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Short Review

RIFM fragrance ingredient safety assessment, 2-butanone, CAS Registry Number 78-93-3

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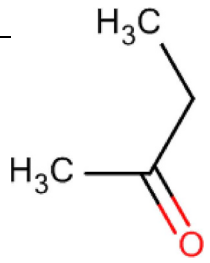


Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions 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; 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
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-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 2-butanone is not genotoxic. Data on 2-butanone provide a calculated MOE > 100 for the repeated dose toxicity and developmental toxicity endpoints. Data on read-across analog 2-pentanone (CAS # 107-87-9) provide a calculated MOE > 100 for the reproductive toxicity endpoint. Available data show that there are no safety concerns for 2-butanone for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-butanone 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-butanone is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 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. (Zeiger and Margolin, 2000; Basler, 1986)
Repeated Dose Toxicity: NOAEL = 1571 mg/kg/day. (Cavender et al., 1983)
Developmental and Reproductive Toxicity:
Developmental toxicity: NOAEL = 781 mg/kg/day. Reproductive toxicity NOAEL = 1297 mg/kg/day.

(Saillenfait et al., 2006; ECHA REACH Dossier: Pentan-2-one; ECHA, 2013)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.
(ECHA REACH Dossier: Butanone; ECHA, 2011; Gad et al., 1986; Descotes, 1988; Klecak, 1985; RIFM, 1975)
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: Critical Measured Value: 98% (OECD 301D) (ECHA REACH Dossier: Butanone; ECHA, 2011)
Bioaccumulation: Screening-level: 3.162 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 3174 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: 3174 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 3.174 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not Applicable; Cleared at Screening-level

1. Identification

1. **Chemical Name:** 2-Butanone
2. **CAS Registry Number:** 78-93-3
3. **Synonyms:** Ethyl methyl ketone; MEK; Methyl ethyl ketone; Butan-2-one; 2-Butanone
4. **Molecular Formula:** C_4H_8O
5. **Molecular Weight:** 72.1
6. **RIFM Number:** 681
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 70.36 °C (EPI Suite)
2. **Flash Point:** < 40 °F; CC (FMA Database), −9 °C (GHS)
3. **Log K_{OW}:** 0.29 (Patel et al., 2002), 0.26 (EPI Suite)
4. **Melting Point**: −80.48 °C (EPI Suite)
5. **Water Solubility:** 76100 mg/L (EPI Suite)
6. **Specific Gravity:** 0.802 (FMA Database)
7. **Vapor Pressure:** 77.9 mm Hg @ 20 °C (EPI Suite v4.0), 75 mm Hg 20 °C (FMA Database), 98.5 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:** Clear, colorless flammable liquid with ethereal, slightly nauseating odor; powerful, fruity-green, herbaceous, and sweet odor of moderate tenacity. There is almost a basil-like spiciness or anisic note of very natural character in this odor (Arctander, 1969)

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.014% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.0000004 mg/kg/day or 0.000028 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.00062 mg/kg/day (RIFM, 2014)

*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:** 75%

OECD, 1997; US EPA, 2003; ATSDR, 1992: 2-Butanone is absorbed through the inhalational route in both humans and rats based on its high blood/air solubility ratio. Humans absorb approximately 75% of inhaled 2-butanone. In a study that estimated the uptake and kinetics of 2-butanone exposure in groups of industrial workers occupationally exposed to < 300 ppm of 2-butanone for 4 h, the results estimated pulmonary retention of 70%. In an experimental study, exposure of human volunteers to 2-butanone at 200 ppm for 4 h in an exposure chamber resulted in an uptake that ranged from 51% to 55% of exposure concentration.

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:** 2-Pentanone (CAS # 107-87-9)
   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

2-Butanone is a normal constituent of human urine that arises from the catabolism of isoleucine (US EPA, 2003). 2-Butanone is rapidly absorbed through both the inhalation and oral routes. Metabolism of 2-butanone is similar in humans and animals including rats and guinea pigs. 2-Butanone is metabolized by both oxidative (major pathway) and

