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Short Review

RIFM fragrance ingredient safety assessment, 3-heptanone, CAS Registry Number 106-35-4

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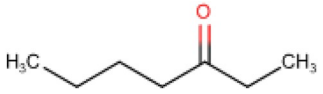
Version: 110818. This version replaces any previous versions.
Name: 3-Heptanone
CAS Registry Number: 106-35-4



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 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

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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.
3-Heptanone 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 3-heptanone is not genotoxic and that there are no safety concerns for 3-heptanone for skin sensitization under the current declared levels of use. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints 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; 3-heptanone 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: Screening Level: 3.2 (BIOWIN 3) US EPA (2012a)
Bioaccumulation: Screening Level: 6.42 L/kg US EPA (2012a)
Ecotoxicity: Screening Level: Fish LC50: 280.7 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: 280.7 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.2807 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening-level

1. Identification

1. **Chemical Name:** 3-Heptanone
2. **CAS Registry Number:** 106-35-4
3. **Synonyms:** Butyl ethyl ketone; Ethyl butyl ketone; Heptan-3-one; 3-Heptanone
4. **Molecular Formula:** $C_7H_{14}O$
5. **Molecular Weight:** 114.19
6. **RIFM Number:** 794
7. **Stereochemistry:** No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 146 °C (FMA Database), 141.64 °C (US EPA, 2012a)
2. **Flash Point:** 36 °C (GHS), 97 °F; CC (FMA Database)
3. **Log K_{OW}**: 1.73 (US EPA, 2012a)
4. **Melting Point**: −42.77 °C (US EPA, 2012a)
5. **Water Solubility:** 3511 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.818 (FMA Database), .8155 (EOA, 1976 Sample 76–96)
7. **Vapor Pressure:** 4.31 mm Hg @ 20 °C (US EPA, 2012a), 2.8 mm Hg

20C (FMA), 5.86 mm Hg @ 25 °C (US EPA, 2012a)
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:** A colorless liquid with a fruity, ketonic, sweet with a musty cheese-like note.*

* http://www.thegoodscentscompany.com/data/rw1025651.html, 09/15/17.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.000032% (RIFM, 2016)
3. **Inhalation Exposure*:** < 0.00010 mg/kg/day or 0.00000010 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.00023 mg/kg/day (RIFM, 2016)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015; Safford et al., 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. **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)

3-Heptanone is reported to occur in nature in the following*:

Apple brandy (*Calvados*)	Milk and milk products
Apple processed (*Malus* species)	Olive (*Olea europaea*)
Banana (*Musa sapientum* L.)	Passion fruit (*Passiflora* species)
Beans	Peach (*Prunus persica* L.)
Beef	Peanut (*Arachis hypogaea* L.)
Cheese, various types	Pear (*Pyrus communis* L.)
Chicken	Pecan (*Carya illinoensis* Koch)
Coffee	Plum (*Prunus* species)
Fish	Plum brandy
Grape (*Vitis* species)	Rooibos tea (*Aspalathus linearis*)
Grape brandy	Sesame seed (roasted)
Mangifera species	Shrimps (prawn)
Mentha oils	

*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

Pre-registered for 2010; no dossier available as of 11/08/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, 3-heptanone does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 3-Heptanone was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2014). There are no studies assessing the mutagenic activity of 3-heptanone; however, 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.

There are no studies assessing the clastogenic activity of 3-heptanone; however, read-across can be made to 2-heptanone (CAS # 110-43-0; see Section V). 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 3-heptanone.

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: 08/24/17.

