Food and Chemical Toxicology 110 (2017) S611–S618

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short review

RIFM fragrance ingredient safety assessment, *cis*-3-octen-1-ol, CAS Registry Number 20125-84-2

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http://dx.doi.org/10.1016/j.fct.2017.10.015
Received 31 August 2017; Received in revised form 27 September 2017; Accepted 9 October 2017
Available online 12 October 2017
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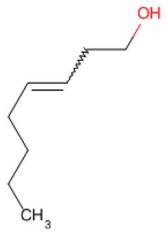
Version: 081617. This version replaces any previous versions.

Name: *cis*-3-Octen-1-ol

CAS Registry Number: 20125-84-2



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
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; Safford et al., 2015; 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
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
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
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- Ultra Violet/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 under the limits 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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.

The material (*cis*-3-octen-1-ol), was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the read across analog *cis*-3-hexenol (CAS # 928-96-1) show that *cis*-3-octen-1-ol is not genotoxic nor does it have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose and developmental and reproductive toxicity endpoints were completed using *cis*-3-hexenol (CAS # 928-96-1) as a read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, *cis*-3-octen-1-ol was found not to be a 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, 2014b; RIFM, 2014a)

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

Developmental and Reproductive Toxicity: NOAEL = 300 mg/kg/day. (ECHA REACH Dossier: *cis*-Hex-3-en-1-ol)

Skin Sensitization: Not sensitizing. (ECHA REACH Dossier: *cis*-Hex-3-en-1-ol; RIFM, 1973; RIFM, 1964)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening Level: 3.37 (BIowin 3) (US EPA, 2012a)
Bioaccumulation: Screening Level: 23.78 l/kg (US EPA, 2012a)
Ecotoxicity: Screening Level: Fish LC50: 53.05 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: 53.05 mg/l (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.05305 μg/l

- **Revised PEC/PNECs (2011 IFRA Volume of Use)**: North America and Europe: Not applicable; Cleared at screening level

1. Identification

1. **Chemical Name**: *cis*-3-Octen-1-ol
2. **CAS Registry Number**: 20125-84-2
3. **Synonyms**: *cis*-3-Octen-1-ol; *cis*-3-Octenol; 3-Octen-1-ol, (Z)-; Oct-3-en-1-ol
4. **Molecular Formula**: $C_8H_{16}O$
5. **Molecular Weight**: 128.22
6. **RIFM Number**: 6725

2. Physical data

1. **Boiling Point**: 73 °C @ 0.5 mm Hg [FMA Database], 206.75 °C (US EPA, 2012a)
2. **Flash Point**: 180 °F; CC [FMA Database]
3. **Log K_{OW}**: 2.59 (US EPA, 2012a)
4. **Melting Point**: −15.22 °C (US EPA, 2012a)
5. **Water Solubility**: 1855 mg/l (US EPA, 2012a)
6. **Specific Gravity**: 0.85 [FMA Database]
7. **Vapor Pressure**: 0.0303 mm Hg @ 20 °C (US EPA, 2012a), 0.1 mm Hg 20 °C [FMA Database], 0.049 mm Hg @ 25 °C (US EPA, 2012a)
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**: A colorless to pale, yellow, clear, liquid with a powerful fresh, fatty, fruity, melon odor while at 1% or less in dipropylene glycol.*

*http://www.thegoodscentscompany.com/data/rw1036361.html, retrieved 3/15/2017.

3. Exposure

1. **Volume of Use (worldwide band)**: < 0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Toothpaste**: 0.0022% (RIFM, 2014c)
   (No reported use in Hydroalcoholics)
3. **Inhalation Exposure***: 0.00000060 mg/kg/day or 0.000040 mg/day (RIFM, 2014c)
4. **Total Systemic Exposure****: 0.000021 mg/kg/day (RIFM, 2014c)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015, 2017; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015, 2017; 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. **Analogues Selected**:
   a. **Genotoxicity**: *cis*-3-hexenol (CAS # 928-96-1)
   b. **Repeated Dose Toxicity**: *cis*-3-hexenol (CAS # 928-96-1)
   c. **Developmental and 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

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

The material, *cis*-3-octen-1-ol is reported to occur in the following foods* and in some natural complex substances (NCS):
Cider (apple wine)
Passion fruit (*Passiflora* species)
*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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 11/30/2010; no dossier available as of 08/21/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current data, *cis*-3-octen-1-ol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. *cis*-3-Octen-1-ol was assessed in the

BlueScreen assay and found to be negative for genotoxicity and cytotoxicity, with and without metabolic activation (RIFM, 2013b). There are no data available for *cis*-3-octen-1-ol. The mutagenic activity of read across analog *cis*-3-hexenol (CAS # 928-96-1; see Section 5) 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.