reductive pathways (minor pathway). 2-Butanone is oxidized by CYP450 to form 3-hydroxy-2-butanone, which is subsequently reduced to 2,3-butanediol. The 2,3-butanediol enters general metabolism, which forms carbon dioxide (CO_2) and water (WHO, 1993). A small portion of absorbed 2-butanone is reduced to 2-butanol, which is rapidly oxidized back to 2-butanone with a minimal amount being eliminated as a glucuronide conjugate (US EPA, 2003). In humans, 200 ppm 2-butanone is reported to metabolize rapidly and completely. Metabolites such as 2-butanol and 2,3-butanediol were identified in serum, whereas 3-hydroxy-2-butanone and 2,3-butanediol have been identified as urinary metabolites (US EPA, 2003). Approximately 30% of the orally administered 2-butanone was metabolized to 2,3-butanediol, 4% was metabolized to 2-butanol, and 4% was metabolized to 3-hydroxy-2-butanone in rats. In another study conducted in rats and guinea pigs, 2-butanone was metabolized by oxidation to 3-hydroxy-2-butanone, which was then reduced to 2,3-butanediol and 2-butanone and further reduced to 2-butanol. In an occupational study where industrial workers were exposed to 2-butanone, the level of 2-butanone in the blood was significantly correlated with the environmental concentrations, indicating rapid transfer from the lungs to the blood (US EPA, 2003). 2-Butanone is a water-soluble and uncharged non-polar substance. Therefore, following absorption, it is expected to uniformly distribute to the various soft tissue compartments, but it is not expected to accumulate in the tissues of humans or rats. It was also reported that 2-butanone can cross the placenta and enter the human fetus (ATSDR, 1992; WHO, 1993). In an occupational study, the distribution of 2-butanone following inhalational exposure to humans was examined, and the tissue or air solubility ratio for kidney, liver, muscle, lung, heart, fat, and brain revealed similar solubility in all of these tissues, with the tissue/air ratio ranging from 147 (lung) to 254 (heart) (US EPA, 2003). In rats exposed to 600 ppm 2-butanone for 6 h for 1 day or for 6–10 h/day for 8 days, blood concentrations of 1041 μmol/L after a single exposure and 1138 μmol/L after repeated exposures were reported. The concentration of 2-butanone in perineal fat was reported to be 0.71 and 0.70 μmol/g after single and repeated exposures, respectively. Similar blood and perineal concentrations after single and repeated exposures revealed that 2-butanone does not accumulate in the body (ATSDR, 1992). The metabolites of 2-butanone in guinea pigs were excreted in the urine as *o*-glucuronides or *o*-sulfates (ATSDR, 1992). The metabolic pathways for 2-butanone in humans and animals are shown in Fig. 1.

In humans, 2-butanone is rapidly cleared from the blood with a plasma half-life ($t_{1/2}$) of 49–96 min exhibiting biphasic elimination and an apparent clearance rate of 0.60 L/min. In addition, 2-butanone was not detected in blood after 20 h after exposure (US EPA, 2003). Therefore, 2-butanone would not be expected to accumulate with chronic exposure (ATSDR, 1992). 2-Butanone excreted completely as metabolites with little excreted as unchanged in both humans (0.1%–3% of the absorbed dose) and animals such as rats, dogs, and guinea pigs. 2-Butanone and its metabolites are mainly excreted through the lungs, although small amounts are excreted through the kidneys (less than 5%) (WHO, 1993). Exposure of 2-butanone through inhalation of human volunteers (200 ppm for 4 h) resulted in 3% exhaled as unchanged 2-butanone, 2% excreted in urine as 2,3-butanediol, and the remainder was metabolized and transformed to simple compounds such as carbon dioxide and water (US EPA, 2003). In contrast, at high dose levels, a proportionally greater amount of unchanged 2-butanone was excreted through the lungs and kidneys due to metabolic saturation (WHO, 1993). In an occupational study, 72 workers exposed to 2-butanone at an average concentration of 47.6 ppm excreted urinary 2-butanone at a range of 0.2–8.1 mg/L (Yoshikawa et al., 1995). Dogs administered orally 338 and 396 g/kg of 2-butanone in water excreted unchanged urinary 2-butanone at 33.1% and 30.3% for 338 and 396 g/kg, respectively (Schwarz, 1898). Rabbits orally administered 2–3 g of 2-butanone in water excreted glucuronide conjugate in urine (Saneyoshi, 1911). Interindividual variability was high in the elimination of 2-butanone among humans. 2-Butanone was exposed to human volunteers through inhalation (whole-body and skin only) for 4 h at a concentration of 200 ppm. It was reported that the pattern of elimination was similar in both the occasions of exposures and that the interindividual variability was high. The average $t_{1/2}$ elimination calculated for 2-butanone was reported to be 1.5 h (whole-body) and 2.7 h (skin only) (Brooke et al., 1998). 2-Butanone has the capacity to competitively inhibit the metabolism of 2,5-hexanedione.