10.1.2. Repeated dose toxicity

The margin of exposure for 3-heptanone is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 3-heptanone. Read-across material 2-heptanone (CAS # 110-43-0; see Section V) has sufficient repeated dose toxicity data to support the repeated dose toxicity endpoint. 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 (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 3-heptanone 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 3-heptanone, 1087/0.00023 or 4726087.**

In addition, the total systemic exposure to 3-heptanone (0.23 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. Reproductive toxicity

The margin of exposure for 3-heptanone is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no developmental toxicity data on 3-heptanone. 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 3-heptanone 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 3-heptanone, 500/0.00023 or 2173913.**

There are no fertility data on 3-heptanone. Read-across material 2-heptanone (CAS # 110-43-0; see Section V) has sufficient fertility data to support the fertility 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 (ECHA, 2012a). 100% inhaled dose was considered for calculating the NOAEL. **Therefore, the 3-heptanone MOE for the fertility endpoint can be calculated by dividing the 2-heptanone NOAEL in mg/kg/day by the total systemic exposure to 3-heptanone, 1239/0.00023 or 5386957.**

In addition, the total systemic exposure to 3-heptanone (0.23 μg/kg/day) is below the TTC (9 μg/kg/day) for the reproductive toxicity endpoint 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), 3-heptanone 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 3-heptanone. Based on the read-across analog 2-heptanone (CAS# 110-43-0; see Section V), 3-heptanone 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 material 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, 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% 3-heptanone (2760 μg/cm^2) (RIFM, 1976). Additionally, no skin sensitization reactions were observed with 4% read-across analog 2-heptanone (2760 μg/cm^2) in a human maximization test (RIFM, 1974).

Based on weight of evidence from structural analysis and read-across analog 2-heptanone, 3-heptanone 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 the available UV/Vis spectra, 3-heptanone 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 3-heptanone 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, 3-heptanone 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 are no inhalation data available on 3-heptanone; however, in a 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 3-heptanone was reported to be 0.00000010 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 0.00000015 mg/kg lung weight/day resulting in a MOE of 132400000000 (i.e., [19860 mg/kg lung weight/day]/[0.00000015 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 0.00000010 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by, Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy", subsection, "Comparative Airway Anatomy."

**W. Bide, R & J. Armour, S & Yee, Eugene. (1997). Estimation of Human Toxicity From Animal Inhalation Toxicity Data: 1. Minute Volume-Body Weight Relationships Between Animals And Man. (Technical report).

***Davies, B. and Morris, T. (1993) Physiological Parameters in Laboratory Animals and Humans. Pharmaceutical Research, 10, 1093–1095. https://doi.org/10.1023/A:1018943613122.

Additional References:

ODonoghue et al., 1984; Carpenter et al., 1949; Smyth et al., 1949; Katz et al., 1980; De Ceaurriz et al., 1984; Smyth et al., 1962; Johnson et al., 1978: Duchamp (1982); Revial et al., 1982; Specht et al., 1940; Hansen and Nielsen, 1994; Korpi et al., 1999.

Literature Search and Risk Assessment Completed On: 09/11/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 3-heptanone 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, 3-heptanone 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 (US EPA, 2012a) did not identify 3-heptanone as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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 (IFRA, 2015), 3-heptanone does not present a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. 3-Heptanone 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)**	<u>280.7</u>			1,000,000	0.2807	

Exposure	Europe	North America
Log K_{ow} used	1.73	1.73
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

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

The RIFM PNEC is 0.2807 μg/L. The revised PEC/PNECs for EU and NA: not applicable; cleared at the screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: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.2019.04.022.

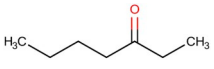
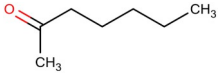
Appendix

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, 2012).
- 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	3-Heptanone	2-Heptanone
CAS No.	106-35-4	110-43-0
Structure		
Similarity (Tanimoto Score)		0.88
Read-across Endpoint		• Genotoxicity • Repeated dose • Developmental and reproductive • Skin sensitization • Respiratory
Molecular Formula	$C_7H_{14}O$	$C_7H_{14}O$

