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Short Review

RIFM fragrance ingredient safety assessment, *p*-isopropyl phenylacetaldehyde, CAS Registry Number 4395-92-0

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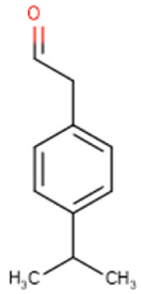
Name: *p*-Isopropyl phenylacetaldehyde CAS Registry Number: 4395-92-0



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,

(*continued on next page*)

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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. *p*-Isopropyl phenylacetaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 3-(*p*-isopropylphenyl)propionaldehyde (CAS # 7775-00-0) show that *p*-isopropyl phenylacetaldehyde is not expected to be genotoxic. Data from 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 from read-across analog 3-(*p*-isopropylphenyl)propionaldehyde (CAS # 7775-00-0) provide *p*-isopropyl phenylacetaldehyde 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; *p*-isopropyl phenylacetaldehyde 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 *p*-isopropyl phenylacetaldehyde is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; *p*-isopropyl phenylacetaldehyde 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 expected to be 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:	
Screening-level: 2.7 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 44.16 kg/L	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 29.51 mg/L	(RIFM Framework; Salvito et al., 2002)
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: Fish LC50: 29.51 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.02951 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level.	

1. Identification

1. **Chemical Name:** p-Isopropyl phenylacetaldehyde
2. **CAS Registry Number:** 4395-92-0
3. **Synonyms:** Benzeneacetaldehyde, 4-(1-methylethyl)-; Cortexal; Cumylacetaldehyde; p-Cymen-7-carboxaldehyde; 4-Isopropylphenylacetaldehyde; (4-Isopropylphenyl)acetaldehyde; Cuminyl acetaldehyde; *p*-Isopropyl phenylacetaldehyde
4. **Molecular Formula:** $C_{11}H_{14}O$
5. **Molecular Weight:** 162.23 g/mol
6. **RIFM Number:** 906
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** >200 °C (Fragrance Materials Association [FMA]), 246.47 °C (EPI Suite v4.11)
2. **Flash Point:** >93 °C (Globally Harmonized System), 200 °F; closed cup (FMA)
3. **Log K_{OW}:** 3 (EPI Suite v4.11)
4. **Melting Point**: 18.38 °C (EPI Suite v4.11)
5. **Water Solubility:** 184 mg/L (EPI Suite v4.11)
6. **Specific Gravity:** 0.990 (FMA)
7. **Vapor Pressure:** 0.0209 mm Hg at 20 °C (EPI Suite v4.0), 0.05 mm Hg at 20 °C (FMA), 0.0329 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:** A colorless liquid

3. Volume of use (Worldwide band)

1. <0.1 metric ton per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.3)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0016% (RIFM, 2023)
2. **Inhalation Exposure*:** 0.0000003 mg/kg/day or 0.000020 mg/day (RIFM, 2023)
3. **Total Systemic Exposure**:** 0.0000084 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 et al., 2015; Safford et al., 2024; Safford et al., 2017; and Comiskey, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2024; Safford et al., 2017; and Comiskey, 2017).

5. Derivation of systemic absorption

1. **Dermal:** SAM 80%

Name	*p*-Isopropyl phenylacetaldehyde
J_{max} (μg/cm^2/h)	12.48[1]
Skin Absorption Class	80%

[1] J_{max} was calculated based on calculated log K_{ow} = 3 (EPI Suite v4.11) and water solubility = 184 mg/L at 25 °C (EPI Suite v4.11).

