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Short review

RIFM fragrance ingredient safety assessment, 2-methyl-3-(p-isopropylphenyl)propionaldehyde, CAS Registry Number 103-95-7

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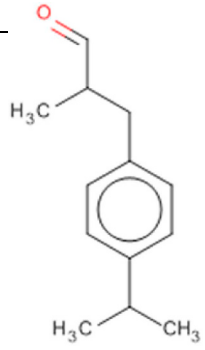
Name: 2-Methyl-3-(*p*-isopropylphenyl)propionaldehyde
CAS Registry Number: 103-95-7



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
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., 2015; Safford et al., 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.

Each endpoint discussed in this safety assessment reviews 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 (i.e., 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.

2-Methyl-3-(*p*-isopropylphenyl)propionaldehyde was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and the read-across analog *p*-*t*-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6) show that this material is not expected to be genotoxic. Data on the target material provided a NESIL of 5900 μg/cm^2 for the skin sensitization endpoint and provided an MOE > 100 for the repeated dose toxicity and developmental and reproductive toxicity endpoints. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde was not found to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on read-across to β-methyl-3-(1-methylethyl)benzenepropanal (CAS # 125109-85-5) and its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1).

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2000a; ECHA REACH Dossier: p-t-butyl-α-methylhydrocinnamic aldehyde; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 25 mg/kg/day.	RIFM, (2011a)
Developmental and Reproductive Toxicity: NOAEL = 25 mg/kg/day.	RIFM, (2011a)
Skin Sensitization: NESIL = 5900 μg/cm^2.	RIFM (2016)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure below TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 85% (OECD 302C) — RIFM (1995)

Bioaccumulation: Screening-level: 175.6 L/kg — (EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 21-day *Daphnia magna* NOEC: 0.71 mg/L read-across to β-methyl-3-(1-methylethyl)benzenepropanal (CAS # 125109-85-5) — RIFM, (2002a)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standard

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1 — (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 21-day *Daphnia magna* NOEC: 0.71 mg/L read-across to β-methyl-3-(1-methylethyl)benzenepropanal (CAS # 125109-85-5) — RIFM, (2002a)

RIFM PNEC is: 14.2 μg/L

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

1. Identification

1. **Chemical Name:** 2-Methyl-3-(p-isopropylphenyl)propionaldehyde
2. **CAS Registry Number:** 103-95-7
3. **Synonyms:** Benzenepropanol, α-methyl-4-(1-methylethyl)-; 3-p-Cumenyl-2-methylpropionaldehyde; Cyclamal; Cyclamen aldehyde; Cyclaviol; Cyclosal; p-Isopropyl-α-methylhydrocinnamaldehyde; α-Methyl-p-isopropylphenylpropylaldehyde; 2-Methyl-3-(pisopropylphenyl)propionaldehyde; Benzenepropanal, α-methyl-4-(1-methylethyl)-; α-Methyl-4-(1-methylethyl)benzenepropanal; 2-ﾒﾁﾙ-3-(p-ｲｿﾌﾟﾛﾋﾟﾙﾌｪﾆﾙ)ﾌﾟﾛﾋﾟｵﾅﾙﾃﾞﾋﾄﾞ; 3-(4-Isopropylphenyl)-2-methylpropanal; Cyclamen aldehyde extra; 2-Methyl-3-(*p*-isopropylphenyl) propionaldehyde
4. **Molecular Formula:** $C_{13}H_{18}O$
5. **Molecular Weight:** 190.28
6. **RIFM Number:** 121

