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Short Review

RIFM fragrance ingredient safety assessment, 2-nonanone, CAS Registry Number 821-55-6

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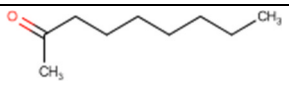

Name: 2-Nonanone
CAS Registry Number: 821-55-6

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor

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BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts

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DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

2-Nonanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-nonanone is not genotoxic. Data on read-across analog 2-heptanone (CAS # 110-43-0) provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 2-nonanone is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog 4-methyl-2-pentanone (CAS # 108-10-1). The environmental endpoints were evaluated; 2-nonanone was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	Kreja (2002)
Repeated Dose Toxicity: NOAEL = 1087 mg/kg/day.	Lynch (1981)
Reproductive Toxicity: Developmental Toxicity NOAEL = 500 mg/kg/day. Fertility NOAEL = 1239 mg/kg/day.	(US EPA, 2020a; ECHA REACH Dossier: Heptan-2-one; ECHA, 2012b)
Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: NOEC = 205 mg/m^3.	Phillips (1987)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Screening-level: 3.16 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 54.8 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 46.27 mg/L	(RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 46.27 mg/	(RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.04627 μg/L	
Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name**: 2-Nonanone
2. **CAS Registry Number**: 821-55-6
3. **Synonyms**: Methyl heptyl ketone; Nonan-2-one; ｱﾙｷﾙ(C = 1–16) ﾒﾁﾙｹﾄﾝ; 2-Nonanone
4. **Molecular Formula**: $C_9H_{18}O$
5. **Molecular Weight**: 142.24
6. **RIFM Number**: 1136
7. **Stereochemistry**: No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 192 °C @ 742 mm Hg (Fragrance Materials Association [FMA]), 184.65 °C (EPI Suite)
2. **Flash Point:** 153 °F; CC (FMA), 67 °C (Globally Harmonized System)
3. **Log K_{OW}:** 2.71 (EPI Suite)
4. **Melting Point**: 18.94 °C (EPI Suite)
5. **Water Solubility:** 170.6 mg/L (EPI Suite)
6. **Specific Gravity:** 0.83 (FMA)
7. **Vapor Pressure:** 0.449 mm Hg @ 20 °C (EPI Suite v4.0), 0.3 mm Hg 20 °C (FMA), 0.647 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A clear liquid fruity-floral, slightly fatty, and herbaceous odor (Arctander, Volume II 1969)

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. 95th Percentile Concentration in Hydroalcoholics: 0.0024% (RIFM, 2019)
2. Inhalation Exposure*: 0.000014 mg/kg/day or 0.0011 mg/day (RIFM, 2019)
3. Total Systemic Exposure**: 0.00072 mg/kg/day (RIFM, 2019)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015a, 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section V. 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, 2015, 2017; Safford, 2015a, 2017).

5. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

6. 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: None
   b. Repeated Dose Toxicity: 2-Heptanone (CAS # 110-43-0)
   c. Reproductive Toxicity: 2-Heptanone (CAS # 110-43-0)
   d. Skin Sensitization: None
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: 4-methyl-2-pentanone (CAS # 108-10-1)
   g. Environmental Toxicity: None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References:
None.

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

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

Beef	Coconut (*Cocos nucifera* L.)
Cheese, various types	Mastic (*Pistacia lentiscus*)
Citrus fruits	Pork
Clam	Strawberry (*Fragaria* species)
Cloves (*Eugenia caryophyllata* Thunberg)	*Vaccinium* species

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

9. REACH dossier

Available; accessed 07/29/19 (ECHA, 2016a).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. The mutagenic activity of 2-nonanone was evaluated in an *in vitro* alkaline Comet assay conducted using 2 different cell lines such as human lung carcinoma epithelial cell line (A549) and Chinese hamster fibroblasts cell line (V79). 2-Nonanone (CAS # 821-55-6) was dissolved in dimethyl sulfoxide (DMSO) incubated with cell culture at concentrations of 6 and 14 mM at 37 °C for 4 h. The treated cells were subjected to alkaline lysis for 60 min and electrophoresis for 30 min at 25 V and 300 mA. The treated slides were scored for DNA migration by olive tail moment. The extent of DNA damage evaluated revealed no significant increase when compared to positive controls (Kreja, 2002). Based on these findings, under the given test conditions, 2-nonanone was found to be negative for DNA damage in the Comet assay.