Brooke et al., 1998; HSDB, 2018: 2-Butanone was exposed to 4 human volunteers through inhalation (whole-body and skin only) in 2 separate occasions at a concentration of 200 ppm for 4 h to assess the dermal absorption. For dermal exposure, the volunteers wore air-fed masks so that the inhalation route was excluded as a source of uptake. 2-Butanone uptake was assessed by monitoring parent or metabolites in blood, single breath, or urine following exposure by using gas chromatography and mass spectrometry. Blood samples were withdrawn from the antecubital vein before and after each exposure (0 and 4 h), urine samples were taken before and after each exposure (0, 4, 6, 8, 10, 12, and 22 h), and breath samples were taken before and immediately after (0 and 4 h) exposure and then at 10–15-min intervals thereafter for a further 3 h. The results of the study suggested that 2-butanone absorbed significantly from the skin, contributing to around 3%–3.5% of the body burden, and it was also reported that there was a relatively high degree of both inter and intraindividual variability. Following both whole-body and dermal-only exposure, 2-butanone levels in breath fell relatively rapidly with similar patterns of elimination. Urinary monitoring data suggest that there is a delay in the post-exposure peak excretion between the 2 exposure regimens. Peak elimination following whole-body exposure was reported in the immediate post-exposure sample (2-h mid-point sample). In contrast, for skin-only exposure the peak of elimination appears to be in the 2-h post-exposure sample (5-h mid-point) with extended elimination. The mean urinary elimination half-life ($t_{1/2}$) calculated for 2-butanone from the 2–6 h post-exposure samples (6-, 8-, and 10-h sampling points) were $t_{1/2}$ of 1.5 h whole-body (range 1–2.3 h) and $t_{1/2}$ of 2.7 h skin (range 1.3–4.3 h).

Additional References: Liira et al., 1984; Dietz et al., 1979; ODonoghue et al., 1984

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

2-Butanone is reported to occur in the following foods by the VCF*:

Allium species
Banana (*Musa sapientum* L.)
Black currants (*Ribes nigrum* L.)
Cabbage (*Brassica oleracea*)
Cheese, various types
Citrus fruits
Egg
Licorice (*Glycyrrhiza glabra* L.)
Oats (*Avena sativa* L.)
Potato (*Solanum tuberosum* L.)

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that

have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. 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 and use levels, 2-butanone does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Multiple genotoxicity studies have been conducted with 2-butanone, and the data indicate that this compound, with or without metabolic activation, is not a bacterial or mammalian cell mutagen. In addition, there are *in vitro* and *in vivo* data indicating that 2-butanone is not clastogenic under the test conditions used. Although many of these studies were not conducted using current OECD protocols or as GLP-compliant studies, the weight of evidence supports the view that 2-butanone is unlikely to be a concern for genotoxicity.

The mutagenic activity of 2-butanone was evaluated in several Ames assays conducted according to guidelines similar to OECD TG 471. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, TA1538, and *E. coli* strain WP2uvrA were evaluated across multiple studies. At least 1 of these studies was conducted at a contract laboratory and was likely conducted as a GLP-compliant study (O'Donoghue et al., 1988), and a second study was conducted by the US National Toxicology Program (NTP) (Zeiger and Margolin, 2000). The results of these studies indicate that 2-butanone, with or without metabolic activation, was not mutagenic in the Ames assay. The mutagenic activity of 2-butanone has been evaluated by the NTP in a bacterial reverse mutation assay conducted according to guidelines similar to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 were treated with 2-butanone in water 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 (Zeiger and Margolin, 2000). Under the conditions of the study, 2-butanone was not mutagenic in the Ames test.

The clastogenic activity of 2-butanone was evaluated in an *in vivo* micronucleus test. 2-Butanone was administered in corn oil via a single intraperitoneal dose of 1.96 mg/kg to groups of male and female CD-1 mice. Mice were euthanized at 12, 24, and 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes (PCEs). The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes (MN-PCEs) in the bone marrow (O'Donoghue et al., 1988). Under the conditions of the study, 2-butanone was considered to be not clastogenic in the *in vivo* micronucleus test. A second study conducted in hamsters supported this conclusion. 2-Butanone was administered in corn oil via a single intraperitoneal dose of 411 mg/kg to groups of male and female Chinese hamsters. Hamsters were euthanized at 12, 24, 48, and 72 h, and the bone marrow was extracted and examined for PCEs. The test material did not induce a statistically significant increase in the incidence of MN-PCEs in the bone marrow (Basler, 1986). Under the conditions of the study, 2-butanone was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, 2-butanone does not present a concern for genotoxic potential.

