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Short Review

RIFM fragrance ingredient safety assessment, *cis*-4-decenol, CAS Registry Number 57074-37-0

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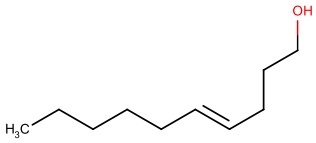


Abbreviation/Definition List:

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., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use, but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*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.

(*continued on next column*)

(*continued*)

cis-4-Decenol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog *cis*-3-hexenol (CAS # 928-96-1) show that *cis*-4-decenol is not expected to be genotoxic and provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from read-across analog *cis*-3-hexenol (CAS # 928-96-1) show that there are no safety concerns for *cis*-4-decenol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; *cis*-4-decenol 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 *cis*-4-decenol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; *cis*-4-decenol 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, 2014a; RIFM, 2014b)

Repeated Dose Toxicity: NOAEL = 125 mg/kg/day. Gaunt et al. (1969)

Reproductive Toxicity: Developmental toxicity: 300 mg/kg/day; Fertility: 300 mg/kg/day. (ECHA REACH Dossier: *cis*-Hex-3-en-1-ol; ECHA, 2013)

Skin Sensitization: Not a concern for skin sensitization at the current, declared use levels. (ECHA REACH Dossier: *cis*-Hex-3-en-1-ol; ECHA, 2013)

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: 3.3 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 105.7 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 9.08 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: 9.08 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.00908 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe (No VoU): Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** *cis*-4-Decenol
2. **CAS Registry Number:** 57074-37-0
3. **Synonyms:** (Z)-4-Decenol; Dec-4-en-1-ol; *cis*-4-Decenol
4. **Molecular Formula:** $C_{10}H_{20}O$
5. **Molecular Weight:** 156.26
6. **RIFM Number:** 577
7. **Stereochemistry:** *Cis* isomer specified. One Stereocenter and 2 total stereoisomers possible

2. Physical data

1. **Boiling Point:** 244.14 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 3.57 (EPI Suite)
4. **Melting Point**: 6.97 °C (EPI Suite)
5. **Water Solubility:** 204.8 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00474 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Hydroalcoholics:** 0.38 (RIFM, 2017)
2. **Inhalation Exposure*:** 0.0011 mg/kg/day or 0.082 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.0095 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, 2017; Safford et al., 2015, 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, 2017; Safford et al., 2015, 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	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** *cis*-3-Hexenol (*cis*-hex-3-en-1-ol; CAS # 928-96-1)
   b. **Repeated Dose Toxicity:** *cis*-3-Hexenol (CAS # 928-96-1)
   c. **Reproductive Toxicity:** *cis*-3-Hexenol (CAS # 928-96-1)
   d. **Skin Sensitization:** *cis*-3-Hexenol (CAS # 928-96-1)
   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)

cis-4-Decenol is reported to occur in the following foods by the VCF*:
Banana (Musa sapientum L.)
Buchu oil.
Citrus fruits.
Passion fruit (*Passiflora* species).
Turpentine oil (Pistacia terebinthus).
*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

Pre-registered for 2010; no dossier available as of 04/15/20.

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, *cis*-4-decenol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of *cis*-4-decenol; however, read-across can be made to *cis*-3-hexenol (CAS # 928-96-1); see Section VI). The mutagenic activity of *cis*-3-hexenol 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 *cis*-3-hexenol in dimethyl sulfoxide (DMSO) at concentrations of 16–5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2014a). Under the conditions of the study, *cis*-3-hexenol was not mutagenic in the Ames test, and this can be extended to *cis*-4-decenol.

The clastogenic activity of *cis*-3-hexenol 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 *cis*-3-hexenol in DMSO at concentrations up to 1002 μg/mL in the presence and absence of metabolic activation for 3 and 24 h *cis*-3-Hexenol did not induce binucleated cells with micronuclei when tested up to the maximum dose in either non-activated or S9-activated test systems (RIFM, 2014b). Under the conditions of the study, *cis*-3-hexenol was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to *cis*-4-decenol.

Based on the data available, *cis*-3-hexenol does not present a concern for genotoxic potential, and this can be extended to *cis*-4-decenol.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/07/19.