Molecular Weight	114.19	114.19
Melting Point (°C, EPI Suite)	−42.77	−42.77
Boiling Point (°C, EPI Suite)	141.64	141.64
Vapor Pressure (Pa @ 25 °C, EPI Suite)	781	655
Log Kow (KOWWIN v1.68 in EPI Suite)	1.73	1.98
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	4300	4300
J_{max} (μg/cm^2/h, SAM)	246.755	215.198
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.54E-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)	● No alert found	● 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 3-heptanone (CAS # 106-35-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 2-heptanone (CAS # 110-43-0) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- 2-Heptanone (CAS # 110-43-0) was used as a read-across analog for the target material 3-heptanone (CAS # 106-35-4) for the genotoxicity, repeated dose, developmental and reproductive, skin sensitization and respiratory endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the class of ketones.
  - o The target substance and the read-across analog share a common saturated aliphatic ketone fragment.
  - o The key difference between the target substance and the read-across analog is that the target has a ketone substitution on the 3rd position of the aliphatic chain while the read-across material has a ketone group on the 2nd position of the aliphatic chain. This structural difference is toxicologically insignificant.
  - o 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.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance 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.

References

Albro, P.W., Corbett, J.T., Schroeder, J.L., 1984. Metabolism of methyl n-amyl ketone (2 heptanone) and its binding to DNA of rat liver in vivo and in vitro. Chem. Biol. Interact. 51 (3), 295–308.

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

Bide, W., Armour, R.J., Eugene, S., Yee, 1997. Estimation of Human Toxicity from Animal Inhalation Toxicity Data: 1. Minute Volume-Body Weight Relationships between Animals and Man. (Technical report).

Carpenter, C.P., Smyth Jr., H.F., Pozzani, U.C., 1949. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Toxicol. 31 (6), 343–346.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. 4 (Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Davies, B., Morris, T., 1993. Physiological parameters in laboratory animals and humans. Pharmaceut. Res. 10, 1093–1095. https://doi.org/10.1023/A:1018943613122.

De Ceaurriz, J., Micillino, J.C., Marignac, B., Bonnet, P., Muller, J., Guenier, J.P., 1984. Quantitative evaluation of sensory irritating and neurobehavioral properties of aliphatic ketones in mice. Food Chem. Toxicol. 22 (7), 545–549.

Duchamp, A., 1982. Electrophysiological responses of olfactory bulb neurons to odour stimuli in the frog. A comparison with receptor cells. Chem. Senses 7 (2), 191–210.

ECHA, 2012a. Registration Dossier Heptan-2-One. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/10230/1.

ECHA, 2012b. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. Read-across Assessment Framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Gaunt, I.F., Carpanini, F.M.B., Wright, M.G., Grasso, P., Gangolli, S.D., 1972. Short-term toxicity of methyl amyl ketone in rats. Food Cosmet. Toxicol. 10 (5), 625–636.

Hansen, L.F., Nielsen, G.D., 1994. Sensory irritation, pulmonary irritation of n-methyl ketones. Receptor activation mechanisms and relationships with threshold limit values. Arch. Toxicol. 68 (3), 193–202.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Johnson, B.L., Setzer, J.V., Lewis, T.R., Hornung, R.W., 1978. An electrodiagnostic study of the neurotoxicity of methyl n-amyl ketone. AIHAJ (Am. Ind. Hyg. Assoc. J.) 39, 866–872.

Katz, G.V., O'Donoghue, J.L., DiVincenzo, G.D., Terhaar, C.J., 1980. Comparative neurotoxicity and metabolism of ethyl n-butyl ketone and methyl n-butyl ketone in rats. Toxicol. Appl. Pharmacol. 52 (1), 153–158.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. In: Current Problems in Dermatology, vol 14. pp. 152–171.

Korpi, A., Kasanen, J.-P., Alarie, Y., Kosma, V.-M., Pasanen, A.L., 1999. Sensory irritating potency of some microbial volatile organic compounds (MVOCs) and a mixture of five MVOCs. Arch. Environ. Health 54 (5), 347–352.

