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Short Review

RIFM fragrance ingredient safety assessment, 2-octanone, CAS Registry Number 111-13-7

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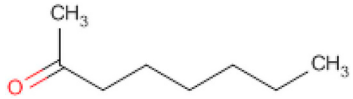
Version: 110918. This version replaces any previous versions.
Name: 2-Octanone
CAS Registry Number: 111-13-7



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., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

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NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

2-octanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-heptanone (CAS # 110-43-0) show that 2-octanone is not genotoxic and that there are no safety concerns for 2-octanone for skin sensitization under the current declared levels of use. The repeated dose, developmental and reproductive, and local respiratory toxicity were completed using data from read-across analog 2-heptanone (CAS # 110-43-0), which provided an MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, 2-octanone was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment	
Genotoxicity: Not expected to be genotoxic.	(EPA HPVIS; US EPA, 1998; ECHA Dossier: Heptan-2-one; ECHA, 2012a)
Repeated Dose Toxicity: NOAEL = 1087 mg/kg/day.	(Lynch et al., 1981)
Reproductive Toxicity: Developmental Toxicity NOAEL = 500 mg/kg/day. Fertility NOAEL = 1239 mg/kg/day.	(US EPA Pilot Prenatal Developmental Study of 2-Heptanone; US EPA, 1993; ECHA Dossier: Heptan-2-one; ECHA, 2012a)
Skin Sensitization: No safety concerns under the current, declared levels of use.	(ECHA Dossier: Heptan-2-one; ECHA, 2012a)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic.	(UV Spectra, RIFM DB)
Local Respiratory Toxicity: NOAEC = 4787.11 mg/m^3.	(Lynch et al., 1981)

Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 94.3% (OECD 301B)	RIFM (1995)
Bioaccumulation: Screening-level: 17.01 L/kg	US EPA (2012a)
Ecotoxicity: Screening-level: 96-h Algae EC50: 31.34 mg/L	US EPA (2012a)
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: 96 h Algae EC50: 31.34 mg/L	US EPA (2012a)
RIFM PNEC is: 3.134 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1	

1. Identification

1. **Chemical Name:** 2-Octanone
2. **CAS Registry Number:** 111-13-7
3. **Synonyms:** Hexyl methyl ketone; Methyl hexyl ketone; アルキル（C＝1～16）メチルケトン; Octan-2-one; 2-Octanone
4. **Molecular Formula:** $C_8H_{16}O$
5. **Molecular Weight:** 128.22
6. **RIFM Number:** 462
7. **Stereochemistry:** Isomer not specified. 0 stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 173 °C (FMA Database), 163.6 °C (US EPA, 2012a)
2. **Flash Point:** 52 °C (GHS), 125 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.22 (US EPA, 2012a)
4. **Melting Point:** −30.72 °C (US EPA, 2012a)
5. **Water Solubility:** 884.2 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.813–0.818 (FMA), 0.815–0.820 (FMA Database)
7. **Vapor Pressure:** 1.33 mmHg @ 20 °C (US EPA, 2012a), 0.8 mm Hg 20C (FMA), 1.87 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})

9. **Appearance/Organoleptic:** Colorless to pale yellow clear liquid with a musty, ketonic, bleu and parmesan cheese-like with earthy and dairy nuances.*

*http://www.thegoodscentscompany.com/data/rw1001751.html, 09/15/17.

