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RIFM fragrance ingredient safety assessment, cedrol, CAS Registry Number 77-53-2

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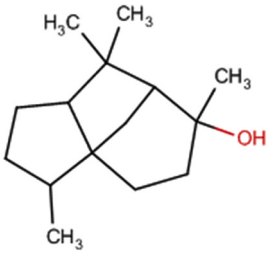

Name: Cedrol
CAS Registry Number: 77-53-2

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Safford et al., 2015a; Safford et al., 2017; Comiskey 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 Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
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,

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(*continued*)

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.

Cedrol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from cedrol and read-across analog patchouli alcohol (CAS # 5986-55-0) show that cedrol is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to cedrol is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data provided cedrol a No Expected Sensitization Induction Level (NESIL) of 2000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; cedrol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; cedrol 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 expected to be genotoxic.	(RIFM, 2001b; RIFM, 2014a; RIFM, 2013b)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.	
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.	
Skin Sensitization: NESIL = 2000 μg/cm^2.	RIFM (2014b)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.	

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 85% (OECD 301F)	RIFM (2007)
Bioaccumulation: Screening-level: 332 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 96-h Fish LC50: 1.048 mg/L	(ECOSAR; US EPA, 2012b)
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: 96-h Fish LC50: 1.048 mg/L	(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.1048 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: <1

1. Identification

1. **Chemical Name:** Cedrol
2. **CAS Registry Number:** 77-53-2
3. **Synonyms:** Cedar camphor; Cedarwood oil alcohols; Cypress camphor; 1H-3a,7-Methanoazulene-6-ol, octahydro-3,6,8,8-tetramethyl-,[3R-(3.α,3a.β,6.α,7.β,8aa]; セドロール; Cedran-8-ol; (+)-Cedrol; 1H-3a,7-Methanoazulen-6-ol, octahydro-3,6,8,8-tetramethyl-, (3R,3aS,6R,7R,8aS)-; 8-β-H-Cedran-8-ol; α-Cedrol; Cedrol cryst; [3R-(3α,3aβ,6α,7β,8aα)]-octahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-6-ol; (1S,2R,5S,7S,8R)-2,6,6,8-tetramethyltricyclo [5.3.1.01,5]undecan-8-ol; Produit AC; Reaction mass of (1S,2R,5S,7S,8R)-2,6,6,8-tetramethyltricyclo[5.3.1.01,5]undecan-8-ol and [3R-(3α,3aβ,6α,7β,8aα)]-octahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl acetate; Reaction Mass of (1S,2R,5S,7S,8R)- 2,6,6,8- tetramethyltricyclo[5.3. 1.01,5]undecan-8-ol and (1S,2R,5S,7S,8R)- 2,6,6,8- tetramethyltricyclo[5.3. 1.01,5] undec-8-yl acetate; Cedrol

4. **Molecular Formula:** $C_{15}H_{26}O$
5. **Molecular Weight:** 222.37 g/mol
6. **RIFM Number:** 129
7. **Stereochemistry:** Isomer not specified. Five chiral centers available and a total of 32 enantiomers possible.

2. Physical data

1. **Boiling Point:** 294 °C; (S) (Fragrance Materials Association [FMA]), >200 °C; (CS) (FMA), 280.2 °C (EPI Suite), 283–286 °C at 1013 hPa (RIFM, 2016b)
2. **Flash Point:** 88 °C (Globally Harmonized System), 190 °F; CC; (S) (FMA), >200 °F; CC; (CS) (FMA), 149.5 °C at 1013 hPa (average corrected and rounded down to nearest multiple of 0.5 °C) (RIFM, 2016a)
3. **Log K_{OW}:** 4.33 (EPI Suite), 2.71–6.86 (RIFM, 2017)
4. **Melting Point**: 39 °C; (CS) (FMA), 79 °C; (S) (FMA), 75.52 °C (EPI Suite), −58.7 °C at 1013 hPa (RIFM, 2016b)
5. **Water Solubility:** 21.88 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0000604 mm Hg at 20 °C (EPI Suite v4.0), 0.000124 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:** EOA Spec. no. 171 White crystals with a very faint odor or cedarwood type. When pure, almost odorless

3. Volume of use (Worldwide band)

1. 10–100 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.33% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.00051 mg/kg/day or 0.037 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0019 mg/kg/day (RIFM, 2018)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (RIFM, 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 (RIFM, 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 v4.2
I	III	I

*See the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** Patchouli alcohol (CAS # 5986-55-0)
   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: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.

