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Short Review

RIFM fragrance ingredient safety assessment, cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime, CAS registry number 19096-86-7

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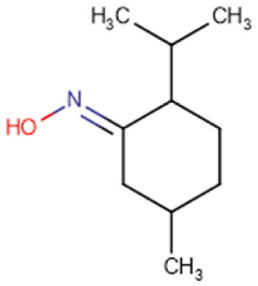

Abbreviation/Definition List:

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

(*continued on next column*)

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UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

Cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data from read-across material 5-methyl-3-heptanone oxime (CAS # 22457-23-4) show that cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class III material, and the exposure to cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime is below the TTC (0.0015 mg/kg/day, 0.0015 mg/kg/day, and 0.47 mg/day, respectively). 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 photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime is not expected to be photoirritating/photoallergenic. The environmental endpoints were evaluated; cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime 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 (VoU) 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. (RIFM, 2003; RIFM, 2014b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
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: 2.8 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation:
Screening-level: 26.31 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity:
Screening-level: Fish LC50: 60.86 mg/L (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

(*continued on next page*)

(*continued*)

Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 60.86 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.06086 μg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not available; cleared at the screening-level	

1. Identification

1. **Chemical Name:** Cyclohexanone,5-methyl-2-(1-methylethyl)-, oxime
2. **CAS Registry Number:** 19096-86-7
3. **Synonyms:** (Z)-(2R,5R)-5-methyl-2-(1-methylethyl)cyclohexanone oxime and (E)-(2R,5R)-5-methyl-2-(1-methylethyl)cyclohexanone oxime and (Z)-(2R,5R)-5-methyl-2-(1-methylethyl)cyclohexanone oxime; Rosoxime; Cyclohexanone,5-methyl-2-(1-methylethyl)-, oxime
4. **Molecular Formula:** $C_{10}H_{19}NO$
5. **Molecular Weight:** 169.26 g/mol
6. **RIFM Number:** 7276
7. **Stereochemistry:** Two stereocenters and 4 possible stereoisomers.

2. Physical data

1. **Boiling Point:** 265.73 °C (EPI Suite v4.11)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 2.66 (KOWWIN v1.68 in EPI Suite v4.11)
4. **Melting Point**: 16.33 °C (EPI Suite v4.11)
5. **Water Solubility:** 333.6 mg/L at 25 °C (WSKOW v1.42 in EPI Suite v4.11)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.000654 mm Hg at 20 °C (EPI Suite v4.0), 0.00117 mm Hg (0.156 Pa) at 25 °C (EPI Suite v4.11)
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:** Not Available

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 v3.1.5)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0046% (RIFM, 2021)
2. **Inhalation Exposure*:** 0.0000044 mg/kg/day or 0.00027 mg/day (RIFM, 2021)
3. **Total Systemic Exposure**:** 0.000021 mg/kg/day (RIFM, 2021)

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. *Cramer Classification: Class III, High* (Expert Judgment)*

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
III	III	I

*See the Appendix below for details.

6.2. *Analogs Selected:*

a. **Genotoxicity:** 5-Methyl-3-heptanone oxime (CAS # 22457-23-4)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Photoirritation/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

Cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime is not reported to occur in foods by the VCF*.

*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.

9. Reach dossier

Available; accessed on 12/07/21 (ECHA, 2012).

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, cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime 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,

Table 1
Summary of existing data on cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) µg/cm²	NOEL-HMT (induction) µg/cm²	LOEL[2] (induction) µg/cm²	WoE NESIL[3] µg/cm²	LLNA[4] Weighted Mean EC3 Value µg/cm²	GPMT[5]	Buehler[5]
Human potency category unknown; Current exposure level below the DST for non-reactive materials.	NA	NA	NA	NA	NA	NA	NA
	In vitro Data[6]				*In silico* protein binding alerts (OECD Toolbox v4.2)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	NA	NA	NA		No alert found	No alert found	No alert found

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; GPMT = Guinea Pig Maximization Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; KE = Key Event; NA = Not Available.
[1]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).
[2]Data derived from CNIH or HMT.
[3]WoE NESIL limited to 2 significant figures.
[4]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[5]Studies conducted according to the OECD TG 406 are included in the table.
[6]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

2014a). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no data assessing the mutagenic or clastogenic activity of cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime; however, read-across can be made to 5-methyl-3-heptanone oxime (CAS # 22457-23-4; see Section VI).

The mutagenic activity of 5-methyl-3-heptanone oxime has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 5-methyl-3-heptanone oxime in dimethyl sulfoxide (DMSO) at concentrations up to 2500 µg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2003). Under the conditions of the study, 5-methyl-3-heptanone oxime was not mutagenic in the Ames test, and this can be extended to cyclohexanone,5-methyl-2-(1-methylethyl)-, oxime.

The clastogenic activity of 5-methyl-3-heptanone oxime was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 5-methyl-3-heptanone oxime in DMSO at concentrations up to 1430 µg/mL in the dose range finding (DRF) study. Micronuclei analysis was conducted at 500 µg/mL in the presence and absence of S9 for 4 h and in the absence of metabolic activation for 24 h 5-Methyl-3-heptanone oxime did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2014b). Under the conditions of the study, 5-methyl-3-heptanone oxime was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to cyclohexanone,5-methyl-2-(1-methylethyl)-, oxime.