There are no studies assessing the clastogenic activity of *cis*-3-octen-1-ol, however, read across can be made to *cis*-3-hexenol (CAS # 928-96-1; see Section 5). 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.

Based on the data available, *cis*-3-hexenol does not present a concern for genotoxic potential and this can be extended to *cis*-3-octen-1-ol.

Additional References: RIFM, 2013a.

Literature Search and Risk Assessment Completed on: 3/10/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for *cis*-3-octen-1-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on *cis*-3-octen-1-ol. Read across material, *cis*-3-hexenol (CAS # 928-96-1; see section 5) 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 for 98 days. Observations included mortality, clinical signs, bodyweight, food intake and water consumption. Gross pathology, organ weight, and histopathology were conducted, as well as hematological and urinary analysis parameters examined at weeks 6 and 14. The most conservative NOEL was considered to be 1250 ppm or 125 mg/kg/day, based on reduction in hemoglobin content among the high dose females (Gaunt et al., 1969). In another study, following the OECD/GLP 422 guidelines, test material, *cis*-3-hexenol was administered via 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 cause of death was considered to be aspiration of the test material during the gavage procedures and not related to the systemic toxicity of the test material. The NOAEL for systemic toxicity was thus considered to be 1000 mg/kg/day, the highest dose tested (ECHA REACH Dossier: *cis*-Hex-3-en-1-ol, CAS # 928-96-1). The most conservative NOEL of 125 mg/kg/day was considered for this safety assessment. **Therefore, the *cis*-3-octen-1-ol 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*-3-octen-1-ol, 125/0.000021 or 5952381.**

In addition, the total systemic exposure to *cis*-3-octen-1-ol (0.021 μg/kg/day) is below the TTC (30 μg/kg bw/dayl; 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: 03/07/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for *cis*-3-octen-1-ol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on *cis*-3-octen-1-ol. Read across material, *cis*-3-hexenol (CAS # 928-96-1; see section 5) has sufficient developmental and reproductive toxicity data. In an OECD/GLP 422 study, groups of 11 RCCHan™:WIST(SPF) rats/sex/dose were administered via gavage test material, *cis*-3-hexenol 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 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 day 2 and 3 post-partum for a single dam; this isolated occurrence was considered to be incidental. The authors determined the NOAELs for general, reproductive and developmental toxicity to be 1000 mg/kg/day (ECHA REACH Dossier: *cis*-Hex-3-en-1-ol, CAS # 928-96-1). The Expert Panel for Fragrance Safety* concluded that although the finding in one litter from one dam is most likely incidental, the more conservative NOAEL of 300 mg/kg/day should be selected for the developmental and reproductive toxicity endpoints. **Therefore, the *cis*-3-octen-1-ol MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the *cis*-3-hexenol NOAEL in mg/kg/day by the total systemic exposure to *cis*-3-octen-1-ol, 300/0.000021 or 14285714.**

In addition, the total systemic exposure to *cis*-3-octen-1-ol (0.021 μg/kg/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 for a Cramer Class I material at the current level of use**.

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

Additional References: RIFM, 1974.

Literature Search and Risk Assessment Completed on: 03/07/2017.

10.1.4. Skin sensitization

Based on the existing data for read across *cis*-3-hexenol (CAS # 928-96-1), *cis*-3-octen-1-ol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. No skin sensitization data are available for *cis*-3-octen-1-ol, however, read across material (see Section 5) *cis*-3-hexenol (CAS # 928-96-1) has been evaluated in animal and human studies. The chemical structure indicates that these materials are not expected to react significantly with skin proteins (Toxtree 2.6.6, OECD toolbox v3.3). In a local lymph node assay, read across material *cis*-3-hexenol did not result in sensitization (ECHA REACH Dossier: *cis*-Hex-3-en-1-ol). In a human maximization test, no reactions indicative of sensitization were observed with 4% or 2760 μg/cm^2 *cis*-3-Hexenol (RIFM, 1973). Moreover, no sensitization reactions were observed when 969 μg/cm^2 *cis*-3-hexenol was evaluated in a confirmatory human repeat insult patch test (RIFM, 1964). Based on weight of evidence from structural analysis and available animal and human studies on read across material *cis*-3-hexenol, *cis*-3-octen-1-ol does not

present a concern for skin sensitization.

Additional References: Klecak, 1985.

