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Short Review

# RIFM fragrance ingredient safety assessment, 2-tridecanone, CAS Registry Number 593-08-8

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ABSTRACT

The existing information supports the use of this material as described in this safety assessment. 2-Tridecanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-heptanone (CAS # 110-43-0) show that 2-tridecanone is not expected to be genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog 2-heptanone (CAS # 110-43-0) show that there are no safety concerns for 2-tridecanone for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-tridecanone is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 2-tridecanone is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 2-Tridecanone 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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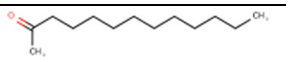
## Conflicts of interest

The authors declare that they have no conflicts of interest.



Version: 062322. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety assessments are published if new relevant data become available. Open access to all RIFM Fragrance Ingredient Safety Assessments is here: fragrancematerialsafetyresource.elsevier.com.

**Name**: 2-Tridecanone

**CAS Registry Number**: 593-08-8

**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

**CNIH** – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)

**Creme RIFM Model** - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford et al., 2017) compared to a deterministic aggregate approach

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

**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 Observed 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

(*continued on next column*)

(*continued*)

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-Tridecanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-heptanone (CAS # 110-43-0) show that 2-tridecanone is not expected to be genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog 2-heptanone (CAS # 110-43-0) show that there are no safety concerns for 2-tridecanone for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; 2-tridecanone is not expected to be photoirritating/photoallergenic. The local respiratory toxicity endpoint was evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class II material, and the exposure to 2-tridecanone is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 2-Tridecanone 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.

**Human Health Safety Assessment**

**Genotoxicity:** Not expected to be genotoxic. (ECHA REACH Dossier: Heptan-2-one; ECHA (2012b))

**Repeated Dose Toxicity:** NOAEL = 20 mg/kg/day. (Gaunt et al., 1972)

**Reproductive Toxicity:** Developmental Toxicity NOAEL = 1547 mg/kg/day. Fertility NOAEL = 1239 mg/kg/day. (ECHA REACH Dossier: Heptan-2-one; ECHA, 2012b)

**Skin Sensitization:** Not a concern for skin sensitization. (ECHA REACH Dossier: Heptan-2-one; ECHA, 2012b)

**Photoirritation/Photoallergenicity:** Not expected to be photoirritating/photoallergenic.
(UV/Vis Spectra; RIFM Database)

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

**Environmental Safety Assessment**

**Hazard Assessment:**

**Persistence:**
Screening-level: 3.0 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

**Bioaccumulation:**
Screening-level: 23.9 L/kg (EPI Suite v4.11; US EPA, 2012a)

**Ecotoxicity:**
Screening-level: Fish LC50: 1.244 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 1.244 mg/L ((RIFM Framework; Salvito et al., 2002)

**RIFM PNEC is:** 0.001244 μg/L

- **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

## 1. Identification

1. **Chemical Name:** 2-Tridecanone
2. **CAS Registry Number:** 593-08-8
3. **Synonyms:** Hendecyl methyl ketone; Methyl undecyl ketone; Tridecan-2-one; 2-Tridecanone
4. **Molecular Formula:** $C_{13}H_{26}O$
5. **Molecular Weight:** 198.35 g/mol
6. **RIFM Number:** 6159
7. **Stereochemistry:** No stereoisomer possible.

## 2. Physical data

1. **Boiling Point:** 263 °C (Fragrance Materials Association [FMA]), 259.8 °C (EPI Suite)
2. **Flash Point:** >93 °C (Globally Harmonized System [GHS]), >200 °F; CC (FMA)
3. **Log $K_{OW}$:** 4.68 (EPI Suite)
4. **Melting Point**: 30 °C (FMA), 25.54 °C (EPI Suite)
5. **Water Solubility:** 4.53 mg/L (EPI Suite)
6. **Specific Gravity:** 0.82 (FMA)
7. **Vapor Pressure:** 0.0118 mm Hg at 20 °C (EPI Suite v4.0), 0.003 mm Hg at 20 °C (FMA), 0.0203 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1}$ • $cm^{-1}$)
9. **Appearance/Organoleptic:** White waxy mass or colorless crystal leaves. Warm oily herbaceous or delicately spicy nut-like odor of considerable tenacity (Arctander, 1969)

## 3. Volume of use (Worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2019)

## 4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.2)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.00020% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.0000011 mg/kg/day or 0.000076 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.000064 mg/kg/day (RIFM, 2021)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015; Safford et al., 2015; Safford, 2017; and Comiskey, 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; Safford et al., 2015; Safford, 2017; and Comiskey, 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 v3.1 | OECD QSAR Toolbox v4.2 |
|---|---|---|
| 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. **Photoirritation/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

## 7. Metabolism

No relevant data available for inclusion in this safety assessment.