Based on the data available, 5-methyl-3-heptanone oxime does not present a concern for genotoxic potential, and this can be extended to cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime.

Additional References: None.

Table 2
Supported concentrations for cyclohexanone,5-methyl-2-(1-methylethyl)-, oxime that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Supported Concentrations[b] (%) in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069	NRU[c]
2	Products applied to the axillae	0.021	2.7×10^{-5}
3	Products applied to the face using fingertips	0.41	7.3×10^{-5}
4	Fine fragrance products	0.39	0.0039
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10	9.8×10^{-5}
6	Products with oral and lip exposure	0.23	NRU[c]
7	Products applied to the hair with some hand contact	0.79	7.7×10^{-5}
8	Products with significant ano-genital exposure	0.041	No Data[d]
9	Products with body and hand exposure, primarily rinse-off	0.75	0.0013
10	Household care products with mostly hand contact	2.7	7.8×10^{-4}
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5	No Data[d]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	No Restriction	0.099

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] These levels represent supported concentrations based on the DST. However, additional studies may show it could be used at higher levels.
[c] No reported use.
[d] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

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

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime or any read-across materials. The total systemic exposure to cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime is below the TTC for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime (0.021 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/15/22.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime or any read-across materials. The total systemic exposure to cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime is below the TTC for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime (0.021 μg/kg/day) is below the TTC (1.5 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/15/22.

11.1.4. Skin sensitization

Based on the existing data and the application of DST, cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Limited skin sensitization data are available for cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime (Table 1). The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford, 2011; Roberts et al., 2015; Safford, 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 2 provides the supported concentrations for cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent supported 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: 01/06/22.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime 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 cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime 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, cyclohexanone, 5-methyl-2-(1-methylethyl)-,oxime 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: 01/11/22.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime 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 cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime. Based on the Creme RIFM Model, the inhalation exposure is 0.00027 mg/day. This exposure is 1740.7 times lower than the Cramer Class III TTC value of 0.47 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: 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 cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime 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 cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 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).

11.2.2. Risk assessment

Based on the current VoU (2019), cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation:

No data available.

Ecotoxicity:

No data available.

11.2.1.3. Other available data. Cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime has been registered under REACH with no additional data 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.

	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>60.86</u>			1000000	0.06086	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.66	2.66
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional VoU 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 0.06086 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
- **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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 ChemView:** https://chemview.epa.gov/chemview/
- **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://pubchem.ncbi.nlm.nih.gov/source/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 06/20/22.

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.2023.114272.

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	Cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime	5-Methyl-3-heptanone oxime
CAS No.	19096-86-7	22457-23-4

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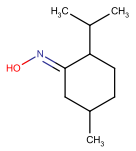
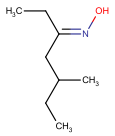
	Target Material	Read-across Material
Structure		
Similarity (Tanimoto Score)		0.74
Read-across Endpoint		• Genotoxicity
Molecular Formula	$C_{10}H_{19}NO$	$C_8H_{17}NO$
Molecular Weight (g/mol)	169.26	143.23
Melting Point (°C, EPI Suite)	16.33	−22.85
Boiling Point (°C, EPI Suite)	265.73	225.87
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.156	2.01
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	2.66	3.58
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	333.6	70.54
J_{max} (μg/cm^2/h, SAM)	12.54	10.47
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.915E-002	3.26E+000
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)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found
Oncologic Classification	• C-Nitroso- and Oxime-type Compounds	• C-Nitroso- and Oxime-type Compounds
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
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 cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime (CAS # 19096-86-7). 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, 5-methyl-3-heptanone oxime (CAS # 22457-23-4) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 5-Methyl-3-heptanone oxime (CAS # 22457-23-4) was used as a read-across analog for the target material, cyclohexanone,5-methyl-2-(1-methylethyl)-,oxime (CAS # 19096-86-7), for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of alkyl oximes.
    - oThe key difference between the target material and the read-across analog is that whereas the target material is a saturated cyclic ketoxime, the read-across analog is a branched, saturated ketoxime. These structural differences are 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 Both the target material and the read-across analog display oncologic classification and repeated dose alerts due to the oxime group. Data are consistent with *in silico* alerts.
  - 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.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree.

Q1 A normal constituent of the body? No
Q2 Contains functional groups associated with enhanced toxicity? No
Q3 Contains elements other than C, H, O, N, and divalent S? No
Q5 Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6 Benzene derivative with certain substituents? No
Q7 Heterocyclic? No

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Q16	Common terpene? (see Cramer et al., 1978 for a detailed explanation) No
Q17	Readily hydrolyzed to a common terpene? No
Q19	Open chain? NO
Q23	Aromatic? No
Q24	Monocarbocyclic with simple substituents? No
Q25	Cyclopropane (see explanation in Cramer et al., 1978)? No
Q26	Monocycloalkanone or a bicyclo compound? No
Q22	A common component of food? NO
Q33	Has a sufficient number of sulfonate or sulfamate groups for every 20 or fewer carbon atoms, without any free primary amines except those adjacent to the sulphonate or sulphamate? No. Class III (Class high)

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