2. Physical data

1. **Boiling Point:** 270 °C (FMA), (calculated) 270.29 °C (EPI Suite)
2. **Flash Point:** 75 °C, 190 °F; CC (FMA)
3. **Log K_{OW}:** 4.0 at 35 °C (RIFM, 2006), 3.91 (EPI Suite)
4. **Melting Point**: 29.1 °C (EPI Suite)
5. **Water Solubility:** 66 mg/L (water) & 75 mg/L (recon water) at 20 °C (RIFM, 2011b), 266 mg/L (RIFM, 2000c), (calculated) 22.59 mg/L (EPI Suite)
6. **Specific Gravity:** 0.95 (RIFM, 1994a), 0.9479 (RIFM), 0.946–0.952 (FMA), 0.948–0.954 (FMA), 0.947–0.953 @ 20 °C (Givaudan88)
7. **Vapor Pressure:** 15.4 mm Hg @ 20 °C (EPI Suite v4.0), 0.004 mm Hg 20 °C (FMA), 22.7 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance in the region of 290–700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless to pale yellow, slightly viscous liquid with strong, sweet, floral odor

3. Exposure

1. **Volume of Use (worldwide band):** > 1000 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics*****:** 0.14% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.00085 mg/kg/day or 0.060 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.0055 mg/kg/day (RIFM, 2015)

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

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

***See IFRA Category 4 in Section IX for maximum acceptable concentrations in finished products.

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** *p-t*-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** β-methyl-3-(1-methylethyl)benzenepropanal (CAS # 125109-85-5)
3. Read-across Justification: See Appendix below

6. Metabolism

A metabolism study was conducted to compare the *in vitro* metabolism by hepatocytes of the test material between 4 species (mouse, rat, rabbit, and human). The analytical method utilized HPLC coupled with mass spectrometry (LC-MS) to profile and identify metabolites generated. Interspecies comparison incubations of the test material (1, 10, and 100 μM) using cryopreserved hepatocytes from mouse, rat, rabbit, and human (1×10^6 viable cells) were conducted in duplicate at incubation times of 0, 1, and 4 h. For most hepatocyte incubations with cyclamen aldehyde, a glucuronide conjugate of cyclamen aldehyde was the largest component. Other main components were cyclamen carboxylic acid, a glucuronide conjugate of hydroxylated cyclamen alcohol, and the glucuronide conjugate of parent cyclamen aldehyde. 4-Isopropylbenzoic acid was only observed in the rat, and a hexose conjugate was exclusive to the mouse (RIFM, 2011c). The metabolic scheme is provided below (See Fig. 1).

