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Short Review

RIFM fragrance ingredient safety assessment, *p*-isobutyl-α-methyl hydrocinnamaldehyde, CAS Registry Number 6658-48-6

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Version: 032420. This version replaces any previous versions.
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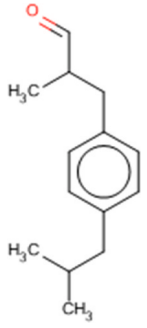
CAS Registry Number: 6658-48-6



Abbreviation/Definition List:

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2-Box Model - A RIFM, Inc. Proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model

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(*continued*)

EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on RIFM's Criteria Document (Api, 2015) and 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 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-Isobutyl-α-methyl hydrocinnamaldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across material *p*-t-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6) show that this material is not expected to be genotoxic. Data from *p-i*sobutyl-α-methyl hydrocinnamaldehyde provide a calculated margin of exposure (MOE) > 100 for the repeated dose and reproductive toxicity endpoints and a No Expected Sensitization Induction Level (NESIL) of 2300 μg/cm^2 for the skin sensitization endpoint. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material (1.4 mg/day), and exposure to *p-i*sobutyl-α-methyl hydrocinnamaldehyde is below the TTC. The phototoxicity/photoallergenicity endpoint was completed based on data and (ultraviolet) UV spectra; *p-i*sobutyl-α-methyl hydrocinnamaldehyde is not phototoxic/photoallergenic. The environmental endpoints were evaluated; *p*-isobutyl-α-methyl hydrocinnamaldehyde 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 in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(RIFM, 1987a; RIFM, 2000a)
Repeated Dose Toxicity: NOAEL = 33.33 mg/kg/day.	RIFM (2018c)
Reproductive Toxicity: Developmental toxicity: NOAEL = 300 mg/kg/day. Fertility: NOAEL = 1000 mg/kg/day.	RIFM (2018d)
Skin Sensitization: NESIL = 2300 μg/cm^2.	RIFM (2008b)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM Database; RIFM, 1987b)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 76% (OECD 301F)	RIFM (2014a)
Bioaccumulation: Screening-level: 370.3 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.315 mg/L	(ECOSAR; US EPA, 2012b)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 48-h *Daphnia magna* LC50: 0.315 mg/L	(ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0315 μg/L	
Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1	

1. Identification

1. **Chemical Name:** *p*-Isobutyl-α-methyl hydrocinnamaldehyde
2. **CAS Registry Number:** 6658-48-6
3. **Synonyms:** 3-(*p*-Cumenyl)-2-methylpropionaldehyde; Rhodial; Suzaral; Silvial; *p*-ｱﾙｷﾙ(C = 3 ~ 4)ﾌｪﾆﾙｱﾙｷﾙ(C = 2 ~ 3)ｱﾙﾃﾞﾋﾄﾞ; Benzenepropanal, α-methyl-4-(2-methylpropyl)-; 3-(4-Isopropylphenyl)-2-methylpropanal; *p*-Isobutyl-α-methyl hydrocinnamaldehyde
4. **Molecular Formula:** $C_{14}H_{20}O$
5. **Molecular Weight:** 204.31
6. **RIFM Number:** 905

2. Physical data

1. **Boiling Point:** 286.25 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 4.4 (EPI Suite)
4. **Melting Point**: 39.4 °C (EPI Suite)
5. **Water Solubility:** 7.299 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0015 mm Hg @ 20 °C (EPI Suite v4.0), 0.00299 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless clear liquid with a medium, floral, green, aldehydic, muguet, and lily odor*

*http://www.thegoodscentscompany.com/data/rw1418091.html; retrieved 06/06/17

3. Volume of use (Worldwide Band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.16% (RIFM, 2018a)

2. **Inhalation Exposure*:** 0.00049 mg/kg/day or 0.036 mg/day (RIFM, 2018a)
3. **Total Systemic Exposure**:** 0.0058 mg/kg/day (RIFM, 2018a)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree (v2.6.0)	OECD QSAR Toolbox (v3.2)
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** *p*-t-Butyl-α-methylhydrocinnamic aldehyde (lilial; CAS # 80-54-6)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

