

Short Review

RIFM fragrance ingredient safety assessment, 4-(p-hydroxyphenyl)-2-butanone, CAS Registry Number 5471-51-2



A.M. Api^a, D. Belsito^b, S. Biserta^a, D. Botelho^a, M. Bruze^c, G.A. Burton Jr.^d, J. Buschmann^e, M.A. Cancellieri^a, M.L. Dagli^f, M. Date^a, W. Dekant^g, C. Deodhar^a, A.D. Fryer^h, S. Gadhia^a, L. Jones^a, K. Joshi^a, A. Lapczynski^a, M. Lavelle^a, D.C. Lieblerⁱ, M. Na^a, D. O'Brien^a, A. Patel^a, T.M. Penning^j, G. Ritacco^a, F. Rodriguez-Ropero^a, J. Romine^a, N. Sadekar^a, D. Salvito^a, T.W. Schultz^k, F. Siddiqi^a, I.G. Sipes^l, G. Sullivan^{a,*}, Y. Thakkar^a, Y. Tokura^m, S. Tsang^a

^a Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA

^b Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA

^c Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE-20502, Sweden

^d Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 48109, USA

^e Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany

^f Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil

^g Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany

^h Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA

ⁱ Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA

^j Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA

^k Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

^l Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

^m Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

A B S T R A C T

The existing information supports the use of this material as described in this safety assessment. 4-(p-Hydroxyphenyl)-2-butanone 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-(p-hydroxyphenyl)-2-butanone is not genotoxic. Data on 4-(p-hydroxyphenyl)-2-butanone provide a calculated MOE > 100 for the repeated dose toxicity endpoint. The developmental and reproductive toxicity and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to 4-(p-hydroxyphenyl)-2-butanone is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from 4-(p-hydroxyphenyl)-2-butanone show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 4-(p-hydroxyphenyl)-2-butanone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4-(p-hydroxyphenyl)-2-butanone 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.

* Corresponding author.

E-mail address: gsullivan@rifm.org (G. Sullivan).

<https://doi.org/10.1016/j.fct.2019.110948>

Received 18 April 2019; Accepted 5 November 2019

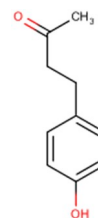
Available online 20 November 2019

0278-6915/ © 2019 Elsevier Ltd. All rights reserved.

Version: 031419. This version replaces any previous versions.

Name: 4-(*p*-Hydroxyphenyl)-2-butanone

CAS Registry Number: 5471-51-2



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

Creame RIFM Model - The Creame 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; Safford et al., 2017) compared to a deterministic aggregate approach

DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

DST - Dermal Sensitization Threshold

ECHA - European Chemicals Agency

ECOSAR - Ecological Structure-Activity Relationships Predictive Model

EU - Europe/European Union

GLP - Good Laboratory Practice

IFRA - The International Fragrance Association

LOEL - Lowest Observable Effect Level

MOE - Margin of Exposure

MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

NA - North America

NESIL - No Expected Sensitization Induction Level

NOAEC - No Observed Adverse Effect Concentration

NOAEL - No Observed Adverse Effect Level

NOEC - No Observed Effect Concentration

NOEL - No Observed Effect Level

OECD - Organisation for Economic Co-operation and Development

OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines

PBT - Persistent, Bioaccumulative, and Toxic

PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration

QRA - Quantitative Risk Assessment

QSAR - Quantitative Structure-Activity Relationship

REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals

RfD - Reference Dose

RIFM - Research Institute for Fragrance Materials

RQ - Risk Quotient

Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test

TTC - Threshold of Toxicological Concern

UV/Vis spectra - Ultraviolet/Visible spectra

VCF - Volatile Compounds in Food

VoU - Volume of Use

vPvB - (very) Persistent, (very) Bioaccumulative

WoE - Weight of Evidence

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

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

4-(*p*-Hydroxyphenyl)-2-butanone 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-(*p*-hydroxyphenyl)-2-butanone is not genotoxic. Data on 4-(*p*-hydroxyphenyl)-2-butanone provide a calculated MOE > 100 for the repeated dose toxicity endpoint. The developmental and reproductive toxicity and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to 4-(*p*-hydroxyphenyl)-2-butanone is below the TTC (0.03 mg/kg/day and 1.4 mg/day, respectively). Data from 4-(*p*-hydroxyphenyl)-2-butanone show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 4-(*p*-hydroxyphenyl)-2-butanone is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 4-(*p*-hydroxyphenyl)-2-butanone 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.