As additional weight of evidence (WoE), data on another straight chain ketone, 2-heptanone (CAS# 110-43-0) can be considered for mutagenicity. 2-heptanone when tested in an Ames assay conducted in accordance with OECD TG 471 and was negative (ECHA, 2012b).

The clastogenic activity of 2-nonanone was evaluated in an *in vitro* micronucleus test conducted using Chinese hamster lung fibroblasts (V79) treated with 2-nonanone in DMSO at concentrations of 6 and 14 mM in the presence and absence of metabolic activation (S9) for 4 h 2-Nonanone did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (Kreja, 2002). Under the conditions of the study, 2-nonanone was considered to be non-clastogenic in the *in vitro* micronucleus test.

As additional WoE, data on the straight chain ketone 2-heptanone (CAS# 110-43-0) can be considered for clastogenicity. 2-heptanone when tested in a chromosomal aberration study in accordance with OECD TG 473 using a Chinese hamster ovary cell line for 3 and 18 h in the presence and absence of metabolic activation. The material was negative for clastogenic effects (ECHA, 2012b).

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

Additional References: ECHA, 2016a.

Literature Search and Risk Assessment Completed On: 09/12/19.

11.1.2. Repeated dose toxicity

The MOE for 2-nonanone is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 2-nonanone. Read-across material 2-heptanone (CAS # 110-43-0; see Section VI) 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 gavage 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, 1972; also available at ECHA, 2012b).

In a subchronic inhalation study conducted prior to GLPs, groups of 50 male Sprague Dawley rats and 8 male Cynomolgus monkeys (strain: *Macaca fascicularis*) 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 rats and monkeys 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 (MV) and body weight 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 MV and body weight values (body weight of 4.5 kg, MV of 1.729 L/min), the calculated NOAEL was considered to be 662 mg/kg/day (Lynch, 1981; data also available at US EPA, 2020a; ECHA, 2012b [001 key/-experimental results]; ECHA, 2012b [002 key/experimental results]).

In an OECD/GLP 421 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 days (GDs), 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, but it declined over the course of exposure as the animals appeared to acclimate to the vapor. The mean body weight 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 on 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 MV and body weight values for Sprague Dawley rats in a subchronic study, the calculated NOAEL was considered to be 1239 mg/kg/day (ECHA, 2012b; data also available at US EPA, 2020a; US EPA, 2020b).

Since the effects of an increase in urine cellularity and organ weight changes from the oral gavage study were not seen in the OECD 421 inhalation study for both male and female rats, 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. Therefore, the 2-nonanone 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-nonanone, 1087/0.00072, or 1509722.

In addition, the total systemic exposure to 2-nonanone (0.72 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

Additional References: Johnson (1978); Spencer (1978); Misumi (1984); RIFM, 1980b.

Literature Search and Risk Assessment Completed On: 09/04/19.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. An OECD 421/GLP reproduction/developmental toxicity screening test was conducted in Sprague Dawley rats. 2-Nonanone was treated via inhalation route at concentrations of 0, 78.6, 405.8, or 1022.6 ppm (0,7.86, 40.58 and 102.26 mg/kg/day). Males were exposed for 50 days, while females were dosed for 37–47 days (through day 19 of gestation) for 6 h/day and 7 days/week. Reduction in food consumption was observed in male rats from 0 to 7 days at 102.6 mg/kg/day. Minimal reductions in activity level were observed at 40.58 and 102.26 mg/kg/day. No changes in body weight or weight gain were observed in treated rats as compared to the control. In addition, no changes in organ weight, gross pathology, histopathology, and sperm measures were observed in treated rats as compared to the control. For pups, no clinical signs were observed in treated rats as compared to the control. In addition, no changes in bodyweight gain or gross pathology were observed in pups. Thus, in this study, the NOAEL for fertility was considered to be 78.6 ppm, corresponding to a reduction in activity level at 405.8 and 1022.6 ppm. This concentration was equal to 7.86 mg/kg/day. The NOAEL for developmental toxicity in this study was considered to be 1022.6 ppm, the highest dose tested. This concentration was equal to 102.26 mg/kg/day (ECHA, 2016a). As the number of animals was not mentioned in this study, the data were considered insufficient.