3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.006% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.00026 mg/kg/day or 0.019 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:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class II, Intermediate

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
II	II	II

2. Analogs Selected:
   a. **Genotoxicity:** 2-heptanone (CAS # 110-43-0)
   b. **Repeated Dose Toxicity:** 2-Heptanone (CAS # 110-43-0)
   c. **Developmental and Reproductive Toxicity:** 2-Heptanone (CAS # 110-43-0)
   d. **Skin Sensitization:** 2-heptanone (CAS # 110-43-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** 2-heptanone (CAS # 110-43-0)
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

2-Octanone is reported to occur in the following foods by the VCF*:
Acerola (*Malpighia*)
Allium species.
Apple brandy (*Calvados*)
Apple processed (*Malus* species)
Apricot (*Prunus armeniaca* L.)
Babaco fruit (*Carica pentagona* Heilborn)
Banana (*Musa sapientum* L.)
Beans.
Beef.
Beer.
Blue cheeses.
Buckwheat.
Capsicum species.
Caviar.
Cheddar cheese.
Cheese, various types.
Chicken.
Clam.
Cloves (*Eugenia caryophyllata* Thunberg)
Cocoa category.
Coffee.
Crab.
Crayfish.
Crispbread.
Date (*Phoenix dactylifera* L.)
Egg.
Fig (*Ficus carica* L.)
Filbert, hazelnut (*Corylus avellano*)
Fish.
Grape (*Vitis* species)
Grape brandy.
Guinea hen.
Honey.
Hop (*Humulus lupulus*)
Katsuobushi (dried bonito)
Krill.
Maize (*Zea mays* L.)
Malt.
Mastic (*Pistacia lentiscus*)
Mate (*Ilex paraguayensis*)
Milk and milk products.
Mountain papaya (*C. candamarcensis, C. pubescens*)
Mushroom.
Oats (*Avena sativa* L.)
Olive (*Olea europaea*)
Origanum (Spanish) (*Coridothymus cap.*(L.) Rchb.)
Papaya (*Carica papaya* L.)
Peach (*Prunus persica* L.)
Peanut (*Arachis hypogaea* L.)
Peas (*Pisum sativum* L.)
Pecan (*Carya illinoensis* Koch)
Plum brandy.
Pork.
Potato chips (American)
quince, marmelo (*Cydonia oblonga* Mill.)
Raspberry, blackberry and boysenberry.
Rice (*Oryza sativa* L.)
Rooibos tea (*Aspalathus linearis*)
Rye bread.
Shrimps.
Soybean (*Glycine max*. L. merr.)
Strawberry (*Fragaria* species)
Strawberry.
Swiss cheeses.
Tea.
Tomato (*Lycopersicon esculentum* Mill.)
Trassi (cooked)
Truffle.
Turkey.
Vaccinium species.

Vanilla.
Walnut (*Juglans* species)
Wheaten bread.
Wine.

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

8. IFRA standard

None.

9. REACH dossier

Available 09/15/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. The mutagenic activity of 2-octanone (CAS # 111-13-7) was evaluated using the gradient-plate modification of the bacterial reverse mutation assay. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *Escherichia coli* strain WP2uvrA were treated with 2-octanone containing a concentration gradient of 0.1–1000 μg/plate. The study was conducted with and without Aroclor 1254–induced rat liver S9. The results of the study indicated that 2-octanone was not mutagenic; however, specific data for the material are not provided (McMahon et al., 1979). This assay was designed for screening large numbers of compounds and does not provide a definitive evaluation of the mutagenic potential of 2-octanone. As a weight-of-evidence approach, read-across can be made to 2-heptanone (CAS # 110-43-0; see Section V). The mutagenic activity of 2-heptanone has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were treated with 2-heptanone 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 dose in the presence or absence of S9 (US EPA, 1998). Under the conditions of the study, 2-heptanone was not mutagenic in the Ames test.

The clastogenicity of 2-heptanone was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovary cells were treated with 2-heptanone in DMSO at concentrations up to 1200 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any dose of the test item, either with or without S9 metabolic activation (ECHA, 2012a). Under the conditions of the study, 2-heptanone was considered to be non-clastogenic in the *in vitro* chromosome aberration assay.

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

Additional References: Kreja and Seidel, 2002; Kreja and Seidel, 2001; Albro et al., 1984; Nakajima et al., 2006.