Repeated Dose Toxicity: NOAEL = 70 mg/kg/day.

Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.

Skin Depigmentation: NOAEL = 10%; Maximum Safe-Use Level: 1%.

Skin Sensitization: No safety concerns at current, declared use levels.

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

(RIFM, 2003a; RIFM, 2003b; RIFM, 2001b)
RIFM (2004a)

RIFM (2017)
(ECHA Dossier4-(4-Hydroxyphenyl)butan-2-one; ECHA, 2015)
(UV Spectra, RIFM Database)

Hazard Assessment:**Persistence:** Critical Measured Value: 89% (OECD 301F) (RIFM, 1996a)**Bioaccumulation:** Screening-level: 4.4 L/kg (EPI Suite v4.11; US EPA, 2012a)**Ecotoxicity:** Screening-level: Fish LC50: 5462 mg/L (RIFM Framework; Salvito et al., 2002)**Conclusion:** Not PBT or vPvP 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: 5462 mg/L (RIFM Framework; Salvito et al., 2002)

(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 5.462 µg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: Not applicable; cleared at screening-level

1. Identification

- 1. Chemical Name:** 4-(*p*-Hydroxyphenyl)-2-butanone
- 2. CAS Registry Number:** 5471-51-2
- 3. Synonyms:** 2-Butanone, 4-(4-hydroxyphenyl)-; Frambinon; *p*-Hydroxybenzylacetone; 1-*p*-Hydroxyphenyl-3-butanone; 4-(4-Hydroxyphenyl)butan-2-one; **Oxanone**; Oxyphenylon; Raspberry ketone; Corps N 112; 4-(4-ヒトキシフェニル)-2-ブタンオン; 4-(*p*-Hydroxyphenyl)-2-butanone
- 4. Molecular Formula:** C₁₀H₁₂O₂
- 5. Molecular Weight:** 164.2
- 6. RIFM Number:** 605
- 7. Stereochemistry:** No isomeric center and no isomers possible.

2. Physical data

- 1. Boiling Point:** > 200 °C (FMA Database), 280.39 °C (EPI Suite)
- 2. Flash Point:** > 200 °F; CC (FMA Database)
- 3. Log K_{ow}:** 1.22 (Smith et al., 2002), 0.4 at 25 °C (RIFM, 1996b), 1.48 (EPI Suite)
- 4. Melting Point:** 82 °C (FMA Database), 72.49 °C (EPI Suite)
- 5. Water Solubility:** 13,460 mg/L (EPI Suite)
- 6. Specific Gravity:** Not Available
- 7. Vapor Pressure:** 0.000373 mm Hg @ 20 °C (EPI Suite v4.0), 0.003 mm Hg 20 °C (FMA Database), 0.000716 mm Hg @ 25 °C (EPI Suite)
- 8. UV Spectra:** Minor absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol⁻¹ · cm⁻¹)
- 9. Appearance/Organoleptic:** White needle-like crystals or granular crystalline material; very sweet, fruity and warm odor resembling raspberry preserve and having a moderate tenacity; sweet-fruity taste but not very powerful; concentrations below 10 ppm are hardly characteristic and not easy to identify the material by.

3. Exposure

- 1. Volume of Use (worldwide band):** 100–1000 metric tons per year (IFRA, 2015)
- 2. 95th Percentile Concentration in Hydroalcoholics:** 0.17% (RIFM, 2013b)
- 3. Inhalation Exposure*:** 0.00053 mg/kg/day or 0.038 mg/day (RIFM, 2013b)
- 4. Total Systemic Exposure**:** 0.0040 mg/kg/day (RIFM, 2013b)

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

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

2015; Safford et al., 2017; and Comiskey et al., 2017).

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 (OECD, 2018)
I	I	I

2. Analogs Selected:

- a. Genotoxicity:** None
 - b. Repeated Dose Toxicity:** None
 - c. 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

4-(*p*-Hydroxyphenyl)2-butanone is expected to be rapidly absorbed from the gastrointestinal tract and rapidly metabolized mainly by conjugation and excreted as glucuronic and sulfate conjugates, which is illustrated in many *in vivo* studies. In a 90-day toxicity study on SPF-derived CFE rats, 4-(*para*-hydroxyphenyl)-2-butanone was administered at 0%, 0.1%, 0.2%, 0.4%, or 1.0% (equivalent to 0, 50, 100, 200, and 500 mg/kg/day, as per the conversion factors for old rat, available in the JECFA Guidelines for the preparation of toxicological working papers (WHO, 2000) for 13 weeks. Ketones were detected in the urine of all treated animals at both 7 and 13 weeks and were excreted within 12 h. In another study, administration of 4-(*para*-hydroxyphenyl)-2-butanone at a dose of 1 mM to rats, rabbits, and guinea pigs, showed that the metabolic pattern is similar in all 3 species. In total, 15 metabolites (Table 1) were identified in rats and rabbits, whereas in guinea pigs, some of the metabolites were not detected.