Read-across material 2-heptanone (CAS # 110-43-0; see Section VI) has sufficient developmental toxicity data to support the developmental toxicity endpoint. In an OECD 414/GLP prenatal developmental screening study, 2-heptanone was administered via inhalation (whole-body) to groups of 25 female Crl:CD(SD) rats for 6 h/day from GD 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 treatment-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 maternal and developmental toxicity was considered to be 1251 ppm, based on the lack of adverse maternal and developmental effects. Using standard MV and body weights for female Sprague Dawley rats in a subchronic study, the calculated maternal and developmental toxicity NOAEL was considered to be 1547 mg/kg/day, the highest dose tested (ECHA, 2012b).

A pilot prenatal developmental toxicity study conducted in 1993 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 GD 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 were 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, 2020a). The most conservative NOAEL of 500 mg/kg/day was selected for the developmental toxicity endpoint. Therefore, the 2-nonanone 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-nonanone, 500/0.00072, or 694444.

Read-across material 2-heptanone (CAS # 110-43-0; see Section VI) 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, gestation, and early lactation for a total of 50 exposure days for males and 34–47 exposure days for females. There were no effects on 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 MV and body weight 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, 2012b; data also available at US EPA, 2020a; US EPA, 2020b). Therefore, the 2-nonanone MOE for the fertility endpoint can be calculated by dividing the 2-heptanone NOAEL in mg/kg/day by the total systemic exposure to 2-nonanone, 1239/0.00072, or 1720833.

In addition, the total systemic exposure to 2-nonanone (0.72 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) 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: 09/06/19.

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.3). No predictive skin sensitization studies are available for 2-nonanone. However, in a human maximization test, no skin sensitization reactions were observed at 5% or 3450 μg/cm^2 of 2-nonanone (ECHA, 2016a; RIFM, 1980a). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 2-nonanone that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/13/19.

Table 1
Maximum acceptable concentrations for 2-nonanone that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	8.2×10^{-7}%
2	Products applied to the axillae	0.021%	0.0014%
3	Products applied to the face using fingertips	0.41%	1.4×10^{-4}%
4	Fine fragrance products	0.39%	0.0024%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.0077%
6	Products with oral and lip exposure	0.23%	0.022%
7	Products applied to the hair with some hand contact	0.79%	1.8×10^{-4}%
8	Products with significant ano-genital exposure	0.041%	No Data[b]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.0020%
10	Household care products with mostly hand contact	2.7%	0.0031%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[b]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	0.28%

[b] No reported use.

[a] Note: [a]For a description of the categories, refer to the IFRA/RIFM Information Booklet.

[b] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-nonanone 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, 2009). Based on the lack of absorbance, 2-nonanone does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. 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, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/13/

19.