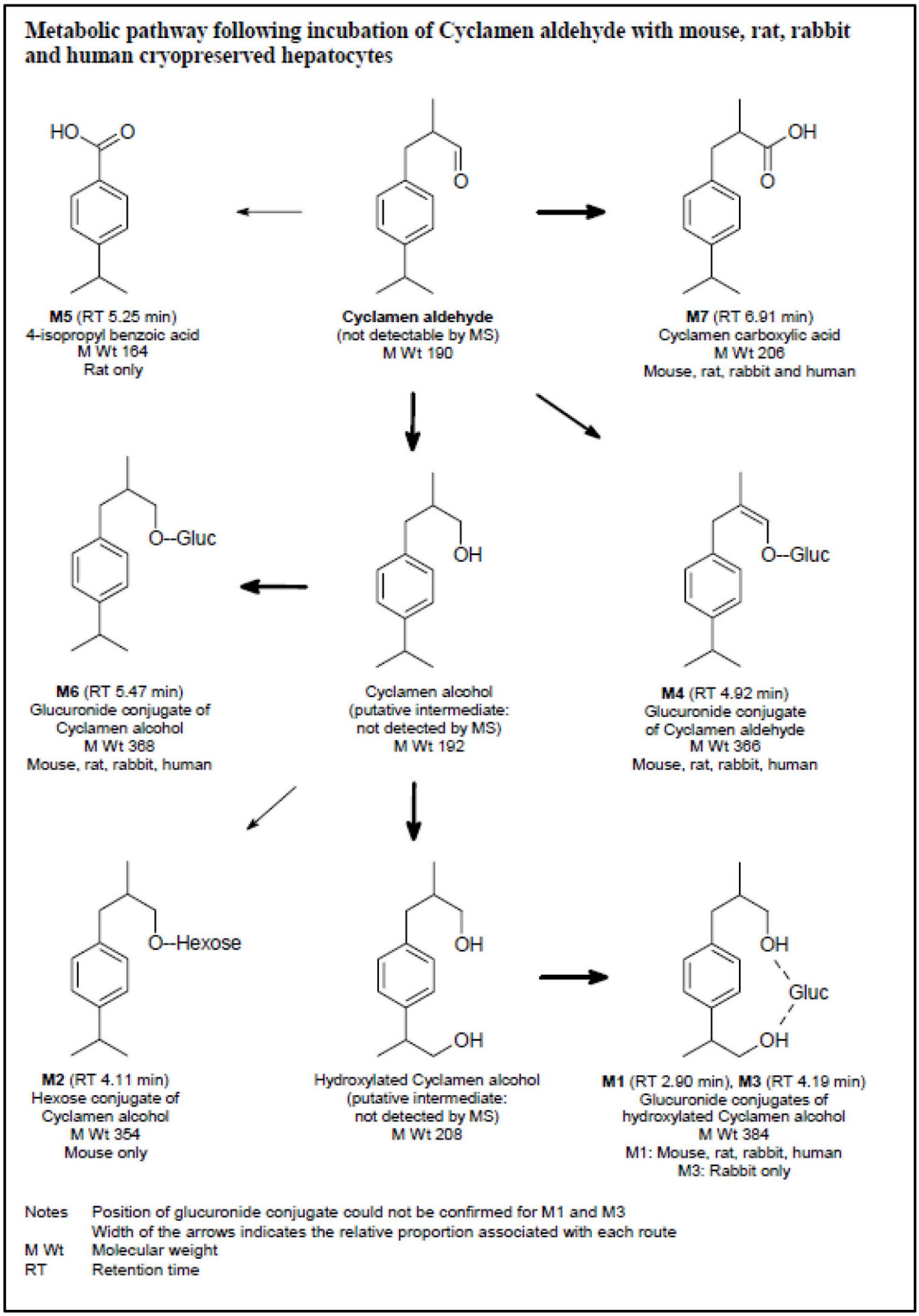


Fig. 1. (Adapted from RIFM, 2011c).

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

2-Methyl-3-(*p*-isopropylphenyl)propionaldehyde is reported to occur in the following foods by the VCF*:

Nutmeg (*Myristica fragrans* Houtt.)

Starfruit (*Averrhoa carambola* L.)

*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.

8. REACH dossier

Available; accessed 04/08/19.

9. Conclusion

The maximum acceptable concentrations[a] in finished products for 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.11
2	Products applied to the axillae	0.14
3	Products applied to the face/body using fingertips	0.038
4	Products related to fine fragrances	0.95
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.46
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.076
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.076
5D	Baby cream, oil, talc	0.025
6	Products with oral and lip exposure	0.076
7	Products applied to the hair with some hand contact	0.076
8	Products with significant ano-genital exposure (tampon)	0.025
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.23
10A	Household care products with mostly hand contact (hand dishwashing detergent)	0.23
10B	Aerosol air freshener	0.72
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.025
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	16

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 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde, the basis was the reference dose of 0.25 mg/kg/day, a predicted skin absorption value of 80%, and a skin sensitization NESIL of 5900 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde has been evaluated in a bacterial reverse mutation assay (Ames test) conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA97a, TA98, TA100, TA1535, and TA102 were treated with 2-methyl-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, 2000a). Under the conditions of the study, 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde was not mutagenic in the Ames test.