The metabolic pathway of 4-(*p*-hydroxyphenyl)-2-butanone is as follows (Fig. 1.):

All of these metabolites were excreted as glucuronide and/or sulfate conjugates; however, acidic metabolites like 4-hydroxybenzoic acid, 4-hydroxyphenylacetic acid, and 3-(4-hydroxyphenyl) propionic acid (and also traces of parent compound) were excreted in unconjugated form. Overall, among all metabolites identified, 4-hydroxy-4-(4-hydroxyphenyl) butan-2-one, 1-hydroxy-4-(4-hydroxyphenyl) butan-2-one, and 4-(4-hydroxyphenyl)butan-1,2-diol were reported as minor metabolites across all species tested.

These results and several other studies lead to the conclusion that 4-

Table 1

Urinary excretion of 4-(*p*-hydroxyphenyl)-2-butanone in rats, guinea pigs, and rabbits (Sportstol and Scheline, 1982).

		Excretion (0–24 h) (%dose)		
Compound number	Chemical name	Rat	Guinea-pig	Rabbit
1	2-(4-Hydroxyphenyl)ethanol	2.4 ± 0.8	0.4 ± 0.1	0.2
2	4-(4-Hydroxyphenyl)butan-2-one	59 ± 3	70 ± 8	38
3	4-Hydroxybenzoic acid	0.4 ± 0.1	trace	0.6
4	4-Hydroxyphenylacetic acid	8 ± 1	trace	1.5
5	4-(4-Hydroxyphenyl)butan-2-ol	10 ± 1	15 ± 3	31
6	4-(4-Hydroxy-3-methoxyphenyl)butan-2-one	0.7 ± 0.1	trace	1.8
7	4-Hydroxy-4-(4-hydroxyphenyl)butan-2-one	trace	0	0.2
8	3-(4-Hydroxyphenyl)propionic acid	1.2 ± 0.5	0	0.2
9	4-(3,4-Dihydroxyphenyl)butan-2-one	1.7 ± 0.9	2.5 ± 0.6	8.2
10	Unidentified	2 ± 1	1.4 ± 0.2	0
11	4-(4-Hydroxy-3-methoxyphenyl)butan-2-ol	0.2 ± 0.1	0.5 ± 0.2	1.4
12	4-(4-Hydroxyphenyl)butan-2,3-diol	1.4 ± 0.3	trace	2.0
13	4-(3,4-Dihydroxyphenyl)butan-2-ol	0.5 ± 0.2	1.3 ± 0.7	4.8
14	1-Hydroxy-4-(4-hydroxyphenyl)butan-2-one	trace	0	0.2
15	4-(4-Hydroxyphenyl)butan-1,2-diol	0.1 ± 0.1	trace	0.2
Total		88 ± 6	93 ± 7	90

(*p*-hydroxyphenyl)-2-butanone followed the ketone→ carbinol→ diol pathway (Sportstol and Scheline, 1982; Gaunt et al., 1970; EFSA, 2016; NIH, 2014; WHO, 2014).

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

4-(*p*-Hydroxyphenyl)-2-butanone is reported to occur in nature in the following foods by the VCF*:

Blackberry (fresh)

Buckwheat honey (*Fagopyrum esculentum*)

European cranberry (*Vaccinium oxycoccus* L.)

Honey loganberry (*Rubus ursinus* var. *loganobaccus*)

Raspberry (*Rubus idaeus* L.)

Raspberry, blackberry, and boysenberry.

Sea Buckthorn (*Hippophae rhamnoides* L.)

Vaccinium species.