Kreja, L., Seidel, H.J., 2001. Toxicology study of some often detected microbial volatile organic compounds (MVOC). Umweltmed. Forsch. Prax. 6 (3), 159–163.

Kreja, L., Seidel, H.-J., 2002. Evaluation of the genotoxic potential of some microbial volatile organic compounds (MVOC) with the comet assay, the micronucleus assay and the HPRT gene mutation assay. Mutat. Res. Genet. Toxicol. Environ. Mutagen 513 (1–2), 143–150.

Lynch, D.W., Lewis, T.R., Moorman, W.J., Plotnick, H.B., Schuler, R.L., Smallwood, A.W., Kommineni, C., 1981. Inhalation toxicity of methyl n-amyl ketone (2-heptanone) in rats and monkeys. Toxicol. Appl. Pharmacol. 58 (3), 341–352.

Misumi, J., Nagano, M., 1984. Neurophysiological studies on the relation between the structural properties and neurotoxicity of aliphatic hydrocarbon compounds in rats. Br. J. Ind. Med. 41 (4), 526–532.

Nakajima, D., Ishii, R., Kageyama, S., Onji, Y., Mineki, S., Morooka, N., Takatori, K., Goto, S., 2006. Genotoxicity of microbial volatile organic compounds. J. Health Sci. 52 (2), 148–153.

ODonoghue, J.L., Krasavage, W.J., DiVincenzo, G.D., Katz, G.V., 1984. Further studies on ketone neurotoxicity and interactions. Toxicol. Appl. Pharmacol. 72 (2), 201–209.

OECD, 2012. The OECD QSAR Toolbox, V 3.4. Retrieved from. http://www.qsartoolbox.org/.

OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA(2015), vol 7 Retrieved from. http://www.oecd.org/.

Patel, H., ten Berge, W., Cronin, M.T.D., 2002. Quantitative structure-activity relationships (QSARs) for the prediction of skin permeation of exogenous chemicals. Chemosphere 48 (6), 603–613.

Phalen, R.F., 2009. Inhalation Studies. Foundations and Techniques, second ed. Informa Healthcare USA, Inc., New York, NY.

Revial, M.F., Sicard, G., Duchamp, A., Holley, A., 1982. New studies on odour discrimination in the frog's olfactory receptor cells. I. Experimental results. Chem. Senses 7 (2), 175–190.

RIFM (Research Institute for Fragrance Materials, Inc), 1974. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1801. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1976. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1796. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2014. Report on the Testing of 3-heptanone in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 67396. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2016. Exposure Survey 13 November 2016.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., et al., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74 (12), 164–176.

Smyth Jr., H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., 1962. Range-finding toxicity data: list VI. AIHAJ (Am. Ind. Hyg. Assoc. J.) 23, 95–107.

Smyth, H.F., Carpenter, C.P., Weil, C.S., 1949. Range-finding toxicity data, list III. The journal of industrial hygiene and toxicolology. J. Ind. Hyg. Toxicol. 31 (1), 60–63.

Specht, H., Miller, J.W., Valaer, P.J., Sayers, R.R., 1940. Acute response of Guinea pigs to the inhalation of ketone vapors. Natl. Inst. Health Bull. 176, 1–66.

Spencer, P.S., Bischoff, M.C., Schaumburg, H.H., 1978. On the specific molecular configuration of neurotoxic aliphatic hexacarbon compounds causing central-peripheral distal axonopathy. Toxicol. Appl. Pharmacol. 44 (1), 17–28.

US EPA, 1993. US EPA High Production Volume Information System (HPVIS): pilot prenatal developmental toxicity study of 2-Heptanone. Retrieved from. https://chemview.epa.gov/chemview.

US EPA, 1998. High Production Volume Information System (HPVIS): 2-Heptanone Genetic Toxicity in Vitro. Retrieved from https://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionId=24977038&epcount=2&epname=Genetic+Toxicity+in+vitro&epdiscp=Mammalian+Health+Effects+SIDS&selchemid=null&CategorySingle=null.

US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.