating and gestation periods, and up to day 4 of lactation). Females in the recovery group were not subjected to mating. In addition to systemic toxicity, the reproductive toxicity parameters were also assessed. No treatment-related adverse effects were observed on fertility or the development of the fetuses up to the highest dose tested. The NOAEL for fertility and developmental toxicity was considered to be 300 mg/kg/day, the highest dose tested (ECHA, 2011b).

Taken altogether, the most conservative reproductive toxicity NOAEL (for both fertility effects and on the development of pups) of 300 mg/kg/day from the OECD 422 study on isoamyl alcohol was selected for the reproductive toxicity endpoint. **Therefore, the isoamyl benzoate MOE for the reproductive toxicity endpoint can be calculated by dividing the isoamyl alcohol NOAEL in mg/kg/day by the total systemic exposure to isoamyl benzoate, 300/0.0005 or 600000.**

In addition, the total systemic exposure to isoamyl benzoate (0.5 μg/kg bw/day) is below the TTC (30 μg/kg bw/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: ECHA, 2011a; OECD, 2001; SCCP, 2005; IPCS, 2018; ECHA, 2011b; WHO, 2005; RIFM, 1988c; Carpanini et al., 1973; Schilling et al., 1997; RIFM, 1991; Gibel et al., 1975; Dow (1992); RIFM, 1988b; Klimisch and Hellwig, 1995; RIFM, 1988a; RIFM, 2010b; RIFM, 2010a; Meyer (1965); McLaughlin et al., 1964; Kimmel et al., 1971.

Literature Search and Risk Assessment Completed On: 01/30/19.

10.1.4. Skin sensitization

Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3), isoamyl benzoate does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for isoamyl benzoate. Based on the existing data and read-across material methyl benzoate (CAS # 93-58-3; see Section V), isoamyl benzoate does not present a concern for skin sensitization under the current, declared levels of use. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material methyl benzoate was found to be non-sensitizing up to 100% (ECHA, 2013). In a guinea pig Freund's Complete Adjuvant test (FCAT), read-across material methyl benzoate did not present reactions indicative of sensitization (Hausen et al., 1995). In a guinea pig Open Epicutanous Test (OET), isoamyl benzoate and read-across material methyl benzoate did not present reactions indicative of sensitization (Klecak, 1985). In human maximization tests, no skin sensitization reactions were observed with isoamyl benzoate at 6% (4140 μg/cm^2) or read-across material methyl benzoate at 4% (2760 μg/cm^2) (RIFM, 1971; RIFM, 1970).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material methyl benzoate, isoamyl benzoate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: RIFM, 1962.

Literature Search and Risk Assessment Completed On: 01/21/19.

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for isoamyl benzoate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, isoamyl benzoate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On:
01/15/19.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are insufficient inhalation data available on isoamyl benzoate. Based on the Creme RIFM Model, the inhalation exposure is 0.0078 mg/day. This exposure is 179.5 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Smyth et al., 1969; RIFM, 1979; RIFM, 2009.

Literature Search and Risk Assessment Completed On: 01/29/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of isoamyl benzoate 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 Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, isoamyl benzoate 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 isoamyl benzoate as 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, 2012). 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).

10.2.2. Risk assessment

Based on the current Volume of Use (2015), isoamyl benzoate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Isoamyl benzoate has been registered under REACH with the following additional data available.

The algae growth inhibition test was conducted according to the OECD 201 method. The 72-h ErC50 was reported to be greater than 15.1 mg/L.

10.2.3. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	8.27			1,000,000	0.00827	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.547	4.404	1.428	10,000	0.1428	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	4.514	3.004	4.313			Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.72	3.72
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
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 0.1428 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 volumes of use.

Literature Search and Risk Assessment Completed On: 01/31/19.

11. 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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **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/

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 05/31/19.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110970.

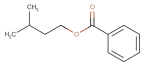
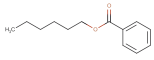
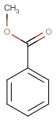
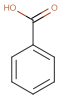
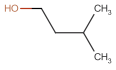
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also 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, 2016).

- 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 v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Isoamyl benzoate	Hexyl benzoate	Methyl benzoate	Benzoic acid	Isoamyl alcohol
CAS No.	94-46-2	6789-88-4	93-58-3	65-85-0	123-51-3
Structure					
Similarity (Tanimoto Score)		0.86	0.66	N/A	N/A
Read-across Endpoint		• Genotoxicity	• Skin Sensitization	• Reproductive Toxicity	• Reproductive Toxicity

