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Short Review

RIFM fragrance ingredient safety assessment, cyclohexanol, CAS Registry Number 108-93-0

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ARTICLE INFO

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ABSTRACT

Summary: The existing information supports the use of this material as described in this safety assessment. Cyclohexanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cyclohexanol is not genotoxic. Data on cyclohexanol provide a calculated margin of exposure (MOE) >100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for cyclohexanol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; cyclohexanol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to cyclohexanol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; cyclohexanol 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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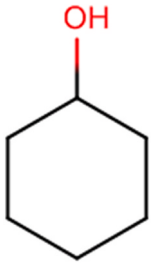

Name: Cyclohexanol
CAS Registry Number: 108-93-0

Abbreviation/Definition List:

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

(*continued on next column*)

(*continued*)

*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.

Cyclohexanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that cyclohexanol is not genotoxic. Data on cyclohexanol provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for cyclohexanol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; cyclohexanol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to cyclohexanol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; cyclohexanol 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 genotoxic.	(ECHA REACH Dossier: Cyclohexanol; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 159 mg/kg/day.	(US EPA, 2005)
Reproductive Toxicity: Developmental toxicity: 600 mg/kg/day Fertility: 159 mg/kg/day.	(RIFM, 2013; US EPA, 2006)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(Environmental Protection Agency, 1990; RIFM, 1974b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 94–99% (OECD 301C Modified MITI Test I)	(ECHA REACH Dossier: Cyclohexanol; ECHA, 2011)
Bioaccumulation: Screening-level: Fish BCF: 3.01 L/kg	(EPI Suite v4.11; US ECHA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 631.8 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: 631.8 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.6318 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Cyclohexanol
2. **CAS Registry Number:** 108-93-0
3. **Synonyms:** Hexahydrophenol; Hexalin; Cyclohexanol
4. **Molecular Formula:** $C_6H_{12}O$
5. **Molecular Weight:** 100.16
6. **RIFM Number:** 519
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 161 °C (Fragrance Materials Association [FMA]), 161.73 °C (EPI Suite)

2. **Flash Point:** 64 °C (Globally Harmonized System)
3. **Log K_{OW}:** 1.23 (Abraham and Rafols, 1995), 1.64 (EPI Suite)
4. **Melting Point**: −33.4 °C (EPI Suite)
5. **Water Solubility:** 33660 mg/L (EPI Suite)
6. **Specific Gravity:** 0.963 (FMA)
7. **Vapor Pressure:** 0.387 mm Hg @ 20 °C (EPI Suite v4.0), 0.5 mm Hg 20 °C (FMA), 0.65 mm Hg at 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:** Colorless, viscous liquid or hygroscopic crystals, or sticky solid, depending on temperature, faint camphor-like odor

3. Volume of use (worldwide band)

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

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

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0063% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.0000079 mg/kg/day or 0.00053 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.000074 mg/kg/day (RIFM, 2017)

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

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

1. **Cramer Classification:** Class I*, Low (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v3.2
I	II	I

*Due to potential discrepancies with 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 (Cramer et al., 1978). See the Appendix below for further details.

2. Analogs Selected:

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** None
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. **Read-across Justification:** None

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

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

Cyclohexanol is reported to occur in the following foods by the VCF*:
Acerola (Malpighia).
Beans.
Black Currants (*Ribes nigrum* L.)
Chestnut (*Castanea* species).
Chicken.
*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 03/27/20 (ECHA, 2011).

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, cyclohexanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenicity of cyclohexanol was assessed in a bacterial reverse mutation assay (Ames test) conducted using *Salmonella typhimurium* strains TA98, TA1535, TA1537, and TA1538 in the presence and absence of S9 with doses up to 15000 μg/plate and was negative (ECHA, 2011).