There are no studies assessing the clastogenicity 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde. The clastogenic activity of read-across analog *p-t*-butyl-α-methylhydrocinnamic aldehyde (CAS # 80-54-6; see Section V) was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in 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 body weight (bw) were administered. Mice were euthanized at 24 or 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. A statistically significant increase in micronucleated polychromatic erythrocytes (MNPCEs) relative to the vehicle control group was observed in male mice at 48 h after treatment with 600 mg/kg bw. This response was not considered biologically relevant since the numbers of MNPCEs in all animals tested were well within the historical control range (3 MNPCE/2000 PCE/animal). Additionally, the frequency of MNPCEs in the control group was considered lower than average, which may have enhanced the statistical significance of the treated animals. No statistically significant increases were observed in females at 48 h with 600 mg/kg bw. No significant increase or dose-response increase was observed in any other treated group regardless of dose level, sex, or collection time (ECHA, 2011). 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 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde.

Based on the available data, 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde does not present a concern for genotoxic potential.

Additional References: RIFM, 2002b.

Literature Search and Risk Assessment Completed On: 05/14/17.

10.1.2. Repeated Dose Toxicity

The margin of exposure (MOE) for 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde (cyclamen aldehyde). An enhanced oral gavage 1-generation reproductive study was conducted in rats in accordance with OECD TG 415 and in compliance with GLP guidelines. Groups of 25 Crl:CD(SD) rats/sex/dose were administered the test material at doses of 0, 25, 75, or 150 mg/kg/day in corn oil. The treated male and female rats were cohabitated for a maximum of 21 days with untreated cohort female and male rats, respectively. Male P generation rats were gavaged once daily 83 days prior to cohabitation, through cohabitation, and continuing through the day before euthanasia. Female P generation rats were gavaged once daily 14 days before cohabitation, through cohabitation, and at day of gestation (DG) 25 (rats that did not deliver) or day 22 postpartum (rats that delivered a litter). F1 generation rats were not directly dosed but may have been exposed to the test material *in utero* during gestation and through maternal milk postpartum. There was a significant reduction in bodyweight gains among high-dose P generation males and females as compared to the controls. The bodyweight gains were also reduced in mid-dose females, which did

not reach statistical significance. Terminal body weights among high-dose P generation males were significantly reduced as compared to the controls, while the terminal body weights among P generation females were unaffected by treatment. At 150 mg/kg/day, treatment with the test material caused infertility in males following mating with untreated females. Macroscopic examination revealed an increase in the incidences of grossly visible masses on one or both cauda epididymides among the high-dose P generation males. There were no macroscopic alterations reported among treated females. There was a significant increase in the absolute and relative weights of the epididymides among high-dose P generation males. Microscopic examination of the epididymis revealed moderate to marked sperm granulomas. Effects of treatment on male reproductive function are considered and described in the reproductive toxicity section of the safety assessment. The absolute and relative liver weights were significantly increased among mid- and high-dose P generation males. There was a significant decrease in the absolute weight of the adrenals among mid- and high-dose P generation males as compared to the controls. Microscopic examination revealed minimal adrenal cortical atrophy affecting the zona fasciculata and zona reticularis among mid- and high-dose males. There was a significant increase in the absolute and relative weights of the liver among treated dams. It was not possible to determine the toxicological significance of the increased liver weights due to a lack of correlated histopathological alterations during microscopic examination among the treated animals. Thus, the NOAEL for general toxicity in P generation male rats was considered to be 75 mg/kg/day, based on decreased body weights and bodyweight gains among the high-dose group, and gross lesions among high-dose males. The NOAEL for general toxicity in P generation female rats was considered to be 25 mg/kg/day, based on decreased bodyweight gains and decreased body weights among the higher-dose treatment groups. The most conservative NOAEL of 25 mg/kg/day was considered for the repeated dose toxicity endpoint (RIFM, 2011a). **Therefore, the MOE for 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde is equal to the 2-methyl-3-(p-isopropylphenyl)propionaldehyde NOAEL in mg/kg/day divided by total systemic exposure to 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde, 25/0.0055 or 4545.**

In addition, the total systemic exposure to 2-methyl-3-(p-isopropylphenyl)propionaldehyde (5.5 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.

