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RIFM fragrance ingredient safety assessment, acetophenone, CAS Registry Number 98-86-2

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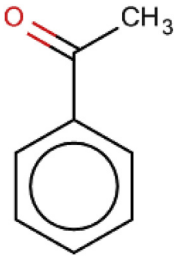
Version: 051418. This version replaces any previous versions.
Name: Acetophenone
CAS Registry Number: 98-86-2



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.

Acetophenone was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that acetophenone is not genotoxic. Data on acetophenone provide a calculated MOE >100 for the repeated dose toxicity and developmental and reproductive toxicity endpoints. The local respiratory toxicity endpoint was completed using the TTC for a Cramer Class I material, and the exposure to acetophenone was below the TTC (1.4 mg/day). The skin sensitization endpoint was completed by utilizing the non-reactive DST; exposure is below the DST. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; acetophenone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; acetophenone was not found to be PBT as per 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. (ECHA REACH Dossier: Acetophenone)

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.	(ECHA REACH Dossier: Acetophenone)
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: 64.7% (OECD 301C)	(REACH Dossier; Accessed 4/27/17)
Bioaccumulation: Screening-level: 1.3 L/kg	(EPI Suite; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 341.1 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	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 341.1 mg/L	(Salvito et al., 2002)
RIFM PNEC is: 0.3411 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. Chemical Name: Acetophenone
2. CAS Registry Number: 98-86-2
3. Synonyms: Acetylbenzol; Acetylbenzene; Benzoyl methide; Ethanone, 1-phenyl-; Methyl phenyl ketone; Phenyl methyl ketone; アセトフェノン; 1-Phenylethanone; Acetophenone
4. Molecular Formula: C_8H_8O
5. Molecular Weight: 120.15
6. RIFM Number: 151

2. Physical data

1. **Boiling Point:** 202 °C (FMA), 189.81 °C (EPI Suite)
2. **Flash Point:** 105 °C (GHS), 170 °F; CC (FMA)
3. **Log K_{OW}:** LogK pdms/w = 1.352 (n = 12) (Xia et al., 2007), 1.63 (Abraham and Rafols, 1995), 1.67 (EPI Suite)
4. **Melting Point**: −9.86 °C (EPI Suite)
5. **Water Solubility:** 4484 mg/L (EPI Suite)
6. **Specific Gravity:** 1.025–1.028 (FMA), 1.027–1.030 (FMA)
7. **Vapor Pressure:** 0.221 mm Hg @ 20 °C (EPI Suite v4.0), 0.2 mm Hg 20 °C (FMA), 0.326 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:** Almost colorless water, white to very pale yellow liquid, or white crystals with sweet pungent odor and bitter, aromatic flavor

3. Exposure

1. **Volume of Use (Worldwide Band):** 10–100 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.010% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.00014 mg/kg/day or 0.010 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00053 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, 2017; Safford et al., 2015, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 5. 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, 2017; Safford et al., 2015, 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:** None
   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:** None
3. **Read-across Justification:** None

6. Metabolism

Not considered for this risk assessment.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Acetophenone is reported to occur in the following foods by the VCF* and is found in some natural complex substances (NCS):

Acerola (*Malpighia*)
Allium species
Apple brandy (calvados)
Apple fresh (*Malus* species)

Apricot (*Prunus armeniaca* L.)
Aubergine, eggplant (*Solanum melongena* L.)
Banana (*Musa sapientum* L.)
Beans
Beef
Black choke berry juice (*Aronia melanocarpa* Ell.)
Blue cheeses
Brown algae
Buckwheat
Capers (*Capparis spinoza*)
Capsicum species
Cashew apple (*Anacardium occidentale*)
Cauliflower and broccoli
Cheese, various types
Chinese liquor (baijiu)
Cider (apple wine)
Cinnamomum species
Citrus fruits
Clam
Cloudberry (*Rubus chamaemorus* L.)
Cloves (*Eugenia caryophyllata* Thunberg)
Cocoa category
Crayfish
Date (*Phoenix dactylifera* L.)
Egg
Elderberry (*Sambucus nigra* L.)
Endive (*Cichorium endivia* L.)
Filbert, hazelnut (*Corylus avellano*)
Fish
Grape (*Vitis* species)
Grape brandy
Guava and feyoa
Guava wine
Honey
Katsuobushi (dried bonito)
Krill
Kumazasa (*Sasa albo-marginata*)
Lamb's lettuce (*Valerianella locusta*)
Lentils
Licorice (*Glycyrrhiza* species)
Loquat (*Eriobotrya japonica* Lindl.)
Macadamia nut (*Macadamia integrifolia*)
Maize (*Zea mays* L.)
Mangifera species
Mastic (*Pistacia lentiscus*)
Matsutake (*Tricholoma matsutake*)
Melon
Mentha oils
Milk and milk products
Mountain papaya (*C. candamarcensis, C. pubescens*)
Mushroom
Nectarine
Olive (*Olea europaea*)
Papaya (*Carica papaya* L.)
Passion fruit (*Passiflora* species)
Peach (*Prunus persica* L.)
Peanut (*Arachis hypogaea* L.)
Peas (*Pisum sativum* L.)
Pecan (*Carya illinoensis* Koch)
Plum (*Prunus* species)
Pomegranate juice (*Punica granatum* L.)
Pork
Potato (*Solanum tuberosum* L.)
Potato chips (American)
Prickly pear (*Opuntia ficus indica*)
Quince, marmelo (*Cydonia oblonga* Mill.)
Rambutan (*Nephelium lappaceum* L.)
Raspberry, blackberry, and boysenberry
Rice (*Oryza sativa* L.)
Rooibos tea (*Aspalathus linearis*)
Rum
Sauerkraut
Scallop
Sherry
Shoyu (fermented soya hydrolysate)
Shrimps (prawn)
Southernpea (*Vinga unguiculata* L.)
Soybean (*Glycine max*. L. Merr.)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species)
Sweet grass oil (*Hierochloe odorata*)
Swiss cheeses
Syzygium species
Tamarind (*Tamarindus indica* L.)
Tea
Tomato (*Lycopersicon esculentum* Mill.)
Trassi (cooked)
Turkey
Vaccinium species
Vanilla
Vinegar
Walnut (*Juglans* species)
Wild rice (*Zizania aquatica*)
Wine

