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Short Review

# RIFM fragrance ingredient safety assessment, 3-(*p*-isopropylphenyl) propionaldehyde, CAS registry number 7775-00-0

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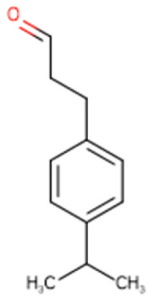
Name: 3-(*p*-Isopropylphenyl)propionaldehyde CAS Registry Number: 7775-00-0




**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor
**CAESAR -** Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
**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; B. Safford et al., 2015; B. Safford et al., 2024; B. Safford et al., 2017; Comiskey 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
**ECOSAR** - Ecological Structure-Activity Relationships Predictive Model
**EU** - Europe/European Union
**GLP** - Good Laboratory Practice
**HESS -** Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
**IFRA** - The International Fragrance Association
**ISS -** Instituto Superiore di Sanita (Italian National Institute of Health)
**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
**OASIS -** OASIS Laboratory of Mathematical Chemistry (LMC)
**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
**Toxtree** - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
**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.**

3-(*p*-Isopropylphenyl)propionaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity,

(*continued on next page*)

(*continued*)

skin sensitization, and environmental safety. Data show that 3-(*p*-isopropylphenyl)propionaldehyde is not genotoxic. Data on read-across analog *p-tert*-butyldihydrocinnamaldehyde (CAS # 18127-01-0) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data provide 3-(*p*-isopropylphenyl) propionaldehyde a No Expected Sensitization Induction Level (NESIL) of 1100 μg/cm$^2$ for the skin sensitization endpoint. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 3-(*p*-isopropylphenyl)propionaldehyde 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 3-(*p*-isopropylphenyl)propionaldehyde is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 3-(*p*-isopropylphenyl)propionaldehyde 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, 2013a; RIFM, 2013c) |
| **Repeated Dose Toxicity:** NOAEL = 4.5 mg/kg/day | RIFM (2017a) |
| **Reproductive Toxicity:** NOAEL = 5 mg/kg/day | (RIFM, 2004; RIFM, 2017a) |
| **Skin Sensitization:** NESIL = 1100 μg/cm$^2$ | RIFM (2000) |
| **Photoirritation/Photoallergenicity:** Not expected to be photoirritating/photoallergenic. | (UV/Vis Spectra, RIFM Database) |
| **Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC. | |
| **Environmental Safety Assessment** | |
| **Hazard Assessment:** | |
| **Persistence:** | |
| Critical Measured Value: 71% (OECD 301D) | RIFM (2017f) |
| **Bioaccumulation:** | |
| Screening-level: 93.12 L/kg (EPI Suite v4.11; US EPA, 2012a) | |
| **Ecotoxicity:** | |
| Screening-level: 48-h *Daphnia magna* LC50: 1.285 mg/L | (ECOSAR v2.0; US EPA, 2012b) |
| **Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards | |
| **Risk Assessment:** | |
| **Screening-level:** PEC/PNEC (North America and Europe) > 1 | (RIFM Framework; Salvito et al., 2002) |
| **Critical Ecotoxicity Endpoint:** 48-h *Daphnia magna* LC50: 1.285 mg/L | (ECOSAR v2.0; US EPA, 2012b) |
| **RIFM PNEC is:** 0.1285 μg/L | |
| • **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: <1 | |

## 1. Identification

1. **Chemical Name:** 3-(*p*-Isopropylphenyl)propionaldehyde
2. **CAS Registry Number:** 7775-00-0
3. **Synonyms:** Benzenepropanal, 4-(1-methylethyl)-; 3-(*p*-Cumenyl) propionaldehyde; Cuminylacetaldehyde; *p*-Cumenylpropanal; *p*-Isopropylhydrocinnamaldehyde; Cyclemax; 3-(4-Isopropylphenyl) propanal; 3-(*p*-Isopropylphenyl)propionaldehyde
4. **Molecular Formula:** $C_{12}H_{16}O$
5. **Molecular Weight:** 176.25 g/mol
6. **RIFM Number:** 5049
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

## 2. Physical data

1. **Boiling Point:** 263.7 °C (EPI Suite v4.11)
2. **Flash Point:** 94 °C (Globally Harmonized System)
3. **Log $K_{OW}$:** 3.49 (EPI Suite v4.11)
4. **Melting Point**: 29.05 °C (EPI Suite v4.11)
5. **Water Solubility:** 60.17 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00686 mm Hg at 20 °C (EPI Suite v4.0), 0.0121 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol$^{-1}$ • cm$^{-1}$)
9. **Appearance/Organoleptic:** Not Available

## 3. Volume of use (WORLDWIDE BAND)

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

## 4. EXPOSURE to fragrance ingredient (Creme RIFM aggregate exposure model v3.3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.072% (RIFM, 2023)
2. **Inhalation Exposure*:** 0.00021 mg/kg/day or 0.015 mg/day (RIFM, 2023)
3. **Total Systemic Exposure**:** 0.0014 mg/kg/day (RIFM, 2023)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford, 2015; Safford, 2024; Safford, 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, 2015; Safford, 2024; Safford, 2017; Comiskey et al., 2017).

## 5. Derivation of systemic absorption

1. Dermal

13.5% for hydroalcoholic-based fragrances and deodorant/antiperspirant products; 8.9% for oil-in-water-based products like make-up products, body lotions, hair styling, and bath cleansing products; 10.5% for water-in-oil-based products like face and hand cream products.

Since the Scientific Committee on Consumer Safety (SCCS) Submission II study (described below) follows GLP and OECD TG 428 and accounts for test material penetration and recovery more accurately, dermal absorption for read-across analog *p-t*-butyl-

α-methylhydrocinnamic aldehyde (BMHCA; CAS # 80-54-6; see Section VI) was determined using these results instead of those of Hawkins (RIFM, 1994). The 13.5% dermal absorption was determined to be conservative and has been considered to calculate maximum acceptable concentrations (see Section X).

