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Short Review

RIFM fragrance ingredient safety assessment, 4′-methylacetophenone, CAS Registry Number 122-00-9

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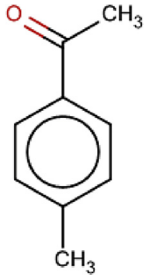
Version: 050918. This version replaces any previous versions.
Name: 4′-Methylacetophenone
CAS Registry Number: 122-00-9



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

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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 under the limits 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 use of this material under current conditions is supported by existing information.

4′-Methylacetophenone was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 4′-methylacetophenone is not genotoxic. Data on read-across analog acetophenone (CAS# 98-86-2) provided an MOE > 100 for the repeated dose toxicity and the developmental and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The local respiratory toxicity endpoint was completed using the TTC for a Cramer Class I material; the exposure to 4′-methylacetophenone is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; 4′-methylacetophenone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4′-methylacetophenone 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, 1998c; RIFM, 2013b)

Repeated Dose Toxicity: NOAEL = 250 mg/kg/day. (ECHA REACH Dossier: Acetophenone)

Developmental and Reproductive Toxicity: NOAEL = 125 mg/kg/day and 750 mg/kg/day, respectively.

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: Critical Measured Value: 92% (OECD 301F) (RIFM, 1998a)

Bioaccumulation: Screening-level: 2.93 L/kg (EPI Suite v4.1; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 148.1 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: 148.1 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.1481 μg/L

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 4′-Methylacetophenone
2. **CAS Registry Number:** 122-00-9
3. **Synonyms:** 1-Acetyl-4-methylbenzene; *p*-Acetyltoluene; Ethanone, 1-(4-methylphenyl)-; *p*-Methylacetophenone; 1-Methyl-4-acetyl benzene; Methyl *p*-tolyl ketone; *p*-Tolyl methyl ketone; Methyl 4-methylphenyl ketone; 4-Acetyltoluene; 1-(4-Methylphenyl)ethanone; p-Methyl acetophenone; Methyl acetophenone; ﾒﾁﾙｱｾﾄﾌｪﾉﾝ; Methyl acetophenone-para; 4′-Methylacetophenone
4. **Molecular Formula:** $C_9H_{10}O$
5. **Molecular Weight:** 134.18
6. **RIFM Number:** 172

2. Physical data

1. **Boiling Point:** 226.3 °C (2012c), 226 °C (FMA), 209.72 °C (EPI Suite)
2. **Flash Point:** 93 °C (GHS), 93 °C (2012b), > 200F; CC (FMA)
3. **Log K_{ow}:** 2.1 at 35 °C (RIFM, 1998b), 2.22 (EPI Suite)
4. **Melting Point**: 7.85 °C (EPI Suite)
5. **Water Solubility:** 1424 mg/L (EPI Suite)
6. **Specific Gravity:** 0.996–1.004 (FMA), 0.998–1.006 (FMA)
7. **Vapor Pressure:** 0.0504 mm Hg @ 20 °C (EPI Suite v4.0), 0.09 mm Hg 20 °C (FMA), 0.0849 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless or nearly colorless liquid with fruity, floral odor resembling acetophenone colorless needles, or opaque crystalline mass; pungent, almost harsh but warm sweet and floral odor of moderate tenacity; sweet, woody floral taste, only in extreme dilution becoming fruity, vaguely reminiscent of strawberry (Arctander, 1969).

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.015% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00011 mg/kg/day or 0.0084 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00060 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
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2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Acetophenone (CAS # 98-86-2)
   c. **Developmental and Reproductive Toxicity:** Acetophenone (CAS # 98-86-2)
   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)

4′-Methylacetophenone is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):

Black currants (*Ribes nigrum* L.)
Buckwheat.
Calabash nutmeg (*Monodora myristica* Dunal).
Capsicum species.
Cauliflower and broccoli.

Celery (*Apium graveolens* L.)
Cheese, various types.
Cherimoya (*Annona cherimolia* Mill.)
Cherry (*Prunus avium* [sweet], *Pr. cerasus* [sour])
Citrus fruits.
Cloudberry (*Rubus chamaemorus* L.)
Cocoa.
Endive (*Cichorium endivia* L.)
Fish.
Grape brandy.
Guava and feyoa
Honey.
Katsuobushi (dried bonito).
Mangifera species.
Mastic (*Pistacia lentiscus*).
Mentha oils.
Parsley (*Petroselium* species).
Passion fruit (*Passiflora* species).
Peach (*Prunus persica* L.)
Pepper (*Piper nigrum* L.)
Potato (*Solanum tuberosum* L.)
Pumpkin seed oil.
Raspberry, blackberry, and boysenberry.
Rice (*Oryza sativa* L.)
Rooibos tea (*Aspalathus linearis*).
Soybean (*Glycine max*. L. merr.)
Tea.
Tomato (*Lycopersicon esculentum* Mill.)
Turpentine oil (*Pistacia terebinthus*).
Whisky.