Additional References: Florin et al., 1980; Nestmann et al., 1980; Douglas et al., 1980; Shimizu et al., 1985; O'Donoghue et al., 1988; Perocco et al., 1983; Shirasu et al., 1976; Chen et al., 1984; Brooks et al., 1988; Muller et al., 1993; Zimmermann et al., 1985a; Zimmermann et al., 1989; Zeiger and Margolin, 2000; Kreja and Seidel, 2002; Kreja and Seidel, 2001; Nakajima et al., 2006; Zimmermann et al., 1985b.

Literature Search and Risk Assessment Completed On: 01/27/19.

10.1.2. Repeated dose toxicity

The MOE is adequate for the repeated dose endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 2-butanone. In a GLP-compliant subchronic inhalation toxicity study (similar to OECD TG 413), 10 Fischer 344 rats/sex/dose (main study) and 5/sex/dose (neuropathology study) were administered 2-butanone (purity: > 99.5%) through whole-body inhalation at concentrations of 0 (control: air), 1250, 2500, and 5000 ppm (equivalent to 1047.6, 2095.3, and 4190.5 mg/kg/day) for 6 h/day, 5 days/week, for a period of 13 weeks. No treatment-related adverse effects were reported for mortality, clinical signs, body weight, food consumption, ophthalmoscopy, neurological examinations, urinalysis, gross pathology, and histopathology at any of the dose levels. However, relative and absolute liver weights were increased in animals at the highest dose along with other significant differences in organ weights such as decreased brain weights (females), spleen weights (females), and increased kidney weights (males and females). Although these changes were not accompanied by histopathological changes, the NOAEL was considered to be 2500 ppm (Cavender et al., 1983; US EPA, 2003).

In another single-dose study (non-GLP-compliant and non-guideline), 6 male Sprague Dawley rats/dose were administered 2-butanone (purity: 99.98%) through inhalation at the concentrations of 0 (control: air) or 550 ppm (equivalent to 1350.9 mg/kg/day) for a period of 22 h/day, 7 days per week, for 6 months. Two animals were euthanized following 2, 4, and 6 months of exposure and were subjected to neuropathological examinations (cerebellar vermis, cervicomedullary junction, lumbar cord, dorsal and ventral spinal roots, spinal ganglia, sciatic notch, and 3 levels of tibial nerve). A transient decrease in bodyweight gain was reported in the initial 8 weeks, but a similar effect was also observed in the control group animals. Hence, this change was not considered to be treatment-related. No morphologic changes in the central and peripheral nervous system were reported. Based on no treatment-related changes reported at 550 ppm dose group, the NOAEL for neurotoxicity was considered to be 550 ppm (equivalent to 1350.9 mg/kg/day).

To account for bioavailability following inhalation, data from regulatory authorities indicated that humans absorbed approximately 75% of inhaled 2-butanone (OECD, 1997; US EPA, 2003; ATSDR, 1992; see Section IV). The data were used to revise the NOAEL of 2095 mg/kg/day to reflect the systemic dose. At a predicted inhalational absorption of 75% of the inhaled dose, the revised repeated dose toxicity NOAEL is 1571.25 mg/kg/day. (See Table 1. Additional studies that were not reported to be GLP-compliant or conducted according to guidelines.)

Table 1
Additional studies that were not reported to be GLP-compliant or conducted according to guidelines.