11.1.2. Repeated dose toxicity

The MOE for *cis*-4-decenol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on *cis*-4-decenol. Read-across material *cis*-3-hexenol (CAS # 928-96-1; see Section VI) has sufficient repeated dose toxicity data. Test material *cis*-3-hexenol was administered via drinking water to groups of 15 SPF-derived CFE weanling rats/sex/dose at doses of 0, 310, 1250, or 5000 ppm (equivalent to 0, 31, 125, and 500 mg/kg/day) for 98 days. Observations included mortality, clinical signs, body weight, food intake, and water consumption. Gross pathology, organ weight analysis, and histopathology were conducted, and hematological and urinary analysis parameters were examined at weeks 6 and 14. There was a decrease in hemoglobin concentration among females at week 6, but no significant changes in hematocrit values or in erythrocyte or reticulocyte counts were reported. This was not considered to be significant since this finding was not observed at week 14 or in any of the male animals. An increase in specific gravity and a decrease in the volume of urine produced during the first 2 h after a water load were observed in males at the highest dose after 14 weeks; this effect was not seen in week 6 treated males or in females after 6 or 14 weeks of treatment. The most conservative NOEL was considered to be 1250 ppm or 125 mg/kg/day, based on a reduction in hemoglobin content among high-dose females (Gaunt et al., 1969). In another study, following the OECD 422/GLP guidelines, the test material *cis*-3-hexenol was administered via oral gavage to groups of 11 RCCHan:WIST (SPF) rats/sex/dose at doses of 0, 100, 300, or 1000 mg/kg/day. The male and female rats were treated for a total of 41 and 53 days, respectively. Mortality was reported among the highest-dose group animals: 1 male and 4 female rats were found dead at different points. The deaths were considered by the authors to be caused by aspiration during the gavage procedures and not related to the systemic toxicity of the test material. The NOAEL for systemic toxicity was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013). The most conservative NOEL of 125 mg/kg/day obtained from the 98-day study was considered for the safety assessment of *cis*-3-hexenol.

Therefore, the *cis*-4-decenol MOE for the repeated dose toxicity endpoint can be calculated by dividing the *cis*-3-hexenol NOEL in mg/kg/day by the total systemic exposure to *cis*-4-Decenol, 125/0.0095, or 13158.

In addition, the total systemic exposure to *cis*-4-decenol (9.5 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: RIFM, 1974.

Literature Search and Risk Assessment Completed On: 10/14/19.

11.1.3. Reproductive toxicity

The MOE for *cis*-4-decenol is adequate for the fertility and developmental toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on *cis*-4-decenol. Read-across material *cis*-3-hexenol (*cis*-hex-3-en-1-ol; CAS # 928-96-1; see section VI) has sufficient developmental and fertility toxicity data. In an OECD 422/GLP study, groups of 11 RCCHan:WIST (SPF) rats/sex/dose were administered test material *cis*-hex-3-en-1-ol via gavage at doses of 0, 100, 300, or 1000 mg/kg/day. The male and female rats were treated for a total of 41 and 53 days, respectively. There were no effects on reproductive parameters, which included precoital times, fertility index, and the conception rate, and the mean number of corpora lutea per dam. There were no effects on litter size, birth index, or sex ratio. The mean postnatal loss was 1.6%, 1.2%, 1.6%, and 9.6% in dose groups 0, 100, 300, and 1000 mg/kg/day, respectively. The cause of the slightly higher postnatal loss in the 1000 mg/kg/day group was the loss of 7 pups on days 2 and 3 post-partum for a single dam; this isolated occurrence was considered to be incidental. The authors determined the NOAELs for general fertility and developmental toxicity to be 1000 mg/kg/day (ECHA, 2013). It was concluded that, although the finding in 1 litter from 1 dam is most likely incidental, the more conservative NOAEL of 300 mg/kg/day should be selected for the fertility and developmental toxicity endpoints.

In another OECD 414/GLP prenatal developmental toxicity study, groups of 20 female Sprague Dawley rats were administered *cis*-3-hexenol via oral gavage at doses of 0, 100, 300, or 1000 mg/kg/day. Females were treated once daily from gestation days (GDs) 6–19 and were euthanized on GD 20. There were no treatment-related adverse effects observed on dams or the development of pups up to the highest dose tested, thus, NOAEL for maternal and developmental toxicity was considered to be 1000 mg/kg/day (ECHA, 2013).

The more conservative NOAEL of 300 mg/kg/day from the OECD 422 study was selected for the reproductive toxicity endpoint.

Therefore, the *cis*-4-decenol MOE for the fertility and developmental toxicity endpoints can be calculated by dividing the *cis*-hex-3-en-1-ol NOAEL in mg/kg/day by the total systemic exposure to *cis*-4-decenol, 300/0.0095, or 31578.

