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Short review

RIFM fragrance ingredient safety assessment, 2-hydroxyacetophenone, CAS Registry Number 118-93-4

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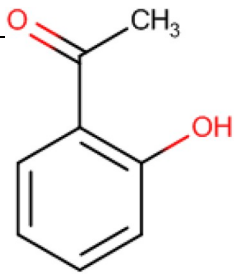
CAS Registry Number: 118-93-4



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., 2015a, 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.

2-Hydroxyacetophenone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 4-hydroxyacetophenone (CAS # 99-93-4) show that 2-hydroxyacetophenone is not expected to be genotoxic. Data on read-across analog 4-hydroxyacetophenone (CAS # 99-93-4) provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the DST for reactive materials (64 $\mu g/cm^2$); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-hydroxyacetophenone is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to 2-hydroxyacetophenone is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2-hydroxyacetophenone 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 expected to be genotoxic. (Florin et al., 1980; ECHA REACH Dossier: 4′-Hydroxyacetophenone; ECHA, 2013)
Repeated Dose Toxicity: NOAEL = 45 mg/kg/day. (ECHA REACH Dossier: 4′-Hydroxyacetophenone; ECHA, 2013)
Reproductive Toxicity: NOAEL = 600 mg/kg/day. (ECHA REACH Dossier: 4′-Hydroxyacetophenone; ECHA, 2013)
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence:
Screening-level: 90% (OECD 301 B) (ECHA REACH Dossier: 2′-Hydroxyacetophenone; ECHA, 2017)
Bioaccumulation:
Screening-level: 2.2 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 195.04 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: 195.04 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.19504 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 2-Hydroxyacetophenone
2. **CAS Registry Number:** 118-93-4
3. **Synonyms:** o-Acetylphenol; Ethanone, 1-(2-hydroxyphenyl)-; o-Hydroxyacetophenone; 1-(2-Hydroxyphenyl)ethanone; 2-Hydroxyacetophenone
4. **Molecular Formula:** $C_8H_8O_2$
5. **Molecular Weight:** 136.15
6. **RIFM Number:** 6697
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 213 °C @ 717 mm Hg (FMA Database), 246.89 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA Database)
3. **Log K_{OW}:** 1.92 (Smith et al., 2002), 1.92 (Smith et al., 2002), 1.97 (EPI Suite)
4. **Melting Point**: 4 °C (FMA Database), 51.94 °C (EPI Suite)
5. **Water Solubility:** 7571 mg/L (EPI Suite)
6. **Specific Gravity:** 1.131 (FMA Database)
7. **Vapor Pressure:** 0.03 mm Hg 20 °C (FMA Database), 0.0448 mm Hg @ 20 °C (EPI Suite v4.0), 0.0702 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:** Not Available

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.000034% (RIFM, 2016)
3. **Inhalation Exposure*:** < 0.0001 mg/kg/day or 0.0000006 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0000002 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., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; 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-Hydroxyacetophenone (CAS # 99-93-4)
   b. **Repeated Dose Toxicity:** 4-Hydroxyacetophenone (CAS # 99-93-4)
   c. **Reproductive Toxicity:** 4-Hydroxyacetophenone (CAS # 99-93-4)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

6.1. Additional References

None.

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

2-Hydroxyacetophenone is reported to occur in nature in the following*:

Beef
Black chokeberry (*Aronia melanocarpa* Ell.)
Cinnamomum species
Coca
Coffee
Rum
Sherry
Tea
Tomato (*Lycopersicon esculentum* Mill.)
Whiskey

*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. This is a partial list.

8. REACH Dossier

Available; accessed 12/19/18.