**RIFM, 1994**: $^{14}$C-BMHCA, *p-t*-butyl-α-methylhydrocinnamic aldehyde, was applied to a 100–cm$^2$ area on the backs of 3 human volunteers and the applications were occluded with gauze dressings. After 6 h, the dressings were removed, and the residual dose material was removed with cotton wool swabs moistened with ethanol. Five successive samples of adhesive "stripping" tape were then applied to 2.5 × 2.5–cm areas of skin and removed. Treated areas of skin were then occluded with fresh gauze dressings until 120 h of application when they were removed, and 5 similar samples of adhesive "stripping" tape were applied and removed. A mean of 1.4% of the applied radioactivity was excreted in urine by the 3 subjects within 24 h. Radioactivity was below the limit of detection in all urine samples collected between 24 h and 120 h after application. Radioactivity was below the limit of detection in feces collected from subjects during hours 0–120 after application. Radioactivity in plasma samples was below the limit of detection at any time after application, corresponding to concentrations of less than 0.025 μg/mL. A mean 63.12% ± 4.95 standard deviation (SD) of the applied radioactivity was recovered from gauze dressings used to occlude the site of application during hours 0–6, and a further mean of 3.76% of dose ± 1.95 SD was removed by washing the skin with an ethanol-moistened swab at 6 h, and 3.06% ± 2.77 SD was recovered from gauze dressing used to occlude treated areas of skin during hours 6–120. Results indicate that very little of applied $^{14}$C-BMHCA was absorbed through the skin into the systemic circulation. While the dermal absorption studies conducted in humans *in vivo* showed that only 1.4% of the applied radioactive dose was absorbed, only 71% of the overall dose was recovered. Based on the presented data combined with the lack of 100% recovery of the test material, an extremely conservative assessment has been taken that approximately 30% of a dermal dose is absorbed.

SCCS Submission II (SCCS, 2019): Dermal absorption of BMHCA has been studied in rats, guinea pigs, and humans *in vitro* and *in vivo*. The BMHCA dermal absorption profile was found to be similar among guinea pigs and humans. In an OECD TG 428/GLP-compliant *in vitro* human skin absorption study, [$^{14}$C]-BMHCA in ethanol-in-water (1.9%), silicone-in-water (0.1%), water-in-oil (0.1%), and oil-in-water (0.1%) was used to represent a variety of commercial cosmetic formulations. Dermal absorption of BMHCA was assessed by a 2-step experimentation process. Following a single topical (semi-occluded) application on split-thickness human skin membrane mounted on modified Franz-type diffusion cells, absorption was measured 24 h post-dosing as well as 72 h post-dosing. The amounts absorbed at the end of 24 h and 72 h following BMHCA treatment were comparable, suggesting that the extent of absorption does not change over time following a single topical application. After 24 h, 7.52%, 5.1%, 6.3%, and 6.24% of [$^{14}$C]-BMHCA was absorbed under the test conditions used for the hydroalcoholic solution, silicone-in-water, water-in-oil, and oil-in-water formulations, respectively. These experiments were designed to differentiate between extractable (potentially absorbable) and non-extractable (bound, non-absorbable) residues of the test material; 21%, 27%, 28%, and 38% of the fraction was potentially not absorbable in the respective vehicles. The percentage of systemically available BMHCA was calculated based on the absorbed dose and subtracting the non-systemically available fraction from the total applied dose. The systemically available portion was lower and ranged between 5% and 7%, with the highest values obtained for the hydroalcoholic vehicle. However, the treatment material recovery for ethanol-in-water, silicone-in-water, water-in-oil, and oil-in-water were 80%–85%, 83%–89%, 91%–97%, and 88%–96%, respectively. Despite the high recovery, a portion of treatment material remained unaccounted for. For 2 formulations, 50%–60% of the applied dose was found in the charcoal filter, demonstrating the volatility of BMHCA. Importantly, a decrease in the total recovery was not correlated with a decrease in the percentage of the BMHCA dose absorbed.

The percentage of systemically available [$^{14}$C]-BMHCA was calculated by the SCCS as mean + SD, including the non-absorbable fraction for water-in-oil and oil-in-water phases, to be 10.5% and 8.9%, respectively. However, for the ethanol-in-water and silicone-in-water phases, SCCS used a more conservative approach to calculate the systemically available percent [$^{14}$C]-BMHCA by using mean + 2 SD and including the non-absorbable fraction. Hence, the percent [$^{14}$C]-BMHCA available systemically following ethanol-in-water and silicone-in-water formulations was calculated to be 13.5% and 8.5%, respectively. Considering percutaneous absorption of BMHCA in humans is minimal, dermal absorption of 13.5% was considered for calculating the systemic exposure to the target material 3-(*p*-isopropylphenyl)propionaldehyde based on the key *in vitro* study with human skin.

RIFM, 1995: A comparative oral and dermal absorption study was performed in male rats following GLP with standards comparable to OECD 417 and 427 guidelines. Dermal absorption of [$^{14}$C]-BMHCA was measured following topical application of the material on the shaved backs of the animals. The animals were observed for up to 120 h following treatment application. At the end of the observation period, 14.6% (cumulative) of the dose was excreted in the urine, 2% in the feces, and 0.8% was recovered in the cage washings. Overall, approximately 19% of the applied dose was found in excreta and tissues, representative of the extent of absorption. However, there are no data on the amount of treatment material recovered following topical application.