Literature Search and Risk Assessment Completed On: 08/24/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for 2-octanone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. In a 13-week oral gavage study conducted prior to GLPs, groups of 15 CFE rats/sex/dose were administered 2-heptanone via oral intubation at doses of 0, 20, 100, or 500 mg/kg/day in corn oil. An additional 5 rats/sex/dose receiving daily doses of 0, 100, or 500 mg/kg/day 2-heptanone were examined after 2 and 6 weeks. There were statistically significant increases in the number of cells excreted in the urine of both males and females at the mid- and high-dose groups after 13 weeks and in the high-dose group after 6 weeks, along with pale kidneys observed in the animals. A significant increase in the absolute liver weight (females) and relative kidney weights (males) was reported at the mid-dose. A significant increase in the absolute and relative liver weights (males and females, and males at week 6), absolute and relative kidney weights (males), and absolute stomach weights (females) were reported at the high-dose. Although organ weight changes were observed in the mid- and high-dose groups, no histopathological alterations or clinical chemistry changes were noted that might also be reflective of renal or hepatic toxicity. The NOAEL in this study was considered to be 20 mg/kg/day, based on the observed increase in urine cellularity and organ weight changes in the mid- and high-dose groups (Gaunt et al., 1972).

In a subchronic inhalation study conducted prior to GLPs, groups of 50 male Sprague Dawley rats and 8 male Cynomolgus monkeys (*Macaca fascicularis* strain) were exposed via inhalation to 0, 100, or 1000 ppm of 2-heptanone for 6 h/day, 5 days/week, for up to 10 months in whole-body chambers. Actual exposure levels were reported to be approximately 0, 131 ± 30 ppm or 1025 ± 136 ppm. No treatment-related effects in clinical signs, body weight, overall cardiopulmonary status, and gross or histopathological alterations were observed for both species. Thus, the NOAEC for both the rat and monkey was considered to be 1025 ppm, the highest dose tested based on the absence of any dose-dependent changes indicative of toxicity. Using standard minute volume and bodyweight values for male Sprague Dawley rats in a chronic study, the calculated NOAEL for repeated dose toxicity was considered to be 1087 mg/kg/day. For the monkeys, using standard minute volume and bodyweight values (BW of 4.5 kg, MV of 1.729 L/min), the calculated NOAEL was considered to be 662 mg/kg/day (Lynch et al., 1981).

In an OECD 421/GLP combined reproductive/developmental screening study, 2-heptanone was administered to groups of 12 Sprague Dawley rats/sex via inhalation at target concentrations of 0, 80, 400, or 1000 ppm (actual measured concentrations of 0, 79, 406, or 1023 ppm) for 6 h/day, 7 days/week during premating, mating, gestation day (GD) and early lactation for a total of 50 exposure days for males and 34–47 exposure days for females. A dose-related reduction in activity (less movement, decreased alertness and slower response to tapping on the chamber wall) was observed at 400 and 1000 ppm animals, that declined over the course of exposure as the animals appeared to acclimate to the vapor. The mean bodyweight change for the 400 ppm dam between GDs 0 and 7 was significantly lower than the controls. Males and females at 1000 ppm exhibited significantly decreased food consumption during days 0–7 only. There were no effects in any of the selected organs that were weighed or examined grossly or histologically. Thus, the parental NOAEL was considered to be 1023 ppm, the highest dose tested. Using standard minute volume and bodyweight values for Sprague Dawley rats in a subchronic study, the calculated NOAEL was considered to be 1239 mg/kg/day (https://echa.europa.eu/registration-dossier/-/registered-dossier/10230/7/9/2, ECHA, 2012a).

