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Short Review

RIFM fragrance ingredient safety assessment, *p*-isopropylacetophenone, CAS Registry Number 645-13-6

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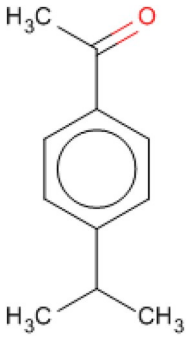
Name: *p*-Isopropylacetophenone
CAS Registry Number: 645-13-6



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, 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
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
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.
p-Isopropylacetophenone was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 4′-methylacetophenone (CAS # 122-00-9) show that *p*-isopropylacetophenone is not expected to be genotoxic. The skin sensitization endpoint was completed using data from read-across analog acetophenone (CAS # 98-86-2) and the application of DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material; the exposure to *p*-isopropylacetophenone is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; *p*-isopropylacetophenone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; *p*-isopropylacetophenone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 1998; RIFM, 2013)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment
Hazard Assessment:
Persistence: Screening-level: 2.74 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 11.17 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 22.75 mg/L (RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 22.75 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.02275 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** *p*-Isopropylacetophenone
2. **CAS Registry Number:** 645-13-6
3. **Synonyms:** *p*-Acetylcumene; Ethanone, 1-[4-(1-methylethyl) phenyl]-; *p*-Isopropylacetylbenzene; 1-(4-(1-Methylethyl)phenyl) ethan-1-one; Methyl *p*-isopropylphenyl ketone; 1-(4-Isopropylphenyl)ethanone; *p*-Isopropylacetophenone
4. **Molecular Formula:** $C_{11}H_{14}O$
5. **Molecular Weight:** 162.23
6. **RIFM Number:** 6264

2. Physical data

1. **Boiling Point:** 262 °C (FMA), 236.04 °C (EPI Suite)
2. **Flash Point:** 200 °F; CC (FMA)
3. **Log K_{ow}:** 3.13 (EPI Suite)
4. **Melting Point**: 19.3 °C (EPI Suite)
5. **Water Solubility:** 190.6 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0138 mm Hg @ 20 °C (EPI Suite 4.0), 0.02 mm Hg 20 °C (FMA), 0.022 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A colorless clear liquid with a medium, orris, spicy, woody, herbal odor.*

*http://www.thegoodscentscompany.com/data/rw1033991.html#toorgano, retrieved 12/1/2015.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.00035% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000000 mg/kg/day or 0.0000027 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0000038 mg/kg/day (RIFM, 2016)

*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 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** 4′-Methylacetophenone (CAS # 122-00-9)
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** Acetophenone (CAS # 98-86-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

p-Isopropylacetophenone is reported to occur in the following foods by the VCF*:
Honey.
Katsuobushi (dried bonito).
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. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 05/09/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. *p*-Isopropylacetophenone was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2014). There are no studies assessing the mutagenicity of *p*-isopropylacetophenone. The mutagenic potential of read-across material 4′-methylacetophenone (CAS # 122-00-9; see Section 5) was evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate-incorporation and preincubation methods. *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 were treated with 4′-methylacetophenone 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, 1998). Under the conditions of the study, 4′-methylacetophenone was not mutagenic in the Ames test.

There are no studies assessing the clastogenicity of *p*-isopropylacetophenone. The clastogenic activity of read-across material 4′-methylacetophenone (CAS # 122-00-9) was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 4′-methylacetophenone in DMSO at concentrations up to 1400 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h 4′-Methylacetophenone did not induce binucleated cells with micronuclei when tested up to the maximum dose in either non-activated or S9-activated test systems (RIFM, 2013). Under the conditions of the study, 4′-methylacetophenone was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the available data, 4′-methylacetophenone does not present a concern for genotoxic potential, and this can be applied to *p*-isopropylacetophenone.

Additional References: RIFM, 2014.