*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

Full and intermediate use dossiers available; accessed 05/10/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 4′-methylacetophenone does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 4′-methylacetophenone has been 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 increase in the mean number of revertant colonies was observed at any tested dose in the presence or absence of S9 (RIFM, 1998c). Under the conditions of the study, 4′-methylacetophenone was not mutagenic in the Ames test.

The clastogenic activity of 4′-methylacetophenone 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, 2013b). 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.

Additional References: RIFM, 2013a.

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

10.1.2. Repeated dose toxicity

The margin of exposure for 4′-methylacetophenone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 4′-methylacetophenone. Read-across material, acetophenone (CAS # 98-86-2; see Section 5) has sufficient repeated dose toxicity data. Groups of 10 male and 10 female weanling Osborne-Mendel rats were administered acetophenone via the diet for 17 weeks in nominal concentrations of 0, 1000, 2500, or 10000 ppm (equivalent to doses of 0, 75, 188, or 750 mg/kg/day, neglecting 31% loss within 1 week due to evaporation). Body weight, food intake, and general conditions were recorded weekly. Hematology, gross pathology, and microscopic examination were conducted at the end of the study. There were no effects on growth, hematology, or macroscopic or microscopic changes in tissue. Thus, the NOEL was reported to be 10000 ppm or 750 mg/kg/day. The US EPA IRIS online summary has derived a NOAEL of 423 mg/kg/day, taking into account the loss by evaporation from food (Hagan et al., 1967). In an OECD 422 gavage study, groups of 10 male and 5 female (additional 10 females for the reproductive toxicity part of the study) Sprague Dawley rats/dose were administered acetophenone at doses of 0, 75, 225, or 750 mg/kg/day daily for a minimum of 14 days before mating and throughout the mating and gestation periods up to lactation day 3. There was no parental mortality. At the 750 mg/kg/day dose, reductions in body weight and food consumption were observed. Wobbly gait and urine stains appeared in both males and females, while hair loss was limited to 3/5 females. Mean forelimb grip strength and mean motor activity of males were statistically lower than the controls. Thus, the NOAEL for the repeated dose toxicity endpoint was considered to be 225 mg/kg/day, based on clinical and neurobehavioral findings among high-dose animals (ECHA REACH Dossier: Acetophenone; data also available in Kapp et al., 2003). In another study, acetophenone was administered to groups of 10 Wistar rats/sex/dose at doses of 0, 125, 250, and 500 mg/kg/day in a corn oil vehicle. The study was conducted according to the OECD 408 guidelines and in accordance with GLP regulations. At 500 mg/kg/day, the mean bodyweight gain was significantly lower among the males, while no toxicologically relevant effect for body weight was observed for females. Clinical signs related to the known hypnotic effect of acetophenone (decreased spontaneous activity) were observed mainly in the male and female groups treated with 500 mg/kg/day. A significantly higher mean percent of reticulocytes was observed for males and females of the highest dose group, which was considered an adverse effect due to the administration of the test material. Furthermore, statistically significantly lower red blood cell count and hemoglobin were also observed in the female animals at 500 mg/kg/day. Thus, the NOAEL was considered to be 250 mg/kg/day, based on decreased bodyweight gains, reduced activity, and increased reticulocyte levels (ECHA REACH Dossier: Acetophenone). The NOAEL of 250 mg/kg/day from the OECD 408 gavage study was considered for this safety assessment.

Therefore, the 4′-methylacetophenone MOE for the repeated dose

toxicity endpoint can be calculated by dividing the acetophenone NOAEL in mg/kg/day by the total systemic exposure to 4′-methylacetophenone, 250/0.0006 or 416667.