*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 that contains 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

Available; accessed 05/08/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the existing data, acetophenone does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of acetophenone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP and OECD TG 471 using the standard plate incorporation/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with acetophenone in ethanol 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 (ECHA: REACH Dossier on acetophenone). Under the conditions of the study, acetophenone was not mutagenic in the Ames test.

The clastogenicity of acetophenone was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP and OECD TG 473. Chinese hamster lung cells were treated with acetophenone in ethanol at concentrations up to 1100 μg/mL in the presence and absence of exogenous metabolic activation. No significant

increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item without S9 metabolic activation. However, there was a statistically significant increase in chromosomal aberrations in the 4-h treatment in the presence of S9 at 1035 μg/mL. This increase was observed in a repeat experiment using a narrower concentration range (900–1100 μg/mL). It was concluded that acetophenone was clastogenic in the presence of metabolic activation (ECHA: REACH Dossier on acetophenone). In contrast, there was no indication of a clastogenic effect *in vivo*. The clastogenic activity of acetophenone was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP and OECD TG 474. The test material was administered in cotton seed oil via intraperitoneal injection to groups of male and female NMRI mice (5/sex/dose). Doses of 103, 257.5, or 515 mg/kg were administered. Mice from each dose level were euthanized at 44 or 68 h. Bone marrow was then extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA: REACH Dossier on acetophenone). Under the conditions of the study, acetophenone was not clastogenic in the *in vivo* micronucleus test.

Based on the available data acetophenone does not present a concern for genotoxic potential.

Additional References: RIFM, 2013.

Literature Search and Risk Assessment Completed On: 2/17/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for acetophenone is adequate for repeated dose toxicity at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on acetophenone. Groups of 10 male and 10 female weanling Osborne-Mendel rats were administered via the diet containing test material acetophenone 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 750 mg/kg/day, reductions in body weight and food consumption as well as wobbly gait and urine stain appeared in both males and females, while hair loss were 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 and GLP guidelines. 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 reticulocytes was observed for males and females of the highest dose group, which was considered as an adverse effect due to the administration of the test material. Furthermore, a 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 acetophenone 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 acetophenone, 250/0.00053, or 471698.

In addition, the total systemic exposure to acetophenone (0.53 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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/20/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for acetophenone is adequate for developmental and reproductive toxicity at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental toxicity data on acetophenone. 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 acetophenone MOE for the developmental toxicity endpoint can be calculated by dividing the acetophenone NOAEL in mg/kg/day by the total systemic exposure to acetophenone, 125/0.00053 or 235849.

There are sufficient reproductive toxicity data on acetophenone. 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 acetophenone MOE for reproductive toxicity can be calculated by dividing the acetophenone NOAEL in mg/kg/day by the total systemic exposure to acetophenone, 750/0.00053 or 1415094.

In addition, the total systemic exposure to acetophenone (0.53 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: 04/20/2017.

10.1.4. Skin sensitization

Based on existing data and application of DST, acetophenone does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. The chemical structure of acetophenone indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD Toolbox v3.4). 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 with 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 product categories indicated in the table. Table 1 provides the acceptable concentration for acetophenone, which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: Sharp, 1978; RIFM, 1970.

Literature Search and Risk Assessment Completed On: 05/01/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, acetophenone 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 acetophenone in experimental models. UV/Vis absorption spectra indicate minor absorbance 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, acetophenone does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/20/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, acetophenone, 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 acetophenone. Based on the Creme RIFM Model, the inhalation exposure is 0.010 mg/day. This exposure is 140 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: Ovchagov, 1965; Smyth and Carpenter,

Table 1
Acceptable concentrations for acetophenone 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	0.07%	0.02%
2	Products applied to the axillae	0.02%	0.01%
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%	0.00%[b]
8	Products with significant ano-genital exposure	0.04%	No data
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.01%
10	Household care products with mostly hand contact	2.70%	0.03%
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	0.642%

Note.

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.

[b] Negligible exposure (< 0.01%).

1944; Duchamp, 1982; Revial et al., 1982; Pinching and Doving, 1974; Zissu, 1995; Tkach, 1967; Helmig et al., 1999a, b; Helmig et al., 1999a, b; Johnson et al., 2005.

Literature Search and Risk Assessment Completed On: 12/13/2016

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of acetophenone 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, acetophenone 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 acetophenone as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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), acetophenone does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Acetophenone has been registered under REACH, and the following key data is available:

Biodegradation of the test material was evaluated according to the OECD 301C method. After 14 days, biodegradation of 64.7% was observed.

A *Daphnia magna* immobilization test was conducted under static conditions, and the 48-h LC50 was reported to be 528 mg/L.

A fish (Fathead minnow) acute toxicity test was conducted according to the OECD 203 guidelines under flow-through conditions. The 96-h LC50 was 162 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50s were 40 mg/L and 86.4 mg/L for biomass and growth rate, respectively.

10.2.3. Risk assessment refinement

Since acetophenone has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>341.1</u>			1,000,000	0.3411	

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.63	1.63
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 the available data, the RQ for this class of material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.3411 μg/L. The revised PEC/PNECs for EU and NA: not applicable; cleared at the screening-level; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 04/27/

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
- **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.

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