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

6. Computational toxicology evaluation

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

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

2. **Analogs Selected**:
a. **Genotoxicity:** 3-(*p*-Isopropylphenyl)propionaldehyde (CAS # 7775-00-0)
b. **Repeated Dose Toxicity:** *p-tert*-Butyldihydrocinnamaldehyde (CAS # 18127-01-0); *p-t*-Butyl-α-methylhydrocinnamic aldehyde (BMHCA; CAS # 80-54-6) for Weight of Evidence (WoE)
c. **Reproductive Toxicity:** *p-tert*-Butyldihydrocinnamaldehyde (CAS # 18127-01-0); *p-t*-Butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6) for WoE
d. **Skin Sensitization:** 3-(*p*-Isopropylphenyl)propionaldehyde (CAS # 7775-00-0)
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None
3. **Read-across Justification**: See Appendix below

7. Metabolism

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

8. Natural occurrence

p-Isopropyl phenylacetaldehyde 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

p-Isopropyl phenylacetaldehyde has been pre-registered for 2010; no dossier available as of 11/10/23.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for *p*-isopropyl phenylacetaldehyde are detailed below.

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(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.0040
2	Products applied to the axillae	0.025
3	Products applied to the face/body using fingertips	0.0081
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	0.10
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.0040
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.032
5D	Baby cream, oil, talc	0.0013
6	Products with oral and lip exposure	0.0040
7	Products applied to the hair with some hand contact	0.028
8	Products with significant ano-genital exposure (tampon)	0.0013
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.12
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.024
10B	Aerosol air freshener	0.089
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.0013
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	0.95

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 *p*-isopropyl phenylacetaldehyde, the basis was the subchronic reference dose of 0.045 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 1100 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.3.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, *p*-isopropyl phenylacetaldehyde does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. *p*-Isopropyl phenylacetaldehyde was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and 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 on an appropriate 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 or clastogenic activity of *p*-isopropyl phenylacetaldehyde. The mutagenic activity of read-across material 3-(*p*-isopropylphenyl)propionaldehyde (CAS # 7755-00-0; see Section VI) 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.

There are no studies assessing the clastogenic activity of *p*-isopropyl phenylacetaldehyde; however, read-across can be made to 3-(*p*-isopropylphenyl)propionaldehyde (CAS # 7755-00-0; see Section VI). 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 available data, 3-(*p*-isopropylphenyl)propionaldehyde does not present a concern for genotoxic potential, and this can be applied to *p*-isopropyl phenylacetaldehyde.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for *p*-isopropyl phenylacetaldehyde 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 p-isopropyl phenylacetaldehyde. 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; see Section VI) 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. 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. Since no adverse effects were reported in an extended 1-generation study (OECD TG 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 *p*-isopropyl phenylacetaldehyde 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 p-isopropyl phenylacetaldehyde, 4.5/0.0000084, or 535714.

When correcting for skin absorption (see Section V) calculated using the RIFM SAM (Shen et al., 2014), the total systemic exposure to 3-(p-isopropylphenyl)propionaldehyde (0.0084 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.

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 reference dose (RfD) of 0.045 mg/kg/day.

11.1.2.1.1. Derivation of subchronic RfD. The RIFM Criteria Document (Api et al., 2015) calls for a default MOE of 100 (10 × 10) based on uncertainty factors applied for interspecies (10 ×) and intraspecies (10 ×) differences. The subchronic RfD for *p*-isopropyl phenylacetaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose Toxicity 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 p-isopropyl phenylacetaldehyde is adequate for the reproductive toxicity endpoints at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on *p*-isopropyl phenylacetaldehyde. 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 reproductive 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 100 or 25 mg/kg/day (RIFM, 2009).

BMHCA (CAS # 80-54-6; see Section VI) 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 *p-tert*-Butyl Benzoic Acid (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

Table 1
Summary of existing data on 3-(*p*-isopropylphenyl)propionaldehyde as a read-across for *p*-isopropyl phenylacetaldehyde.

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.
[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).
[2]WoE NESIL limited to 2 significant figures.
[3]Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).
[4]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

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).

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, 5/0.0000084, or 595238.