Since the effects of an increase in urine cellularity and organ weight changes from the oral gavage study (Gaunt et al., 1972) were not seen in the OECD 421 inhalation study for both male and female rats, thus the NOAEL of 1087 mg/kg/day from the subchronic inhalation study of male Sprague Dawley rats was considered for the repeated dose toxicity endpoint. 100% inhaled dose was considered for calculating the

NOAEL. **Therefore, the 2-octanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-heptanone NOAEL in mg/kg/day by the total systemic exposure to 2-octanone, 1087/0.00062 or 1753226.**

In addition, the total systemic exposure to 2-octanone (0.62 μg/kg/day) is below the TTC (9 μg/kg/day) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: Johnson et al., 1978; Spencer et al., 1978; Misumi and Nagano, 1984.

Literature Search and Risk Assessment Completed On: 09/06/17.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 2-octanone is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 2-octanone. Read-across material, 2-heptanone (CAS # 110-43-0; see Section V) has sufficient developmental toxicity data to support the developmental toxicity endpoint. In an OECD 414/GLP prenatal developmental toxicity study, 2-heptanone was administered via inhalation (whole-body) to groups of 25 female Crl:CD (SD) rats for 6 h/day from GDs 6 through 19, at target concentrations of 0 (filtered air), 300, 600, or 1200 ppm (actual measured concentrations of 0, 303, 613, or 1251 ppm). No test material–related macroscopic findings were observed in the dams and treatment did not affect intrauterine growth and survival. Examination of the fetuses revealed no external, visceral or skeletal malformations or developmental variations that could be attributed to the test material. Thus, the NOAEC for developmental toxicity was considered to be 1251 ppm, based on the lack of adverse developmental effects. The NOAEC for maternal toxicity was considered to be 613 ppm, due to decreased mean bodyweight gain, mean net bodyweight gain and food consumption. Using standard minute volume and body weights for female Sprague Dawley rats in a subchronic study, the calculated developmental toxicity NOAEL was considered to be 1547 mg/kg/day, the highest dose tested and the maternal toxicity was considered to be 758 mg/kg/day (ECHA, 2012a).

A pilot prenatal developmental toxicity study was summarized by the US EPA in their hazard assessment of 2-heptanone, but was not presented in the US EPA HPV submission. According to the US EPA, 2-heptanone was administered via oral gavage to pregnant Crj:CD (SD) rats (12–13/dose) at doses of 0, 100, 250, 500, or 1000 mg/kg/day in corn oil on GDs 6 to 15. Observations included mortality, clinical signs, body weight, and food consumption. The gravid uterine weights, number of corpora lutea, implantations, fetal survival, sex, and fetal weights were assessed. All fetuses were examined for external abnormalities, and half of the fetuses from each litter were examined for skeletal and visceral abnormalities. Ataxia was observed in dams treated at 500 and 1000 mg/kg/day. Furthermore, bradypnea, lacrimation, and prone position was observed at 1000 mg/kg/day. Maternal bodyweight gain was significantly decreased at 1000 mg/kg/day in the absence of changes in the mean body weight and food consumption. At 1000 mg/kg/day, live fetal body weight and the number of ossified sacrococcygeal vertebral bodies in males were significantly decreased. At 500 mg/kg/day, the sex ratio (male/alive) was significantly increased. There were no other treatment-related effects on the number of corpora lutea, implantations and live fetuses, sex ratio, embryo, and fetal mortality. No other effect on external, visceral, or skeletal anomalies or variations were observed. The NOAEL for maternal toxicity was considered to be 250 mg/kg/day, based on ataxic gait. The NOAEL for developmental toxicity was considered to be 500 mg/kg/day, based on effects on fetal body weight and skeletal ossification at the highest dose (US EPA, 1993). The most conservative NOAEL of 500 mg/kg/day was considered for the developmental toxicity endpoint. **Therefore, the 2-octanone MOE for the developmental toxicity endpoint can be calculated by dividing the 2-heptanone NOAEL in mg/kg/day by the total systemic exposure to 2-octanone, 500/0.00062 or 806452.**