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. These factors can be refined based on availability of data. Due to insufficient intraspecies susceptibility data for 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde, the factor of 10 remains unchanged. For interspecies variability, the factor of 10 can be further sub-divided into 4 and 2.5 based on toxicokinetic and toxicodynamic differences, respectively (Renwick, 1993). The addition of a supplementary uncertainty factor for the endocrine disturbance potential of 2-methyl-3-(p-isopropylphenyl)propionaldehyde was considered unnecessary. The uncertainty factors are based on the Scientific Committee on Consumer Safety (SCCS) guidance document for testing of cosmetic ingredients and their safety evaluation (2018). Based on this, the Expert Panel for Fragrance Safety has approved the uncertainty factor of 100 for RIFM safety assessments of 2-methyl-3-(p-isopropylphenyl)propionaldehyde.

10.1.2.1.1. Derivation of reference dose (RfD). Section IX 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, 2008; 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, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.25 mg/kg/day.

The RfD for 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde was calculated by dividing the lowest NOAEL (from the Repeated Dose and Developmental and Reproductive Toxicity sections) of 25 mg/kg/day by the uncertainty factor, 100 = 0.25 mg/kg/day.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/31/17.

10.1.3. Developmental and Reproductive Toxicity

The MOE for 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient reproductive and developmental toxicity data on 2-methyl-3-(*p*-isopropylphenyl) propionaldehyde (cyclamen aldehyde). An enhanced oral gavage 1-generation reproductive study was conducted in rats in accordance with OECD TG 415 and in compliance with GLP guidelines. Groups of 25 Crl:CD(SD) rats/sex/dose were administered the test material at doses of 0, 25, 75, or 150 mg/kg/day in corn oil. The treated male and female rats were cohabitated for a maximum of 21 days with untreated cohort female and male rats, respectively. Male P generation rats were gavaged once daily 83 days prior to cohabitation, through cohabitation, and continuing through the day before euthanasia. Female P generation rats were gavaged once daily 14 days before cohabitation, through cohabitation and at DG 25 (rats that did not deliver) or day 22 postpartum (rats that delivered a litter). F1 generation rats were not directly dosed but may have been exposed to the test material *in utero* during gestation and through maternal milk postpartum. In addition to the systemic toxicity effects reported in the repeated dose toxicity section, the test material was reported to affect the reproductive function among treated animals. High-dose P generation males were reported to be infertile following mating with untreated females. Grossly visible masses were reported on one or both cauda epididymides among high-dose P generation males. Microscopic examination of the epididymis revealed moderate to marked sperm granulomas. The sperm motility evaluation revealed that 13/25 males of the mid-dose and 25/25 males of the high-dose group had no motile sperm. Sperm morphology was also affected. The sperm counts among mid-dose P generation males reflected a significant reduction in number and density from the cauda epididymides. The average values for sperm counts and density from the cauda epididymides among mid-dose males were significantly reduced as compared to the historical control values. Pregnancy occurred in 23, 24, 23, and 1 of the 25 to 28 untreated female rats that were assigned to mate with treated male rats in the 0, 25, 75, and 150 mg/kg/day dose groups, respectively. All pregnant dams in the 0, 25, and 75 mg/kg/day dose groups delivered litters. The one pregnant dam in the 150 mg/kg/day paternal dose group did not deliver a litter. Natural delivery and litter observations were unaffected by the dose levels of the test material, up to 75 mg/kg/day. There was a significant increase in pup mortality among high-dose group P generation males. In addition, the average pup body weight per litter was significantly reduced at 75 and 150 mg/kg/day at each tabulated interval between days 1 and 22 postpartum, as compared to the control group values. For the F1 generation pups obtained from treated males