11.1.6. Local respiratory toxicity

There are insufficient inhalation data available on 2-nonanone; however, in a 2-week inhalation study for the read-across analog 4-methyl-2-pentanone (CAS # 108-10-1; see Section VI), a NOEC of 205 mg/m^3 was reported (Phillips, 1987).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 14-week whole-body inhalation exposure study, Fischer 344 rats (14/sex/group) were exposed to either 0, 205, 1033, or 4106 mg/m^3 MIBK for 6 h/day, 5 days/week (Phillips, 1987). Endpoints evaluated included clinical signs, body and organ weights (kidneys, heart, liver, lungs, and testes), urinalysis, hematology, serum chemistry (glucose and hepatic enzyme levels), complete gross pathology, and targeted histopathology (nasal cavity, trachea, liver, kidneys, and lungs) in all animals. Complete histopathology was conducted for the control (sham) and high-exposure (4106 mg/m^3) groups. Across all endpoints, no effects were documented in the low-exposure group (205 mg/m^3) for males or females. All adverse treatment-related effects were systemic (localized primarily to the kidney and liver) and occurred within the mid- and high-exposure groups (1033 or 4106 mg/m^3 MIBK). Treatment-related effects included increased body weights, increased platelet counts, decreased eosinophil counts, increased serum cholesterol, increased liver weights, increased urine glucose and protein levels, and hyaline droplet accumulation in the kidneys (severity was concentration-dependent). No lung, nasal cavity, or tracheal lesions were reported. Therefore, the NOEC was determined to be 205 mg/m^3.

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

- (205 mg/m^3) × (1 m^3/1000L) = 0.205 mg/L
- MV of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.205 mg/L) × (61.2 L/day) = 12.55 mg/day
- (12.55 mg/day)/(0.0016 kg lung weight of rat*) = 7844 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0011 mg/day; this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015; Safford, 2015a). 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, 2009) to give 0.0017 mg/kg lung weight/day resulting in a MOE of 4614118 (i.e., [7844 mg/kg lung weight of rat/day]/[0.0017 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.0011 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."

Additional References: NIOSH, 2006; NTP, 2005; DeCeaurriz (1984); Smyth (1951); DeCeaurriz (1981); Tyl (1987); Silverman (1946); McOmie (1949); Habig (1989); Lam (1990); Hjelm (1990); Abou-Donia (1991); Exxon (1982a); Exxon (1982b); Exxon (1982c); Hagmar, 1988; Dick (1992); Specht (1940); MacEwen (1971); MacEwen (1970); Duguay (1995); Gagnon (1994); Iregren (1993); Geller (1978); Spencer (1975); Duckett (1979); Duguay (1997a); Bernard (1997); Duguay (1997b); Kumagai (1999); Jang (2001); David (1999); Nemec (2004); Stout (2008); Tsai (2009).

Literature Search and Risk Assessment Completed On: 10/07/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-nonanone was performed following the RIFM Environmental Framework (Salvito, 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-nonanone 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 2-nonanone 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012a). 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), 2-nonanone presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. No data available

11.2.2.2. Biodegradation. No data available.

11.2.2.3. Ecotoxicity. No data available.

11.2.2.4. Other available data. 2-Nonanone has been registered for REACH with no additional data available at this time.

11.2.3. 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.

Exposure information and PEC calculation (following RIFM

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	46.27			1000000	0.04627	

Environmental Framework: Salvito, 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	2.71	2.71
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.04627 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 09/16/19.

13. Literature Search*

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 01/31/20.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111934.

Appendix

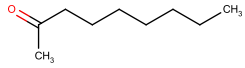
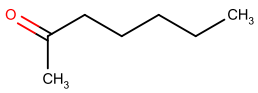
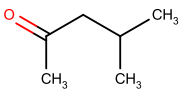
Read-across Justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).

- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

Principal Name	Target Material	Read-across Material	Read-across Material
	2-Nonanone	2-Heptanone	4-Methyl-2-pentanone
CAS No.	821-55-6	110-43-0	108-10-1
Structure			
Similarity (Tanimoto Score)		0.90	0.56
Read-across Endpoint		• Reproductive Toxicity • Repeated Dose Toxicity	• Local Respiratory Toxicity
Molecular Formula	$C_9H_{18}O$	$C_7H_{14}O$	$C_6H_{12}O$
Molecular Weight	142.24	114.18	100.16
Melting Point (°C, EPI Suite)	−7.50	−35.00	−84.00
Boiling Point (°C, EPI Suite)	195.30	151.00	116.50
Vapor Pressure (Pa @ 25 °C, EPI Suite)	83.19	513.29	2653.11
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.14	1.98	1.31
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	3.71E+02	4.30E+03	1.90E+04
J_{max} (μg/cm^2/h, SAM)	40.922	215.198	489.547
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.72E+01	1.71E+01	1.40E+01
Repeated Dose Toxicity			
Repeated Dose (HESS)	• Not categorized	• Not categorized	
Reproductive Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)	
Local Respiratory Toxicity			
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	• No alert found		• No alert found
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