Duration in detail	GLP/ Guideline	No. of animals/dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
12 weeks; 7 h/day, 5 days/week	Not reported	15 male Guinea pigs	Inhalation	0 (control), 235 ppm (172.9 mg/kg/day) (purity: 99.5%)	NOAEL derived as 173 mg/kg/day	Based on no treatment-related effects reported	LaBelle and Brieger, 1955
12 weeks; 7 h/day, 5 days/week	Not reported	25 rats (strain not reported)	Inhalation	0 (control), 235 ppm (197.9 mg/kg/day) (purity: 99.5%)	NOAEL derived as 198 mg/kg/day	Based on no treatment-related effects reported	LaBelle and Brieger, 1955
7 weeks; 8 h/day, 5 days/week	Not reported	Rats (5 animals/group) (strain not reported)	Inhalation	0 (control), 6000 ppm (equivalent to 5775.1 mg/kg/day) (purity is 99%)	LOAEL-5775.1 mg/kg/day	All animals were found dead by week 7 because of bronchial pneumonia	Altenkirch et al., 1978a
4 weeks; 6 h/day, 5 days/week	Not reported	4 male Sprague Dawley rats	Inhalation	800 ppm for (equivalent to 604.4 mg/kg/day)	NOAEL derived as 604.4 mg/kg/day	Based on no treatment-related changes reported	US EPA (2003)
30 days; (duration of exposure was not reported, so, assumed as 6 h/day)	Not reported	Sherman rats (15 animals/group)	Inhalation	0 (control), 125, 250, 500, and 1000 ppm (equivalent to 90.3, 180.5, 361., and 721.9 mg/kg/day)	NOAEL derived as 721.9 mg/kg/day	Based on no histopathological changes reported in the lung, liver, and kidney	NTRL (1989)
30 days; (duration of exposure was not reported, so, assumed as 6 h/day)	Not reported	Guinea pigs mixed strains (10/group)	Inhalation	0 (control), 125, 250, 500, and 1000 ppm (equivalent to 78.8, 157.7, 315.3, and 630.6 mg/kg/day)	NOAEL derived as 630.6 mg/kg/day	Based on no histopathological changes reported in the lung, liver, and kidney	NTRL (1989)
16 weeks; 8 h/day 5 days/week	Not reported	Wistar white rats (20 animals/group)	Inhalation	0 (control), 700 ppm (equivalent to 673.8 mg/kg/day) (purity −99.98%)	NOAEL for neurotoxicity was considered to be 673.8 mg/kg/day	Based on no treatment-related changes reported	Duckett et al., 1979
17 weeks; 8 h/day 5 days/week	Not reported	Wistar white rats (20 animals/group)	Inhalation	0 (control), 200 ppm (equivalent to 192.5 mg/kg/day)	NOAEL for neurotoxicity was considered to be 192.5 mg/kg/day	Based on no treatment-related changes reported	Duckett et al., 1979
7–9 weeks; 24 h/day, 7 days/week	Not reported	4 rats (Strain not reported)	Inhalation	1500 ppm, (calculated dose was 4331.4 mg/kg/day)	NOAEL for neurotoxicity was considered to be 4331.4 mg/kg/day	Based on no paralysis reported and no histopathological changes reported in the nerves	US EPA (2003)
7–9 weeks; 24 h/day, 7 days/week	Not reported	5 mice (strain not reported)	Inhalation	1500 ppm (calculated dose was 6853.8 mg/kg/day)	NOAEL for neurotoxicity was considered to be 6853.8 mg/kg/day	Based on no paralysis reported and no histopathological changes reported in the nerves	US EPA (2003)

Therefore, the 2-butanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the NOAEL in mg/kg/day by the total systemic exposure to 2-butanone, 1571.25/0.00062 or 2534274.

In addition, the total systemic exposure to 2-butanone (0.62 μg/kg/day) is below the TTC (30 μg/kg/day) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: NICNAS, 2013; NTRL, 1989; ATSDR, 1992; HSDB, 2018; OECD, 1997; ECHA, 2011; ODonoghue et al., 1984; Saida et al., 1976; Takeuchi et al., 1983; Ralston et al., 1985; ATSDR, 1992.

Literature Search and Risk Assessment Completed On: 01/14/19.

10.1.3. Developmental and reproductive toxicity

The MOE for 2-butanone is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental toxicity data on 2-butanone. An inhalation developmental toxicity study was conducted in pregnant female Sprague Dawley rats. Groups of 19–23 rats/dose were exposed via inhalation to 2-butanone (methyl ethyl ketone; MEK) at concentrations of 0 (filtered air), 1000, 2000, 4000, or 6000 ppm (equivalent to 0, 781, 1561, 3122, and 4684 mg/kg/day, respectively, as per standard minute volume and body weights for female Sprague Dawley rats) for 6 h per day on gestation days (GD) 6–20. All animals were euthanized on GD 21, and cesarean sectioning was performed. Reduced bodyweight gains were reported among 4000 ppm dam during the first half of the study and during the entire study period for 6000 ppm dam. Furthermore, statistically significant decreased body weight was reported for 4000 and 6000 ppm dam. The decreased body weight was accompanied by a statistically significant reduction in feed consumption throughout the study at 4000 and 6000 ppm. Statistically significant decreases in fetal body weights were reported at ≥2000 ppm (4%, 15%, and 19%–20% at 2000, 4000, and 6000 ppm, respectively). Incidences of skeletal variations such as delayed ossification of sternebrae (statistically significant) and rudimentary cervical ribs were reported at 4000 and 6000 ppm. The NOAEL for maternal toxicity was considered to be 2000 ppm or 1561 mg/kg/day, based on the significantly reduced bodyweight gain among higher dose group dams. The NOAEL for developmental toxicity was considered to be 1000 ppm or 781 mg/kg/day, based on decreased fetal body weights at ≥2000 ppm and increased incidence of delayed ossification of sternebrae and rudimentary cervical ribs at 4000 and 6000 ppm (Saillenfait et al., 2006).