and untreated females, there were no treatment-related effects except for no litters produced by the females mated with high-dose group P generation males. In addition to the systemic effects reported among treated P generation females described in the repeated dose toxicity section, there were no effects of treatment on the female reproductive cycles, mating, or fertility parameters among treated P generation females up to the highest dose tested. For the F1 generation offspring of treated P generation female rats, *in utero* and lactation exposure to the test material at 150 mg/kg/day caused an increase in lenticular opacities during the pre-weaning period that persisted into the post-weaning period. There was a significant decrease in body weights and bodyweight gains among F1 generation animals at doses of 75 mg/kg/day and higher. There was also an increase in the anogenital distance at 150 mg/kg/day based on covaried analysis. Thus, the NOAEL for viability and growth of the F1 generation offspring of treated P generation female rats was considered to be 25 mg/kg/day. The NOAEL for P generation female reproductive toxicity was considered to be 25 mg/kg/day, based on decreased implantation sites, delivered pups, pup survival, and litter size at 150 mg/kg/day; an increase in pup mortality at 150 mg/kg/day; and a decrease in pup body weight at 75 and 150 mg/kg/day dose groups. The NOAEL for P generation male reproductive toxicity was considered to be 25 mg/kg/day, based on the reduction in sperm motility and density among higher-dose group animals. Thus, the NOAEL for the reproductive and developmental toxicity was considered to be 25 mg/kg/day (RIFM, 2011a). The addition of a supplementary uncertainty factor for the endocrine disturbance potential of 2-methyl-3-(*p*-isopropylphenyl) propionaldehyde was considered unnecessary. The uncertainty factors are based on the Scientific Committee on Consumer Safety (SCCS) guidance document for testing of cosmetic ingredients and their safety evaluation (2018). Based on this, the Expert Panel for Fragrance Safety has approved the uncertainty factor of 100 for RIFM safety assessments of 2-methyl-3-(p-isopropylphenyl)propionaldehyde.

Therefore, the MOE for 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde is equal to the 2-methyl-3-(p-isopropylphenyl)propionaldehyde NOAEL in mg/kg/day divided by total systemic exposure to 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde, 25/0.0055 or 4545.

In addition, the total systemic exposure to 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde (5.5 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/17.

10.1.4. Skin Sensitization

Based on the existing data, 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde is considered to be a weak skin sensitizer with a defined NESIL of 5900 μg/cm^2.

10.1.4.1. Risk assessment. Based on the existing data, 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde 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). 2-Methyl-3-(*p*-isopropylphenyl)propionaldehyde was found to be positive in *in vitro* KeratinoSens, the U937-CD86 test, and the human Cell Line Activation Test but negative in the Direct Peptide Reactivity Assay (DPRA) (Natsch et al., 2013; Piroird et al., 2015; Nukada et al., 2011). However, in a murine local lymph node assay (LLNA), 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde was found to be a weak sensitizer with reported EC3 values ranging from 20.5% (5125 μg/cm^2) to 22.3% (5575 μg/cm^2) (Basketter et al., 2001; Gerberick et al., 2004; ECHA, 2013). Similarly, in a guinea pig maximization test, 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde was found to be a weak sensitizer (RIFM, 1988). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1971). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 5905 μg/cm^2 of 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde in 1:3 ethanol:diethyl phthalate, no reactions indicative of sensitization were observed in any of the 114 volunteers (RIFM, 2016). Based on the available data, summarized in Table 1, 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde is considered to be a weak skin sensitizer with a defined NESIL of 5900 μg/cm^2. Section IX 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, 2008; 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, http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final–september-2016.pdf) and a reference dose of 0.25 mg/kg/day.

Table 1
Data summary for 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde.

LLNA Weighted Mean EC3 Value [No. Studies] μg/cm^2	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
5575 [1]	Weak	5905	2070	NA	5900[d]

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; 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 two significant figures.

[d] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL.

Additional References: RIFM, 1964a; RIFM, 1964b; RIFM, 1980.

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

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, 2-methyl-3-(*p*-isopropylphenyl) propionaldehyde would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

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

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde. Based on the Creme RIFM Model, the inhalation exposure is 0.060 mg/day. This exposure is 23.3 times lower than the Cramer Class I TTC value of 1.4 mg/day based on human lung weight of 650 g (Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

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

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-methyl-3-(*p*-isopropylphenyl) propionaldehyde was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio 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, 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.1 (US EPA, 2012a) did identify 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde as possibly 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 et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.1).