9. Conclusion

The existing information supports the use of this material as described in this safety assessment.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2-hydroxyacetophenone does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 2-hydroxyacetophenone has been evaluated in a bacterial reverse mutation assay equivalent to OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with 2-hydroxyacetophenone in ethanol at concentrations of 3 μmol/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Florin et al., 1980). Under the conditions of the study, 2-hydroxyacetophenone was not mutagenic in the Ames test. Additionally, the mutagenic potential of read-across material 4-hydroxyacetophenone (CAS # 99-93-4; see Section V) was assessed in an Ames assay conducted equivalent to OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 4-hydroxyacetophenone in dimethyl sulfoxide (DMSO) at concentrations up to 10000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2013). Under the conditions of the study, 4-hydroxyacetophenone was not mutagenic in the Ames test, and this can be extended to 2-hydroxyacetophenone.

There are no data assessing the clastogenic activity of 2-hydroxyacetophenone; however, read-across can be made to 4-hydroxyacetophenone (CAS # 99-93-4; see Section V). The clastogenic activity of 4-hydroxyacetophenone was evaluated in an *in vivo* micronucleus test equivalent to OECD TG 474. The test material was administered in corn oil via the intraperitoneal route to groups of male and female ICR mice. Doses of 113, 225, and 450 mg/kg were administered. Mice from each dose level were euthanized, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2013). Under the conditions of the study, 4-hydroxyacetophenone was considered to be not clastogenic in the *in vivo* micronucleus test, and this can be extended to 2-hydroxyacetophenone.

Based on the data available, 4-hydroxyacetophenone does not present a concern for genotoxic potential, and this can be extended to 2-hydroxyacetophenone.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/30/19.

10.1.2. Repeated dose toxicity

The MOE for 2-hydroxyacetophenone 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 2-hydroxyacetophenone. Read-across material 4-hydroxyacetophenone (CAS # 99-93-4; see Section V) has sufficient repeated dose toxicity data. A 90-day oral toxicity study (similar to OECD 408 guidelines; GLP-compliance unknown) was conducted on 20 Sprague Dawley rats/sex/dose that were administered 4-hydroxyacetophenone through gavage at doses of 0, 5, 15, and 45 mg/kg/day. There were no treatment-related effects observed in physical health, body weight, food consumption, clinical chemistry, hematology, urinalysis, ophthalmology, gross pathology, and histopathology. Based on the absence of treatment-related effects up to the highest tested dose, the NOAEL for repeated dose toxicity was considered to be 45 mg/kg/day (ECHA, 2013).

In another OECD 407/GLP compliant toxicity study (conducted within an OECD 422/GLP compliant study), groups of 5 Crl:WI(Han) outbred rats/sex/dose were administered 4-hydroxyacetophenone via oral gavage at doses of 0, 40, 150, and 600 mg/kg/day. Males were treated for 30 days (beginning 2 weeks prior to mating until study day 30), while females were treated for 43–46 days (beginning 2 weeks prior to mating up to at least lactation day 4). No treatment-related mortality was reported during the study. Increased salivation due to the palatability of the test material was observed in both sexes at the highest dose. No treatment-related effects were reported for body weight, food consumption, microscopic examinations, or gross pathology in either sex. However, in females treated with 150 mg/kg/day a significant increase in body weight without changes in food consumption was reported during study days 1–8 of the premating period. A dose-dependent increase in hyaline droplets without tubular degeneration was observed during histopathological analysis in male rats from all groups. This effect was attributed to male rat-specific α-2u-globulin nephropathy and was not considered a human health concern (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990). Hematopoietic foci in the spleen were observed in female rats of both control and treated groups with similar incidence but a dose-dependent increase in severity of the foci. However, the severities were considered to be within background levels of pregnant or lactating females and therefore were not considered to be toxicologically relevant. Based on the absence of treatment-related adverse effects up to the highest tested dose, the NOAEL for repeated dose toxicity was considered to be 600 mg/kg/day (ECHA, 2013). Based on the lack of adverse effects, the most conservative NOAEL of 45 mg/kg/day was determined for the repeated dose toxicity.

Therefore, the 2-hydroxyacetophenone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 4-hydroxyacetophenone NOAEL in mg/kg/day by the total systemic exposure to 2-hydroxyacetophenone, 45/0.0000002 or 225000000.

In addition, the total systemic exposure to 2-hydroxyacetophenone (0.0002 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/24/19.