7.1. Additional References

None.

8. Natural occurrence

Cedrol is reported to occur in the following foods by the VCF*:

Calamus (sweet flag) (*Acorus calamus* L.)	Mastic (*Pistacia lentiscus*)
Cinnamomum species	Pistachio oil (*Pistacia vera*)
Citrus fruits	Soybean (*Glycine max*. L. merr.)
Cocoa	Tea
Guava and feyoa	Turpentine oil (*Pistacia terebinthus*)
Katsuobushi (dried bonito)	

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

9. Reach dossier

Available; accessed on 11/05/21 (ECHA, 2019).

10. Conclusion

The maximum acceptable concentrations[a] in finished products for cedrol are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
1	Products applied to the lips (lipstick)	0.15
2	Products applied to the axillae	0.046
3	Products applied to the face/body using fingertips	0.92
4	Products related to fine fragrances	0.86
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.22
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.22
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.22
5D	Baby cream, oil, talc	0.22
6	Products with oral and lip exposure	0.51
7	Products applied to the hair with some hand contact	1.8
8	Products with significant ano-genital exposure (tampon)	0.090
9	Products with body and hand exposure, primarily rinse-off (bar soap)	1.7
10A	Household care products with mostly hand contact (hand dishwashing detergent)	6.0

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(*continued*)

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)
10B	Aerosol air freshener	6.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	3.3
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For cedrol, the basis was a skin sensitization NESIL of 2000 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, cedrol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of cedrol 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, TA102, and TA97a were treated with cedrol 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, 2001b). Under the conditions of the study, cedrol was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of cedrol; however, read-across can be made to patchouli alcohol (CAS # 5986-55-0; see Section VI).

The clastogenic activity of patchouli alcohol 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 patchouli alcohol in DMSO at concentrations up to 1112 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 192 μg/mL in the presence and absence of metabolic activation. Patchouli alcohol did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation system (RIFM, 2014a). Under the conditions of the study, patchouli alcohol was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to cedrol.

Based on the data available, patchouli alcohol does not present a concern for genotoxic potential, and this can be extended to cedrol.

Additional References: RIFM, 2013b; RIFM, 2013a; RIFM, 2016d.

Literature Search and Risk Assessment Completed On: 11/06/20.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on cedrol or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (1.9 μg/kg/day) is below the TTC for cedrol (30 μg/kg/day; Kroes et al., 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/21/20.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are no reproductive toxicity data on cedrol or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (1.9 μg/kg/day) is below the TTC for cedrol (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/20/20.

11.1.4. Skin sensitization

Based on the existing data, cedrol is considered a skin sensitizer with a defined NESIL of 2000 μg/cm^2.

11.1.4.1. Risk assessment. Based on the existing data, cedrol is 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). Cedrol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and LuSens test (ECHA, 2019; 001 key study; ECHA, 2019; 002 key study). In a murine local lymph node assay (LLNA), cedrol was found to be sensitizing with an EC3 value of 19% (4750 μg/cm^2) (RIFM, 2016c). In a guinea pig open epicutaneous test (OET), cedrol at 8% did not lead to skin sensitization reactions (Klecak, 1979). Similarly, in a guinea pig closed epicutaneous test (CET), cedrol at 10% did not lead to skin sensitization reactions (Ishihara et al., 1986). In a human maximization test, skin sensitization reactions were observed when 8% or 5520 μg/cm^2 of cedrol in petrolatum was used (RIFM, 1973). In another human maximization test, no skin reactions were observed at 8% or 5520 μg/cm^2. Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 1.7% or 2008 μg/cm^2 of cedrol in 1:3 ethanol: diethyl phthalate (1:3 EtOH:DEP), no reactions indicative of sensitization were observed in any of the 106 volunteers (RIFM, 2014b).