Summary

There are insufficient toxicity data on 2-nonanone (CAS # 821-55-6). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 2-heptanone (CAS # 110-43-0) and 4-methyl-2-pentanone (CAS # 108-10-1) were identified as read-across analogs 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-nonanone (CAS # 821-55-6) for the repeated dose toxicity and reproductive toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of straight chain saturated aliphatic ketones.
  - o The target material and the read-across analog share a carbonyl group in position 2 within an aliphatic straight chain.
  - o The key difference between the target material and the read-across analog is that the target material is a C9 straight chain, whereas the read-across analog is a C7 straight chain. This structural difference is toxicologically insignificant.
  - o The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 4-Methyl-2-pentanone (CAS # 108-10-1) was used as a read-across analog for the target material 2-nonanone (CAS # 821-55-6) for the local respiratory toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic ketones.
  - o The target material and the read-across analog share a carbonyl group in position 2 within an aliphatic saturated chain.

- The key difference between the target material and the read-across analog is that the target material is a C9 straight chain, whereas the read-across analog is a C6 branched chain. The physical-chemical properties (log Kow, vapor pressure, and aqueous solubility) of the target material and the read-across analog do not have significant differences to affect the potential of each material to cause local respiratory toxicity. The mechanism of metabolism in lung tissue for any class of chemicals is not well-known. The molecular structure and physical-chemical properties profoundly affect the ADME properties of any molecule. Therefore, acting conservatively, we can conclude that the present differences in the structure and the physical-chemical properties between the two materials will not significantly affect the local respiratory toxicity endpoint, and the structural differences between the target material and the read-across analog are insignificant in the context of local respiratory toxicity.
- The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material 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.

References

Abou-Donia, M.B., Hu, Z., Lapadula, D.M., Gupta, R.P., 1991. Mechanisms of joint neurotoxicity of n-hexane, methyl isobutyl ketone and o-ethyl o-4-nitrophenyl phenylphosphonothioate in hens. J. Pharmacol. Exp. Therapeut. 257 (1), 282–289.

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.

Arctander, S., 1969. Perfume and Flavor Chemicals (Aroma Chemicals), vols. I and II. Published by the author: Montclair, NJ (USA).

Bernard, L., David, R.M., Tyler, T.R., Banton, M.I., Topping, D.C., O'Donoghue, J.L., 1997. A thirteen-week inhalation schedule-controlled operant behavior study of methyl iso-butyl ketone in the rat. Toxicologist 36 (1), 62 part 2.

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.

David, R.M., Bernard, L.G., Banton, M.I., Tyler, T.R., Topping, D.C., Gill, M.W., O'Donoghue, J.L., 1999. The effect of repeated methyl iso-butyl ketone vapor exposure on schedule-controlled operant behavior in rats. Neurotoxicology 20 (4), 583–594.

De Ceaurriz, J.C., Micillino, J.C., Bonnet, P., Guenier, J.P., 1981. Sensory irritation caused by various industrial airborne chemicals. Toxicol. Lett. 9, 137–143.

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.

Dick, R.B., Krieg Jr., E.F., Setzer, J., Taylor, B., 1992. Neurobehavioral effects from acute exposures to methyl isobutyl ketone and methyl ethyl ketone. Fund. Appl. Toxicol. 19 (3), 453–473.

Duckett, S., Streletz, L.J., Chambers, R.A., Auroux, M., Galle, P., 1979. 50 ppm MnBK Subclinical neuropathy in rats. Experientia 35 (10), 1365–1367.