10.1.3. Reproductive toxicity

The MOE for 2-hydroxyacetophenone is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-hydroxyacetophenone. Read-across material 4-hydroxyacetophenone (CAS # 99-93-4; see Section V) has sufficient reproductive toxicity data. In an OECD 422/GLP combined repeated dose toxicity study with a reproduction/developmental toxicity screening test, groups of 5 Crl: WI (Han) rats/sex/dose were administered via oral gavage 4-hydroxyacetophenone at doses of 0, 40, 150, or 600 mg/kg/day in propylene glycol for 7 days per week. The animals were dosed 2 weeks

Table 1
Acceptable concentrations for 2-hydroxyacetophenone that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	NRU[b]
2	Products applied to the axillae	0.0015%	3.3×10^{-7}%
3	Products applied to the face using fingertips	0.029%	1.7×10^{-9}%
4	Fine fragrance products	0.027%	3.0×10^{-5}%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	7.0×10^{-6}%
6	Products with oral and lip exposure	0.016%	NRU[b]
7	Products applied to the hair with some hand contact	0.056%	2.6×10^{-9}%
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	2.4×10^{-6}%
10	Household care products with mostly hand contact	0.19%	7.2×10^{-7}%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	3.3×10^{-5}%

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

prior to mating and continued through the day before euthanasia for males (30 days) and until lactation day 4 for females (43–46 days). In addition to systemic toxicity parameters, reproductive toxicity parameters were also assessed. No treatment-related adverse effects were observed on fertility or on the development of pups up to the highest dose level. The NOAEL for reproductive toxicity was considered to be 600 mg/kg/day (ECHA, 2013). **Therefore, the 2-hydroxyacetophenone MOE for the reproductive toxicity endpoint can be calculated by dividing the 4-hydroxyacetophenone NOAEL in mg/kg/day by the total systemic exposure to 2-hydroxyacetophenone, 600/0.0000002 or 3000000000.**

In addition, the total systemic exposure to 2-hydroxyacetophenone (0.0002 μg/kg/day) is below the TTC (30 μg/kg/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.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/21/19.

10.1.4. Skin sensitization

Based on the existing data and the application of the DST, 2-hydroxyacetophenone does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; OECD Toolbox v4.2). In a guinea pig maximization test, 2-hydroxyacetophenone did not present reactions indicative of sensitization up to 100% (ECHA, 2017). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Roberts et al., 2015; Safford, 2008; Safford et al., 2011; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentrations for 2-hydroxyacetophenone that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/17/19.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-hydroxyacetophenone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-hydroxyacetophenone in experimental models. UV/Vis absorption spectra indicate minor absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-hydroxyacetophenone 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 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: 01/11/19.

10.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-hydroxyacetophenone is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2-hydroxyacetophenone. Based on the Creme RIFM Model, the inhalation exposure is 0.0000006 mg/day. This exposure is 2333333 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: 01/29/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-hydroxyacetophenone was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient

(RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 2-hydroxyacetophenone 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).

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	195.04			1000000	0.19504	

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 2-hydroxyacetophenone as 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 v4.11).

10.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 2-hydroxyacetophenone does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. No data available.

10.2.1.2.2. Ecotoxicity. No data available.

10.2.1.3. Other available data. 2-Hydroxyacetophenone has been registered for REACH, and the following data is available:

The ready biodegradability of the test material was evaluated according to the OECD 301 B (CO_2 evolution test) method. After 28 days, biodegradation of 90% was observed.

The fish acute toxicity test was conducted according to the EPA OTS 797.1400 method under static conditions. The 96-h LC50 value with *Lepomis macrochirus* was 115 mg/L.

A *Daphnia magna* immobilization study was conducted according to the EPA OTS 797.1300 method under static conditions. The 48-h EC50 based on nominal concentration was reported to be 56.5 mg/L.

The algal toxicity test was conducted according to the EPA OPP 123-3 method under static conditions. The 120-h IC50 value was reported to be greater than 100 mg/L (ECHA, 2017).