Literature Search and Risk Assessment Completed On: 2/18/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on *p*-isopropylacetophenone or any read-across materials. The total systemic exposure to *p*-isopropylacetophenone is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on *p*-isopropylacetophenone or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to *p*-isopropylacetophenone (0.0038 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on *p*-isopropylacetophenone or any read-across materials. The total systemic exposure to *p*-isopropylacetophenone is below the TTC for the developmental and reproductive toxicity endpoint of a Cramer Class II material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on *p*-isopropylacetophenone or any read-across materials that can be used to support the developmental toxicity endpoint. The total systemic exposure to *p*-isopropylacetophenone (0.0038 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental toxicity endpoint of a Cramer Class I material at the current level of use.

There are no reproductive toxicity data on *p*-isopropylacetophenone or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to *p*-isopropylacetophenone (0.0038 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.4. Skin sensitization

Based on read-across to acetophenone (CAS # 98-86-2) and application of DST, *p*-isopropylacetophenone does not present a safety concern for skin sensitization under current, declared levels of use.

10.1.4.1. Risk assessment. No skin sensitization studies are available on *p*-isopropylacetophenone. Based on limited existing animal and human data on acetophenone (CAS # 98-86-2; see Section 5) and application of DST, *p*-isopropylacetophenone does not present a concern for skin sensitization. The chemical structure indicates that these materials would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). In predictive guinea pig test methods, no results indicative of sensitization were observed with acetophenone (Klecak et al., 1977; Klecak, 1985; Sharp, 1978). Additionally, no reactions indicative of skin sensitization were observed in a human maximization test with 4′-methylacetophenone (RIFM, 1970a). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2. The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentration for *p*-isopropylacetophenone which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: RIFM, 1970b.

Literature Search and Risk Assessment Completed On: 03/09/17.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, *p*-isopropylacetophenone 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 *p*-isopropylacetophenone in experimental models. UV/Vis

Table 1
Acceptable concentration limits for *p*-isopropylacetophenone based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	95th Percentile Concentration
1	Products applied to the lips	0.069%	0.00%
2	Products applied to the axillae	0.021%	0.00%
3	Products applied to the face using fingertips	0.41%	0.00%
4	Fine fragrance products	0.39%	0.00%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%[b]
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No Data
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.00%[b]
10	Household care products with mostly hand contact	2.70%	0.00%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.00%[b]

Notes.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet. (www.rifm.org/doc).
[b] Negligible exposure (< 0.01%).

absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, *p*-isopropylacetophenone does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis

UV/Vis absorption spectra (OECD TG 101) for *p*-isopropylacetophenone were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark, 1000 L $mol^{-1} \cdot cm^{-1}$, of concern for phototoxic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/21/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, *p*-isopropylacetophenone, exposure level 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 *p*-isopropylacetophenone. Based on the Creme RIFM Model, the inhalation exposure is 0.0000027 mg/day. This exposure is 518518 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: 3/10/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of *p*-isopropylacetophenone 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, *p*-isopropylacetophenone was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.1 (US EPA, 2012a) identified *p*-isopropylacetophenone 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2011), *p*-isopropylacetophenone does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

Other available data: p-Isopropylacetophenone has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	22.75			1,000,000	0.02275	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.13	3.13
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.02275 µg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 1/15/16.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

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.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110565.

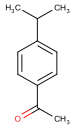
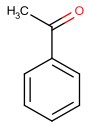
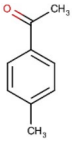
Appendix

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). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework.

