Short Review

RIFM fragrance ingredient safety assessment, 2-cyclohexylcyclohexanone, CAS Registry Number 90-42-6

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ABSTRACT

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

2-Cyclohexylcyclohexanone was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data and read-across to 2-tert-butylycyclohexanone (CAS # 1728-46-7) show that 2-cyclohexylcyclohexanone is not expected to be genotoxic. Data on read-across material 2-sec-butylcyclohexanone (CAS # 14765-30-1) provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for non-reactive materials (900 µg/cm²); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-cyclohexylcyclohexanone 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 II material, and the exposure to 2-cyclohexylcyclohexanone is below the TTC (0.47 mg/day). The environmental endpoints were evaluated; 2-cyclohexylcyclohexanone was found not to be persistent, biocumulative, 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.

Version: 102820. This version replaces any previous versions.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2013; RIFM, 2000s; RIFM, 2017a; RIFM (2018))

Repeated Dose Toxicity: NOAEL = 16 mg/kg/day.

Reproductive Toxicity: Developmental toxicity: 226 mg/kg/day; Fertility: 226 mg/kg/day.

Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST. (RIFM (2018))

Phototoxicity/Photosensitization: Not expected to be phototoxic/photosensitizing. (UV Spectra; RIFM Database)

Local Respiratory Toxicity: NO AEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 3% after 21 days

Bioaccumulation: Screening level: 152.4 L/kg

Ecotoxicity: Screening level: Fish LC50: 6.48 mg/L

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening level: PEC/PNEC (North America and Europe) < 1

Critical Ecotoxicity Endpoint: Fish LC50: 6.48 mg/L

RIFM PNEC is: 0.00648 µg/L

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

1. Identification

1. Chemical Name: 2-Cyclohexylocyclohexanone
2. CAS Registry Number: 90-42-6
3. Synonyms: Bicyclohexanone; [1,1'-Bicyclohexyl]-2-one; 1,1'-Bi (cyclohexyl)-2-one; Cyclohexyl cyclohexanone; 2-Cyclohexylocyclohexanone
4. Molecular Formula: C15H24O
5. Molecular Weight: 180.29
6. RIFM Number: 356
7. Stereocchemistry: No isomer specified. One stereocenter and 2 total stereoisomers possible.
2. Physical data

1. Boiling Point: 272.41 °C (EPI Suite)
2. Flash Point: > 200 °F; CC (FMA), >93 °C (GHS)
3. Log Kow: 3.81 (EPI Suite)
4. Melting Point: 40.11 °C (EPI Suite)
5. Water Solubility: 30.41 mg/L (EPI Suite)
6. Specific Gravity: Not Available
7. Vapor Pressure: 0.0136 mm Hg @ 20 °C (EPI Suite v4.0), 0.0215 mm Hg @ 25 °C (EPI Suite)
8. UV Spectra: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ · cm⁻¹)

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v3.0)

1. 95th Percentile Concentration in Hydralcoholics: 0.000% (RIFM, 2017b)
   Reported use in Household products only.

2. Inhalation Exposure*: 0.00000021 mg/kg/day or 0.000015 mg/day (RIFM, 2017b)
3. Total Systemic Exposure**: 0.0000048 mg/kg/day (RIFM, 2017b)

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

<table>
<thead>
<tr>
<th>Expert Judgment</th>
<th>Toxicity v 2.6</th>
<th>OECD QSAR Toolbox v 3.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>II</td>
<td>II</td>
</tr>
</tbody>
</table>

2. Analogs Selected:
   a. Genotoxicity: 2-tert-butylocyclohexane (CAS # 1728-46-7)
   b. Repeated Dose Toxicity: 2-sec-butylocyclohexane (CAS # 14765-30-1)
   c. Reproductive Toxicity: 2-sec-butylocyclohexane (CAS # 14765-30-1)
   d. Skin Sensitization: None
   e. Phototoxicity/Photoallergenicity: None
   f. Local Respiratory Toxicity: None
   g. Environmental Toxicity: None
3. Read-across Justification: See Appendix below

7. Metabolism

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

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

2-Cyclohexylcyclohexanone is not reported to occur in foods by the VCF*.