Another inhalation developmental toxicity study was conducted in pregnant female Sprague Dawley rats. Groups of 25 rats/dose were exposed via inhalation to 2-butanone (MEK) at concentrations of 400, 1000, or 3000 ppm (equivalent to 364, 911, and 2732 mg/kg/day, respectively, as per standard minute volume and body weight for female Sprague Dawley rats) for 7 h per day on days 6–15 of gestation. Simultaneously, a group of 35 rats was exposed to filtered room air to serve as the control group. Animals were observed from GD 6 for incidences of toxicity and bodyweight changes. Cesarean section was performed on GD 21. Maternal toxicity was exhibited by a decrease in bodyweight gain and increased water consumption; however, no changes in food consumption were observed. At 3000 ppm, statistically significant increased incidences of extra lumbar ribs and delayed ossification of the skull and cervical centra were observed. The NOAEL for developmental toxicity was considered to be 1000 ppm or 911 mg/kg/day, based on increased incidences of skeletal variant and a delay in the ossification of fetal bones among high-dose group fetuses (Deacon et al., 1981; #4224; also available at ECHA, 2011).

Additional developmental toxicity studies were conducted in both rats and mice (see table below). Taken together, the major effects reported in both rats and mice were characterized by delayed ossification of the sternebrae and vertebrae, and skeletal variations such as misaligned sternebrae (mice) and rudimentary cervical ribs (rat). The NOAEL of 1000 ppm was determined for all studies (Saillenfait et al., 2006; Deacon et al., 1981; Schwetz et al., 1974; NTRL, 1989). All these effects were observed in the presence of maternal toxicity (Saillenfait et al., 2006; Deacon et al., 1981) in rats and also in the absence of maternal toxicity (Schwetz et al., 1974; NTRL, 1989) in both rats and mice. Given the range of concentrations tested, both the Saillenfait et al. (2006) (range tested: 1000–6000 ppm) and Deacon et al. (1981) (range tested: 400–3000 ppm) studies were considered for the risk assessment for developmental toxicity. Therefore, the most conservative developmental toxicity NOAEL of 781 mg/kg/day from the Saillenfait study was selected for the developmental toxicity endpoint. **Therefore, the 2-butanone MOE for the developmental toxicity endpoint can be calculated by dividing the 2-butanone NOAEL in mg/kg/day by the total systemic exposure to 2-butanone, 781/0.00062 or 1259677.**

Duration in detail	GLP/ Guideline	No. of animals/ dose (Species, strain, sex)	Route (vehicle)	Doses (in mg/kg/day; purity)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
GD 6–15 days; 7 h/day	Not mentioned	21-23 Pregnant female Sprague Dawley rats/group	Inhalation (air)	0 (filtered air), 1000, and 3000 ppm (equivalent to 911 and 2732 mg/kg/day, as per standard minute volume and body weights for female Sprague Dawley rats)	Maternal toxicity NOAEL = 3000 ppm or 2732 mg/kg/day Developmental toxicity NOAEL = 1000 ppm or 911 mg/kg/day	No maternal toxicity observed up to the highest dose tested Based on delayed ossification of the sternebrae, as was the total number of litters with soft tissue anomalies and low incidence of acaudate fetuses, imperforate anus, brachygnathia at 3000 ppm	Schwetz et al., 1974; Leong et al., 1974
GD 6–15, 7 h/day; 7 days/week	Non-GLP	Female Swiss albino Crl:CD-1 mice (10 virgin and 33 plug-positive mice/group)	Inhalation (air)	0 (filtered air), 400, 1000, and 3000 ppm (equivalent to 0, 533, 1333, and 3998 mg/kg/day, as per standard minute volume and body weights for mouse)	Maternal toxicity NOAEL = 3000 ppm or 1333 mg/kg/day Developmental toxicity NOAEL = 1000 ppm or 1333 mg/kg/day	No maternal toxicity observed up to the highest dose tested Based on the decreased fetal body weights and increased skeletal variations in fetuses exposed at 3000 ppm	NTRL, 1989; Schwetz et al., 1991