10.2.2. Risk assessment

Based on current VoU (2015), 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 1994a**:** An OECD 301B ready biodegradability study (28-day) was conducted at a nominal concentration of 10 mg/L. The reported biodegradation at the end of the study was 65.5%.

RIFM, 1995**:** In a modified MITI test based on OECD 302C guideline, the inherent biodegradability of cyclamen aldehyde was found to be 85% at the end of the 28-day study.

RIFM, 1994b**:** In a ready biodegradability study according to the OECD 301F guideline, cyclamen aldehyde's biodegradation reached 58% after 28 days.

10.2.3.2. Ecotoxicity. RIFM, 2000b**:** A *Daphnia magna* immobilization study was conducted according to the OECD 202 method under static conditions. The reported 48-h EC50 was 4.19 mg/L.

RIFM, 2012b: A *Daphnia magna* immobilization study was conducted according to the OECD 202 method under semi-static conditions. Under the conditions of this study, the 48-h EC50 based on the time-weighted mean measured test concentrations was 1.4 mg/L.

RIFM, 2013**:** The algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50s based on geometric mean measured concentration were 4.3 mg/L for growth rate and 2.7 mg/L for yield and biomass.

10.2.4. Other available data

This material has been registered for REACH with no additional data available.

The following data is available for the read-across material:

RIFM, 1991a: A 96-h fish (*Salmo gairdneri*) acute toxicity test was conducted according to the OECD 203 method. The LC50 was reported to be 1.082 mg/L.

RIFM, 1991b**:** A 48-h *Daphnia magna* acute toxicity test was conducted following the OECD 202 method. The EC50 was determined to be 7.70 mg/L (Logit-model) at 48 h with a 95% confidence interval of 6.27–10.21 mg/L.

RIFM, 1999**:** An algae inhibition test was conducted according to OECD 201 guideline. The EC50 for growth rate was 11 mg/L (95% CI 7.4–20); the EC50 was not determined for biomass. The 72-h NOEC was reported to be 3.2 mg/L for biomass and growth rate.

RIFM, 2002a**:** A 21-day *Daphnia magna* chronic study was conducted according to the OECD 211 method under semi-static conditions. The NOEC and LOEC (measured concentrations) were determined to be 0.71 mg/L and 2.6 mg/L, respectively.

10.2.5. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	4.67			1,000,000	0.00467	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	1.092	0.681	1.600	10,000	0.0681	Aldehydes (Mono)
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	3.032	2.303	2.160			Neutral Organics
Tier 3: Measured Data (including read-across data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	1.1					
Daphnia		4.19	0.71	50	14.2	
Algae		8.4	3.2			

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.9	3.9
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
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 14.2 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: 03/13/19.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/29/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. 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.2020.111267.

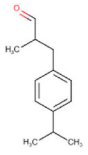
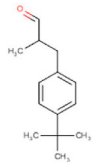
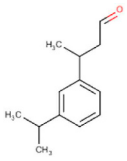
Appendix