9. REACH dossier

2-cyclohexylcyclohexanone has been pre-registered for 2010; no dossier available as of 01/02/20.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

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

The mutagenic activity of 2-cyclohexylcyclohexanone 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 method. Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 2-cyclohexylcyclohexanone in dimethyl sulfoxide (DMSO) at concentrations up to 1500 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, 2000a). Under the conditions of the study, 2-cyclohexylcyclohexanone was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 2-cyclohexylcyclohexanone; however, read-across can be made to 2-tert-butylocyclohexanone (CAS # 1728-46-7; see Section VI). The clastogenic activity of read-across material 2-tert-butylocyclohexanone 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 2-tert-butylocyclohexanone in DMSO at concentrations up to 1543 µg/ml in a dose
range finding (DRF) study, and micronuclei analysis was conducted at concentrations up to 300 μg/mL in the presence and absence of S9 for 3 h and in the absence of S9 for 24 h. 2-tet-Butylcyclohexanone did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RFIM, 2017a). Under the conditions of the study, 2-tet-butylcyclohexanone was considered to be non-clastogenic in the in vitro micronucleus test.

Based on the data on read-across material 2-tet-butylcyclohexanone, 2-cyclohexylcyclohexanone does not present a concern for genotoxic potential.

Additional References: None.


11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-cyclohexylcyclohexanone. Read-across material 2-sec-butylcyclohexanone (CAS # 14765-30-1; see Section VI) has sufficient reproductive toxicity data.

In an OECD 422 and GLP compliant study, 10 Wistar Han rats/sex/dose were fed 2-sec-butylcyclohexanone (purity: >97%) orally with diet at doses of 0, 650, 2000, and 6000 ppm. Mean daily intakes of the test material at 650 ppm were 48 mg/kg/day for males and 88 mg/kg/day for females, at 2000 ppm they were 151 mg/kg/day for males and 226 mg/kg/day for females, and at 6000 ppm they were 377 mg/kg/day for males and 508 mg/kg/day for females. Dosing in male and female rats started 2 weeks prior to mating and lasted up to euthanasia in males (at least 28 days) and up to 13 days in females post-partum (about 51–56 days for females with offspring and 42 days for females without offspring). No treatment-related mortalities were observed at any dose level. Treatment-related clinical signs such as piloerection were observed in all females at 2000 ppm and in both sexes at 6000 ppm along with hunched posture in 1 male and most females at 6000 ppm from study week 3 onwards. Following week 4, there was a significant decrease in bodyweight gain in males and females at 2000 and 6000 ppm as well as a decrease in food consumption at these doses. Treatment-related effects were observed in hematologic, biochemistry, organ weights, and histopathology parameters. These were considered to be secondary to weight loss and presented with low severity. Based on the observed clinical signs at doses ≥2000 ppm, the NOAEL was considered to be 650 ppm (48 mg/kg/day) for both sexes (RFIM, 2018).

A default safety factor of 3 was used when deriving a NOAEL from the OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety. The derived NOAEL for the repeated dose toxicity data is 48/3 or 16 mg/kg/day.

Therefore, the 2-cyclohexylcyclohexanone MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-sec-butylcyclohexanone NOAEL (mg/kg/day) by the total systemic exposure (mg/kg/day) for 2-cyclohexylcyclohexanone, 16/0.0000048 or 333333.

In addition, the total systemic exposure to 2-cyclohexylcyclohexanone (0.0048 μg/kg/day) is below the TTC threshold (9 μg/kg/day) for the repeated dose toxicity endpoint of a Cancer II material at the current level of use.

**The Expert Panel for Fragrance Safety** is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.


Literature Search and Risk Assessment Completed On: 01/08/20.

11.1.4. Skin sensitization

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

11.1.4.1. Risk assessment. The chemical structure of this material
indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.3). In a guinea pig open epicutaneous test (OET) with 2-cyclohexylcyclohexanone, no reactions indicative of skin sensitization were found (Kleczek, 1985). In a human maximization test, no skin sensitization reactions were observed at 20% 2-cyclohexylcyclohexanone (RIFM, 1972). Additionally, in a confirmatory human repeat insult patch test (HRRIPT) with 2.5% or 1938 μg/cm² of 2-cyclohexylcyclohexanone in alcohol SDA 39C, no reactions indicative of sensitization were observed in any of the 37 volunteers (RIFM, 1973). Acting conservatively due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm² (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for the non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 2-cyclohexylcyclohexanone that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Table 1