Duguay, A.B., Plaa, G.L., 1995. Tissue concentrations of methyl isobutyl ketone, methyl n-butyl ketone and their metabolites after oral or inhalation exposure. Toxicol. Lett. 75 (1–3), 51–58.

Duguay, A.B., Plaa, G.L., 1997a. Ketone potentiation of intrahepatic cholestasis: effect of two aliphatic isomers. J. Toxicol. Environ. Health 50 (1), 41–52.

Duguay, A., Plaa, G.L., 1997b. Altered cholesterol synthesis as a mechanism involved in methyl isobutyl ketone-potentiated experimental cholestasis. Toxicol. Appl. Pharmacol. 147 (2), 281–288.

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

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

ECHA, 2016a. Nonan-2-one Registration Dossier. Retrieved from. https://echa.europa.eu/lt/registration-dossier/-/registered-dossier/17523/1.

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

Exxon Chemical Americas, 1982a. Submission to. EPA, Unpublished.

Exxon Chemical Americas, 1982b. Submission to. EPA, Unpublished.

Exxon Chemical Americas, 1982c. Submission to. EPA, Unpublished.

Gagnon, P., Mergler, D., Lapare, S., 1994. Olfactory adaptation, threshold shift and recovery at low levels of exposure to methyl isobutyl ketone (MIBK). Neurotoxicology 15 (3), 637–642.

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 Chem. Toxicol. 10 (5), 625–636.

Geller, I., Martinez, R.L., Hartmann, R.J., Kaplan, H.L., 1978. Effects of ketones on a match to sample task in the baboon. Proceedings west. pharmac. Soc. 21, 439–442.

Habig, C., Abou-Donia, M.B., Lapadula, D.M., 1989. Cytochrome P-450 induction in chickens exposed simultaneously to n-hexane and methyl iso-butyl ketone. Toxicologist 9 (1), 194.

Hagmar, L., Bellander, T., Hogstedt, B., Hallberg, T., Attewell, R., Raihle, G., Au, W.W., Legator, M.S., Mitelman, F., Skerfving, S., 1988. Biological effects in a chemical factory with mutagenic exposure. I. Cytogenetic and haematological parameters. Int. Arch. Occup. Environ. Health 60 (6), 437–444.

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.

Hjelm, E.W., Hagberg, M., Iregren, A., Lof, A., 1990. Exposure to methyl isobutyl ketone: toxicokinetics and occurrence of irritative and CNS symptoms in man. Int. Arch. Occup. Environ. Health 62 (1), 19–26.

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

Iregren, A., Tesarz, M., Wigaeus-Hjelm, E., 1993. Human experimental MIBK exposure: effects on heart rate, performance, and symptoms. Environ. Res. 63 (1), 101–108.

Jang, J.-Y., Droz, P.O., Kim, S., 2001. Biological monitoring of workers exposed to ethylbenzene and co-exposed to xylene. Int. Arch. Occup. Environ. Health 74 (1), 31–37.

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

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. Mutation Research. Genetic Toxicology and Environmental Mutagenesis 513 (1–2), 143–150.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Kumagai, S., Oda, H., Matsunaga, I., Kosaka, H., Akasaka, S., 1999. Uptake of 10 polar organic solvents during short-term respiration. Toxicol. Sci. 48 (2), 255–263.

Lam, C.-W., Galen, T.J., Boyd, J.F., Pierson, D.L., 1990. Mechanism of transport and distribution of organic solvents in blood. Toxicol. Appl. Pharmacol. 104 (1), 117–129.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

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.

MacEwen, J.D., Vernot, E.H., 1970. Toxic Hazards Research Unit Annual Technical Report: 1970. Unpublished.

MacEwen, J.D., Venot, E.H., Haun, C.C., 1971. Effect of 90-day continuous exposure to methylisobutylketone on dogs, monkeys, and rats, p. 730291. Unpublished. NTIS AD Rep.