RIFM, 2012: A metabolism study was conducted with *p*-isobutyl-α-methyl hydrocinnamaldehyde (silvial) to compare the *in vitro* metabolism by hepatocytes of the test material between 4 species (mouse, rat, rabbit, and human). Following hepatocyte incubations of silvial, a total of 7 components were observed. Interspecies differences were small, and the glucuronide conjugate of silvial alcohol was generally the largest component (in terms of the percentage of total peak area). Metabolites silvial acid and the glucuronide conjugate of hydroxylated silvial alcohol were also observed in most hepatocyte incubations. The remaining metabolites of silvial were typically observed at low levels (<5% of the total peak area) and/or in a limited number of incubations. Metabolites of the glucuronide conjugate of silvial alcohol and silvial acid were observed at low levels in all 0-h (control) incubations. The metabolic scheme is provided below. (See Fig. 1)

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

p-Isobutyl-α-methyl hydrocinnamaldehyde is not reported to occur in food 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; accessed on 03/24/20.

10. Conclusion

The maximum acceptable concentrations[a] in finished products for *p*-isobutyl-α-methyl hydrocinnamaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.080
2	Products applied to the axillae	0.053
3	Products applied to the face/body using fingertips	0.80
4	Products related to fine fragrances	0.99
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.25
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.25
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.25
5D	Baby cream, oil, talc	0.083
6	Products with oral and lip exposure	0.080
7	Products applied to the hair with some hand contact	0.72
8	Products with significant ano-genital exposure (tampon)	0.083
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.9
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.9
10B	Aerosol air freshener	5.4
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.083
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction

Note.

[a] Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For *p*-isobutyl-α-methyl hydrocinnamaldehyde, the basis was the reference dose of 0.33 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 2300 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).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, *p*-isobutyl-α-methyl hydrocinnamaldehyde does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of *p*-isobutyl-α-methyl hydrocinnamaldehyde has been evaluated in a bacterial reverse mutation assay conducted in accordance with guidelines similar to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain

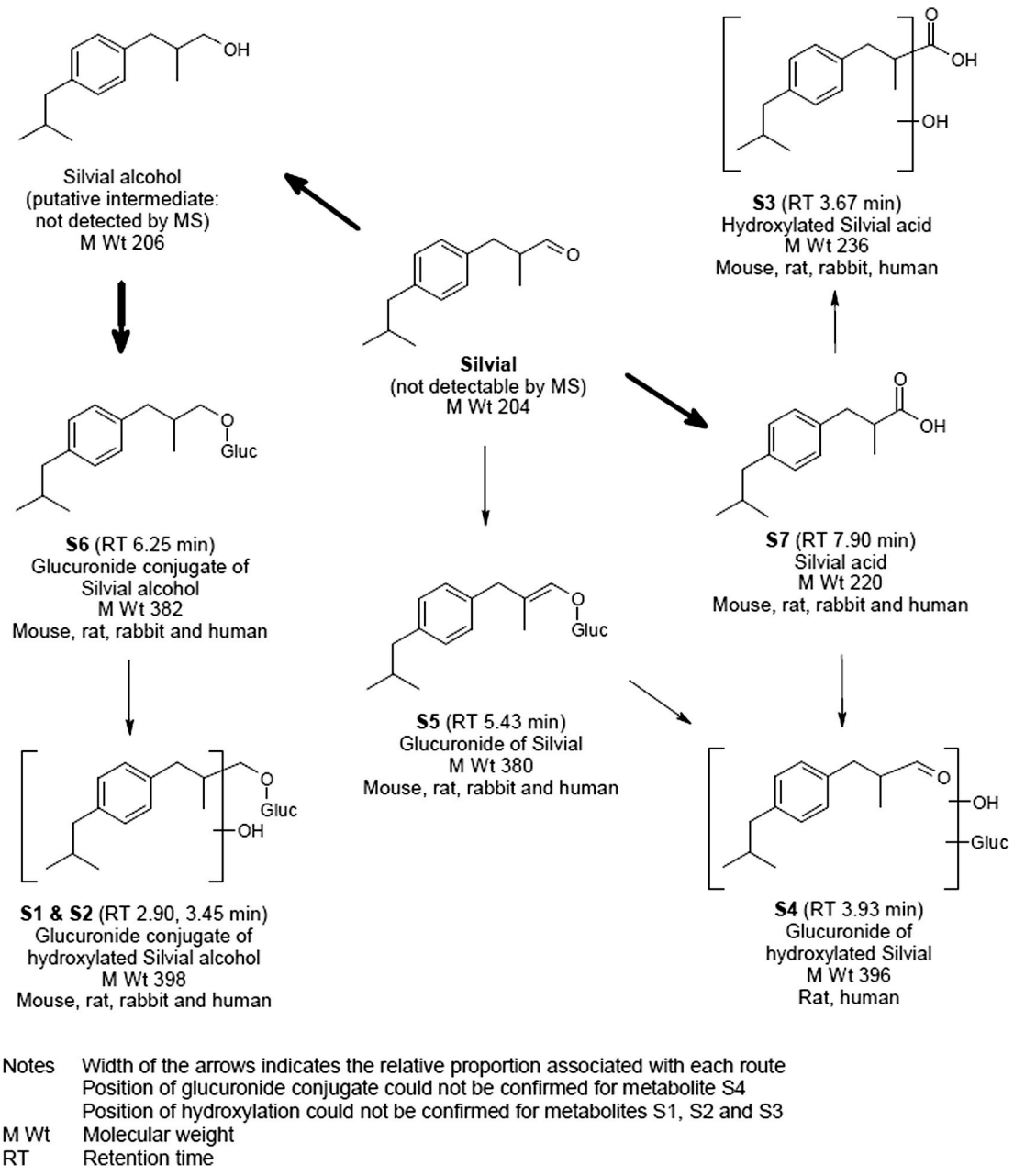


Fig. 1. Metabolic pathway following incubation of Silvial with mouse, rat, rabbit and human crypreserved hepatocyclesAdapted from (RIFM, 2012).

WP2uvrA were treated with *p*-isobutyl-α-methyl hydrocinnamaldehyde in dimethyl sulfoxide (DMSO) at concentrations up to 50 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, 1987a). Under the conditions of the study, *p*-isobutyl-α-methyl hydrocinnamaldehyde was not mutagenic in the Ames test.

There are no clastogenicity data available for *p*-isobutyl-α-methyl hydrocinnamaldehyde. The clastogenic activity of read-across material *p*-t-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6; see Section VI) was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and accordance with OECD TG 474. The test material was administered in corn oil via a single intraperitoneal injection to groups of male and female ICR mice. Doses of 150, 300, or 600 mg/kg were administered. Mice from each dose level were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2000a). Under the conditions of the study, *p*-t-butyl-α-methylhydrocinnamic aldehyde was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to *p*-isobutyl-α-methyl hydrocinnamaldehyde.

Based on the available data, *p*-isobutyl-α-methyl hydrocinnamaldehyde does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/27/17.

11.1.2. Repeated dose toxicity

The MOE for *p*-isobutyl-α-methyl hydrocinnamaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data for *p*-isobutyl-α-methyl hydrocinnamaldehyde. In an OECD 410 and

