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Short Review

RIFM fragrance ingredient safety assessment, 2-cyclohexylpropanal, CAS Registry Number 2109-22-0

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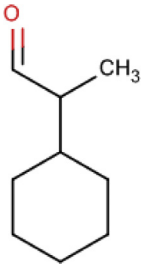
Version: 091318. This version replaces any previous versions.
Name: 2-Cyclohexylpropanal
CAS Registry Number: 2109-22-0



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, 2017) compared to a deterministic aggregate approach
DEREK	Derek Nexus is an *in silico* tool used to identify structural alerts
DST	Dermal Sensitization Threshold
ECHA	European Chemicals Agency
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

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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
QRA	Quantitative Risk Assessment
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).

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

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

2-Cyclohexylpropanal was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from 2-cyclohexylpropanal show that it is not genotoxic. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to 2-cyclohexylpropanal is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using DST for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-cyclohexylpropanal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-cyclohexylpropanal was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment	
Genotoxicity	Not Genotoxic. (RIFM, 2017a; RIFM, 2017b)
Repeated Dose Toxicity	No NOAEL available. Exposure is below the TTC.
Developmental and Reproductive Toxicity	No NOAEL available. Exposure is below the TTC.
Skin Sensitization:.	No safety concerns at current, declared use levels; exposure is below the DST
Phototoxicity/Photoallergenicity	Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM Database)
Local Respiratory Toxicity	No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment	
Hazard Assessment	
Persistence	Screening-level: 2.91 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation	Screening-level: 45.14 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity	Screening-level: LC50: 25.01 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) (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint	LC50: 25.01 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is	0.02501 μg/L
• Revised PEC/PNECs (2015 IFRA VoU):	North America and Europe: Not Applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 2-Cyclohexylpropanal
2. **CAS Registry Number:** 2109-22-0
3. **Synonyms:** 2-シクロヘキシルプロパナール; 2-Cyclohexylpropanal
4. **Molecular Formula:** $C_9H_{16}O$
5. **Molecular Weight:** 140.22
6. **RIFM Number:** 6530
7. **Stereochemistry:** Isomer not specified. One stereocenter present and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 202.00–203.00 °C @ 760.00 mm Hg*
2. **Flash Point:** 91 °C (GHS)
3. **Log K_{ow}:** Not Available
4. **Melting Point**: Not Available
5. **Water Solubility:** 223.6 mg/L @ 25 °C*
6. **Specific Gravity:** 0.91300 to 0.92300 @ 25.00 °C*
7. **Vapor Pressure:** 0.344 mm Hg @ 20 °C (EPI Suite v4.0)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** A clear, colorless liquid with a medium natural, fresh, green, pollen odor in 10% dipropylene glycol*

*http://www.thegoodscentscompany.com/data/rw1041921.html, retrieved on 3/10/15.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.00006% (RIFM, 2017c)
3. **Inhalation Exposure*:** 0.000053 mg/kg/day or 0.0037 mg/day (RIFM, 2017c)
4. **Total Systemic Exposure**:** 0.00027 mg/kg/day (RIFM, 2017c)

*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 IV. 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).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity**: None
   b. **Repeated Dose** Toxicity: None
   c. **Developmental and 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

6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

2-Cyclohexylpropanal is not reported to occur in food by the VCF*.

*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. Ifra standard

None.

9. Reach dossier: dossier

Available; accessed 04/18/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2-cyclohexylpropanal does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. 2-Cyclohexylpropanal was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: < 80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of 2-cyclohexylpropanal 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 *Escherichia coli* strain WP2uvrA were treated with 2-cyclohexylpropanal in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2017a). Under the conditions of the study, 2-cyclohexylpropanal was not mutagenic in the Ames test.

The clastogenic activity of 2-cyclohexylpropanal 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-cyclohexylpropanal in DMSO at concentrations up to 175 μg/mL in the presence and absence of metabolic activation (S9) for 4 h and in the absence of metabolic activation for 24 h 2-Cyclohexylpropanal did not induce binucleated cells with micronuclei when tested up to cytotoxic concentrations in either the presence or absence of an S9 activation system (RIFM, 2017b). Under the conditions of the study, 2-cyclohexylpropanal was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, 2-cyclohexylpropanal does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/10/2018.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 2-cyclohexylpropanal or on any read-across materials. The total systemic exposure to 2-cyclohexylpropanal is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-cyclohexylpropanal or on any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 2-cyclohexylpropanal (0.27 μg/kg bw/day) is below the TTC (30 μg/kg bw/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: 04/24/18.

10.1.3. Developmental and reproductive toxicity

There are insufficient developmental and reproductive toxicity data on 2-cyclohexylpropanal or on any read-across materials. The total systemic exposure to 2-cyclohexylpropanal is below the TTC for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on 2-cyclohexylpropanal or on any read-across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to 2-cyclohexylpropanal (0.27 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/24/18.

10.1.4. Skin sensitization

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

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins

Table 1
Maximum acceptable concentrations for 2-cyclohexylpropanal that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.005%	0.000%
2	Products applied to the axillae	0.001%	0.000%[b]
3	Products applied to the face using fingertips	0.029%	0.000%
4	Fine fragrance products	0.027%	0.000%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.007%	0.000%[b]
6	Products with oral and lip exposure	0.016%	0.000%
7	Products applied to the hair with some hand contact	0.056%	0.000%[b]
8	Products with significant ano-genital exposure	0.003%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	0.016%
10	Household care products with mostly hand contact	0.192%	0.025%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.107%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.020%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.001%).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

(Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v4.2). No predictive skin sensitization studies are available for 2-cyclohexylpropanal. Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford et al., 2011; Safford et al., 2015b; Roberts et al., 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 2-cyclohexylpropanal that present no appreciable risk for skin sensitization based on the reactive DST. These concentrations are not limits; they represent acceptable concentrations based on the DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/07/18.

10.1.5. Phototoxicity/photoallergenicity

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

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

10.1.5.2. Key studies. There are no studies available on 2-cyclohexylpropanal in experimental models.

10.1.5.3. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 2-cyclohexylpropanal 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.

Literature Search and Risk Assessment Completed On: 03/27/18.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 2-cyclohexylpropanal is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2-cyclohexylpropanal. Based on the Creme RIFM Model, the inhalation exposure is 0.0037 mg/day. This exposure is 378.4 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: 04/24/2018.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-cyclohexylpropanal 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, 2-cyclohexylpropanal was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 2-cyclohexylpropanal 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 BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

10.2.2. Risk assessment

Based on the current Volume of Use (2015), 2-cyclohexylpropanal does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

Other available data.

2-cyclohexylpropanal has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in μg/L).

Endpoints used to calculate PNEC are highlighted.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	25.01			1,000,000	0.02501	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.01	3.01
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	NA
Risk Characterization: PEC/PNEC	**< 1**	**NA**

Based on available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.02501 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 05/02/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 08/27/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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