A mammalian cell gene mutation assay (mouse lymphoma assay) was conducted according to OECD TG 476 and GLP guidelines. Mouse lymphoma L5178Y cells were treated with cyclohexanol in deionized water at concentrations of 1000.0 μg/mL (as determined in a preliminary toxicity assay), for 4 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test material, either with or without metabolic activation (ECHA, 2011). Under the conditions of the study, cyclohexanol was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of cyclohexanol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in aqueous 0.5% CMC (carboxymethyl cellulose) via oral gavage to groups of male and female NMRI mice. Doses of 500, 100, or 1500 mg/kg were administered. Mice from each dose level were euthanized at 16, 24, and

48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011). Under the conditions of the study, cyclohexanol was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, cyclohexanol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/22/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on cyclohexanol. In a modified (extended exposure period) OECD 422-compliant study, 15 Sprague Dawley rats/sex/dose were administered cyclohexanol via whole-body inhalation at doses of 0, 50, 150 and 450 ppm (equivalent to 0, 53, 159, and 478 mg/kg/day, respectively). Males were exposed for 16 weeks, and females were exposed for 13 weeks (6 h/day, 5 days/week for both sexes). However, after 10 weeks of exposure, the 450 ppm level was reduced to 400 ppm due to slight mortality and mating stress on females. After the exposure period, 5 rats/sex/group were selected for a 4-week recovery period. Mortality was seen in males at the high dose on days 37, 38, and 60 of the study, and 1 high-dose female was euthanized in extremis on day 17; these deaths were considered treatment-related. No treatment-related effects were seen in ophthalmoscopic evaluations, functional observational battery, motor activity, bodyweight gain, food consumption, hematology, clinical chemistry, urinalysis, organ weights, or macroscopic and microscopic evaluations at any dose level. Clinical observations conducted immediately post-exposure revealed decreased activity and prostration in both sexes at the high dose. Based on mortality and adverse clinical signs at 478 mg/kg/day (450 ppm), the NOAEL for this study was considered to be 159 mg/kg/day (150 ppm) (US EPA, 2006a).

Because the exposure period of the OECD 422 study was extended to 13–16 weeks, a safety factor of 3 was not applied.

Therefore, the cyclohexanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the cyclohexanol NOAEL in mg/kg/day by the total systemic exposure to cyclohexanol, 159/0.000074, or 2148649.

In addition, the total systemic exposure to cyclohexanol (0.074 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/02/20.

11.1.3. Reproductive toxicity

The MOE for cyclohexanol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on cyclohexanol. In an OECD 414/GLP prenatal developmental toxicity study, 24 female Sprague Dawley rats/group were administered dose levels of 150, 300, and 600 mg/kg/day in corn oil via oral gavage from gestation days (GDs) 6–15. No mortality was observed. Treatment-related clinical signs of hypoactivity and/or salivation were observed in 21 out of 24 dams during different days of gestation at 600 mg/kg dose. No gross lesions were observed in dams during necropsy in any of the doses tested. No treatment-related or toxicologically relevant effects were seen in fetuses with respect to external, visceral, and skeletal examinations. The NOAEL for maternal toxicity was considered to be 300 mg/kg/day, based on treatment-related clinical signs of hypoactivity and/or salivation at 600 mg/kg/day. The NOAEL for developmental toxicity was considered to be 600 mg/kg/day, based on the absence of treatment-related adverse effects on the development of pups up to the highest dose tested (RIFM, 2013).