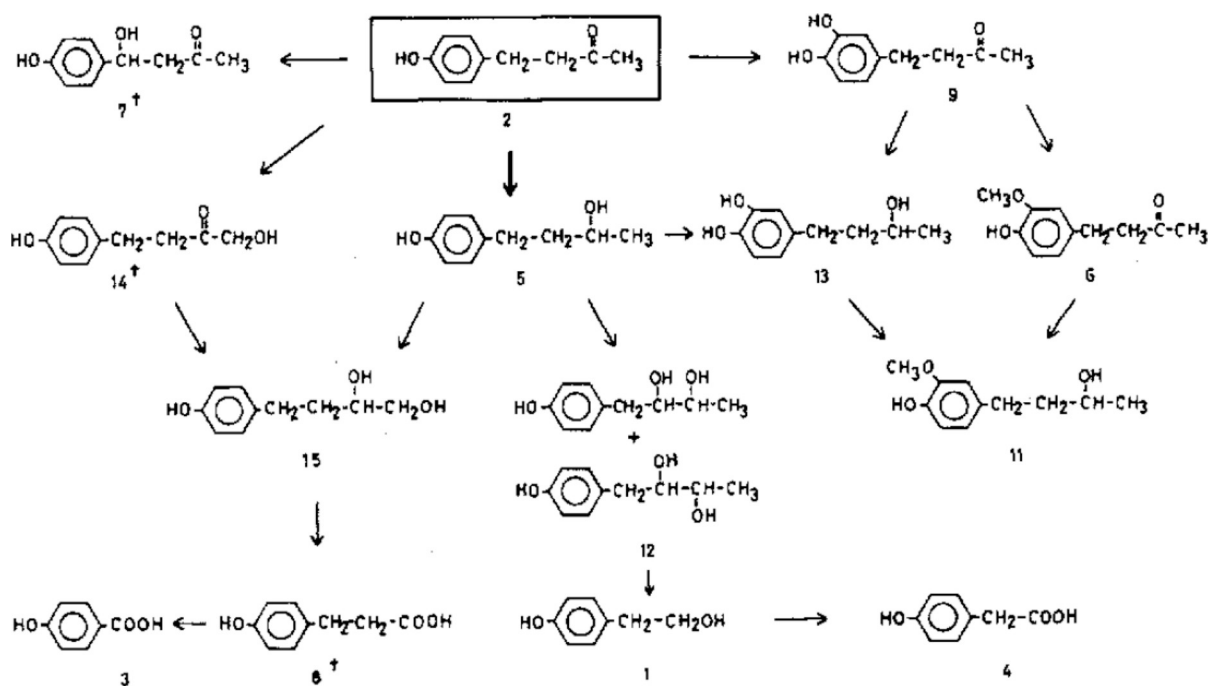
*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. REACH dossier

Dossier available; accessed 04/18/18 (ECHA, 2015).

9. Conclusion

The maximum acceptable concentrations^a in finished products for 4-(*p*-hydroxyphenyl)-2-butanone are detailed below.



† Not excreted by guinea-pigs.

Fig. 1. Proposed metabolic pathway of 4-(*p*-Hydroxyphenyl)-2-butanone in rats, guinea pigs, and rabbits (Sportstol and Scheline, 1982)

IFRA Category ^b	Description of Product Type	Maximum Acceptable Concentrations ^a in Finished Products (%)
1	Products applied to the lips (lipstick)	0.68
2	Products applied to the axillae	1.0
3	Products applied to the face/body using fingertips	0.27
4	Products related to fine fragrances	1.0
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	1.0
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.14
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.27
5D	Baby cream, oil, talc	0.045
6	Products with oral and lip exposure	0.82
7	Products applied to the hair with some hand contact	0.41
8	Products with significant ano-genital exposure (tampon)	0.045
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.0
10A	Household care products with mostly hand contact (hand dishwashing detergent)	1.0
10B	Aerosol air freshener	1.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	0.045
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	78

Note.

^a Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For 4-(*p*-hydroxyphenyl)-2-butanone, the basis was the reference dose of 0.7 mg/kg/day, skin depigmentation NOAEL = 10% (Maximum Safe-Use Level: 1%) and a predicted skin absorption value of 80%.

^b For a description of the categories, refer to the IFRA RIFM Information Booklet. (www.rifm.org/doc).

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 4-(*p*-hydroxyphenyl)-2-butanone does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 4-(*p*-hydroxyphenyl)-2-butanone was assessed in the BlueScreen assay and found positive for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013a). BlueScreen is a screening assay that assesses genotoxic stress through alterations in gene expressions in a human cell line. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 4-(*p*-hydroxyphenyl)-2-butanone 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 TA98, TA100, TA102, TA1535, and TA1537 were treated with 4-(*p*-hydroxyphenyl)-2-butanone in dimethyl sulfoxide (DMSO) at concentrations up to 5000 µg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2003a). Under

the conditions of the study, 4-(*p*-hydroxyphenyl)-2-butanone was not mutagenic in the Ames test.