When correcting for skin absorption (see Section V) calculated using the RIFM SAM (Shen et al., 2014), the total systemic exposure to *p-tert*-butyldihydrocinnamaldehyde (0.0084 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 read-across material 3-(*p*-isopropylphenyl)propionaldehyde, *p*-isopropyl phenylacetaldehyde was assigned a 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. Limited skin sensitization data are available for *p*-isopropyl phenylacetaldehyde. Therefore, a structurally related material, 3-(*p*-isopropylphenyl)propionaldehyde (CAS # 7775-00-0; see Section VI), was used for the risk assessment of *p*-isopropyl phenylacetaldehyde. The data on the read-across material are summarized in Table 1 *p*-Isopropyl phenylacetaldehyde and read-across material are predicted *in silico* to be reactive with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.5). Read-across material 3-(*p*-isopropylphenyl)propionaldehyde was found to be borderline in a direct peptide reactivity assay (DPRA), negative in a KeratinoSens, and positive in a human cell line activation test (h-CLAT) and U-SENS test (RIFM, 2016a; RIFM, 2016b; RIFM, 2017c; 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), read-across material 3-(*p*-isopropylphenyl)propionaldehyde was found to be sensitizing with an EC3 value of 18.6% (4650 μg/cm^2) (RIFM, 2012). In a human maximization test, no reactions indicative of sensitization were observed when *p*-isopropyl phenylacetaldehyde was tested at 2760 μg/cm^2 (RIFM, 1977). Additionally, in a Confirmation of No Induction in Humans (CNIH) test with 1111 μg/cm^2 of read-across material 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 and *in vitro*, animal, and human studies on the read-across material and the target material, *p*-isopropyl phenylacetaldehyde is a sensitizer with a WoE NESIL of 1100 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (2020) and a subchronic RfD of 0.045 mg/kg/day.

Additional References: RIFM, 2017b.

Literature Search and Risk Assessment Completed On: 03/01/23.

11.1.5. Photoirritation/photoallergenicity

Based on available UV/Vis spectra, *p*-isopropyl phenylacetaldehyde 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 *p*-isopropyl phenylacetaldehyde in experimental models. UV/Vis absorption spectra indicate no 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, *p*-isopropyl phenylacetaldehyde 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 material, p-isopropyl phenylacetaldehyde, the exposure level 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 *p*-isopropyl phenylacetaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.000020 mg/day. This exposure is 70000 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 *p*-isopropyl phenylacetaldehyde 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),

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	29.5			1000000	0.02951	

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, *p*-isopropyl phenylacetaldehyde was identified as a fragrance material with no 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 *p*-isopropyl phenylacetaldehyde 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).

11.2.1.1. Risk assessment. Based on the current VoU (2019), *p*-isopropyl phenylacetaldehyde presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies. ***Biodegradation***:
No data available.
Ecotoxicity:
No data available.

11.2.1.3. Other available data. p-Isopropyl phenylacetaldehyde has been pre-registered for REACH with no additional data at this time.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.0	3.0
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.02951 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it 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.Structured

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.2024.114497.

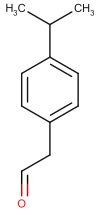
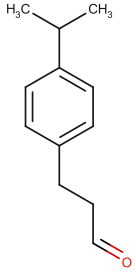
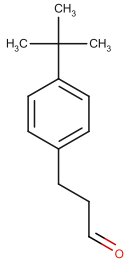
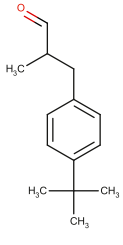
Appendix

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	Read-across Material	WoE Material
Principal Name	*p*-Isopropyl phenylacetaldehyde	3-(*p*-Isopropylphenyl) propionaldehyde	*p-tert*-Butyldihydrocinnamaldehyde	*p-t*-Butyl-α-methylhydrocinnamic aldehyde (BMHCA)
CAS No.	4395-92-0	7775-00-0	18127-01-0	80-54-6
Structure				
Similarity (Tanimoto Score)		0.73	0.73	0.67
SMILES	CC(C)c1ccc(CC═O)cc1	CC(C)c1ccc(CCC═O)cc1	CC(C)(C)c1ccc(CCC═O)cc1	CC(Cc1ccc(cc1)C(C)(C)C)C═O
Endpoint		Genotoxicity Skin sensitization	Repeated dose toxicity Reproductive toxicity	Repeated dose toxicity Reproductive toxicity
Molecular Formula	$C_{11}H_{14}O$	$C_{12}H_{16}O$	$C_{13}H_{18}O$	$C_{14}H_{20}O$
Molecular Weight	162.232	176.259	190.286	204.313
Melting Point (°C, EPI Suite)	18.38	29.05	46.30	46.29
Boiling Point (°C, EPI Suite)	246.47	263.70	273.66	280.03