In an OECD 422 combined repeated dose/reproductive toxicity screening test, Sprague Dawley rats (15/sex/concentration) were treated with cyclohexanol vapors via whole-body inhalation at 0, 50, 150, and 450 ppm (equivalent to 0, 0.21, 0.614, and 1.84 mg/L/day). Animals were exposed for 6 h/day, 5 days/week, for 13 weeks (females) or 16 weeks (males). The only modifications to the original OECD 422 were an extension of the exposure period to 10 weeks prior to mating, a 4-week recovery period for 5 males/group, and sperm motility and concentration measurements. The high dose (450 ppm) was reduced to 400 ppm (equivalent to approximately 1.64 mg/L/day) after 10 weeks of exposure due to the mortality of 3 males on days 37, 38, and 60, as well as 1 female (euthanized in extremis) on day 17. Microscopically, the cause of these deaths could not be determined. However, because these deaths occurred at the highest concentration level, they were considered to be treatment-related. Decreased activity and prostration were reported among animals of the high-dose group immediately following exposure. In the high-dose group, 2/11 pregnancies (18.2%) resulted in no viable pups at parturition and lower mean pup weights (10%–12%) at birth and postnatal day 4. No treatment-related adverse effects were reported during the histological examination. High-dose males showed a reduction in testicular sperm counts, but they were within the historical data range, and recovery groups had sperm counts comparable to controls; hence, this was not considered to be an adverse effect. The NOAEC for fertility and developmental toxicity was considered to be 150 ppm (0.614 mg/L), based on treatment-related effects observed among high-dose group animals with few pregnancies along with no viable fetuses and reduced pup weights (US EPA, 2006b). Using standard minute volume and bodyweight values for male and female Sprague Dawley rats, the calculated NOAEL for fertility and developmental toxicity is 159 mg/kg/day.

In another study, male rabbits (5/group) were treated orally with cyclohexanol (diluted with olive oil) at 25 mg/kg/day (groups 2 and 3) for a period of 40 days. Group 1 animals received the vehicle alone and served as controls. Group 2 was allowed to recover for a period of 70 days following cessation of cyclohexanol administration. On day 40, 24 h after administration, group 1 and group 3 animals were euthanized, and the right testes and epididymides were removed surgically and evaluated. Microscopically, testes showed degenerative changes with loss of type A spermatogonia, spermatocytes, spermatids, and spermatozoa. Spermatids showed morphological changes; cytolysis and chromatolysis were common. Leydig cells were shrunken with scant cytoplasm, and nuclei were reduced in diameter. Reduced luminal epithelium and scanty stereocilia were reported in histopathology of epididymides. The lumen of the cauda epididymides and ductus deferens were devoid of spermatozoa. Degenerating cells were reported in a few tubules. Reversibility was observed for effects observed on testes and epididymides. After the recovery period, no treatment-related effects were reported for spermatogenesis, organ weights, seminiferous tubule, and Leydig cells nuclear dimensions. Histopathology of the liver did not show any effect except for the degranulation of the hepatoplasm. A statistically significant reduction was reported for RNA, protein, sialic acid, and glycogen in testes and epididymides in treated animals. The testicular cholesterol increased significantly, whereas acid phosphatase enzyme activity was reduced. Adrenal ascorbic acid values were also decreased. All these changes were reversed to subnormal values after 70 days of recovery. A statistically significant reduction in serum protein contents and an elevation of serum cholesterol, phospholipids, triglycerides, bilirubin, pyruvate transaminase, and alkaline phosphatase were reported. No treatment-related effects were reported for blood sugar and blood urea. Serum transaminase, triglycerides, and protein

levels showed reversibility after 70 days of recovery, whereas total cholesterol, phospholipids, bilirubin, and phosphatase enzyme activity remained unaltered as compared to the treatment group. Hematological parameters were in the normal range. Therefore, cyclohexanol at the dose of 25 mg/kg/day (daily, for 40 days) produced a brief period of infertility by inhibiting the process of spermatogenesis at the spermatocyte and spermatid levels, which recovered after 70 days of recovery. However, limited details were given in the study report. Data on the test compound (purity), dosing method (means of oral administration), and in-life parameters (body weight, clinical signs) were not mentioned (Dixit et al., 1980).