GLP-compliant study, 5 Wistar rats/sex/dose were administered the test material at doses of 0, 100, 300, and 1000 mg/kg/day through topical application of 5 mL solution for 28 days. No mortality was reported during the study at any doses. However, female rats were found to be more sensitive to the treatment material than their male counterparts. Local effects of slight erythema and/or scales were observed study day 15 onwards in both sexes at higher doses. In the high-dose group, male bodyweight gain was suppressed in the absence of changes in food consumption while higher food consumption was reported in females without any changes in body weight. Hence, these changes were not considered to be toxicologically relevant. In male rats of the 1000 mg/kg/day group, a significant decrease in body weight and absolute adrenal(s) weight as well as increased relative testes weight were reported without any histopathological changes. In the high-dose group female rats, the livers showed pale discoloration accompanied by increased liver weights, microvesicular vacuolation, and hepatocellular hypertrophy. The increased incidence and severity of diffuse hepatocellular hypertrophy and microvesicular vacuolation was also observed in the livers of females at 300 mg/kg/day without alterations in hepatic enzyme activity in the liver. Additionally, minimal single-cell necrosis and centrilobular pigmented cells were also observed in females from the high-dose group. These hepatic alterations in female animals at 300 and 1000 mg/kg/day were considered to be treatment-related effects. In addition, significantly lower platelet counts were reported in females at both 300 and 1000 mg/kg/day doses. Since the lower platelet count was accompanied by a longer prothrombin time and activated partial thromboplastin time in females in the high-dose group, these effects were considered adverse. Furthermore, at the highest dose, additional findings included lower serum levels of total protein, cholesterol, and calcium in both sexes, as well as decreased serum albumin and higher serum total bilirubin and urea level in females. Based on the hepatic toxicity and hematological alterations at 1000 and 300 mg/kg/day in females, the NOAEL for repeated dose toxicity was considered to be 100 mg/kg/day (RIFM, 2018c).

A default safety factor of 3 was used when deriving a NOAEL from the 28-day study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*. The derived NOAEL for the repeated dose toxicity data is 100/3 or 33.33 mg/kg/day.

Therefore, the *p*-Isobutyl-α-methyl hydrocinnamaldehyde MOE for repeated dose toxicity can be calculated by dividing the NOAEL in mg/kg/day for *p*-Isobutyl-α-methyl hydrocinnamaldehyde by the total systemic exposure (mg/kg/day), 33.33/0.0058 or 5747.

In addition, the total systemic exposure to *p-i*sobutyl-α-methyl hydrocinnamaldehyde (5.8 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1.1. Derivation of 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. (RIFM, 2008a; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dose of 0.33 mg/kg/day.

The RIFM Criteria Document (Api, 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 *p*-isobutyl-α-methyl hydrocinnamaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 33.33 mg/kg/day by the uncertainty factor, 100 = 0.33 mg/kg/day.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/04/19.

11.1.3. Reproductive toxicity

The MOE for *p*-isobutyl-α-methyl hydrocinnamaldehyde is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on *p*-isobutyl-α-methyl hydrocinnamaldehyde.

The systemic toxicity and testicular and epididymal toxicity of *p*-isobutyl-α-methyl hydrocinnamaldehyde were evaluated in rats. *p*-Isobutyl-α-methyl hydrocinnamaldehyde was administered once daily for 5 days by oral gavage to groups of sexually mature (12 weeks old) male Crl:CD (SD)IGS BR rats (6/dose) at dose levels of 0, 25, 100, or 250 mg/kg/day in corn oil. The urine from treated males was subjected to bioanalysis for the presence of 4-isobutyl benzoic acid (CAS # 38861-88-0). There was no effect of treatment on the testis or the epididymis among treated animals. Urine analysis revealed the presence of the metabolite 4-isobutyl benzoic acid among all treated animals with dose-response (RIFM, 2009). However, 4-isobutyl benzoic acid was not detected during the *in vitro* metabolism study conducted on hepatocytes derived from rats, mice, humans, or rabbits, and interspecies differences were small (see Section VII; RIFM, 2012).

In another study, *p*-isobutyl-α-methyl hydrocinnamaldehyde was administered to approximately 10-week-old male Crl:CD(SD) rats via oral gavage at doses of 0, 25, 75, or 250 mg/kg/day in corn oil for 14 days. The purpose of the study was to provide information regarding possible adverse effects on the male reproductive system. Sperm evaluation revealed a significant decrease in the average sperm count and sperm density from the cauda epididymis as compared to the control animals. The cauda epididymal sperm count at 25 mg/kg/day was below the ranges observed historically at the testing facility. In addition, the percentage of abnormal sperm, specifically sperm with detached heads or no heads, was increased or significantly increased in the 75 and 250 mg/kg/day dose groups. The increases in abnormal sperm resulted in an overall reduction or significant reduction in the percentage of normal sperm among animals of the mid- and high-dose groups. The NOAEL for general toxicity in male rats was greater than 250 mg/kg/day. The NOAEL for male reproductive organs and sperm was less than 25 mg/kg/day (RIFM, 2010).

An OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Wistar Han rats. Groups of 10 rats/sex/dose received silvial applications via daily dermal exposure at doses of 0, 100, 300, and 1000 mg/kg/day in corn oil for 6–7 h, 7 days per week. Males were treated for a minimum of 29 days (2 weeks prior to mating, during mating, and up to the day before scheduled necropsy), and females were treated for 45–50 days (14 days prior to mating, during mating and pregnancy, up to day 19 post-coitum, and starting on day 4 of lactation, up to and including the day before scheduled necropsy). Females that failed to deliver were treated for 35–38 days. One high-dose dam was euthanized on lactation day 2 due to total litter loss (neglected pups, which resulted in lower viability index); the dam showed no signs of toxicity. No morphological findings were observed in the testes, epididymides, or ovaries, and evaluation of the testes did not show any indication of abnormal spermatogenesis. The length and regularity of the estrous cycle were not affected by treatment. At 1000 mg/kg/day, the total number of dead pups (from the 1 high-dose dam that lacked maternal care and neglected her pups) was statistically significantly higher than the control group. Six male and 6 female pups at 1000 mg/kg/day were euthanized postnatal day (PND) 2 since they were cold, lethargic, and showed a greyish appearance. All other high-dose group pups from the remaining 9 litters survived until the scheduled necropsy, and none of these pups showed clinical signs suggesting deficient maternal care; thus, the pup mortality at 1000 mg/kg/day in a single litter was not considered to be related to treatment. At the first litter check, 3 low-dose pups and 1 mid-dose pup were found dead. This

finding was not considered to be treatment-related as the incidence did not show a dose-response and remained within normal limits. At 1000 mg/kg/day, body weights of male pups were 10% lower (not statistically significant) from birth until the end of the lactation period, and body weight differences of high-dose female pups from controls were 14% at birth and 12% at PND 13 (statistically significant). Although all values were within historical control data, the differences in decreased pup body weight were considered to be adverse. The NOAEL for effects on fertility was considered to be 1000 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity was considered to be 300 mg/kg/day, based on decreased pup body weight among high-dose group animals. The authors of the study report noted that serum T4 levels were decreased for parental animals at 300 mg/kg/day (males: 19%) and 1000 mg/kg/day (males: 43% and females: 31%) and in pups at all dose levels in PND 4 (approximately 25–30%) and PNDs 14–16 (approximately 20–55%). This effect was considered to be treatment-related; however, possible adversity could not be assessed within this type of screening study, and therefore, it was not taken into account when determining the NOAEL levels (RIFM, 2018d).

Therefore, the *p*-isobutyl-α-methyl hydrocinnamaldehyde MOE for the developmental toxicity endpoint can be calculated by dividing the *p*-isobutyl-α-methyl hydrocinnamaldehyde NOAEL in mg/kg/day by the total systemic exposure for *p*-isobutyl-α-methyl hydrocinnamaldehyde, 300/0.0058 or 51724.

Since the dermal route of exposure is considered to be the more relevant route for fragrance exposure, the NOAEL of 1000 mg/kg/day for male and female fertility was selected from the dermal OECD 421 study. **Therefore, the *p*-isobutyl-α-methyl hydrocinnamaldehyde MOE for the fertility endpoint can be calculated by dividing the *p*-isobutyl-α-methyl hydrocinnamaldehyde NOAEL in mg/kg/day by the total systemic exposure for *p*-isobutyl-α-methyl hydrocinnamaldehyde, 1000/0.0058 or 172414.**

In addition, the total systemic exposure to *p*-isobutyl-α-methyl hydrocinnamaldehyde (5.8 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2011.

Literature Search and Risk Assessment Completed On: 01/16/19.