There are no reproductive toxicity data on 2-butanone. Read-across material 2-pentanone (CAS # 107-87-9; see section V) has sufficient reproductive toxicity data. An OECD 421/GLP reproduction and developmental toxicity study was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were exposed via whole-body exposure to concentrations of 0.0, 1.0, 2.5, or 5.0 mg/L (equivalent to 0, 259, 648, and 1297, respectively, as per standard minute volume and body weight values for male and female Sprague Dawley rats) 2-pentanone for 6 h per day, 7 days per week. Females were exposed for a total of 35–48 days (14 days pre-mating, 14 days mating, 21–22 days of gestation, and 4 days of early lactation) and males were exposed for 51 days. A statistically significant increase in the absolute weight of the

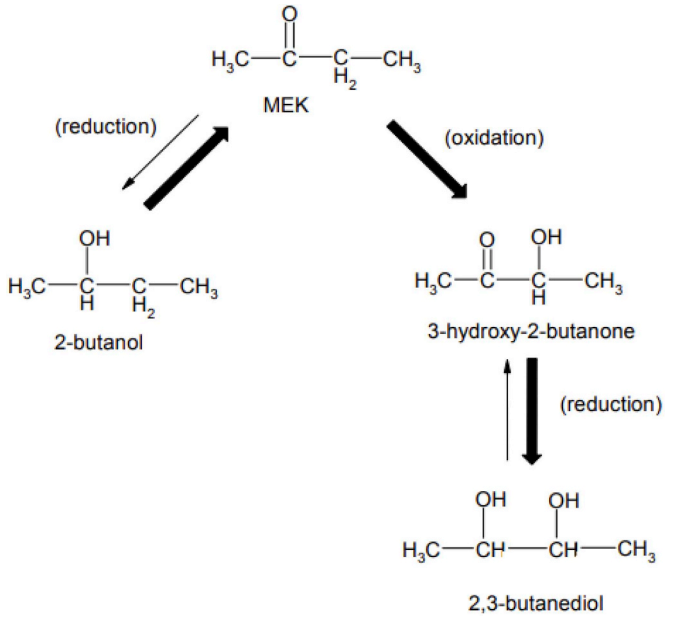


Fig. 1. Proposed metabolic pathways for 2-Butanone (US EPA, 2003).

epididymis with no correlated macroscopic or histopathological changes was reported at 5 mg/L dose group males. No treatment-related adverse effects were reported for sexual maturation, estrous cycle, sperm analysis, and reproductive performance for both male and females at any dose level. No treatment-related effects were reported for gestation length, pup survival, prenatal loss, number of implantations, live and dead pups, and pup body weight at any dose level. The NOAEL for reproductive toxicity was considered to be 5.0 mg/L mg/kg/day or 1297 mg/kg/day, the highest dose tested (ECHA, 2013). **Therefore, the 2-butanone MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-pentanone NOAEL in mg/kg/day by the total systemic exposure to 2-butanone, 1297/0.00062 or 2091935.**

In addition, the total systemic exposure to 2-butanone (0.62 μg/kg/day) is below the TTC (30 μg/kg/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: Stoltenburg-Didinger (1991).

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

10.1.4. Skin sensitization

Based on weight of evidence (WoE) from structural analysis and animal studies and human studies, 2-butanone does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on the existing data, 2-butanone does not present a 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., 2007b; #53620; Toxtree 3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, 2-butanone did not present reactions indicative of sensitization at 100% (Gad et al., 1986). In 2 guinea pig Buehler tests, 2-butanone did not present reactions indicative of sensitization at 50%, 100%, and 100% (ECHA, 2011; Gad et al., 1986). In a guinea pig open cutaneous test (OET), 2-butanone did not present reactions indicative of sensitization at 20% (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with 20% (13800 μg/cm^2) (RIFM, 1975). Based on WoE from structural analysis and animal studies and human studies, 2-butanone does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: Lea et al., 1999; Back and Larsen, 1982; Gad et al., 1986; Descotes (1988).