### 7.1. *Additional references*

None

## 8. Natural occurrence

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

*Allium* species.
Banana (*Musa sapientum* L.)
*Cheese*, various types.
Ginger (*Zingiber* species).
Lamb and mutton.
Malt.
Olive (*Olea europaea*).
Pork.
Rice (*Oryza sativa* L.)
Strawberry (*Fragaria* 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

Pre-registered for 2010; no dossier available as of 01/25/22.

## 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-tridecanone does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* 2-Tridecanone was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) without metabolic activation, negative for cytotoxicity with metabolic activation, and negative for genotoxicity with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on an appropriate read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

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

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

(ECHA, 2012a). Under the conditions of the study, 2-heptanone was not mutagenic in the Ames test, and this can be extended to 2-tridecanone.

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 material, 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, and this can be extended to 2-tridecanone.

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

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

**Literature Search and Risk Assessment Completed On:** 01/21/22.

*11.1.2. Repeated dose toxicity*

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

*11.1.2.1. Risk assessment.* There are no repeated dose toxicity data on 2-tridecanone. Read-across material 2-heptanone (CAS # 110-43-0; see Section VI) has sufficient data to support the repeated dose toxicity endpoint.

In a subchronic toxicity study, groups of 15 CFE rats/sex/dose were administered 2-heptanone via gavage (vehicle: corn oil) at doses of 0, 20, 100, or 500 mg/kg/day for 13 weeks. An additional CFE 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. Absolute kidney weights were increased in males at the high dose, while relative kidney weights were increased in males at the mid and high doses. Absolute liver weights were increased in females at the high dose, while relative liver weights were increased in both sexes at the high dose. Absolute stomach weights were increased in females 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 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 GLP- and OECD 421-compliant study, groups of 12 Sprague Dawley rats/sex/dose were administered 2-heptanone via inhalation at concentrations of 0, 80, 400, or 1000 ppm (actual measured concentrations of 0, 79, 406, or 1023 ppm) 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 (6 h/day, 7 days/week). A dose-related reduction in activity (less movement, decreased alertness, and slower response to tapping on the chamber wall) was observed in the mid- and high-dose animals; however, this effect declined over the course of exposure as the animals appeared to acclimate to the vapor. Mean bodyweight gains were reduced in the mid- and high-dose animals, while food consumption was reduced in the high-dose animals, during GDs 0–7 only. There were no effects in any of the selected organs that were weighed or examined grossly or histologically. Thus, based on no adverse effects seen up to the highest dose, the parental NOAEL for this study was considered to be 1023 ppm. 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, 2012b).

The most conservative NOAEL of 20 mg/kg/day was taken from the subchronic toxicity study.

Therefore, the 2-tridecanone 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-tridecanone, 20/0.000064, or 312500.

In addition, the total systemic exposure to 2-tridecanone (0.064 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class II material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 11/23/21.

*11.1.3. Reproductive toxicity*

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

*11.1.3.1. Risk assessment.* There are no developmental toxicity or fertility data on 2-tridecanone. Read-across material 2-heptanone (CAS # 110-43-0; see Section VI) has sufficient data to support the reproductive toxicity endpoint.

In an OECD 414- and GLP-compliant prenatal developmental toxicity study, 2-heptanone was administered via inhalation (whole-body) to groups of 25 female Crl:CD(SD) rats/sex/dose 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).

In an OECD 421- and GLP-compliant combined reproductive/developmental screening study, 2-heptanone was administered to groups of 12 Sprague Dawley rats/sex/dose via inhalation at concentrations of 0, 80, 400, or 1000 ppm (actual measured concentrations of 0, 79, 406, or 1023 ppm) during premating, mating, GD, and early lactation for a total of 50 exposure days for males and 34–47 exposure days for females (7 days/week, 6 h/day). 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 and developmental toxicity 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).