11.1.4. Skin sensitization

Based on the available data, *p*-isobutyl-α-methyl hydrocinnamaldehyde is considered to be a weak skin sensitizer with a defined NESIL of 2300 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, *p*-isobutyl-α-methyl hydrocinnamaldehyde is considered to be a weak skin sensitizer. The chemical structure of this material indicates that it would be expected to react with skin proteins (Toxtree 2.6.13; OECD Toolbox v3.4). *p*-Isobutyl-α-methyl hydrocinnamaldehyde was found to be negative in the *in vitro* Direct Peptide Reactivity Assay (DPRA) and KeratinoSens test (RIFM, 2014b; RIFM, 2015b) but positive in the human cell line activation test (h-CLAT) and U-Sens (RIFM, 2018b; RIFM, 2015a). However, in a murine local lymph node assay (LLNA), *p*-isobutyl-α-methyl hydrocinnamaldehyde was found to be sensitizing with an EC3 value of <10% (<2500 μg/cm^2; RIFM, 2001). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1977). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 2362 μg/cm^2 of *p*-isobutyl-α-methyl hydrocinnamaldehyde in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 104 volunteers (RIFM, 2008b). Based on the available data (see Table 1 below), *p*-isobutyl-α-methyl hydrocinnamaldehyde is considered to be a weak skin sensitizer with a defined NESIL of 2300 μg/cm^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. (RIFM, 2008a; IDEA [International Dialogue for the Evaluation of Allergens] project Final Report on the QRA2: Skin Sensitization Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016, https://ideaproject.info/documents/QRA2-report.pdf) and a reference dos[a] of 0.33 mg/kg/day.

Additional References: RIFM, 2003; RIFM, 1989; RIFM, 2000b.

Literature Search and Risk Assessment Completed On: 05/22/17.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra along with existing data, *p*-isobutyl-α-methyl hydrocinnamaldehyde does not present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Additionally, no phototoxic effects were observed in a guinea pig study when *p*-isobutyl-α-methyl hydrocinnamaldehyde was tested at concentrations up to 30% in acetone (RIFM, 1987b). Based on the *in vivo* study data and the lack of absorbance, *p*-isobutyl-α-methyl hydrocinnamaldehyde does not present a concern for phototoxicity or photoallergenicity.

UV Spectra Analysis: The available spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/10/17.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for *p*-isobutyl-α-methyl hydrocinnamaldehyde 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*-isobutyl-α-methyl hydrocinnamaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.036 mg/day. This exposure is 38.9 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/28/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *p*-isobutyl-α-methyl

Table 1
Data Summary for *p*-isobutyl-α-methyl hydrocinnamaldehyde.

LLNA Weighted Mean EC3 Value μg/cm^2 [No. Studies][c]	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-HRIPT (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL[b] (induction) μg/cm^2	WoE NESIL[c] μg/cm^2
<2500 [a]	Weak	2362	5520	NA	2300

NOEL = No observed effect level; HRIP[b] = Human Repeat Insult Patch Tes[c]; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from HRIPT or HMT.

[c] WoE NESIL limited to 2 significant figures.

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

11.2.1.1. Risk assessment. Based on current VoU (2015), *p*-isobutyl-α-methyl hydrocinnamaldehyde presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. RIFM, 2014a: Ready biodegradability of the test material was evaluated in a manometric respirometry test according to the OECD 301F method. Biodegradation of 76% was observed after 28 days.

RIFM, 1997: Biodegradation of *p*-isobutyl-α-methyl hydrocinnamaldehyde was evaluated according to the OECD Guidelines for Testing of Chemicals Ready Biodegradability 302C using a modified MITI test (II). The average percentage biodegradation of *p*-isobutyl-α-methyl hydrocinnamaldehyde at 28 days was 69%.

11.2.1.2.2. Ecotoxicity. RIFM, 2017a: A fish (zebrafish) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions. The 96-h LC50 based on geometric mean measured concentration was reported to be 11.3 mg/L.

RIFM, 2017b: A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 was 4.71 mg/L.

RIFM, 2017c: An algae growth inhibition test was conducted according to the OECD 201 method. Based on geometric mean measured test concentration, the 72-h EC10, EC50, and NOEC was 1.16 mg/L, 1.44 mg/L, and 0.6 mg/L for growth rate and 0.884 mg/L, 1.21 mg/L, and 0.6 mg/L based on yield, respectively.