				• Repeated Dose Toxicity	• Repeated Dose Toxicity
Molecular Formula	$C_{12}H_{16}O_2$	$C_{13}H_{18}O_2$	$C_8H_8O_2$	$C_7H_6O_2$	$C_5H_{12}O$
Molecular Weight	192.25	206.28	136.15	122.12	88.15
Melting Point (°C, EPI Suite)	21.57	42.34	−15	122.4	−117.2
Boiling Point (°C, EPI Suite)	261	272	199	249.2	131.1
Vapor Pressure (Pa @ 25 °C, EPI Suite)	2.01	0.79	5.07E+001	7.00E-04	3.16E+002
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	4.15	4.28	2.12	1.87	1.16
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	13.68	8.921	1344	3400	2.67e+004
J_{max} (μg/cm^2/h, SAM)	28.882	6.313	77.618	120.948	733.512
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.09E+001	1.45E+001	3.28E+000	3.86E-003	1.43E+000
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found			
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found			
Carcinogenicity (ISS)	• Non-carcinogen (good reliability)	• Non-carcinogen (good reliability)			
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 alert found	• No alert found			
Oncologic Classification	• Not classified	• Not classified			
Repeated Dose Toxicity					
Repeated Dose (HESS)	• Cocaine (Renal toxicity) Alert • Propanolol (Renal toxicity) Alert			• Alpha-Naphthyl-isothiocyanate (Hepatotoxicity) Alert • Carbamazepine (Hepatotoxicity) Alert • Carbamazepine (Renal Toxicity) Alert • Coumarin (Hepatotoxicity) Alert • Diclofenac (Hepatotoxicity) Alert • Mefenamic Acid (Hepatotoxicity) Alert • Styrene (Renal Toxicity) Alert • Toluene (Renal toxicity) Alert	• Not categorized
Reproductive and Developmental Toxicity					
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group			• Non-binder, without OH or NH2 group	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (moderate reliability)			• Toxicant (low reliability)	• Toxicant (good 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)		• Slightly reactive (GSH)|Slightly reactive (GSH) ≫ Reaction at sp3 carbon atom (SN2)		
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found		
Skin Sensitization Reactivity Domains (-Toxtree v2.6.13)	• No alert found		• No alert found		
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3	• N/A	• See Supplemental Data 4

Summary

There are insufficient toxicity data on isoamyl benzoate (CAS # 94-46-2). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, hexyl benzoate (CAS # 6789-88-4), methyl benzoate (CAS # 93-58-3), benzoic acid (CAS # 65-85-0), and isoamyl alcohol (CAS # 123-51-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Metabolism

The metabolism of the target material isoamyl benzoate (CAS # 94-46-2) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v4.2). The target material is predicted to be metabolized to benzoic acid (CAS # 65-85-0) and isoamyl alcohol (CAS # 123-51-3) in the first step with 0.902 probability. Hence, benzoic acid (CAS # 65-85-0) and isoamyl alcohol (CAS # 123-51-3) can be used as read-across analogs for the target material. Read-across materials benzoic acid (CAS # 65-85-0) and isoamyl alcohol (CAS # 123-51-3) were in domain for the *in vivo* rat and in domain for the *in vitro* rat S9 simulator (OASIS TIMES v2.27.19).

Conclusions

- Hexyl benzoate (CAS # 6789-88-4) was used as a read-across analog for the target material isoamyl benzoate (CAS # 94-46-2) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of aromatic esters.
  - o The target material and the read-across analog share a benzoic acid fragment.
  - o The key difference between the target material and the read-across analog is that the target material has a branched isoamyl C5 alcohol fragment while the read-across analog has a C6 straight chain alcohol fragment. This structural difference is toxicologically insignificant.
  - o 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 comparison of their toxicological properties.
  - o Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq 80\%$ and J_{max} for the read-across analog corresponds to skin absorption $\leq 40\%$. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
  - o According to the OECD QSAR Toolbox v4.2, 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.
- Methyl benzoate (CAS # 93-58-3) was used as a read-across analog for the target material isoamyl benzoate (CAS # 94-46-2) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of aromatic esters.
  - o The target material and the read-across analog share a benzoic acid fragment.
  - o The key difference between the target material and the read-across analog is that the target material has a branched isoamyl C5 alcohol fragment while the read-across analog has a methanol C1 alcohol fragment. This structural difference is toxicologically insignificant.
  - o 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 comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The read-across analog has a Protein Binding Potency SN2 alert, which is not found in the target material. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. Data superseded predictions in this case.
  - o The target material and read-across analog present several alerts for repeated dose toxicity by the HESS categorization scheme. Those alerts are due to the structural similarity between the materials and several toxicants. However, neither the target material nor the read-across analog match with any active structural fragments reported for these alerts. Therefore, the predictions can be ignored.
  - 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.
- Read-across alcohol isoamyl alcohol (CAS # 123-51-3) and read-across acid benzoic acid (CAS # 65-85-0) are used as read-across analogs for the target ester isoamyl benzoate (CAS # 94-46-2) for the reproductive and repeated dose toxicity endpoints.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - o Structural differences between the target material and the read-across analogs are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v4.2, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - o Target material presents several alerts for repeated dose toxicity by HESS categorization scheme. Those alerts are due to structural similarity between the target material and several toxicants. However, the target material does not match with any active structural fragments reported for these alerts. Therefore, predictions can be ignored.
  - o 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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