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


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.
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).

This safety assessment is based on the RIFM Criteria Document (Api 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.

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.

Environmental Safety Assessment

Hazard Assessment:

Persistence/Critical Measured Value: (ECHA REACH Dossier: Cyclohexanol; ECHA, 2011)
Bioaccumulation: Screening-level: Fish BCF: 3.01 L/kg (RIFM, 2013; US ECHA, 2006)
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: 0.6318 mg/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: C₆H₁₂O
5. Molecular Weight: 100.16
6. RIFM Number: 519
7. Stereochemistry: Stereisoromer 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 Kow: 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. 95th 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)

<table>
<thead>
<tr>
<th>Expert Judgment</th>
<th>Toxtree v3.1</th>
<th>OECD QSAR Toolbox v3.2</th>
</tr>
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   *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.


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 poly-
chromatic 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 adminis-
tered 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,
the study, cyclohexanol was considered to be not clastogenic in the
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, hematol-
ology, clinical chemistry, urinalysis, organ weights, or macroscopic and
microscopic evaluations at any dose level. Clinical observations con-
ducted 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 MOE 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 toxicity endpoint
can be calculated by dividing the cyclohexanol MOE in mg/
kg/day by the total systemic exposure to cyclohexanol, 159/0.000074,
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 hypoviscosity 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 hypo-
activity and/or salivation at 600 mg/kg/day. The NOAEL for develop-
mental 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/replicative toxicity
screening test, Sprague Dawley rats (15/sex/concentration) were
exposed to 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 consid-
ered 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 develop-
mental 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. Macroscopically, testes showed degenerative changes with
loss of type A spermatogonia, spermatoocytes, spermatids, and sperma-
tozoa. Spermatozoa showed morphological changes; cytolysis and chro-
matolysis were common. Leydig cells were shrunken with scant
cyttoplasm, and nuclei were reduced in diameter. Reduced luminal
epithelium and scanty stericollia were reported in histopathology of
epididymides. The lumen of the cauda epididymides and ductus defer-
ens 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 ef-
fects 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 hepatopla-
moma. 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 normal values after 70
days of recovery. A statistically significant reduction in serum protein
contents and an elevation of serum cholesterol, phospholipids, tri-
glycerides, 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.

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.

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 Cramer 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.

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 respective VoU, its log Kow, 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.
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 ≥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).

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Europe (EU)</th>
<th>North America (NA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Kow Used</td>
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<td>1.23</td>
</tr>
<tr>
<td>Biodegradation Factor Used</td>
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<td>0</td>
</tr>
<tr>
<td>Dilution Factor</td>
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<td>3</td>
</tr>
<tr>
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<td>&lt;1</td>
</tr>
<tr>
<td>Risk Characterization: PEC/PNEC</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

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.

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/
- **SciFinder**: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **National Library of Medicine’s Toxicology Information Services**:
  - EPI Suite v4.11.
  - ChemIDplus:
  - Google: https://www.google.com
  - SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
  - NTP: https://ntp.niehs.nih.gov/
  - 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
  - Google: https://www.google.com

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.
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.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q18. One of the list? (see Cramer et al., 1978 for a detailed explanation on list of categories). No. Class low (Class I).

References