Literature Search and Risk Assessment Completed on: 3/9/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, *cis*-3-octen-1-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no predictive studies available on *cis*-3-octen-1-ol in experimental models. The available UV/Vis spectra for *cis*-3-octen-1-ol indicate no significant absorbance between 290 and 700 nm. Corresponding molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on the lack of absorbance in the critical range, *cis*-3-octen-1-ol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 02/22/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, *cis*-3-Octen-1-ol, exposure level 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 *cis*-3-Octen-1-ol. Based on the Creme RIFM model, the inhalation exposure is 0.000040 mg/day. This exposure is 35000 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: 3/10/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of *cis*-3-octen-1-ol was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates; US EPA, 2012b) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, *cis*-3-octen-1-ol 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*-3-octen-1-ol as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

10.2.2. Risk assessment

Based on current Volume of Use (2011), *cis*-3-octen-1-ol does not present a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.3. Other available data

cis-3-Octen-1-ol has been pre-registered for REACH with no additional data at this time.

10.2.4. 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)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	<u>53.05 mg/l</u>			1,000,000	0.05305 μg/l	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.59	2.59
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.05305 μg/l. The revised PEC/PNECs for EU and NA: Not Applicable; 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: 5/28/15.

11. Literature search*

- **RIFM database**: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA**: http://echa.europa.eu/
- **NTP**: http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **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://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor**: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS**: http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary**: http://cfpub.epa.gov/hpv-s/
- **Japanese NITE**: http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base**: http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google**: https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.10.015.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.10.015.

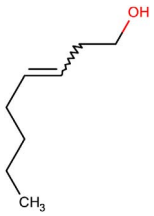
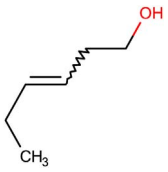
Appendix

Read across justification

Methods

The read across analogs were identified following the strategy for structuring and reporting a read across prediction of toxicity 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 Chemical 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 was 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 substance 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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010) and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target material	Read across material
Principal Name	*cis*-3-Octen-1-ol	*cis*-3-Hexenol
CAS No.	20125-84-2	928-96-1
Structure		
Similarity (Tanimoto score)		0.89
Read across endpoint		• Genotoxicity • Skin Sensitization • Reproductive and Developmental

		• Repeated Dose
Molecular Formula	$C_8H_{16}O$	C6H12O
Molecular Weight	128.22	100.16
Melting Point (°C, EPISUITE)	−15.22	−38.47
Boiling Point (°C, EPISUITE)	206.75	165.73
Vapor Pressure (Pa @ 25°C, EPISUITE)	6.53	125
Log Kow (KOWWIN v1.68 in EPISUITE)	2.59	1.0[a]
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	1855	1.6E+004
J_{max} (mg/cm^2/h, SAM)	150.12	250.19
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	2.76E+000	1.57E+000
Genotoxicitys		
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
In vitro Mutagenicity (Ames test) alerts by ISS	• No alert found	• No alert found
In vivo mutagenicity (Micronucleus) alerts by ISS	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Repeated Dose		
Repeated Dose (HESS)	• Not categorized	• Not categorized
Reproductive and Developmental toxicity		
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity Model by CAESAR v2.1.6	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
Skin Sensitization		
Protein binding by OASIS v1.1	• No alert found	• No alert found
Protein binding by OECD	• No alert found	• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Non-sensitizer (low reliability)	• Non-sensitizer (moderate reliability)
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator and structural alerts for metabolites	See supplemental data 1	See supplemental data 2

[a] RIFM, 1997.

Summary

There are insufficient toxicity data on the target material *cis*-3-octen-1-ol (CAS # 20125-84-2). Hence, *in silico* evaluation was conducted to determine a read across analog for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, *cis*-3-hexenol (CAS # 928-96-1) was identified as read across material with data for their respective toxicological endpoints.

Conclusion/Rationale

- *cis*-3-Hexenol (CAS # 928-96-1) was used as a read across analog for the target material *cis*-3-octen-1-ol (CAS # 20125-84-2) for the skin sensitizaiton, genotoxicity, reproductive and developmental toxicity and repeated dose toxicity endpoints.
  - o The target substance and the read across analog are structurally similar and belong to the structural class of primary non-beta-unsaturated aliphatic alcohols.
  - o The target substance and the read across analog share primary alcohol structures with isolated double bonds.
  - o The key difference between the target substance and the read across analog is that the target substance has a longer aliphatic chain than the read across analog. This structural difference between the target substance and the read across analog does not affect consideration of the toxicological endpoints.
  - o Similarity between the target substance and the read across analog is indicated by the Tanimoto score shown in the table above. Differences between the structures that affect the Tanimoto score do not affect consideration of the toxicological endpoints.
  - o The physical-chemical properties of the target substance and the read across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the QSAR OECD Toolbox (v3.4), structural alerts for toxicological endpoints are consistent between the target substance and the read across analog.
  - o The target substance and the read across analog are expected to be metabolized similarly, as shown by the metabolism simulator.

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