In addition, the total systemic exposure to 4′-methylacetophenone (0.6 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint for a Cramer Class I material at the current level of use (Kroes et al., 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 4′-methylacetophenone is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 4′-methylacetophenone. Read-across material acetophenone (CAS # 98-86-2; see Section 5) has sufficient developmental toxicity data. In an OECD 422 combined repeated dose toxicity and reproduction/developmental screening study, groups of 10 Sprague Dawley rats/sex/dose were administered acetophenone at doses of 0, 75, 225, or 750 mg/kg/day daily via gavage for a minimum of 14 days before mating and throughout the mating and gestation periods up to lactation day 3. There was a significant increase in the number of stillborn offspring among the high-dose group as compared to controls. There was a significant increase in the number of offspring dying, missing and/or cannibalized, along with an increase in the number of litters with total litter loss among the high-dose group during lactation days 1–4. There was a significant decrease in the total number of live born, viability index, and mean number of live pups per litter on lactation days 1–4. The number of mean live pups per litter was significantly lower on lactation days 1–4, and the live birth index was also reported to be out of the historical control range. Clinical signs among the high-dose group offspring included increased incidences of desquamation, cool to the touch, skin with shiny appearance, skin appearing tight with restricted movement, and a slightly increased incidence of gasping and pale skin color. There was a significant decrease in the pup weight per litter among the high-dose group on lactation days 1 and 4; this was reported to be out of the historical control ranges. During gross pathological examination of offspring, high-dose group pups were reported with incidences of cleft palate and edema, atelectasis, dermal hypoplasia, scabbing, desquamation, and 22 dead pups with observed autolysis. Thus, the NOAEL for the developmental toxicity endpoint was considered to be 225 mg/kg/day, based on effects of treatment on viability of the offspring, alterations in clinical signs, body weight, and gross pathological alterations among the high-dose group offspring (ECHA REACH Dossier: Acetophenone). In another study, an OECD 414 prenatal developmental toxicity study was conducted using pregnant female Wistar rats. The test material acetophenone was administered via gavage to groups of 25 rats/dose at 0, 125, 300, and 750 mg/kg/day in a corn oil vehicle. Additional groups of 10 female rats were added to the control and high-dose groups. Females were treated daily from gestation day 5 (GD 5) up to GD 19. At 300 and 750 mg/kg/day, treatment-related clinical signs of reduced activity, ataxia, and salivation (known hypnotic effect of acetophenone), along with statistically significantly reduced body weight and food consumption, were observed. At the same dose levels, a dose-dependent statistically significantly lower uterus weight and adjusted maternal weights (maternal weight minus gravid uterus weight) were observed. The mean fetus and litter weights among the mid- and high-dose groups were dose-dependently and statistically significantly lower when compared to the controls. Furthermore, skeletal examination showed a moderately, statistically significantly higher incidence of bilateral pelvic girdle caudal shift when compared to concurrent controls for pups in the highest dose group. This change of position of pelvic girdle relative to the number of pre-pelvic vertebrae was associated with a moderately higher litter incidence of supernumerary bilateral full fourteenth thoracolumbal rib but without achieving statistical significance. Both findings were observed in greater incidences at 750 mg/kg/day when compared to the maximum litter and fetal incidence of historical data. Under the conditions of the study, the NOAEL for maternal and developmental toxicity was considered to be 125 mg/kg/day (ECHA REACH Dossier: Acetophenone). The most conservative NOAEL from the OECD 414 was selected for the developmental toxicity endpoint.

Therefore, the 4′-methylacetophenone MOE for the developmental toxicity endpoint can be calculated by dividing the acetophenone NOAEL in mg/kg/day by the total systemic exposure to 4′-methylacetophenone, 125/0.0006 or 208333.

There are no reproductive toxicity data on 4′-methylacetophenone. Read-across material, acetophenone (CAS # 98-86-2; see Section 5) has sufficient reproductive toxicity data. In an OECD 422 combined repeated dose toxicity and reproduction/developmental screening study, groups of 10 Sprague Dawley rats/sex/dose were administered acetophenone at doses of 0, 75, 225, or 750 mg/kg/day daily via gavage for a minimum of 14 days before mating and throughout the mating and gestation periods up to lactation day 3. There were no effects of treatment on the reproductive performance of parental animals up to the highest dose tested. Thus, the NOAEL for the reproductive toxicity endpoint was considered to be 750 mg/kg/day, the highest dose tested (ECHA REACH Dossier: Acetophenone).

Therefore, the 4′-methylacetophenone MOE for the reproductive toxicity endpoint can be calculated by dividing the acetophenone NOAEL in mg/kg/day by the total systemic exposure to 4′-methylacetophenone, 750/0.0006 or 1250000.

In addition, the total systemic exposure to 4′-methylacetophenone (0.6 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/10/2017.

10.1.4. Skin sensitization

Based on existing data, read-across to acetophenone (CAS # 98-86-2), and application of DST, 4′-methylacetophenone does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited data exist on 4′-methylacetophenone and read-across analog acetophenone (CAS # 98-86-2; see Section 5). The chemical structure of these materials indicates that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). Read-across analog acetophenone was found to be negative in guinea pig studies (Klecak et al., 1977; Klecak, 1979, 1985; Sharp, 1978). In a human maximization test, no skin sensitization reactions were observed at 6% or 4140 μg/cm^2 4′-methylacetophenone (RIFM, 1970a) or 2% or 1380 μg/cm^2 acetophenone (RIFM, 1971). 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 2-methylundecanal dimethyl acetal 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 UV/Vis absorption spectra, 4′-methylacetophenone would not be expected to present a concern for phototoxicity or photoallergenicity.