10.2.2. Risk assessment refinement

Since 2-hydroxyacetophenone has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.97	1.97
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 0.19504 μg/L. The revised PEC/PNECs for EU and North America are: not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 01/30/19.

11. Literature search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml

- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.
*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 05/31/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.111026.

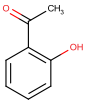
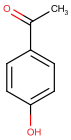
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as 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 material 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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	2-Hydroxyacetophenone	4-Hydroxyacetophenone
CAS No.	118-93-4	99-93-4
Structure		
Similarity (Tanimoto Score)		0.76
Read-across Endpoint		• Genotoxicity • Repeated Dose Toxicity • Reproductive Toxicity
Molecular Formula	$C_8H_8O_2$	$C_8H_8O_2$
Molecular Weight	136.15	136.15
Melting Point (°C, EPI Suite)	5	109.5
Boiling Point (°C, EPI Suite)	218	246.89
Vapor Pressure (Pa @ 25°C, EPI Suite)	9.36	0.261
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	1.92	1.35
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	7571	9900
J_{max} (μg/cm^2/h, SAM)	370.366	108.59
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.30E-001	1.03E-004
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found

DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Carcinogenicity (ISS)	• Non-carcinogen (good reliability)	• Non-carcinogen (good reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• H-acceptor-path3-H-acceptor	• No alert found
Oncologic Classification	• Phenol Type Compounds	• Phenol Type Compounds
Repeated Dose Toxicity		
Repeated Dose (HESS)	• 2-Acetylaminofluorene (Hepatotoxicity) Alert|Mefenamic Acid (Hepatotoxicity) Alert|Menadione (Hepatotoxicity) Alert|N-hydroxy-2-acetylaminofluorene (Hepatotoxicity) Alert|Toluene (Renal toxicity) Alert	• Acetaminophen (Hepatotoxicity) Alert|Acetaminophen (Renal toxicity) Alert|Mefenamic Acid (Hepatotoxicity) Alert|N-(4-Fluoro-4-biphenylyl)acetamide (Renal Toxicity) Alert|Phenacetin (Hepatotoxicity) Alert|Phenacetin (Renal toxicity) Alert
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (low reliability)	• Toxicant (low reliability)
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-hydroxyacetophenone (CAS # 118-93-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 4-hydroxyacetophenone (CAS # 99-93-4) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 4-Hydroxyacetophenone (CAS # 99-93-4) was used as a read-across analog for the target material 2-hydroxyacetophenone (CAS # 118-93-4) for the genotoxicity, reproductive toxicity, and repeated dose toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of phenolic aromatic ketones.
  - o The target material and the read-across analog share a phenolic ring with a C2 ketone branch.
  - o The key difference between the target material and the read-across analog is the position of the hydroxyl group in the phenol ring. The target material has the alcohol group in position 2 while the read-across analog has the alcohol group in position 4. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material has an *In Vivo* Mutagenicity (Micronucleus, ISS) alert for H-acceptor-path3-H-acceptor. This alert is due to the hydroxy and carbonyl groups within 1–4 connectivity. Additionally, both the target and read-across materials display an Oncologic Classification alert for phenol-type compounds. However, a literature search rules out phenolic ketones as carcinogenic compounds. The data described in the genotoxicity section show that the material is safe at the current level of use. Therefore, the predictions are superseded by data.
  - o Both materials present several Repeated Dose (HESS) *in silico* alerts due to Dice structural similarity scores higher than 50% with a wide variety of toxicants. Most of these toxicants are either aromatic amines, toluene, or aromatic macrocycle ketones such as menadione. Pethidine is a macromolecular aromatic ester bearing a tertiary amine ring while phenacetin is a secondary amide. Consequently, those substances are metabolized very differently compared to the target and read-across materials. Therefore, the predictions are superseded by data.
  - o Both the target material and the read-across analog have a Developmental Toxicity (CAESAR v2.1.6) alert as toxicants. The data described in the developmental toxicity section show that the MOE is adequate at the current level of use. The predictions are superseded by data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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