<table>
<thead>
<tr>
<th>IFRA Category</th>
<th>Description of Product Type</th>
<th>Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST</th>
<th>Reported 95th Percentile Use Concentrations in Finished Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Products applied to the lips</td>
<td>0.069%</td>
<td>NRU&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Products applied to the axillae</td>
<td>0.021%</td>
<td>NRU&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Products applied to the face using fingertips</td>
<td>0.41%</td>
<td>NRU&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Fine fragrance products</td>
<td>0.39%</td>
<td>NRU&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Products applied to the face and body using the hands (palms), primarily leave-on</td>
<td>0.10%</td>
<td>NRU&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Products with oral and lip exposure</td>
<td>0.23%</td>
<td>NRU&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Products applied to the hair with some hand contact</td>
<td>0.79%</td>
<td>NRU&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Products with significant anogenital exposure</td>
<td>0.041%</td>
<td>No Data&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>Products with body and hand exposure, primarily time-off</td>
<td>0.75%</td>
<td>NRU&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>Household care products with mostly hand contact</td>
<td>2.7%</td>
<td>0.0115%</td>
</tr>
<tr>
<td>11</td>
<td>Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate</td>
<td>1.5%</td>
<td>No Data&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>Products not intended for direct skin contact, minimal or insignificant transfer to skin</td>
<td>Not Restricted</td>
<td>NRU&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> For a description of the categories, refer to the IFRA/RIFM Information Booklet.

<sup>b</sup> No reported use.

<sup>c</sup> 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: 01/06/20.

11.1.5. Phototoxicity/photoallergenicity

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

11.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-cyclohexylcyclohexanone 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, 2-cyclohexylcyclohexanone 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 minor 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 2-cyclohexylcyclohexanone is below the Cramer Class III° TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are no inhalation data available on 2-cyclohexylcyclohexanone. Based on the Creme RIFM Model, the inhalation exposure is 0.000015 mg/day. This exposure is 31333 times lower than the Cramer Class III° TTC value of 0.47 mg/day (based on human lung weight of 650 g); therefore, the exposure at the current level of use is deemed safe.

<sup>a</sup> As per Carthew et al. (2009), Cramer Class II materials default to Cramer Class III for the local respiratory toxicity endpoint.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/24/20.

11.2. Environmental endpoint summary

11.2.1. Screening level assessment

A screening level risk assessment of 2-cyclohexylcyclohexanone was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiers of screening for aquatic risk. In Tier 1, only the material’s regional 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 QSR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental
Framework, 2-cyclohexylcyclohexanone 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) identified 2-cyclohexylcyclohexanone as possibly persistent but not 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 BOWIN 3 predicts a value <2.2 and either BOWIN 2 or BOWIN 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 BCFAF 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 BOWIN and BCFAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

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

11.2.3. Key studies

11.2.3.1. Biodegradation. RIFM, 2000b: The ready biodegradability of the test material was evaluated using the closed bottle test according to the OECD 301D guideline. Biodegradation of 3% was observed after 21 days and 0% after 28 days.

11.2.3.2. Ecotoxicity. RIFM, 2000c: The *Daphnia* acute immobilization test was conducted according to the OECD 202 guidelines under static conditions. The 48-h EC50 value based on nominal test concentrations was reported to be 15.6 mg/L (95% CI: 14.2–17.0 mg/L).

11.2.4. Other available data

2-Cyclohexylcyclohexanone has been pre-registered for REACH with no additional information available at this time.

11.2.5. Risk assessment refinement

Since 2-cyclohexylcyclohexanone has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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>
<td>3.81</td>
<td>3.81</td>
</tr>
<tr>
<td>Biodegradation Factor Used</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dilution Factor</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Regional Volume of Use Tonnage Band</td>
<td>&lt;1</td>
<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 0.00648 µg/L. The revised PEC/PNECs for EU and NA are not applicable; the material was cleared at the screening-level, and 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:** 01/13/20.

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/
- SciFinder: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- National Library of Medicine’s Toxicology Information Services: https://toxnet.nlm.nih.gov/
- EPA ACTOR: https://actor.epa.gov/actor/home.xhtml
- US EPA HPVIS: https://ofmpub.epa.gov/opthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&👖sجامی=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 05/31/20.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111871.

Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemicals Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical-chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- Jmax values were calculated using RIFM’s Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

<table>
<thead>
<tr>
<th>Principal Name</th>
<th>Target Material</th>
<th>Read-across Material</th>
<th>Read-across Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Cyclohexylcyclohexanone</td>
<td>2-sec-Butylcyclohexanone</td>
<td>2-tert-Butylcyclohexanone</td>
<td></td>
</tr>
<tr>
<td>CAS No.</td>
<td>90-42-6</td>
<td>14765-30-1</td>
<td>1728-46-7</td>
</tr>
<tr>
<td>Structure</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Similarity (Tanimoto Score)</th>
<th>1.00</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read-across Endpoint</td>
<td>Repeated Dose Toxicity</td>
<td>Genotoxicity</td>
</tr>
<tr>
<td>Molecular Formula</td>
<td>C12H20O</td>
<td>C18H26O</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>180.29</td>
<td>154.25</td>
</tr>
<tr>
<td>Melting Point (°C, EPI Suite)</td>
<td>32.00</td>
<td>1.92</td>
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<tr>
<td>Boiling Point (°C, EPI Suite)</td>
<td>264.00</td>
<td>218.54</td>
</tr>
<tr>
<td>Vapor Pressure (Pa @ 25°C, EPI Suite)</td>
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<td>28.26</td>
</tr>
<tr>
<td>Log Kow (ROWWIN v1.68 in EPI Suite)</td>
<td>3.81</td>
<td>2.94</td>
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<tr>
<td>Water Solubility (mg/L @ 25°C, WSKOW v1.42 in EPI Suite)</td>
<td>30.41</td>
<td>222.70</td>
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<tr>
<td>Jmax (μg/cm²/h, SAM)</td>
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<td>48,316</td>
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<td>Henry’s Law (Pa m²/mol, Bond Method, EPI Suite)</td>
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<td>1.61E+001</td>
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<tr>
<td>Genotoxicity</td>
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<td>DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)</td>
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<tr>
<td>DNA Binding (OECD QSAR Toolbox v4.2)</td>
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<td>Carcinogenicity (ISS)</td>
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<td>DNA Binding (Ames, MN, CA, OASIS v1.1)</td>
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<tr>
<td>In Vitro Mutagenicity (Ames, ISS)</td>
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<tr>
<td>In Vivo Mutagenicity (Micronucleus, ISS)</td>
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</tr>
</tbody>
</table>

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Summary

There are insufficient toxicity data on 2-cyclohexylocyclohexane (CAS # 90-42-6). Hence, in silico evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical-chemical properties, and expert judgment, 2-sec-butylcyclohexane (CAS # 14765-30-1) and 2-tert-butylcyclohexane (CAS # 1728-46-7) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 2-sec-Butylcyclohexane (CAS # 14765-30-1) was used as a read-across analog for the target material 2-cyclohexylocyclohexane (CAS # 90-42-6) for the reproductive toxicity and repeated dose toxicity endpoints.
  o The target material and the read-across analog are structurally similar and belong to a class of cyclohexanes.
  o The target material and the read-across analog share a cyclohexane ring.
  o The key difference between the target material and the read-across analog is that the target material has a cyclohexyl ring in position 2, whereas the read-across analog has a sec-butyl substitution in the same position. This structural difference is toxicologically insignificant.
  o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  o The physical-chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  o The Repeated Dose (HESS) alert for the target material is triggered because of a structural similarity above the 50% threshold with perhexiline. However, the target material belongs to a different chemical family as perhexiline. Consequently, this alert can be ignored. The predictions are superseded by the data.
  o Both the target material and the read-across analog are toxicants within the Developmental Toxicity (CAESAR) classification scheme. The data described in the reproductive toxicity section show that the MOE is adequate at the current level of use. Therefore, the predictions are superseded by data.
  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.

- 2-tert-Butylcyclohexane (CAS # 1728-46-7) was used as a read-across analog for the target material 2-cyclohexylocyclohexane (CAS # 90-42-6) for the genotoxicity endpoint.
  o The target material and the read-across analog are structurally similar and belong to a class of cyclohexanes.
  o The target material and the read-across analog share a cyclohexane ring.
  o The key difference between the target material and the read-across analog is that the target material has a cyclohexyl ring in position 2, whereas the read-across analog has a tert-butyl substitution in the same position. This structural difference is toxicologically insignificant.
  o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  o The physical-chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References


OECD. 2016. The OECD QSAR Toolbox. v.3.2-4.2. Retrieved from: http://www.oqtoolebox.org/