11.2.1.2.3. Other available data. *p*-Isobutyl-α-methyl hydrocinnamaldehyde has been registered under REACH with no additional data at this time.

11.2.2. Risk assessment refinement

Since *p*-Isobutyl-α-methyl hydrocinnamaldehyde has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.4	4.4
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on read-across, the RQs for these materials are <1. No further assessment is necessary.

The RIFM PNEC is 0.0315 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 04/03/19.

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**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 03/25/20.

Declaration of competing interest

The authors declare that they have no known competing financial

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.25			1000000	0.00225	
ECOSAR Acute Endpoints **(Tier 2) *Ver 1.11***	0.647	0.315	0.829	10000	0.0315	Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2) *Ver 1.11***	1.173	0.832	1.549			Neutral Organics

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.2020.111686.

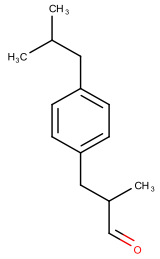
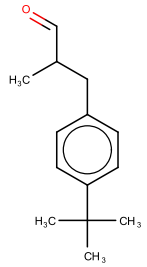
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). 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 v3.4 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2018).

	Target material	Read-across material
Principal Name	*p*-Isobutyl-α-methyl hydrocinnamaldehyde	*p*-*t*-Butyl-α-methylhydrocinnamic aldehyde
CAS No.	6658-48-6	80-54-6
Structure		
Similarity (Tanimoto score)		0.92
Read-across endpoint		• Genotoxicity
Molecular Formula	$C_{14}H_{20}O$	$C_{14}H_{20}O$
Molecular Weight	204.31	204.31
Melting Point (°C, EPI Suite)	39.40	46.29
Boiling Point (°C, EPI Suite)	286.25	280.03
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.399	0.477
Log K_{ow}(KOWWIN v1.68 in EPI Suite)	4.4	4.2[1]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	7.299	33[2]
J_{max} (μg/cm^2/h, SAM)	6.514	3.552
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.53E+000	2.53E+000
Genotoxicity		
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• Michael addition • Schiff base formers	• Michael addition • Schiff base formers
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Carcinogen (low reliability)	• Carcinogen (low reliability)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
***In vitro* Mutagenicity (Ames test) alerts by ISS**	• Simple aldehyde	• Simple aldehyde
***In vivo* mutagenicity (Micronucleus) alerts by ISS**	• Simple aldehyde	• Simple aldehyde
Oncologic Classification	• Aldehyde-type compound	• Aldehyde-type compound
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	• See Supplemental Data 1	• See Supplemental Data 2

1. RIFM, 1994.
2. RIFM, 1995.

Summary

There are insufficient toxicity data on the target material *p*-isobutyl-α-methyl hydrocinnamaldehyde (CAS # 6658-48-6). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, *p*-t-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- *p*-t-Butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6) was used as a read-across analog for the target material *p*-Isobutyl-α-methyl hydrocinnamaldehyde (CAS # 6658-48-6) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the structural class of aromatic branched aldehydes.
  - o The target material and the read-across analog share a 2-methyl-3-phenylpropanal fragment.
  - o The key difference between the target material and the read-across analog is that the target has an isobutane substituent on the 2-methyl-3-phenylpropanal fragment, whereas the read-across analog has a tert-butyl group as a substituent at the para position. This structure difference between the target material and the read-across analog does not affect consideration of the toxicity endpoint.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicity endpoint.
  - 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 QSAR OECD Toolbox (v3.4), structural alerts for toxicity endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have carcinogenicity alerts by the ISS model. Both substances also have DNA binding alerts by OECD, *in vivo* and *in vitro* mutagenicity alerts, and are classified as simple aldehyde type compounds. This shows that the read-across analog is predicted to have comparable reactivity with the target material. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genetic toxicity. Therefore, the alert is superseded by the availability of 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 differences between the target material and the read-across analog do not affect consideration of the toxicity endpoint.

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