Because no adverse effects on developmental toxicity were observed in either study, the higher developmental toxicity NOAEL of 1547 mg/kg/day was taken from the OECD 414 study.

Therefore, the 2-tridecanone 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-tridecanone, 1547/0.000064 or 24171875.

Therefore, the 2-tridecanone MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-heptanone NOAEL in mg/kg/day by the total systemic exposure to 2-tridecanone, 1239/0.000064 or 19359375.

In addition, the total systemic exposure to 2-tridecanone (0.064 μg/kg/day) is below the TTC (9 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoints of a Cramer Class II material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 11/23/21.

### 11.1.4. Skin sensitization

Based on the existing data and read-across 2-heptanone (CAS # 110-43-0), 2-tridecanone does not present a concern for skin sensitization.

*11.1.4.1. Risk assessment.* Limited skin sensitization data are available for 2-tridecanone. Therefore, 2-heptanone (CAS # 110-43-0; see Section VI) was used for the risk assessment of 2-pentadecanone. The data on the read-across material are summarized in Table 1. Based on the existing data on the read-across material, 2-tridecanone is not considered a skin sensitizer. The chemical structure of the read-across material and the target material indicate that they would be expected to react with skin proteins directly (Roberts et al., 2007; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material 2-heptanone was found to be non-sensitizing when tested up to 100% (25000 μg/cm$^2$) (ECHA, 2012b). In guinea pigs, open epicutaneous tests did not present reactions indicative of sensitization with read-across 2-heptanone (Klecak, 1979, 1985). In a human maximization test, no skin sensitization reactions were observed with 2760 μg/cm$^2$ read-across 2-heptanone (RIFM, 1974).

Based on the weight of evidence (WoE) from structural analysis, animal studies, and a human study on the read-across material and the target material, 2-tridecanone does not present a concern for skin sensitization.

**Additional References:** Sharp (1978).

**Literature Search and Risk Assessment Completed On:** 01/17/22.

### 11.1.5. Photoirritation/photoallergenicity

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

*11.1.5.1. Risk assessment.* There are no photoirritation studies available for 2-tridecanone in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for photoirritation and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-tridecanone does not present a concern for photoirritation or photoallergenicity.

*11.1.5.2. UV spectra analysis.* UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for photoirritating effects, 1000 L mol$^{-1}$ • cm$^{-1}$ (Henry et al., 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 01/10/22.

### 11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-tridecanone is below the Cramer Class III* TTC value for inhalation exposure local effects.

*11.1.6.1. Risk assessment.* There are no inhalation data available on 2-tridecanone. Based on the Creme RIFM Model, the inhalation exposure is 0.000076 mg/day. This exposure is 6184 times lower than the Cramer Class III* TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

*As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 01/17/22.

## 11.2. Environmental endpoint summary

### 11.2.1. Screening-level assessment

A screening-level risk assessment of 2-tridecanone was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the

**Table 1**
Summary of existing data on 2-heptanone as a read-across for 2-tridecanone.

| WoE Skin Sensitization Potency Category[a] | Human Data | | | | Animal Data | | |
|---|---|---|---|---|---|---|---|
| | NOEL-CNIH (induction) μg/cm$^2$ | NOEL-HMT (induction) μg/cm$^2$ | LOEL[b] (induction) μg/cm$^2$ | WoE NESIL[c] μg/cm$^2$ | LLNA[d] Weighted Mean EC3 Value μg/cm$^2$ | GPMT[e] | Buehler[e] |
| No evidence of sensitization[g] | NA | 2760 | NA | NA | 25000 | NA | NA |
| | ***In vitro* Data[f]** | | | | ***In silico* protein binding alerts (OECD Toolbox 4.2)** | | |
| | **KE 1** | **KE 2** | **KE 3** | | **Target** | **Autoxidation simulator** | **Metabolism simulator** |
| | NA | NA | NA | | Nucleophilic addition | Nucleophilic addition | Nucleophilic addition |

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.

[a] WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

[d] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[e] Studies conducted according to the OECD TG 406 are included in the table.

[f] Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[g] Determined based on Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients (Api et al., 2015).