Table 1
Acceptable concentrations for 4′-methylacetophenone 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%	0.01%
2	Products applied to the axillae	0.021%	0.02%
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.00%[b]
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%[b]
7	Products applied to the hair with some hand contact	0.79%	0.01%
8	Products with significant ano-genital exposure	0.04%	No Data
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.01%
10	Household care products with mostly hand contact	2.70%	0.01%
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	0.92%

Note:[a]For a description of the categories, refer to the IFRA/RIFM Information Booklet.[b]Negligible exposure (< 0.01%).

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 4′-methylacetophenone 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 lack of absorbance, 4′-methylacetophenone 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: 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, 4′-methylacetophenone, 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 4′-methylacetophenone. Based on the Creme RIFM Model, the inhalation exposure is 0.0084 mg/day. This exposure is 167 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: 12/14/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 4′-methylacetophenone 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, 4′-methylacetophenone 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) did not identify 4′-methylacetophenone as either being possibly persistent nor 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), 4′-methylacetophenone does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation:

RIFM, 1998a: The ready biodegradability of the test substance was determined by the manometric respirometry test according to the OECD 301F method. The test material underwent 92% biodegradation after 28 days.

RIFM, 1999: The ready biodegradability of the test material was evaluated in a closed bottle test. Biodegradation of 60% was observed after 28 days.

Ecotoxicity:

RIFM, 1999: A *Daphnia magna* acute toxicity study was conducted under static conditions. The 48-h EC50 was reported to be 31 mg/L.

(RIFM, 2012a): An algae growth inhibition test was conducted according to the OECD 201 method. Under the test conditions, the 72-h

EC50s, based on mean measured concentrations, were 17 and 36 mg/L for yield (ECy50) and growth rate reduction (ECr50), respectively.

10.2.2.1. Other available data. 4′-Methylacetophenone has been registered under REACH, and the following additional data is available:

A fish (*Brachydanio rerio*) acute toxicity study was conducted according to the OECD 203 method under static conditions. The 96-h LC50 was reported to be 71 mg/L.

10.2.3. Risk assessment refinement

Since 4′-methylacetophenone 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	148.1			1,000,000	0.1481	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.1	2.1
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
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 0.1481 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: 3/1/2017.

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
- **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.

Appendix A. Supplementary data

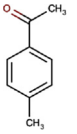
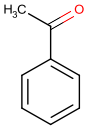
Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.08.023.

AppendixRead-across Justification

Method

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 (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, 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*-Methylacetophenone	Acetophenone
CAS No.	122-00-9	98-86-2
Structure		
Similarity (Tanimoto score)		0.91
Read-across endpoint		• Repeated dose • Reproductive and developmental • Skin sensitization
Molecular Formula	$C_9H_{10}O$	C_8H_8O
Molecular Weight	134.18	120.15
Melting Point (°C, EPI Suite)	7.85	−9.86
Boiling Point (°C, EPI Suite)	209.72	189.81
Vapor Pressure (Pa @ 25°C, EPI Suite)	11.3	43.5
Log Kow (KOWWIN v1.68 in EPI Suite)	2.10	1.58
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	372	6130
J_{max} (mg/cm^2/h, SAM)	13.981	146.789
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.08E-005	9.81E-006
Repeated dose toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder without OH or NH_2 group	• Non-binder without OH or NH_2 group
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (moderate reliability)	• Toxicant (low reliability)
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)	• Non-sensitizer (low 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

Summary

There are insufficient toxicity data on the target material p-methylacetophenone (CAS # 122-00-9). 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, acetophenone (CAS # 98-86-2) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- For target material *p*-methylacetophenone (CAS # 122-00-9), acetophenone (CAS # 98-86-2) was used as a read-across analog for the skin sensitization, repeated dose, and reproductive and developmental toxicity endpoints.
  - oThe target substance and the read-across analog are structurally similar and belong to the structural class of aromatic ketones.
  - o The target substance and the read-across analog share an acetophenone substructure.
  - o The key difference between the target substance and the read-across analog is that the target has a methyl substituent on the aromatic ring para to the acetyl substituent, whereas the read-across analog acetophenone does not. This structure difference between the target substance and the read-across analog does not affect consideration of the toxicological endpoints.
  - o Similarity between the target substance 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 toxicological endpoints.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicity endpoints are consistent between the target substance and the read-across analog.
  - o The CAESAR model for developmental toxicity predicts the target substance and the read-across analog to be toxicants. There are no other alerts for developmental toxicity. The ER binding alert is negative. The data described in the developmental toxicity section show that the margin of exposure for the read-across analog is adequate at the current level of use. Therefore, the alert will be superseded by the availability of data.
  - o The structural alerts for the toxicity endpoints are consistent between the metabolites of the read-across analog and the target material.

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