There are no reproductive toxicity data on 2-octanone. Read-across material, 2-heptanone (CAS # 110-43-0; see Section V) has sufficient reproductive toxicity data to support the reproductive toxicity endpoint. In an OECD 421/GLP combined reproductive/developmental screening study, 2-heptanone was administered to groups of 12 Sprague Dawley rats/sex via inhalation at target concentrations of 0, 80, 400, or 1000 ppm (actual measured concentrations of 0, 79, 406, or 1023 ppm) for 6 h/day, 7 days/week during premating, mating, GD, and early lactation for a total of 50 exposure days for males and 34–47 exposure days for females. There were no effects in any of the reproductive organs that were weighed or examined grossly or histologically. There were no treatment-related effects on litter parameters or reproductive performance observed. No treatment-induced alterations in pup body weight, clinical signs, or external abnormalities were observed. Thus, the NOAEC for effects on fertility was considered to be 1023 ppm, the highest concentration tested. Using standard minute volume and bodyweight values for Sprague Dawley rats in a subchronic study, the calculated NOAEL for effects on fertility was considered to be 1239 mg/kg/day (https://echa.europa.eu/registration-dossier/-/registered-dossier/10230/7/9/2, ECHA, 2012a). 100% inhaled dose was considered for calculating the NOAEL. **Therefore, the 2-octanone MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-heptanone NOAEL in mg/kg/day by the total systemic exposure to 2-octanone, 1239/0.00062 or 1998387.**

In addition, the total systemic exposure to 2-octanone (0.62 μg/kg/day) is below the TTC (9 μg/kg/day) for the developmental and reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/06/17.

10.1.4. Skin sensitization

Based on the existing data and the read-across 2-heptanone (CAS # 110-43-0), 2-octanone does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for 2-octanone. Based on the read-across material 2-heptanone (CAS # 110-43-0; see Section V), 2-octanone does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay (LLNA), read-across 2-heptanone was found to be negative up to the maximum tested concentration of 100%, which resulted in a Stimulation Index (SI) of 1.6 (ECHA, 2012a). In guinea pigs, an open epicutaneous test did not present reactions indicative of sensitization up to 4% read-across material 2-heptanone (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with 4% 2-octanone (2760 μg/cm^2) (RIFM, 1973). Additionally, no skin sensitization reactions were observed with 4% read-across material 2-heptanone (2760 μg/cm^2) in a human maximization test (RIFM, 1974).

Based on weight of evidence from structural analysis and read-across material 2-heptanone, 2-octanone does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: Patel et al., 2002.

Literature Search and Risk Assessment Completed On: 08/28/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, 2-octanone 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-octanone in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, 2-octanone 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: 08/02/17.

10.1.6. Local respiratory toxicity

There is insufficient inhalation data available on 2-octanone; however, in 10 month subchronic whole-body inhalation study for the analog 2-heptanone (CAS # 110-43-0; see Section V), a NOAEC of 4787.11 mg/m^3 is reported by Lynch et al. (1981).

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data from the scientific literature to calculate the MOE for local respiratory toxicity. In a 10-month subchronic whole-body inhalation study conducted in both rats and monkeys, a NOAEC of 4787.11 mg/m^3 was reported for 2-heptanone (Lynch et al., 1981). Both male Sprague Dawley rats (n = 50) and Cynomolgus monkeys (strain: *Macaca fascicularis*; n = 8) were exposed to 0 (filtered air), 611.82, or 4787.11 mg/m^3 (analytical verification: 611.82 ± 140.11 mg/m^3 and 4787.11 ± 635.17 mg/m^3) of the test material (6 h/day, 5 days/week). Clinical observations (body weight and motility), clinical chemistry (blood sample analysis), metabolism study (blood and urine samples), pulmonary function evaluation (monkeys only), as well as gross and histopathology were all considered. Pulmonary function evaluation (monkeys only) included mechanical properties (compliance and resistance), lung volumes, flow-volume dynamics, distribution of ventilation, diffusion, and gas exchange assessment was done before the first exposure, and then again after 6 months of exposure to 2-heptanone. No treatment-related mortality, gross or histopathological alterations were observed for both species. There were no statistically significant changes in pulmonary function following 6 months of exposure to 2-heptanone (monkeys only); although there was a high degree of variability among the treated animals. Therefore, the NOAEC for both the rat and monkey was considered to be 4787.11 mg/m^3.