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. 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-tridecanone 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-tridecanone 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, 2017a). 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).

*11.2.1.1. Risk assessment.* Based on the current Volume of Use (2019), 2-tridecanone does not present a risk to the aquatic compartment in the screening-level assessment.

*11.2.1.2. Key studies*

*11.2.1.2.1. Biodegradation.* No data available.

*11.2.1.3. Ecotoxicity.* No data available.

*11.2.1.4. Other available data.* 2-Tridecanone has been pre-registered for REACH with no additional data at this time.

*11.2.1.5. 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 Environmental Framework: Salvito, 2002).

| Exposure | Europe | North America |
|---|---|---|
| Log $K_{ow}$ Used | 4.68 | 4.68 |
| 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 0.001244 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

**Literature Search and Risk Assessment Completed On:** 05/24/22.

## 12. 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:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
  - **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 06/23/22.

## Declaration of competing interest

The authors declare that they have no known competing financial

| | 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>1.244</u> | | | 1000000 | 0.001244 | |

interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix F. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2022.113408.

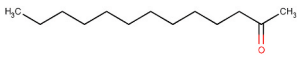
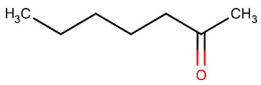
## Appendix

*Read-across Justification*

*Methods*

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017b).

- 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 (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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

| | Target Material | Read-across Material |
|---|---|---|
| **Principal Name** | 2-Tridecanone | 2-Heptanone |
| **CAS No.** | 593-08-8 | 110-43-0 |
| **Structure** |  |  |
| **Similarity (Tanimoto Score)** | | 0.90 |
| **Endpoint** | | • Genotoxicity<br>• Skin Sensitization<br>• Repeated dose toxicity<br>• Reproductive toxicity |
| **Molecular Formula** | $C_{13}H_{26}O$ | $C_7H_{14}O$ |
| **Molecular Weight (g/mol)** | 198.35 | 114.19 |
| **Melting Point (°C, EPI Suite)** | 30.50 | −35.00 |
| **Boiling Point (°C, EPI Suite)** | 263.00 | 151.00 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 1.39 | 513.29 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 4.53 | 4300.00 |
| **Log $K_{OW}$** | 4.68 | 1.98 |
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 0.67 | 215.21 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 85.42 | 17.12 |
| **Genotoxicity** | | |
| **DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)** | No alert found | No alert found |
| **DNA Binding (OECD QSAR Toolbox v4.2)** | No alert found | No alert found |
| **Carcinogenicity (ISS)** | No alert found | No alert found |
| **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 skin sensitization reactivity domain alerts were identified | No skin sensitization reactivity domain alerts were identified |
| **Oncologic Classification** | No alert found | No alert found |
| **Repeated Dose Toxicity** | | |
| **Repeated Dose (HESS)** | Not possible to classify according to these rules | Not possible to classify according to these rules |
| **Reproductive Toxicity** | | |

(*continued on next page*)

(*continued*)

| | Target Material | Read-across Material |
|---|---|---|
| **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) |
| **Skin Sensitization** | | |
| **Protein Binding (OASIS v1.1)** | Out of mechanistic domain | DPRA less than 9% (DPRA 13%)\|DPRA less than 9% (DPRA 13%) ≫ No protein binding alert |
| **Protein Binding (OECD)** | Not possible to classify according to these rules (GSH) | Not possible to classify according to these rules (GSH) |
| **Protein Binding Potency** | Not categorized | Not categorized |
| **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 |
| **Metabolism** | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)** | See Supplemental Data 1 | See Supplemental Data 2 |

*Summary*

There are insufficient toxicity data on 2-tridecanone (CAS # 593-08-8). 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, 2-tridecanone (CAS # 593-08-8), for the genotoxicity, skin sensitization, repeated dose toxicity, developmental toxicity, and fertility endpoints.
  - o The target material and the read-across analog belong to the class of ketones.
  - o The target material and the read-across analog share a common saturated aliphatic ketone fragment.
  - o The key difference between the target material and the read-across analog is that the target has a C13 aliphatic chain, while the read-across analog has a C7 aliphatic 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. The Tanimoto score is mainly driven by the 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 material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown with the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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