Based on weight of evidence (WoE) from structural analysis, animal, and human studies, cedrol is a weak sensitizer with a WoE NESIL of 2000 μg/cm^2 (Table 1). Section X provides the maximum acceptable concentrations in finished products, which take into account skin

Table 1
Data summary for cedrol.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
4750 [1]	Weak	2008	NA	5520	2000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from CNIH or HMT.
[c] WoE NESIL limited to 2 significant figures.

sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b).

Additional References: Klecak (1985); NCBI, 2020).

Literature Search and Risk Assessment Completed On: 11/03/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, cedrol 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 cedrol in experimental models. UV/Vis absorption spectra indicate no significant absorption 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 the lack of absorbance, cedrol 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: 10/23/20.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There is insufficient inhalation data available on cedrol. Based on the Creme RIFM Model, the inhalation exposure is 0.037 mg/day. This exposure is 37.8 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: Kagawa et al., 2003; Dayawansa et al., 2003.

Literature Search and Risk Assessment Completed On: 11/05/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of cedrol 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, cedrol was identified as a fragrance material with the 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 cedrol 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). 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), cedrol presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 2007:** The ready biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301F method. Cedrol underwent an average of 85% biodegradation after 28 days.

RIFM, 2001a: The ready biodegradability of cedrol was determined over a 28-day period with non-adapted activated sludge in a closed bottle test according to the OECD 301D method. Biodegradation of 55% was observed.

11.2.2.1.2. Ecotoxicity. **RIFM, 2000:** A *Daphnia magna* acute immobilization test was conducted according to the OECD 202 method, under static conditions. The 48-h EC50 value based on measured concentration was reported to be 4.3 mg/L (95% CI: 4–4.6 mg/L).

11.2.2.1.3. Other available data. Cedrol has been registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Since Cedrol has passed the screening criteria, measured data are included for completeness and have 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2.818			1000000	0.002818	
ECOSAR Acute Endpoints **(Tier 2)** v1.11	1.489	1.048	1.897	10000	0.1048	Neutral Organics

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	6.86	6.86
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.1048 μg/L. The revised PEC/PNECs for EU and NA are <1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 11/09/20.

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 11/05/21.

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.2022.112998.

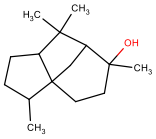
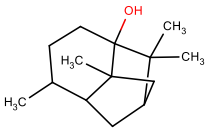
Appendix

Read-across Justification

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020a). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 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 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's skin absorption model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2020).

	Target Material	Read-across Material
Principal Name	Cedrol	Patchouli alcohol
CAS No.	77-53-2	5986-55-0
Structure		
Similarity (Tanimoto Score)		0.90
Endpoint		Genotoxicity
Molecular Formula	$C_{15}H_{26}O$	$C_{15}H_{26}O$
Molecular Weight (g/mol)	222.372	222.372
Melting Point (°C, EPI Suite)	86.00	56.00
Boiling Point (°C, EPI Suite)	280.20	280.20
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.0165	0.0328
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	21.9	42.9
Log K_{OW}	4.33	3.98
J_{max} (μg/cm^2/h, SAM)	2.05	2.89
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.24	1.24
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found
In Vitro Mutagenicity (Ames, ISS)	No alert found	No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	No alert found	No alert found
Oncologic Classification	Not classified	Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on cedrol (CAS 77-53-2). 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, patchouli alcohol (CAS 5986-55-0) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Patchouli alcohol (CAS 5986-55-0) was used as a read-across analog for the target material cedrol (CAS 77-53-2) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to a class of multicyclic sesquiterpene alcohols.
  - o The target substance and the read-across analog share a tertiary alcohol group on a saturated multicyclic hydrocarbon skeleton.
  - o The key difference between the target substance and the read-across analog is the position of the methyl substitutions on the ring system. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target material.
  - o The similarity between the target substance 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 substance 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 substance and the read-across analog.

- There are no *in silico* alerts for the target substance and the read-across analog. The data for the read-across analog confirms that the analog does not pose a concern for genetic toxicity. *In silico* alerts are consistent with data.
- The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies 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.
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation). Yes. Class I (Class low)

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