The clastogenic activity of 4-(*p*-hydroxyphenyl)-2-butanone was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in propylene glycol (PEG 400) via oral gavage to groups of male and female CD1 mice. Doses of 250, 500, or 1000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 or 48 h, 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 (RIFM, 2003b). Under the conditions of the study, 4-(*p*-hydroxyphenyl)-2-butanone was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 4-(*p*-hydroxyphenyl)-2-butanone does not present a concern for genotoxic potential.

Additional References: RIFM, 2001b.

Literature Search and Risk Assessment Completed On: 05/20/18.

10.1.2. Repeated dose toxicity

The margin of exposure for 4-(*p*-hydroxyphenyl)-2-butanone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 4-(*p*-hydroxyphenyl)-2-butanone that can be used to support the repeated dose toxicity endpoint. An OECD 408 dietary 90-day subchronic toxicity study was conducted in Sprague Dawley rats. Groups of 10 rats/sex/dose received 4-(*p*-hydroxyphenyl)-2-butanone in the diet at doses of 0, 70, 275, or 700 mg/kg/day. A statistically significant decrease in bodyweight gain was observed in high-dose males with an overall reduction of 19% as compared to the controls. Food consumption was normal in all dose groups except for a slight (but statistically significant) decreases in the mid- and high-dose males during the first 2 weeks of the study only. A statistically significant increase in the relative liver weight (up to 16%) was observed at 275 and 700 mg/kg/day. Statistically significant increases were observed in alanine aminotransferase (ALT, up to 295%), aspartate aminotransferase (AST, 157%), and alkaline phosphatase (ALP, up to 69%) at 700 mg/kg/day (males and females). The increases in ALT and AST also extended to females at 275 mg/kg/day; however, liver histopathology did not show any evidence of liver degeneration or necrosis at any doses. The NOAEL was considered to be 70 mg/kg/day, based on decreased body weight and alterations in the liver (increased serum liver enzymes and liver weights) among animals of the higher dose groups (RIFM, 2004a; WHO, 2011).

In a 13-week subchronic toxicity study, groups of 15 SPF-derived CFE rats/sex/dose were fed diets containing test material, 4-(*p*-hydroxyphenyl)-2-butanone (purity is 96%) at dose levels of 0%, 0.1%, 0.2%, 0.4%, or 1% (equivalent to 0, 50, 100, 200, and 500 mg/kg/day, as per the conversion factors for old rat, available in the JECFA Guidelines for the preparation of toxicological working papers on Food Additives; WHO, 2000) for 13 weeks. A slight but statistically significant decrease (5%) in bodyweight gain was reported in males at the 1% dose level. Since the decrease in body weight was minimal and no changes were reported in females at this dose level or in both sexes at lower dose levels, the decrease in body weight was not biologically significant. In males, the relative liver and kidney weights were increased at 0.4% and 1% (and the relative adrenals weights at 1%), but no correlation in clinical chemistry and histopathology findings were reported; therefore, these changes were not considered to be treatment-related. The NOAEL for repeated dose toxicity was considered to be 1% or 500 mg/kg/day, based on the absence of treatment-related effects up to the highest dose level tested (Gaunt et al., 1970; EFSA, 2016; WHO, 2014; NIH, 2014).

The most conservative NOAEL of 70 mg/kg/day from the OECD 408 study was selected for this safety assessment. **Therefore, the 4-(p-hydroxyphenyl)-2-butanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 4-(p-hydroxyphenyl)-2-butanone NOAEL in mg/kg/day by the total systemic exposure to 4-(p-hydroxyphenyl)-2-butanone, 70/0.004, or 17,500.**

In addition, the total systemic exposure to 4-(p-hydroxyphenyl)-2-butanone (4.0 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Gaunt et al., 1970; RIFM, 2004b; Sportstol and Scheline, 1982; Fukuda et al., 1998a.

Literature Search and Risk Assessment Completed On: 05/11/18.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on 4-(p-hydroxyphenyl)-2-butanone or on any read-across materials. The total systemic exposure to 4-(p-hydroxyphenyl)-2-butanone is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. An OECD 408 dietary 90-day subchronic toxicity study was conducted in Sprague Dawley rats. Groups of 10 rats/sex/dose received 4-(p-hydroxyphenyl)-2-butanone in the diet at doses of 0, 70, 275, or 700 mg/kg/day. In addition to systemic toxicity parameters, the reproductive organs were also assessed. Organ weight analysis included testes, ovaries, prostate gland, uterus with cervix, and histopathology examination of the testes, epididymides, ovaries, prostate gland, seminal vesicles, uterus with cervix, and vagina for the control and high-dose group animals. No treatment-related effects were reported in the evaluation of reproductive organs. A NOAEL for reproductive toxicity could not be derived since there were no data on spermatology and estrous cycling of the male and female animals (RIFM, 2004a; WHO, 2011).