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

## 6. Computational toxicology evaluation

### 6.1. *Cramer Classification: class I, low*

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.5 (OECD, 2021b) |
|---|---|---|
| I | I | I |

### 6.2. *Analogs selected*

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** *p-tert*-Butyldihydrocinnamaldehyde (Bourgeonal; CAS # 18127-01-0); Weight of Evidence (WoE) material - *p-t*-butyl-α-methylhydrocinnamic aldehyde (BMHCA; CAS # 80-54-6)
c. **Reproductive Toxicity:** *p-tert*-Butyldihydrocinnamaldehyde (Bourgeonal; CAS # 18127-01-0); WoE - *p-t*-butyl-α-methylhydrocinnamic aldehyde (BMHCA; CAS # 80-54-6)
d. **Skin Sensitization:** None

**Table 1**
Metabolites of 3-(*p*-isopropylphenyl)propionaldehyde (cyclemax) by species.

| Metabolites | Species | Amount | Conc (μM) | Time (h) |
|---|---|---|---|---|
| **C1** | Mouse (1 Human Profile) | <20% | 10, 100 | 1, 4 |
| **C2** | All | <5% | 10, 100 | 1, 4 |
| **C3** | Mouse (1 Rabbit Profile) | <5% | 10, 100 | 1, 4 |
| **C4** | All | 1–20% | 10, 100 | 1, 4 |
| **C5** | All | 1–20% | 10, 100 | 1, 4 |
| **C6** | All | Largest component | 1, 10, 100 | 1, 4 |
| **C7** | Mouse, Rat, and Rabbit | <5% | 100 | 4 |
| **C8** | All | 1–20% | 10, 100 | 0, 1, 4 |

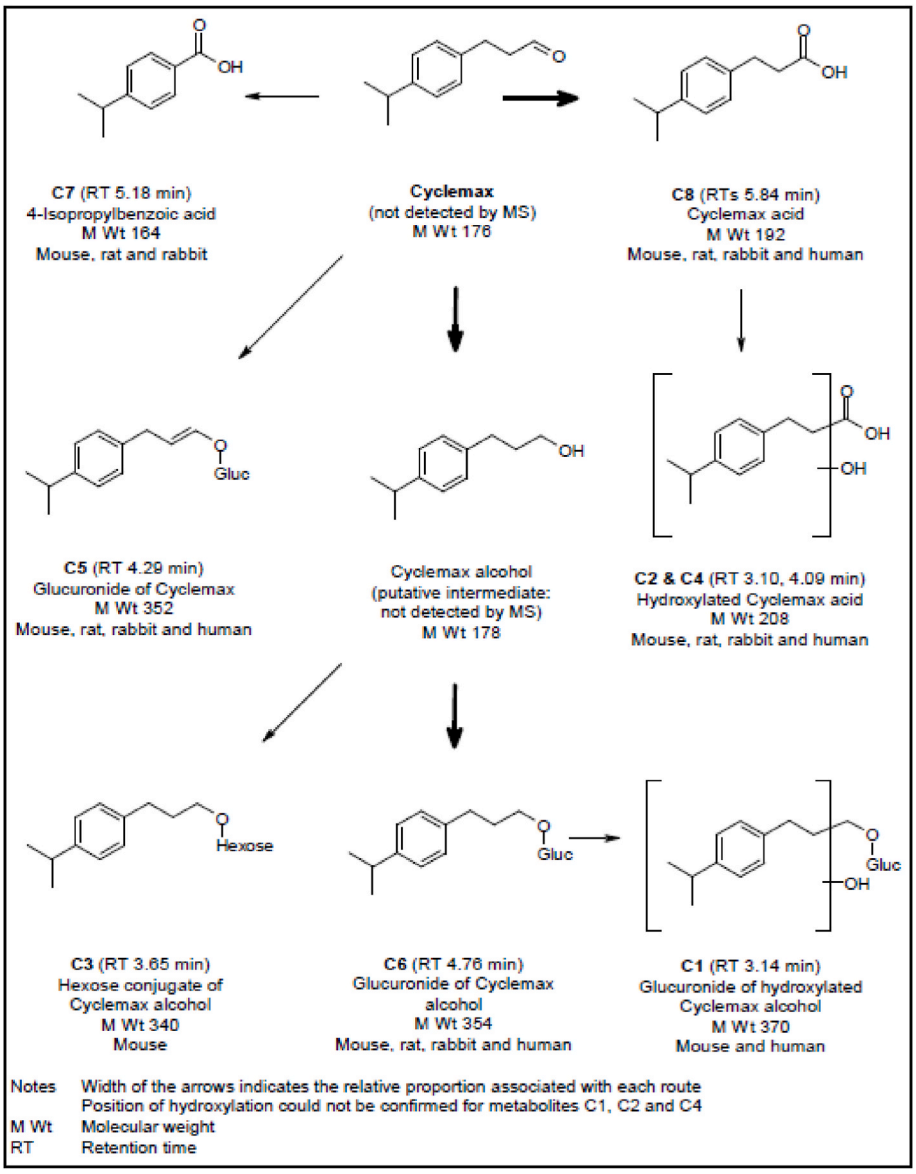



**Fig. 1.** Adapted from RIFM, 2012a.

e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None
3 Read-across justification

See Appendix below.

## 7. Metabolism

RIFM, 2012a: A metabolism study was conducted with 3-(*p*-isopropylphenyl)propionaldehyde (cyclemax) to compare the hepatic *in vitro* metabolism among 4 species (mice, rats, rabbits, and humans). The analytical method utilized HPLC LC-MS to profile and identify metabolites generated. Interspecies comparison incubations of the test material (1, 10, and 100 μM) using cryopreserved hepatocytes from mice, rats, rabbits, and humans were conducted in triplicate at incubation times of 0, 1, and 4 h. Eight components were detected following hepatocyte incubations with 3-(*p*-isopropylphenyl)propionaldehyde (cyclemax), with similar results obtained for all species. The glucuronide conjugate of the metabolite, cyclemax alcohol, was the major metabolite in most of the 1-h and 4-h hepatocyte incubations (Table 1). The metabolite cyclemax acid was observed widely and was the second major component in most mouse, rabbit, and human hepatocyte incubations. It was also the only component detected in the 0-h (control) incubations, although levels were low. The glucuronide conjugate of cyclemax was also detected in most incubations and tended to be the second major component in rat hepatocyte incubations. Most of the remaining metabolites were present at low levels and/or in a limited number of incubations, although hydroxylated cyclemax acid was detected in most incubations. 4-Isopropylbenzoic acid was not detected in any human hepatocyte incubations. The metabolic scheme is presented in Fig. 1 below.

**Additional References**: None.

## 8. Natural occurrence

3-(*p*-Isopropylphenyl)propionaldehyde 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 03/14/23.