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	WoE Material
Vapor Pressure (Pa @ 25°C, EPI Suite)	4.39E+00	1.61E+00	6.65E-01	4.77E-01
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.84E+02	6.02E+01	2.11E+01	7.86E+00
Log KOW	3	3.49	3.94	4.36
J_{max} (μg/cm^2/h, SAM)	12.48	5.36	2.24	0.94
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.08E+00	1.43E+00	1.90E+00	2.52E+00
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.5)	No alert found	No alert found		
DNA Binding (OECD QSAR Toolbox v4.5)	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes|Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes	Michael addition|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals|Michael addition ≫ P450 Mediated Activation to Quinones and Quinone-type Chemicals ≫ Arenes|Schiff base formers|Schiff base formers ≫ Direct Acting Schiff Base Formers|Schiff base formers ≫ Direct Acting Schiff Base Formers ≫ Mono aldehydes		
Carcinogenicity (ISS)	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity	Simple aldehyde (Genotox)|Structural alert for genotoxic carcinogenicity		
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found		
In Vitro Mutagenicity (Ames, ISS)	Simple aldehyde	Simple aldehyde		
In Vivo Mutagenicity (Micronucleus, ISS)	Simple aldehyde	Simple aldehyde		
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds		
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 NH2 group		Non-binder, without OH or NH2 group	Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	Toxicant (low reliability)		Toxicant (low reliability)	Toxicant (low reliability)
Skin Sensitization				
Protein Binding (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes		
Protein Binding (OECD)	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls	Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers|Schiff Base Formers ≫ Direct Acting Schiff Base Formers ≫ Mono-carbonyls		
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)		
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes	Schiff base formation|Schiff base formation ≫ Schiff base formation with carbonyl compounds|Schiff base formation ≫ Schiff base formation with carbonyl compounds ≫ Aldehydes		
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	Alert for Schiff base formation identified.	Alert for Schiff base formation identified.		
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.5)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on *p*-isopropyl phenylacetaldehyde (CAS # 4395-92-0). 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, 3-(*p*-isopropylphenyl)propionaldehyde (CAS # 7775-00-0), *p-tert*-butyldihydrocinnamaldehyde (CAS # 18127-01-0), and *p-t*-butyl-α-methylhydrocinnamic

aldehyde (CAS # 80-54-6) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 3-(*p*-Isopropylphenyl)propionaldehyde (CAS # 7775-00-0) was used as a read-across analog for the target material *p*-isopropyl phenylacetaldehyde (CAS # 4395-92-0) for the genotoxicity and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the group of alkyl cyclic aldehydes.
  - o The key difference between the target material and the read-across analog is that the read-across analog contains an additional methylene carbon separating the aldehyde from the aryl group. The read-across analog 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 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 the percentage of 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 v4.5, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Both the target material and read-across analog have alerts for Michael addition and p450-mediated activation to a quinone. The data from the genotoxicity section shows that the read-across analog is of no concern for the genotoxicity endpoint. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the *in silico* alerts and predictions are superseded by the data.
  - o Both the target material and the read-across analog have Schiff base formation alerts for skin sensitization. According to the data from the skin sensitization section, the read-across analog is a skin sensitizer with a NESIL for WoE. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, *in silico* alerts are consistent with the data.
  - 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.
- *p-tert*-Butyldihydrocinnamaldehyde (CAS # 18127-01-0) and *p-t*-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6) were used as a read-across analog and a WoE material, respectively, for the target material *p*-isopropyl phenylacetaldehyde (CAS # 4395-92-0) 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 aryl 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 and contains an additional methylene carbon in between the aldehyde and the aryl group. The WoE 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 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 the percentage of 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 v4.5, 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.

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