There are insufficient developmental and reproductive toxicity data on 4-(p-hydroxyphenyl)-2-butanone or on any read-across materials that can be used to support the developmental and reproductive toxicity endpoints. The total systemic exposure to 4-(p-hydroxyphenyl)-2-butanone (4.0 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: Gaunt et al., 1970; RIFM, 2004b.

Literature Search and Risk Assessment Completed On: 05/08/18.

10.2. Skin depigmentation

10.2.1. Risk assessment

A depigmentation study was conducted in black mice with 4-(p-hydroxyphenyl)-2-butanone. The potency of this material to induce depigmentation is very weak. Depigmentation was observed following topical exposure to 20% in a hydrophilic ointment (5 days/week for 16 weeks). No depigmentation was observed at 5% or 10% when the vehicle was acetone or when administered via gavage in olive oil. The authors concluded that leukoderma due to 4-(p-hydroxyphenyl)-2-butanone might only occur following high-dose exposure in an occupational setting, and it should be possible to protect workers with standard methods of chemical use management (Fukuda et al., 1998b). Another depigmentation study was conducted in shaved black mice for 3 weeks (Lin et al., 2011). Daily applications of a 0.2% or 2% gel preparation (Vaseline) of 4-(p-hydroxyphenyl)-2-butanone to mouse skin significantly increased the degree of skin-whitening within 1 week of treatment. Depigmentation was investigated in 5 Yucatan minipigs, with 0.2%, 2%, and 10% 4-(p-hydroxyphenyl)-2-butanone in 1:1

ethanol:propylene glycol applied topically, twice a day for 56 consecutive days. Three minipigs were placed in a recovery cohort from the end of the dosing period until day 85 to determine if effects were reversible. The dose site chromametric results showed that there was a large magnitude of variation throughout the study, as expected, including during the recovery period. The findings appeared concentration-dependent and continued through the end of the dosing phase of the study. Chromametric reading differences between the vehicle control and the test groups were generally eliminated after discontinuation of dose administration. The results were interpreted to indicate that the elevated (depigmented) chromametric reading was most likely due to light reflection changes of the skin surface rather than frank depigmentation. In conclusion, topical dose administration twice daily of 4-(p-hydroxyphenyl)-2-butanone (HPB) formulations at 0.2% (2 mg/mL), 2% (20 mg/mL), and 10% (100 mg/mL) for 56 days was not associated with any adverse dermal effects or frank depigmentation in miniature swine (RIFM, 2017). Pig skin is structurally similar to the human epidermal thickness and dermal-epidermal thickness ratios. Pigs and humans have similar hair follicle and blood vessel patterns. Pigs are often used as models for dermatologic studies including vitiligo and depigmentation (Herron, 2009). As such, the NOAEL of 10% from the mini-pig study was considered more relevant than the study conducted with black mice. The NOAEL from the mini-pig study was then further adjusted by a safety factor of 10, to a maximum safe-use level of 1%.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/07/18.

10.2.2. Skin sensitization

Based on the available data, 4-(p-hydroxyphenyl)-2-butanone does not present a safety concern for skin sensitization under the current, declared levels of use.

10.2.2.1. Risk assessment. Based on the existing data, 4-(p-hydroxyphenyl)-2-butanone does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v4.1). In a murine local lymph node assay (LLNA), 4-(p-hydroxyphenyl)-2-butanone was not found to be sensitizing up to 50% with a Stimulation Index (SI) of 1.9 (ECHA, 2015; accessed 03/27/18). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1974). Based on the weight of evidence (WoE) from structural analysis and animal and human studies, 4-(p-hydroxyphenyl)-2-butanone does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/27/18.

10.2.3. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 4-(p-hydroxyphenyl)-2-butanone would not be expected to present a concern for phototoxicity or photoallergenicity.

10.2.3.1. Risk assessment. There are no phototoxicity studies available for 4-(p-hydroxyphenyl)-2-butanone 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 the lack of significant absorbance in the critical range, 4-(p-hydroxyphenyl)-2-butanone does not present a concern for phototoxicity or photoallergenicity.