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for 3-(*p*-isopropylphenyl)propionaldehyde 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) | 0.024 |
| 2 | Products applied to the axillae | 0.025 |
| 3 | Products applied to the face/body using fingertips | 0.094 |
| 4 | Products related to fine fragrances | 0.47 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.12 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.024 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.094 |
| 5D | Baby cream, oil, talc | 0.0079 |
| 6 | Products with oral and lip exposure | 0.024 |
| 7 | Products applied to the hair with some hand contact | 0.047 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.0079 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 0.50 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 0.28 |
| 10B | Aerosol air freshener | 0.61 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 0.0079 |
| 12 | Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin | 15 |

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 3-(*p*-isopropylphenyl)propionaldehyde, the basis was the subchronic reference dose of 0.045 mg/kg/day, a skin absorption value of 13.50%, and a skin sensitization NESIL of 1100 μg/cm$^2$.
bFor 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).
cCalculations by Creme RIFM Aggregate Exposure Model v3.3

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

Based on the current existing data, 3-(*p*-isopropylphenyl)propionaldehyde does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* 3-(*p*-Isopropylphenyl)propionaldehyde was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) with and without metabolic activation, positive for genotoxicity with metabolic activation, and negative for genotoxicity without metabolic activation. These positive results were observed at cytotoxic concentrations that were within the acceptable range for the BlueScreen assay (positive: <80% relative cell density) (RIFM, 2013b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). While the BlueScreen assay on the target material showed positive results, data from additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 3-(*p*-isopropylphenyl)propionaldehyde has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and equivalent to OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 3-(*p*-isopropylphenyl) propionaldehyde 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 dose in the presence or absence of S9 (RIFM, 2013a). Under the conditions of the study, 3-(*p*-isopropylphenyl)propionaldehyde was not mutagenic in the Ames test.

The clastogenic activity of 3-(*p*-isopropylphenyl)propionaldehyde 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 3-(*p*-isopropylphenyl) propionaldehyde in DMSO at concentrations up to 1760 μg/mL in the presence and absence of S9 for 4 h and in the absence of S9 for 24 h 3-(*p*-Isopropylphenyl)propionaldehyde did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2013c). Under the conditions of the study, 3-(*p*-isopropylphenyl)propionaldehyde was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 3-(*p*-isopropylphenyl)propionaldehyde does not present a concern for genotoxic potential.

**Additional References:** RIFM, 2017e.

**Literature Search and Risk Assessment Completed On:** 03/10/23.

#### 11.1.2. Repeated dose toxicity

The MOE for 3-(*p*-isopropylphenyl)propionaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

*11.1.2.1. Risk assessment.* There are no repeated dose toxicity data on 3-(*p*-isopropylphenyl)propionaldehyde. Read-across material *p-tert*-butyldihydrocinnamaldehyde (CAS # 18127-01-0; see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

In a GLP and OECD 422-compliant study, 10 Crl:CD (SD) rats/sex/dose were administered *p-tert*-butyldihydrocinnamaldehyde via gavage at doses of 0, 0.5, 1, and 5 mg/kg/day. Males were treated before cohabitation, through mating, and continuing for approximately 28 days (42–45 days total); females were treated before cohabitation, through parturition until day 12 of lactation (38–56 days total). No treatment-related mortality was observed during the study period. There were no effects on clinical signs, body weight, bodyweight gain, food consumption, functional observation battery, motor activity, organ weights, hematology, clinical chemistry, or coagulation. Based on no effects seen up to the highest dose, the NOAEL for this study was determined to be 5 mg/kg/day (RIFM, 2019).

BMHCA (CAS # 80-54-6) can be used as a WoE material to support the repeated dose toxicity endpoint. Bourgeonal is expected to follow the same metabolic pathway as BMHCA and form a *p-tert*-Butyl Benzoic Acid (tBBA) intermediate, which ultimately conjugates with Coenzyme A. In addition, Laue et al. (2017) demonstrate that the adverse effects of these compounds are not dependent on the aldehyde moiety but on the respective acid derivative. This further confirms the similarity in the mode of action for both bourgeonal and BMHCA. Moreover, bourgeonal is expected to be metabolized more rapidly in comparison to BMHCA,

thereby limiting the accumulation of tBBA-CoA conjugates responsible for male reproductive toxicity. Since no adverse effects were reported in an extended 1-generation study (OECD 443) for BMHCA at doses less than 4.5 mg/kg/day, it is plausible that similar results are observed for bourgeonal in a study with a longer duration. Hence, we propose to use 4.5 mg/kg/day as the point of departure for this risk assessment based on the similarity in metabolism and mode of action of these 2 structurally similar compounds (RIFM, 2017a).

**Therefore, the 3-(*p*-isopropylphenyl)propionaldehyde MOE for the repeated dose toxicity endpoint can be calculated by dividing the *p-tert*-butyldihydrocinnamaldehyde NOAEL in mg/kg/day by the total systemic exposure to 3-(*p*-isopropylphenyl)propionaldehyde, 4.5/0.0014, or 3214.**

**When correcting for skin absorption (see Section V), the total systemic exposure to 3-(*p*-isopropylphenyl)propionaldehyde (1.4 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.**

*11.1.2.2. 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 0.045 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 RfD for 3-(*p*-isopropylphenyl)propionaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose or Reproductive Toxicity sections) of 4.5 mg/kg/day by the uncertainty factor, 100 = 0.045 mg/kg/day.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/14/23.

*11.1.3. Reproductive toxicity*

The MOE for 3-(*p*-isopropylphenyl)propionaldehyde is adequate for the reproductive toxicity endpoint at the current level of use.