Literature Search and Risk Assessment Completed On: 01/29/19.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 2-butanone 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-butanone in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-butanone does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · 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-butanone is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are insufficient inhalation data available on 2-butanone. Based on the Creme RIFM Model, the inhalation exposure is 0.000028 mg/day. This exposure is 50000 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: Couri et al., 1977; Schwetz et al., 1974; ODonoghue et al., 1984; Carpenter et al., 1949; Smyth et al., 1962; Dick et al., 1984; Leong et al., 1974; De Ceaurriz et al., 1981; Deacon et al., 1981; Cavender et al., 1983; DeCeaurriz et al., 1983; Dick et al., 1989; Dick et al., 1988; Liira et al., 1991; Shibata et al., 1990a; Schwetz et al., 1991; Liira et al., 1990a; Liira et al., 1990b; Shibata et al., 1990b; Dahl et al., 1991; Li et al., 1986; Altenkirch et al., 1978a; Brown et al., 1987; Couri et al., 1978; Liira et al., 1988a; Liira et al., 1988b; Takeuchi et al., 1983; Toftgard et al., 1981; Wen et al., 1985; Altenkirch et al., 1977; Altenkirch et al., 1978b; Altenkirch et al., 1982; Geller et al., 1979; LaBelle and Brieger, 1955; Saida et al., 1976; Stoltenburg-Didinger et al., 1990; NTRL, 1989; Stoltenburg-Didinger, 1991; Morrow et al., 1991; Dick et al., 1992; Brondeau et al., 1989; Stone et al., 1981; Shell, 1992; Abdel-Rahman et al., 1976; Specht et al., 1940; Tada et al., 1972; Patty et al., 1935; Frantik et al., 1994; Hetland et al., 1976; Adachi et al., 1993; Yoshikawa et al., 1995; Shamy et al., 1994; Geller et al., 1978; Liira et al., 1984; Miyasaka et al., 1982; Perbellini et al., 1984; Uaki et al., 1995; Callander, 1995; Egan et al., 1980; Duckett et al., 1979; Ashley and Prah, 1997; vanEngelen, 1997; Ghittori et al., 1987; Mitran et al., 1997; Ong et al., 1991; Ichihara et al., 1998; Doty (1994); Karakaya et al., 1999; Muttray et al., 2002; Haumann et al., 2003; Wiesmuller et al., 2002; vanThriel et al., 2003; Saillenfait et al., 2006; Tsai et al., 2009.

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-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, 2-butanone 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 v4.11 did not identify 2-butanone 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 VoU (2015), 2-butanone does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.1.2. Other available data. 2-Butanone has been registered under REACH and the following data is available:

The ready biodegradability of 2-butanone has been evaluated according to the OECD 301D method. After 28 days, biodegradation of 98% was observed.

A fish (*Pimephales promelas*) acute toxicity study was conducted according to the OECD 203 method under static conditions. The 96-h LC50 was reported to be 2993 mg/L.

A *Daphnia magna* acute immobilization study was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be 308 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method under static conditions. The 96-h EC50 (based on growth rate) was reported to be 2029 mg/L (ECHA, 2011).

10.2.1.3. Risk assessment refinement. Since 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 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	3174			1000000	3.174	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	0.26	0.26
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 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 3.174 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at 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.2019.111025.

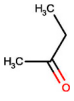
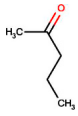
Appendix

Read-across Justification

Methods

The read-across analog was 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).
- 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-Butanone	2-Pentanone
CAS No.	78-93-3	107-87-9
Structure		
Similarity (Tanimoto Score)		0.77
Read-across Endpoint		• Reproductive Toxicity
Molecular Formula	C_4H_8O	$C_5H_{10}O$
Molecular Weight	72.10	86.13
Melting Point (°C, EPI Suite)	−86.67	−76.9
Boiling Point (°C, EPI Suite)	79.6	102.2
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.21E+004	4.72E+003
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	0.29	0.91
Water Solubility (μg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.11e+005	4.3e+004
J_{max} (μg/cm^2/h, SAM)	2224.002	833.107
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.73E+000	8.47E+000
Reproductive and Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (moderate reliability)	• Non-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-butanone (CAS # 78-93-3). 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, 2-pentanone (CAS # 107-87-9) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 2-Pentanone (CAS # 107-87-9) was used as a read-across analog for the target material 2-butanone (CAS # 78-93-3) for the reproductive toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of straight-chain saturated ketones.
  - o The target material and the read-across analog share a fully saturated straight chain with a ketone functionality in position 2.
  - o The key difference between the target material and the read-across analog is that the former is a C4 ketone while the latter is a C5 ketone. 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 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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