10.2.3.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 4-(p-hydroxyphenyl)-2-butanone 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: 04/11/18.

10.2.4. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 4-(p-hydroxyphenyl)-2-butanone is below the Cramer Class I TTC value for inhalation exposure local effects.

10.2.4.1. Risk assessment. There are no inhalation data available on 4-(p-hydroxyphenyl)-2-butanone. Based on the Creme RIFM Model, the inhalation exposure is 0.038 mg/day. This exposure is 36.8 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; #57336); therefore, the exposure at the current level of use is deemed safe.

Key Studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/24/18.

10.3. Environmental endpoint summary

10.3.1. Screening-level assessment

A screening-level risk assessment of 4-(p-hydroxyphenyl)-2-butanone 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-(p-hydroxyphenyl)-2-butanone was not identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 4-(p-hydroxyphenyl)-2-butanone 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 v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.3.1.1. Risk assessment. Based on the current Volume of Use (2015), 4-(p-hydroxyphenyl)-2-butanone does not present a risk to the aquatic compartment.

10.4. Key Studies

10.4.1. Biodegradation

RIFM, 1996a: A study was conducted following the OECD 301F Test Guideline. 100 mg/L of the test material was incubated for a period of 28 days. The test material underwent 89% biodegradation by the end of the study.

RIFM, 2001a: A study was conducted following OECD Test Guideline 301D. 3 mg/L of the test substance was incubated for a period of 28 days. The test material achieved a maximum of 69% biodegradation by the twenty-eighth day.

10.4.2. Ecotoxicity

RIFM, 2000: A *Daphnia* immobilization study following OECD Test Guideline 202 was reported. The reported 48-h EC50 was 18 mg/L.

10.4.3. Other available data

4-(p-hydroxyphenyl)-2-butanone has been registered under REACH with no additional data at this time.

10.5. Risk assessment refinement

Since 4-(p-hydroxyphenyl)-2-butanone 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 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening-level (Tier1)	<u>5462</u>			1,000,000	5.462	

Exposure	Europe (EU)	North America (NA)
Log K _{ow} Used	0.4	0.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	100–1000
Risk Characterization: PEC/PNEC	< 1	< 1

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

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

The RIFM PNEC is 5.462 µg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at the 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: 02/28/19.

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://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/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 03/14/19.

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.