*11.1.3.1. Risk assessment.* There are no reproductive toxicity data on 3-(*p*-isopropylphenyl)propionaldehyde. Read-across material *p-tert*-butyldihydrocinnamaldehyde (CAS # 18127-01-0; see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

In a GLP and OECD 422-compliant study, 10 Crl:CD (SD) rats/sex/dose were administered *p-tert*-butyldihydrocinnamaldehyde via gavage at doses of 0, 0.5, 1, and 5 mg/kg/day. Males were treated before cohabitation, through mating, and continuing for approximately 28 days (42–45 days total); females were treated before cohabitation, through parturition until day 12 of lactation (38–56 days total). No treatment-related mortality was observed during the study period. There were no treatment-related adverse effects on mating or fertility parameters, serum T4 concentrations, or organ weights in the parental (P) generation. There were no treatment-related adverse effects on anogenital distance, nipple retention (males), mean pup body weights, macroscopic observations, microscopic observations, or serum T4 concentrations in the offspring (F1) generation. Based on no adverse effects seen up to the highest dose, the fertility and developmental toxicity NOAEL for this study was considered to be 5 mg/kg/day (RIFM, 2019).

In a GLP-compliant reproductive toxicity study, groups of 6 sexually mature male CD rats/dose were administered *p-tert*-butyldihydrocinnamaldehyde via gavage (vehicle: corn oil) at dose levels of 0, 25, 100, or 250 mg/kg/day for 5 days. Bodyweight changes were observed in all dosage groups. Adverse clinical signs and morbidity were observed at 100 and 250 mg/kg/day. In the high-dose group, mean body weights and testes weights were reduced, and mean absolute epididymides weights were marginally increased. Macroscopic examination revealed enlarged epididymides (3/6 rats) as well as other organ findings. Microscopic changes in the testes included Sertoli cell vacuolation and tubular degeneration/atrophy. In the epididymides, reduced numbers of sperm and sloughed sperm in the tubule lumen were seen. The known metabolite 4-*tert*-butylbenzoic acid (TBBA), which is associated with testicular toxicity, was found in the urine of low- and mid-dose animals (high-dose animals were not evaluated due to morbidity). Treatment of male rats with a single oral dose of the test material for 5 consecutive days was associated with marked systemic toxicity at 250 and 100 mg/kg/day and testicular/epididymal toxicity at 100 mg/kg/day. The known metabolite of the parent substance TBBA, which may be associated with testicular toxicity, was found in the urine of males treated at 25 or 100 mg/kg/day (RIFM, 2009).

BMHCA (CAS # 80-54-6) can be used as a WoE material to support the reproductive toxicity endpoint. Bourgeonal is expected to follow the same metabolic pathway as BMHCA and form a tBBA intermediate, which ultimately conjugates with Coenzyme A. Accumulation of the tBBA-CoA in rat hepatocytes is considered to be the underlying mode of action for male reproductive toxicity. In addition, Laue et al. (2017) demonstrate that the adverse effects of these compounds are not dependent on the aldehyde moiety but on the respective acid derivative. This further confirms the similarity in the mode of action for both bourgeonal and BMHCA. Moreover, bourgeonal is expected to be metabolized more rapidly in comparison to BMHCA, thereby limiting the accumulation of tBBA-CoA conjugates responsible for male reproductive toxicity.

In an OECD 414-compliant study, groups of 25 pregnant female Wistar rats/dose were administered BMHCA via gavage (vehicle: olive oil) at nominal doses of 0, 5, 15, or 45 mg/kg/day (effective doses of 0, 4.1, 12.7, or 40.7 mg/kg/day, respectively) on days 6–20 post-coitum. At 45 mg/kg/day, dams exhibited statistically significant increased resorption rates (post-implantation loss 15.1%), a lower number of live fetuses/dam (7.4 vs. 8.1 in the controls), statistically significant lower mean fetal body weights (about 19% below controls), and a statistically significant increased rate of fetuses/litter with skeletal variations (delays/minor disturbances in ossification, predominantly of skull, vertebrae and sternebrae, supernumerary 14th ribs). At 15 mg/kg/day, statistically significant lower mean fetal body weights (about 8% below controls) and a statistically significant increased rate of fetuses/litter with skeletal variations (delays/minor disturbances in ossification, predominantly of vertebrae and sternebrae, supernumerary 14th ribs) were reported. Clear signs of maternal toxicity, which included reduced food consumption, impaired body weights, and alterations in clinical chemistry accompanied by liver weight changes, were observed among mid- and high-dose dams. Based on reduced fetal body weight and increased incidences of skeletal variation of the fetuses among higher dose group dams, the maternal and prenatal developmental toxicity NOAEL for this study was considered to be the nominal dose of 5 mg/kg/day, or the effective dose of 4.1 mg/kg/day (RIFM, 2004).

In an OECD 443/GLP-compliant study, groups of 35 Wistar rats/sex/dose were administered BMHCA (encapsulated) via diet at target doses of 0, 1, 3, or 10 mg/kg/day (equivalent to an overall mean dose of 0, 1.4, 4.5, or 15.1 mg/kg/day) Based on distinct liver toxicity and corresponding effects on food consumption, body weights, and clinical-pathological parameters (predominantly in females), the repeated dose toxicity NOAEL for this study was considered to be the target dose of 3 mg/kg/day or the overall mean dose of 4.5 mg/kg/day for the F0 and F1 parental generations, as well as adolescent animals. Based on no adverse effects on mating or fertility parameters seen up to the highest dose, the fertility NOAEL for this study was established at the target dose of 10 mg/kg/day or the overall mean dose of 15.1 mg/kg/day, the highest dose tested. Based on reduced pup body weights in the high-dose group F1 and F2 offspring, the developmental toxicity NOAEL for this study was established at the target dose of 3 mg/kg/day, or the overall mean dose of 4.5 mg/kg/day (RIFM, 2017a; SCCS, 2019).

**Table 2**
Summary of existing data on 3-(p-isopropylphenyl)propionaldehyde.

| WoE Skin Sensitization Potency Category[1] | Human Data | | | | Animal Data | | |
|---|---|---|---|---|---|---|---|
| | NOEL-CNIH (induction) µg/cm² | NOEL-HMT (induction) µg/cm² | LOEL (induction) µg/cm² | WoE NESIL[2] µg/cm² | LLNA[3] Weighted Mean EC3 Value µg/cm² | GPMT | Buehler |
| Weak | 1111 | N/A | N/A | 1100 | 4650 | N/A | N/A |
| | *In vitro* Data[4] | | | | *In silico* protein binding alerts (OECD Toolbox v4.5) | | |
| | KE 1 | KE 2 | KE 3 | | Target Material | Autoxidation simulator | Metabolism simulator |
| | Borderline | Negative | Positive | | Schiff base formation | Radical reactions; Schiff base formation | No alert found |

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; N/A = Not Available.
1WoE 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).
2WoE NESIL limited to 2 significant figures.
3Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).
4Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

The NOAEL of 5 mg/kg/day from the OECD 422 study on the read-across material was selected for the developmental toxicity and fertility endpoints.