For the fertility endpoint, a NOAEL of 159 mg/kg/day was derived from OECD 422 study on rats, based on treatment-related effects observed among high-dose group animals with few pregnancies along with no viable fetuses. However, in a study performed on male rabbits produced a brief period of infertility by inhibiting the process of spermatogenesis at the spermatocyte and spermatid levels. These effects were recovered after 70 days, but due to limited details given in the study report, a clear NOAEL was not derived. Hence, taking a conservative approach the fertility endpoint was evaluated using TTC.

There are insufficient or inconclusive fertility data on cyclohexanol or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure for cyclohexanol (0.074 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint at the current level of use.

Furthermore, since there were adverse effects seen OECD 422 study for developmental toxicity, the OECD 414 study was not considered for deriving NOAEL for this safety assessment. Hence, the NOAEL for developmental toxicity was considered to be 159 mg/kg/day.

Therefore, the cyclohexanol MOE for the developmental toxicity endpoint can be calculated by dividing the cyclohexanol NOAEL in mg/kg/day by the total systemic exposure to cyclohexanol, 159/0.000074, or 2148649.

In addition, the total systemic exposure to cyclohexanol (0.074 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/20/20.

11.1.4. Skin sensitization

Based on the existing data, cyclohexanol presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Based on the existing data, cyclohexanol is not considered a skin sensitizer. 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; TIMES-SS v2.28.16). In a guinea pig maximization test, cyclohexanol did not lead to skin sensitization reactions (Environmental Protection Agency, 1990). Moreover, a guinea pig Buehler test did not present reactions indicative of sensitization (RIFM, 1974b). In a human maximization test, no skin sensitization reactions were observed at 4% (2760 μg/cm^2) (RIFM, 1974a).

Based on the weight of evidence (WoE) from structural analysis as well as animal and human studies, cyclohexanol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: Klecak (1985); Environmental Protection Agency, 1990; ECHA, 2011.

Literature Search and Risk Assessment Completed On: 05/06/20.

11.1.5. Phototoxicity/photoallergenicity

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/04/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for cyclohexanol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on cyclohexanol. Based on the Creme RIFM Model, the inhalation exposure is 0.00053 mg/day. This exposure is 2642 times lower than the Cramer Class I TTC value of 1.4 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: 05/04/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cyclohexanol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, cyclohexanol 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 cyclohexanol 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, 2012). 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 predicts a fish BCF $\geq$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), cyclohexanol presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Cyclohexanol has been registered for REACH with the following additional data available at his time (ECHA, 2011):

The ready biodegradability of the test material was evaluated using the modified MITI test (I) according to the OECD 301 C guideline. Biodegradation of 94–99% was observed after 28 days.

A short-term fish toxicity test was performed according to US EPA Committee on Methods for Toxicity (1975) using fathead minnow (*Pimephales promelas*) under flow-through conditions. The 96-h LC50 value based on measured concentration was reported to be 704 mg/L.

The *Daphnia* acute immobilization test was conducted according to the OECD 202 guideline under semi-static conditions. The 48-h LC50 value based on nominal concentration was reported to be17 mg/L (95% CI: 14–20 mg/L).

The *Daphnia magna* reproduction test was conducted according to the OECD 211 guideline under semi-static conditions. The 21-day NOEC values based on measured (TWA) concentrations for reproduction and growth was reported to be 0.953 mg/L. The 21-day EC50 value based on measured (TWA) concentrations was reported to be $>$ 0.953 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 and EC10 values based on nominal concentrations for growth rate were reported to be $>$ 500 mg/L and 1.55 mg/L.

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 Environmental Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	1.23	1.23
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 0.6318 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: 05/05/20.

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 09/30/20.

	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>631.8</u>			1000000	0.6318	

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

Explanation of Cramer Classification

Due to potential discrepancies with 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 (Cramer et al., 1978).

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.
Q19. Open chain? No.
Q23. Aromatic? No.
Q24. Monocarbocyclic with simple substituents? No.
Q18. One of the list? (see Cramer et al., 1978 for a detailed explanation on list of categories). No. Class low (Class I).

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