This NOAEC expressed in mg/kg lung weight/day is:

- (4787.11 mg/m^3) (1m^3/1000L) = 4.79 mg/L
- Minute ventilation (MV) of 1.729 L/min for a monkey** × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 622 L/day
- (4.79 mg/L) (622 L/d) = 2979 mg/day
- (2979 mg/day)/(0.15 kg lung weight of monkey***) = 19860 mg/kg lung weight/day

The 95th percentile calculated exposure to 2-octanone was reported to be 0.019 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; and Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.029 mg/kg lung weight/day resulting in an MOE of 684828 (i.e., [19860 mg/kg lung weight/day]/[0.029 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.019 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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Literature Search and Risk Assessment Completed On: 09/11/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-octanone 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-octanone was 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 2-octanone 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; #68218). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012b). 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.

10.2.2. Risk assessment

Based on the current VoU (2015), 2-octanone presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. RIFM, 1995**:** The ultimate and ready biodegradability of 2-octanone was studied using a sealed vessel test, which was conducted according to OECD TG 301B. 2-Octanone (10 mg/L) and secondary effluent from an unacclimatized activated sludge plant were incubated for 28 days, and CO_2 production was measured. The biodegradation rate of 2-octanone at day 28 was 94.3%.

Ecotoxicity: No data available.

10.2.2.2. Other available data

2-Octanone has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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)**	115.8			1,000,000	0.1158	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	66.75	38.68	31.34	10,000	3.134	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.2	2.2
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 3.134 µg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 8/14/17.

11. Literature search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/31/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.01.029.

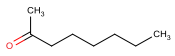
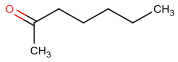
Appendix

Read-across justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material
Principal Name	2-Octanone	2-Heptanone
CAS No.	111-13-7	110-43-0
Structure		
Similarity (Tanimoto Score)		0.95
Read-across Endpoint		• Genotoxicity • Repeated dose • Developmental and reproductive • Skin sensitization • Respiratory
Molecular Formula	$C_8H_{16}O$	$C_7H_{14}O$
Molecular Weight	128.22	114.19
Melting Point (°C, EPI Suite)	−30.72	−42.77
Boiling Point (°C, EPI Suite)	163.60	141.64
Vapor Pressure (Pa @ 25 °C, EPI Suite)	249	655
Log Kow (KOWWIN v1.68 in EPI Suite)	2.37	1.98
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	899	4300
J_{max} (mg/cm^2/h, SAM)	55.809	215.198
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.04E-004	1.54E-004
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify	• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
Local Respiratory Toxicity		
Respiratory Sensitization (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-octanone (CAS # 111-13-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physicochemical properties and expert judgment, 2-heptanone (CAS # 110-43-0) was identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- 2-Heptanone (CAS # 110-43-0) was used as a read-across analog for the target material 2-octanone (CAS # 111-13-7) for the genotoxicity, repeated dose, developmental and reproductive, skin sensitization, and respiratory endpoints.
  - ○ The target substance and the read-across analog are structurally similar and belong to the class of ketones.
  - ○ The target substance and the read-across analog share a common saturated aliphatic ketone fragment.
  - ○ The key difference between the target substance and the read-across analog is that the target has a C8 aliphatic chain, while the read-across analog has a C7 aliphatic chain. This structural difference is toxicologically insignificant.
  - ○ The similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by a common saturated aliphatic ketone fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - ○ The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ 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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