**Therefore, the *p-tert*-butyldihydrocinnamaldehyde MOE for the reproductive toxicity endpoints can be calculated by dividing the *p-tert*-butyldihydrocinnamaldehyde NOAEL in mg/kg/day by the total systemic exposure to *p-tert*-butyldihydrocinnamaldehyde, 5/0.0014, or 3571.**

**When correcting for skin absorption (see Section V), the total systemic exposure to *p-tert*-butyldihydrocinnamaldehyde (1.4 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint at the current level of use.**

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/14/23.

*11.1.4. Skin sensitization*

Based on the existing data, 3-(*p*-isopropylphenyl)propionaldehyde is considered a skin sensitizer with a defined NESIL of 1100 µg/cm$^2$, and the maximum acceptable concentrations in finished products are provided in Section X.

*11.1.4.1. Risk assessment.* Based on the existing data, 3-(*p*-isopropylphenyl)propionaldehyde is considered a skin sensitizer (Table 1). This material is predicted *in silico* to be reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). 3-(*p*-Isopropylphenyl)propionaldehyde was found to be borderline in a direct peptide reactivity assay (DPRA), negative in a KeratinoSens, but positive in a human cell line activation test (h-CLAT) and U-SENS test (RIFM, 2016a; RIFM, 2016b; RIFM, 2017h; RIFM, 2020). These *in vitro* results are inconclusive based on the 2 out of 3 defined approach, following OECD Guideline No. 497: Defined Approaches on Skin Sensitization (OECD, 2021a). In a murine local lymph node assay (LLNA), 3-(p-isopropylphenyl)propionaldehyde was found to be

sensitizing with an EC3 value of 18.6% (4650 μg/cm$^2$) (RIFM, 2012b). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 1111 μg/cm$^2$ of 3-(*p*-isopropylphenyl)propionaldehyde in 3:1 alcohol SD39C:diethyl phthalate, no reactions indicative of sensitization was observed in any of the 99 volunteers (RIFM, 2000).

Based on the WoE from structural analysis, *in vitro* studies, an animal study, and a human study, 3-(*p*-isopropylphenyl)propionaldehyde was assigned a WoE NESIL of 1100 μg/cm$^2$ (Table 2). 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 0.045 mg/kg/day.

**Additional References:** RIFM, 2017c.

**Literature Search and Risk Assessment Completed On:** 02/28/23.

*11.1.5. Photoirritation/photoallergenicity*

Based on the available UV/Vis absorption spectra, 3-(*p*-isopropylphenyl)propionaldehyde would not be expected to present a concern for photoirritation or photoallergenicity.

*11.1.5.1. Risk assessment.* There are no photoirritation studies available for 3-(*p*-isopropylphenyl)propionaldehyde in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 3-(*p*-isopropylphenyl) propionaldehyde does not present a concern for photoirritation or photoallergenicity.

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

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 02/21/23.

*11.1.6. Local Respiratory Toxicity*

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3-(*p*-isopropylphenyl)propionaldehyde 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 3-(*p*-isopropylphenyl)propionaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.015 mg/day. This exposure is 93.3 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:** 06/22/23.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of 3-(*p*-isopropylphenyl)propionaldehyde 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 of 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, 3-(*p*-isopropylphenyl)propionaldehyde 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 3-(*p*-isopropylphenyl)propionaldehyde as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2017a). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

*11.2.2. Risk assessment*

Based on the current VoU (2019), 3-(*p*-isopropylphenyl)propionaldehyde presents a risk to the aquatic compartment in the screening-level assessment.

*11.2.2.1. Key studies. Biodegradation:*

RIFM, 2017f: The biodegradability of the test material was evaluated in a closed bottle test according to the OECD 301D guidelines. Under the conditions of this study, biodegradation of 71% was observed.

*Ecotoxicity:*

RIFM, 2017d: A 72-h algal growth inhibition test was conducted according to the OECD 201 method. Under the conditions of this study and based on geometric mean measured test concentrations, the 0-72-h EC50 values for inhibition of growth rate and yield were 11 (95% CI: 9.1–13) and 7.3 (95% CI: 7.0–7.6) mg/L, respectively. The 72-h NOEC for inhibition of both growth rate and yield was 2.3 mg/L.

RIFM, 2017g: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48h-EC50 was reported to be 0.43 mg/L based on average exposure concentrations (95% confidence interval between 0.29 and 0.68 mg/L).

RIFM, 2017b: A fish (rainbow trout) acute toxicity test was conducted according to the OECD 203 method under semi-static conditions. Based on the geometric mean measured test concentrations, the 96-h LC50 was reported to be 3.9 mg/L.

Other available data

3-(*p*-Isopropylphenyl)propionaldehyde has been registered under REACH with no additional data at this time.

*11.2.3. Risk assessment refinement.* **Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).**

**Endpoints used to calculate PNEC are underlined.**

| | LC50 (Fish) | EC50 (*Daphnia*) | EC50 (Algae) | AF | PNEC | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening-level **(Tier 1)** | 12.26 mg/L | | | 1000000 | 0.01226 μg/L | |
| ECOSAR Acute Endpoints **(Tier 2)** ***v2.0*** | 1.673 mg/L | 1.285 mg/L | 2.747 mg/L | 10000 | 0.1285 μg/L | Aldehydes (Mono) |
| ECOSAR Acute Endpoints **(Tier 2)** ***v2.0*** | 6.660 mg/L | 4.339 mg/L | 5.701 mg/L | | | Neutral Organics |

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{OW}$ Used | 3.48 | 3.48 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional VoU Tonnage Band | 10–100 | 1–10 |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

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

The RIFM PNEC is 0.1285 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:** 03/07/23.