- 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, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- 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, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target material	Read-across material	
Principal Name	*p*-Isopropylacetophenone	Acetophenone	*p*-Methylacetophenone
CAS No.	645-13-6	98-86-2	122-00-9
Structure			
Similarity (Tanimoto score)		0.82	0.74
Read-across endpoint		• Skin sensitization	• Genotoxicity
Molecular Formula	$C_{11}H_{14}O$	C_8H_8O	$C_9H_{10}O$
Molecular Weight	162.23	120.15	134.18
Melting Point (°C, EPI Suite)	19.30	−9.86	7.85
Boiling Point (°C, EPI Suite)	236.04	189.81	209.72
Vapor Pressure (Pa @ 25 °C, EPI Suite)	2.93	43.5	11.3
Log Kow (KOWWIN v1.68 in EPI Suite)	2.98	1.58	2.10
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	190.6	6130	372
J_{max} (μg/cm^2/h, SAM)	37.779	146.789	13.981
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.91E-005	9.81E-006	1.08E-005
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)	• No alert found		• No alert found
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Non-carcinogen (low reliability)		• Non-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	• No alert found		• No alert found
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found		• No alert found
Oncologic Classification	• Not classified		• Not classified
Skin Sensitization			
Protein binding by OASIS v1.4	• No alert found	• No alert found	
Protein binding by OECD	• No alert found	• No alert found	
Protein binding potency	• Not possible to classify	• Not possible to classify	
Protein binding alerts for skin sensitization by OASIS v1.4	• No alert found	• No alert found	
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (good reliability)	• Non-sensitizer (good reliability)	
Metabolism			
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on the target material *p*-isopropylacetophenone (CAS # 645-13-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties and expert judgment, analogs acetophenone (CAS # 98-86-2) and *p*-methylacetophenone (CAS # 122-00-9) were identified as read-across materials with sufficent data for toxicological evaluation.

Conclusions

- For the target material *p*-isopropylacetophenone (CAS # 645-13-6), acetophenone (CAS # 98-86-2) was used as a read-across analog for the skin sensitization endpoint, and *p*-methylacetophenone (CAS # 122-00-9) was used as a read-across analog for the genotoxicity endpoint.
  - o The target substance and the read-across analogs are structurally similar and belong to the structural class of aromatic ketones.
  - o The target substance and the read-across analogs share an acetophenone substructure.
  - o The key difference between the target substance and the read-across analogs is that the target substance has a *p*-isopropyl substitution on the aromatic ring, while the read-across analog acetophenone does not have a substitution on the aromatic ring, and the analog *p*-methylacetophenone has an n-propyl group on the ketone moiety compared to a methyl on the target substance. These structural differences between the target substance and the read-across analogs do not affect consideration of the toxicological endpoints.
  - o Similarity between the target substance and the read-across analogs 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 toxicological endpoints.
  - o The physical–chemical properties of the target substance and the read-across analogs are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target substance and the read-across analogs.
  - o The CAESAR model for skin sensitization predicts the target substance to be a sensitizer, while it predicts the read-across analog acetophenone to be a non-sensitizer. Other skin sensitization related protein binding alerts are not found for the target substance. The data described in the skin sensitization section for the read-across analog shows that it does not pose a concern for the skin sensitization endpoint. Therefore, from the structural similarity and data availability for the read-across analog, the alert for the target substance is superseded.
  - o The target substance and the read-across analogs are expected to be metabolized similarly, as shown by the metabolism simulator.

XII. References

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

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

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

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

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

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

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

IFRA (International Fragrance Association), 2011. Volume of Use Survey, 2011.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. In: Current Problems in Dermatology, vol. 14. pp. 152–171.

Klecak, G., Geleick, H., Frey, J.R., 1977. Screening of fragrance materials for allergenicity in the Guinea pig. I. Comparison of four testing methods. J. Soc. Cosmet. Chem. Jpn. 28, 53–64.

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

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

OECD, 2012. The OECD QSAR Toolbox, v3.4. Retrieved from. http://www.qsartoolbox.org/.

OECD, 2015. *Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

RIFM (Research Institute for Fragrance Materials, Inc), 1970a. The Contact Sensitizing Potential of Fragrance Materials in Humans. Report to RIFM. RIFM Report Number 1760. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1970b. Toxicological Studies of Acetanisole and Acetophenone. Unpublished report from Fritzsche, Dodge and Olcott, Inc. RIFM report number 13834. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1998. 4'-Methylacetophenone: Reverse Mutation in Salmonella typhimurium. Unpublished Report from Symrise. RIFM Report Number 56087. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2013. 4'-Methylacetophenone (methyl acetophenone-para): In vitro micronucleus test in human lymphocytes. Unpublished report from Symrise. RIFM report number 67878. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2014. Report on the Testing of P-Isopropylacetophenone in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 67024. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016. Expo. Surv. 10 March 2016.

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

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

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

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

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

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

Sharp, D.W., 1978. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9 (3), 261–271.

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

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

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.