McOmie, W.A., Anderson, H.H., 1949. Comparative Toxicologic Effects of Some Isobutyl Carbinols and Ketones, vol. 2. University California Publications Pharmacology, pp. 217–230, 17.

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.

Nemec, M.D., Pitt, J.A., Topping, D.C., Gingell, R., Pavkov, K.L., Rauckman, E.J., Harris, S.B., 2004. Inhalation two-generation reproductive toxicity study of methyl isobutyl ketone in rats. Int. J. Toxicol. 23 (2), 127–143.

National Institute for Occupational Safety and Health, Kanwal, R., Kullman, G., Fedan, K., Kreiss, K., 2006. NIOSH Health Hazard Evaluation Report. Unpublished.
National Toxicology Program, 2005. Toxicology and Carcinogenesis Studies of Methyl Isobutyl Ketone (CAS No. 108-10-1) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP-TR-538. NIH Publication No. 07-4476.
OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA, vol. 2015, p. 7. Retrieved from. http://www.oecd.org/.
OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.
Phillips, R.D., Moran, E.J., Dodd, D.E., Fowler, E.H., Kary, C.D., O'Donoghue, J., 1987. A 14-week vapor inhalation toxicity study of methyl isobutyl ketone. Fund. Appl. Toxicol. 9 (3), 380–388.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980a. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1790. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980b. 90-Day Repeated Oral Administration of Five Ketones and N-Heptane to Rats. Private Communication to FEMA. Unpublished Report from O'Donohogue, J.L. & Krasavage, W.J. RIFM Report Number 23424. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 2019. Exposure Survey 23. January 2019.
Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.
Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.
Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.
Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.
Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.
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., 2015a. 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, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015b. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.
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., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 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, 164–176.
Silverman, L., Schultz, H.F., First, M.W., 1946. Further studies on sensory response to certain industrial solvent vapors. The Journal of Industrial Hygiene and Toxicolology. The Journal of Industrial Hygiene and Toxicology 28, 262–266.
Smyth Jr., H.F., Carpenter, C.P., Weil, C.S., 1951. Range finding toxicity data: list IV. A. M.A. Archives of Industrial Hygiene and Occupational Medicine 4 (2), 119–122.
Specht, H., Miller, J.W., Valaer, P.J., Sayers, R.R., 1940. Acute response of Guinea pigs to the inhalation of ketone vapors. In: National Institute Health Bulletin, 176, pp. 1–66.
Spencer, P.S., Schaumberg, H.H., Raleigh, R.L., Terhaar, C.J., 1975. Nervous system degeneration produced by the industrial solvent methyl n-butyl ketone. Arch. Neurol. 32 (4), 219–222.
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.
Stout, M.D., Herbert, R.A., Kissling, G.E., Suarez, F., Roycroft, J.H., Chhabra, R.S., Bucher, J.R., 2008. Toxicity and carcinogenicity of methyl isobutyl ketone in F344N rats and B6C3F1 mice following 2-year inhalation exposure. Toxicology 244 (2–3), 209–219.
Tsai, C.-J., Chen, M.-L., Chang, K.-F., Chang, F.-K., Mao, I.-F., 2009. The pollution characteristics of odor, volatile organochlorinated compounds and polycyclic aromatic hydrocarbons emitted from plastic waste recycling plants. Chemosphere 74 (8), 1104–1110.
Tyl, R.W., France, K.A., Fisher, L.C., Pritts, I.M., Tyler, T.R., Philips, R.D., Moran, E.J., 1987. Developmental toxicity evaluation of inhaled methyl isobutyl ketone in Fisher 344 rats and CD-1 mice. Fund. Appl. Toxicol. 8 (3), 310–327.
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.
US EPA, 2020a. Assessment of 2-Heptanone (CAS 110-43-0). Retrieved from. https://chemview.epa.gov/chemview.
US EPA, 2020b. HPV Query Result (CAS 110-43-0). Retrieved from. https://ofmpub.epa.gov/oppthpv/public_search.publiclist.