## 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
- **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 01/03/24.

## 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.2024.114555.

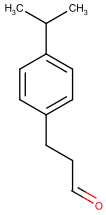
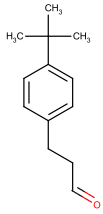
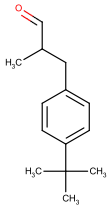
## Appendix

*Read-across Justification*

*Methods*

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- $J_{max}$ values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.5 (OECD, 2021b).
- ER binding and repeat dose categorization were generated using the 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 | WoE Material |
|---|---|---|---|
| **Principal Name** | 3-(*p*-Isopropylphenyl) propionaldehyde | *p-tert*-Butyldihydrocinnamaldehyde | *p-t*-Butyl-α-methylhydrocinnamic aldehyde |
| **CAS No.** | 7775-00-0 | 18127-01-0 | 80-54-6 |
| **Structure** |  |  |  |
| **Similarity (Tanimoto Score)** | | 1.00 | 0.91 |
| **SMILES** | CC(C)c1ccc (CCC═O)cc1 | CC(C) (C)c1ccc (CCC═O)cc1 | CC(Cc1ccc (cc1)C(C) (C)C)C═O |
| **Endpoint** | | Repeated dose toxicity<br>Reproductive toxicity | Repeated dose toxicity<br>Reproductive toxicity |
| **Molecular Formula** | $C_{12}H_{16}O$ | $C_{13}H_{18}O$ | $C_{14}H_{20}O$ |
| **Molecular Weight (g/mol)** | 176.259 | 190.286 | 204.313 |
| **Melting Point (°C, EPI Suite)** | 29.05 | 46.30 | 46.29 |
| **Boiling Point (°C, EPI Suite)** | 263.70 | 273.66 | 280.03 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 1.61E+00 | 6.65E-01 | 4.77E-01 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 6.02E+01 | 2.11E+01 | 7.86E+00 |
| **Log $K_{OW}$** | 3.49 | 3.94 | 4.36 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 5.36 | 2.24 | 0.94 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 1.43E+00 | 1.90E+00 | 2.52E+00 |
| ***Repeated Dose Toxicity*** | | | |
| **Repeated Dose (HESS)** | Not categorized | Chlorphentermine (Hepatotoxicity) Alert | Chlorphentermine (Hepatotoxicity) Alert |
| ***Reproductive Toxicity*** | | | |
| **ER Binding (OECD QSAR Toolbox v4.5)** | Non-binder, without OH or $NH_2$ group | Non-binder, without OH or $NH_2$ group | Non-binder, without OH or $NH_2$ group |
| **Developmental Toxicity (CAESAR v2.1.6)** | Toxicant (low reliability) | Toxicant (low reliability) | Toxicant (low reliability) |
| ***Metabolism*** | | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)** | See Supplemental Data 1 | See Supplemental Data 2 | See Supplemental Data 3 |

*Summary*

There are insufficient toxicity data on 3-(*p*-isopropylphenyl)propionaldehyde (CAS # 7775-00-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, *p-tert*-butyldihydrocinnamaldehyde (CAS # 18127-01-0) and *p-t*-butyl-α-methylhydrocinnamic aldehyde (80-54-6) were identified as read-across analogs

with sufficient data for toxicological evaluation.

*Conclusions*

- *p-tert*-Butyldihydrocinnamaldehyde (CAS # 18127-01-0) and *p-t*-butyl-α-methylhydrocinnamic aldehyde (80-54-6) were used as a read-across analog and WoE material, respectively, for the target material 3-(*p*-isopropylphenyl)propionaldehyde (CAS # 7775-00-0) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the group of alkylated cyclic aldehydes.
  - o The key difference between the target material and the read-across analog is that the read-across analog has a tert-butyl group on the aryl ring rather than an isopropyl. The weight of the evidence material is also an aldehyde with alkylation on the α carbon next to the aldehyde group. The read-across analog, combined with the WoE material, contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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, read-across analog, and WoE material all have alerts for non-binders and toxicants. Data from the reproductive toxicity section confirms that the MOE for the target materials is under the current usage. The structural similarity between the target material and the read-across analogs is considered. The predictions are superseded by the data.
  - o The read-across analog and WoE material have alerts for hepatotoxicity. Data from the repeated dose toxicity section confirms that the MOE for the target material is under the current usage. The structural similarity between the target material and read-across analogs is considered. 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 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.

## References


Api, A.M., Basketter, D., Bridges, J., Cadby, P., et al., 2020. Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials. Regul. Toxicol. Pharmacol. 118, 104805.

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cottrez, F., Boitel, E., Ourlin, J.C., Peiffer, J.L., et al., 2016. A 3D reconstituted epidermis based model for quantifying chemical sensitization potency: reproducibility and predictivity results from an inter-laboratory study. Toxicol. Vitro 32, 248–260.

Date, M.S., O'Brien, D., Botelho, D.J., Schultz, T.W., et al., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. 33 (7), 1709–1718.

ECHA, 2017a. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.11: PBT Assessment. Retrieved from. https://echa.europa.eu/en/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

ECHA, 2017b. Read-across Assessment Framework (RAAF). Retrieved from. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a.

ECHA, 2018. 3-(*p*-Cumenyl)propionaldehyde Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/22566/1/2.

European Centre for Ecotoxicology and Toxicology of Chemicals, 2003. Contact Sensitisation: Classification According to Potency. ECETOC. Technical Report No. 87.

Forreryd, A., Zeller, K.S., Lindberg, T., Johansson, H., Linstedt, M., 2016. From genome-wide arrays to tailor-made biomarker readout - progress towards routine analysis of skin sensitizing chemicals with GARD. Toxicol. Vitro 37, 178–188.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2019. Volume of Use Survey, January-December 2019.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laue, H., Kern, S., Badertscher, R., Ellis, G., Natsch, A., 2017. *p*-Alkyl-Benzoyl-CoA conjugates as relevant metabolites of aromatic aldehydes with rat testicular toxicity—studies leading to the design of a safer new fragrance chemical. Toxicol. Sci. 160 (2), 244–255. Retrieved from. https://academic.oup.com/toxsci/article/160/2/244/4098089.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2021. Fragrance skin sensitization evaluation and human testing: 30-year experience. Dermatitis 32 (5), 339–352.

OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA, p. 7, 2015. https://one.oecd.org/document/ENV/JM/HA(2015)7/en/pdf.

OECD, 2021a. Guideline No. 497: Defined Approaches on Skin Sensitisation, OECD Guidelines for the Testing of Chemicals, Section, vol. 4. OECD Publishing, Paris. https://doi.org/10.1787/b92879a4-en.

OECD, 2021b. The OECD QSAR Toolbox, v3.2–4.5. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1994. The Dermal Absorption of (14)C-BMHCA, (14)C-Para-Tert-Butyl-Alpha-Methylhydrocinnamaldehyde in Man. Report to RIFM. RIFM Report Number 23500. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1995. Studies of the Oral and Dermal Absorption of (14)C-Par-Tert-Butyl-Alpha Methylhydrocinnamaldehyde (BMHCA) in the Rat. Report to RIFM. RIFM Report Number 23697. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000. Repeated Insult Patch Test with 3-(p-Isopropylphenyl)propionaldehyde (Cyclemax). Unpublished Report from International Flavors and Fragrances. RIFM Report Number 48332. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. p-t-Butyl-alpha-methylhydrocinnamic Aldehyde (Lysmeral): Prenatal Developmental Toxicity Study in Wistar Rats. Unpublished Report from BASF. RIFM Report Number 52014. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Bourgeonal, Silvial and Cyclamen Aldehyde: Toxicity Study by Oral Gavage Administration to Sexually Mature Male CD Rats for 5 Days. Unpublished Report from Givaudan. RIFM Report Number 57411. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2012a. p-Isobutyl-a-methyl Hydrocinnamaldehyde, 3-(p-Isopropylphenyl)propionaldehyde, Isopropylphenylbutanal, P-Methoxybenzaldehyde and Hydratropic Aldehyde: Comparative in Vitro Metabolism Using Mouse, Rat, Rabbit and Human Hepatocytes. RIFM Report Number 63976. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2012b. 3-(4-Isopropylphenyl) propanal (Cyclemax): Local Lymph Node Assay in the Mouse. Unpublished Report from IFF. RIFM Report Number 65004. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. 3-(p-Isopropylphenyl) propionaldehyde: Reverse Mutation Assay "Ames Test" Using Salmonella typhimurium and Escherichia coli. RIFM Report Number 65019. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Report on the Testing of 3-(para-Isopropylphenyl)propionaldehyde in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 65068. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013c. 3-(p-Isopropylphenyl) propionaldehyde: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). [Amendment Attached] RIFM Report Number 66023. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. Direct Peptide Reactivity Assay (DPRA) in Fragrance Materials. RIFM Report Number 72227. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Induction of Antioxidant-Response-Element Dependent Gene Activity and Cytotoxicity (Using MTT) in the Keratinocyte ARE-Reporter Cell Line KeratinoSens. RIFM Report Number 72235. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017a. p-t-Butyl-α-methylhydrocinnamic Aldehyde (Lysmeral): Modified Extended One-Generation Reproduction Toxicity Study in Wistar Rats. Unpublished Report from BASF. RIFM Report Number 72036. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017b. 3-(p-Isopropylphenyl) propionaldehyde (Cyclemax): Acute Toxicity to Fish. Unpublished Report from International Flavors & Fragrances, Inc. RIFM Report Number 72097. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017c. Evaluation of the Sensitization Potential Using the SENS-IS Test of Multiple Materials. RIFM Report Number 72532. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017d. 3-(p-Isopropylphenyl) propionaldehyde (Cyclemax): Algal Growth Inhibition Test. Unpublished Report from International Flavors & Fragrances, Inc. RIFM Report Number 73606. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017e. 3-(p-Isopropylphenyl) propionaldehyde (Cyclemax): L5178Y TK +/- Mouse Lymphoma Assay. Unpublished Report from International Flavors & Fragrances, Inc. RIFM Report Number 74184. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017f. 3-(p-Isopropylphenyl) propionaldehyde (Cyclemax): Biodegradability in the Closed Bottle Test. Unpublished Report from International Flavors & Fragrances, Inc. RIFM Report Number 74697. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017g. 3-(p-Isopropylphenyl) propionaldehyde (Cyclemax): Daphnia sp., 48-hour Acute Immobilization Test. Unpublished Report from International Flavors & Fragrances, Inc. RIFM Report Number 75396. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2017h. 3-(p-Isopropylphenyl) propionaldehyde: in Vitro Sensitization: Dendritic Cell Line Activation Assay Human Cell Line Activation Test (H-CLAT) Unpublished Report from BASF. RIFM Report Number 77115. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2019. p-tert-Butyldihydrocinnamaldehyde (Bourgeonal): Oral (Gavage) Combined Repeated Dose Toxicity Study with the Reproduction/developmental Toxicity Screening in Rats.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020. Evaluation of in Vitro Skin Sensitization Potential of Several Fragrance Materials with the U937 Cell Line Activation Test (U-SENS™) Assay - (Non-GLP) Part 2. RIFM Report Number 77316. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2023. Exposure Survey 39. January 2023.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2024. Corrigendum to "Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products" [Regul. Toxicol. Pharmacol. 72 (3), 673-68]. Regul. Toxicol. Pharmacol., 105545

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

SCCS, 2019. Scientific committee on consumer safety SCCS OPINION ON the safety of butylphenyl methylpropional (p-BMHCA) in cosmetic products: submission II. Retrieved from. https://health.ec.europa.eu/system/files/2021-08/sccs_o_213_0.pdf .

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

Thakkar, Y., Joshi, K., Hickey, C., Wahler, J., et al., 2022. The BlueScreen HC assay to predict the genotoxic potential of fragrance materials. Mutagenesis 37 (1), 13–23.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v2.0. United States Environmental Protection Agency, Washington, DC, USA.