Read-across Justification

Methods

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

- The materials were first clustered based on their structural similarity. In the second step, data availability and data quality on the selected cluster were examined. Finally, appropriate read-across analogs from the cluster were confirmed by using 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 analog were calculated using EPI Suite v4.11 developed by US EPA (US EPA, 2012a).
- J_{max} values were calculated using the RIFM skin absorption model (SAM), and the parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification were generated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2018).
- Developmental toxicity and skin sensitization were estimated using CAESAR v.2.1.7 and 2.1.6 respectively (Cassano et al., 2010).
- Protein binding was estimated 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	Read-across Material
Principal Name	2-Methyl-3-(*p*-isopropylphenyl)propionaldehyde	*p*-*t*-butyl-α-methylhydrocinnamic aldehyde	β-methyl-3-(1-methylethyl)benzenepropanal
CAS No.	103-95-7	80-54-6	125109-85-5
Structure			
Similarity (Tanimoto score)		0.92	0.66
Read-across endpoint		• Genotoxicity	• Environmental toxicity
Molecular Formula	$C_{13}H_{18}O$	$C_{14}H_{20}O$	$C_{13}H_{18}O$
Molecular Weight	190.28	204.31	190.29
Melting Point (°C, EPI Suite)	29.10	46.29	29.10
Boiling Point (°C, EPI Suite)	270.29	280.03	270.29
Vapor Pressure (Pa @ 25 °C, EPI Suite)	3.03E+003	0.477	1.24
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	4.0	4.2	3.91
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	266	33	22.59
J_{max} (μg/cm^2/h, SAM)	14.653	4.165	16.117
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.90E+000	2.53E+000	1.90E+000
Genotoxicity			
DNA binding (OASIS v 1.4 QSAR Toolbox v3.4)	• No alert found	• No alert found	
DNA binding by OECD QSAR Toolbox (v3.4)	• Michael addition • Schiff base formers	• Michael addition • Schiff base formers	
Carcinogenicity (genotox and non-genotox) 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	

Environmental toxicity			
BIOWIN 3	• 2.65 (possibly persistent)		• 2.48 (possibly persistent)
ECOSAR (96 h Fish LC50) for aldehydes mono in mg/L	• 1.092		• 0.679
ECOSAR (48-hr Dapnhia LC50) for aldehydes mono in mg/L	• 0.681		• 0.338
ECOSAR (96-hr algae LC50) for aldehydes mono in mg/L	• 1.600		• 0.879
Metabolism			
OECD QSAR Toolbox (v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3
Rat liver S9 metabolism simulator and structural alerts for metabolites			

Summary

There are insufficient toxicity data on the target material 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde (CAS # 103-95-7). Hence, *in silico* evaluation was conducted by determining a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analog read-across material *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 target material 2-methyl-3-(*p*-isopropylphenyl) propionaldehyde (CAS # 103-95-7) for the genotoxicity endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - ○ The target material and the read-across analog share a 2-methyl-3-phenylpropanal fragment.
  - ○ The key difference between the target material and the read-across analog is that the target material has an isopropyl substituent on the 2-methyl-3-phenylpropanal fragment, whereas the read-across analog has a *tert*-butyl group substituent. This structural difference between the target material and the read-across analog does not affect consideration of the toxicological endpoint.
  - ○ The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the aromatic branched aldehydes fragment. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoint.
  - ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - ○ The target material and the read-across analog have a carcinogenicity alert by the ISS model. Both substances also have a DNA binding alert 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 will be superseded by the availability of the data.
  - ○ The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural differences between the target material and the read-across analog do not affect consideration of the toxicological endpoints.
- β-methyl-3-(1-methylethyl)benzenepropanal (CAS # 125109-85-5) was used as a read-across analog for the target material 2-methyl-3-(*p*-isopropylphenyl)propionaldehyde (CAS # 103-95-7) for the environmental toxicity endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to the structural class of aldehydes.
  - ○ The target material and the read-across analog share a 2-methyl-3-phenylpropanal fragment.
  - ○ The key difference between the target material and the read-across analog is that the target material has an isopropyl substituent on 4 position of the bbenzene ring, whereas the read-across analog has a the same substituent on 3 position. This structural difference between the target material and the read-across analog does not affect consideration of the toxicological endpoint.
  - ○ The similarity between the target material and the read-across analog is indicated by the Tanimoto score in the above table. The Tanimoto score is mainly driven by the aromatic branched aldehydes fragment. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoint.
  - ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the BIOWIN 3 and ECOSAR model for predicting aquatic toxicity, for the toxicological endpoints are consistent between the target material and the read-across analog.
  - ○ The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural differences between the target material and the read-across analog do not affect consideration of the toxicological endpoints.

References

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