In addition, the total systemic exposure to *cis*-4-decenol (9.5 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the fertility and developmental toxicity endpoint for a Cramer Class I material at the current level of use.

Additional References: RIFM, 1974.

Literature Search and Risk Assessment Completed On: 10/14/19.

11.1.4. Skin sensitization

Based on read-across material *cis*-3-hexenol (CAS # 928-96-1), *cis*-4-decenol does not present a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. No skin sensitization studies are available for *cis*-4-decenol. Based on read-across material *cis*-3-hexenol (CAS # 928-96-1), *cis*-4-decenol is not considered a skin sensitizer. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.3). In a murine local lymph node assay, read-across material *cis*-3-hexenol was not found to be sensitizing when tested up to 100% (ECHA, 2013). In a guinea pig open epicutaneous test, no sensitization reactions were observed with read-across material *cis*-3-hexenol at 4% (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with 4% or 2760 μg/cm^2 of read-across material *cis*-3-hexenol (RIFM, 1973). Additionally, in a confirmatory human repeat insult patch test with 1.25% or 968.99 μg/cm^2 of read-across material *cis*-3-hexenol in 95% ethanol, no reactions indicative of sensitization was observed in any of the 38 volunteers (RIFM, 1964).

Based on the weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material *cis*-3-hexenol, *cis*-4-decenol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/20/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, *cis*-4-decenol 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 *cis*-4-decenol 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, *cis*-4-decenol 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: 09/30/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for *cis*-4-decenol 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 *cis*-4-decenol. Based on the Creme RIFM Model, the inhalation exposure is 0.082 mg/day. This exposure is 17.1 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: 10/10/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of *cis*-4-decenol 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, *cis*-4-decenol 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 *cis*-4-decenol 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).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), *cis*-4-decenol presents no risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.3. Other available data. *cis*-4-Decenol has been pre-registered for REACH with no additional data available at this time.

11.2.2. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>9.08</u>			1000000	0.00908	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	3.57	3.57
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	No VoU	<1
Risk Characterization: PEC/PNEC	**NA**	**< 1**

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

The RIFM PNEC is 0.00908 μg/L. The revised PEC/PNECs for EU (No VoU) and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 09/25/19.

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**
- **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 04/15/20.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111545.

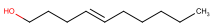
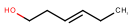
Appendix

Read-across Justification

Methods

The read-across analog was 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, 2016).

- 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).
- 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, 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 material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	*cis*-4-Decenol	*cis*-3-Hexenol
CAS No.	57074-37-0	928-96-1
Structure		
Similarity (Tanimoto Score)		0.76
Read-across Endpoint		• Genotoxicity • Repeated dose toxicity • Reproductive toxicity • Skin sensitization
Molecular Formula	$C_{10}H_{20}O$	$C_6H_{12}O$
Molecular Weight	156.26	100.16
Melting Point (°C, EPI Suite)	6.97	−38.47
Boiling Point (°C, EPI Suite)	244.14	165.73
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.632	125
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	3.57	1.61
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	2.05E+002	1.6E+004
J_{max} (μg/cm^2/h, SAM)	25.95	446.29
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	4.87E+000	1.57E+000
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
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Slightly reactive (GSH)|Slightly reactive (GSH) ≫ Alkenes (AN)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
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 *cis*-4-decenol (CAS # 57074-37-0). 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, *cis*-3-hexenol (CAS # 928-96-1) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- *cis*-3-Hexenol (CAS # 928-96-1) was used as a read-across analog for the target material *cis*-4-decenol (CAS # 57074-37-0) for the genotoxicity, repeated dose toxicity, reproductive toxicity, and skin sensitization endpoints.
  - o The target material and the read-across analog are structurally similar and belong to the class of unsaturated primary aliphatic alcohols.
  - o The target material and the read-across analog share a vinylene unsaturation and a primary hydroxy group.
  - o The key difference between the target material and the read-across analog is that the read-across analog has a shorter aliphatic chain by 4 carbons compared to the target material and a vinylene unsaturation in position 3, while the target material has a vinylene unsaturation in position 4. This structural difference is toxicologically insignificant.
  - o The 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 read-across analog has a Protein Binding Potency alert for slightly reactive alkene. Even though the target material is also an unsaturated primary alcohol but with 4 more carbons, this alert is not seen in the target material. The data described in the skin sensitization section show that there are no concerns for skin sensitization at the current level of use. The predictions are superseded by the 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.

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