References

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

- Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. *Food Chem. Toxicol.* 47 (6), 1287–1295.
- Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. *Regul. Toxicol. Pharmacol.* 72 (3), 660–672.
- Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. *Regul. Toxicol. Pharmacol.* 88, 144–156.
- ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. <http://echa.europa.eu/>.
- ECHA, 2015. Registration Dossier 4-(4-Hydroxyphenyl)butan-2-One. Retrieved from. <https://echa.europa.eu/registration-dossier/-/registered-dossier/12633/1>.
- EFSA, 2016. Safety and efficacy of aromatic ketones, secondary alcohols and related esters belonging to chemical group 21 when used as flavourings for all animal species. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). *EFSA J.* 14 (8), 4557.
- Fukuda, Y., Nagano, M., Futatsuka, M., Arimatsu, Y., 1998a. An experimental study on depigmenting activity of 4-(p-hydroxyphenyl)-2-butanone in C57 black mice. *J. Occup. Health* 40 (2), 97–102.
- Fukuda, Y., Nagano, M., Tsukamoto, K., Futatsuka, M., 1998b. In vitro studies on the depigmenting activity of 4-(p-hydroxyphenyl)-2-butanone. *J. Occup. Health* 40 (2), 137–142.
- Gaunt, I.F., Sharratt, M., Colley, J., Lansdown, A.B.G., Grasso, P., 1970. Acute and short-term toxicity of p-hydroxybenzyl acetone in rats. *Food Cosmet. Toxicol.* 8 (4), 349–358.
- Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? *J. Photochem. Photobiol. B Biol.* 96 (1), 57–62.
- Herron, A., 2009. Pigs as Dermatologic Models of Human Skin Disease. In: *Proceeding of the ACVP/ASVCP Concurrent Annual Meetings*.
- IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.
- Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. *Food Chem. Toxicol.* 45 (12), 2533–2562.
- Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. *Regul. Toxicol. Pharmacol.* 62 (1), 160–182.
- Lin, V.C.-H., Ding, H.-Y., Kuo, S.-Y., Chin, L.-W., Wu, J.-Y., Chang, T.-S., 2011. Evaluation of in vitro and in vivo depigmenting activity of raspberry ketone from *Rheum officinale*. *Int. J. Mol. Sci.* 12 (8), 4819–4835.
- NIH, 2014. U.S. National library of medicine hazardous substances data bank: raspberry ketone. Retrieved from. <https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+8163>.
- OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. <http://www.qsartoolbox.org/>.
- RIFM (Research Institute for Fragrance Materials, Inc), 1974. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1779. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1996. Ready Biodegradability of 4-(p-Hydroxyphenyl)-2-Butanone (Corps N 112). Unpublished report from Givaudan. RIFM report number 51403. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 1996. Partition Coefficient N-Octanol/water of 4-(p-Hydroxyphenyl)-2-Butanone (Corps N 112). Unpublished report from Givaudan. RIFM report number 51404. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2000. 4-(p-Hydroxyphenyl)-2-butanone: Acute Immobilisation Test (48 H) to *Daphnia Magna* STRAUS. Unpublished report from Symrise. RIFM report number 61064. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2001. 4-(p-Hydroxyphenyl)-2-butanone: Ready Biodegradability Closed Bottle Test. Unpublished report from Symrise. RIFM report number 61063. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2001. 4-(p-Hydroxyphenyl)-2-butanone: Reverse Mutation Assay (Ames Test) with *Salmonella typhimurium*. Unpublished report from Symrise. RIFM report number 61066. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2003. 4-(p-Hydroxyphenyl)-2-butanone: Reverse Mutation Test "Ames Test" with *S. typhimurium* and *E. coli*. Unpublished report from Takasago International Corporation. RIFM report number 50968. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2003. 4-(p-Hydroxyphenyl)-2-butanone: Mouse Micronucleus Test. Unpublished report from Takasago International Corporation. RIFM report number 50969. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2004. A 90-day Dietary Toxicity Study of 4-(p-Hydroxyphenyl)-2-Butanone (raspberry Ketone) in Rats. Unpublished report from Takasago International Corporation. RIFM report number 50863. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2004. 4-(p-Hydroxyphenyl)-2-butanone: A 14-Day Dietary Range-Finding Toxicity Study in Rats. Unpublished report from Takasago International Corporation. RIFM report number 50971. RIFM, Woodcliff Lake, NJ, USA.

- RIFM (Research Institute for Fragrance Materials, Inc), 2013. Report on the Testing of 4-(para-Hydroxyphenyl)-2-Butanone in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 65025. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc), 2013. Exposure Survey 02, November 2013.
- RIFM (Research Institute for Fragrance Materials, Inc), 2017. 4-(p-Hydroxyphenyl)-2-butanone: Depigmentation assessment study after topical dermal dose administration in miniature swine. [Amendment attached] RIFM report number 73036. RIFM, Woodcliff Lake, NJ, USA.
- Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. *Chem. Res. Toxicol.* 20 (7), 1019–1030.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. *Regul. Toxicol. Pharmacol.* 72, 673–682.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. *Regul. Toxicol. Pharmacol.* 86, 148–156.
- Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. *Environ. Toxicol. Chem.* 21 (6), 1301–1308.
- Smith, C.J., Perfetti, T.A., Morton, M.J., Rodgman, A., Garg, R., Selassie, C.D., Hansch, C., 2002. The relative toxicity of substituted phenols reported in cigarette mainstream smoke. *Toxicol. Sci.* 69 (1), 265–278.
- Sportstol, S., Scheline, R.R., 1982. The metabolism of 4-(4 hydroxyphenyl)butan-2-one (raspberry ketone) in rats Guinea-pigs and rabbits. *Xenobiotica* 12 (4), 249–257.
- US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
- US EPA, 2012b. The ECOSAR (ECological Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
- WHO, 2000. Guidelines for the preparation of toxicological working papers for the joint FAO/WHO expert committee on food additives (JECFA). Retrieved from: https://www.who.int/foodsafety/chem/jecfa/en/tox_guidelines.pdf.
- WHO, 2011. WHO Food Additives Series: 64. Safety evaluation of certain food additives and contaminants. Retrieved from <http://www.inchem.org/documents/jecfa/jecmono/v64je01.pdf>.
- WHO, 2014. WHO food additive series 46. Phenol and phenol derivatives. Joint FAO/WHO expert committee on food additives (JECFA): benzyl derivatives. Retrieved from: <http://www.inchem.org/documents/jecfa/jecmono/v46je09.htm>.