Food and Chemical Toxicology 149 (2021) 111868

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Short Review

RIFM fragrance ingredient safety assessment, 3-octanol, CAS Registry Number 589-98-0

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ARTICLE INFO

Keywords:
Genotoxicity
Repeated dose
Developmental
And reproductive toxicity
Skin
Sensitization
Phototoxicity/photoallergenicity
Local respiratory toxicity
Environmental safety

ABSTRACT

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

3-Octanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 3-hexanol (CAS # 623-37-0) show that 3-octanol is not expected to be genotoxic. Data on 3-octanol provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across analog 2-octanol (CAS # 123-96-6) provide a calculated MOE >100 for the reproductive toxicity endpoint and show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 3-octanol 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; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 3-octanol 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.

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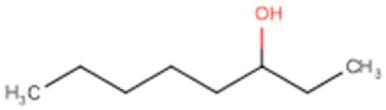
https://doi.org/10.1016/j.fct.2020.111868
Received 16 September 2020; Received in revised form 22 October 2020; Accepted 12 November 2020
Available online 18 November 2020

Version: 091,620. This version replaces any previous versions.



Name: 3-Octanol
CAS Registry Number: 589-98-0

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a; Safford 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 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.

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(*continued*)

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

3-Octanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 3-hexanol (CAS # 623-37-0) show that 3-octanol is not expected to be genotoxic. Data on 3-octanol provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity endpoint. Data on read-across analog 2-octanol (CAS # 123-96-6) provide a calculated MOE >100 for the reproductive toxicity endpoint and show that there are no safety concerns for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 3-octanol 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; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 3-octanol 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, 2017b; RIFM, 2017a)
Repeated Dose Toxicity: NOAEL = 25 mg/kg/day.	(Lindecrona et al., 2003)
Reproductive Toxicity: Developmental toxicity: 100 mg/kg/day Fertility: 300 mg/kg/day.	ECHA REACH Dossier: Octan-2-ol; ECHA (2011)
Skin Sensitization: Not a concern for skin sensitization at the current, declared use levels.	(ECHA REACH Dossier: Octan-2-ol, ECHA, 2011; RIFM, 1977)
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: 3.37 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 29.48 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 40.7 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: 40.7 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.0470 μg/L

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

1. Identification

1. **Chemical Name**: 3-Octanol
2. **CAS Registry Number**: 589-98-0
3. **Synonyms**: Amyl ethyl carbinol; Ethyl n-amyl carbinol; Octanol-3; アルカノール(C = 5 ~ 38); Octan-3-ol; 3-Octanol
4. **Molecular Formula**: $C_8H_{18}O$
5. **Molecular Weight**: 130.23

6. **RIFM Number**: 918
7. **Stereochemistry**: One chiral center and 2 stereoisomers.

2. Physical data

1. **Boiling Point:** 175 °C (Fragrance Materials Association [FMA]), 181.87 °C (EPI Suite)
2. **Flash Point:** 69 °C (Globally Harmonized System), 157 °F; CC (FMA)
3. **Log K_{OW}:** 2.73 (EPI Suite)
4. **Melting Point**: 27.45 °C (EPI Suite)
5. **Water Solubility:** 1379 mg/L (EPI Suite)
6. **Specific Gravity:** 0.820 (FMA)
7. **Vapor Pressure:** 0.0627 mm Hg @ 20 °C (EPI Suite v4.0), 0.0996 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:** Colorless liquid, with a sweet, herbaceous, oily-nutty warm odor

3. Volume of use (worldwide band)

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

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v2.0)

1. 95th Percentile Concentration in Hydroalcoholics: 0.0021% (RIFM, 2019)
2. Inhalation Exposure*: 0.000013 mg/kg/day or 0.00090 mg/day (RIFM, 2019)
3. Total Systemic Exposure**: 0.00030 mg/kg/day (RIFM, 2019)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 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 (Comiskey et al., 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 v3.2
I	II	I

*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). See the Appendix below for further details.

2. Analogs Selected:
   a. **Genotoxicity:** 3-Hexanol (CAS # 623-37-0)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** 2-Octanol (CAS # 123-96-6)
   d. **Skin Sensitization:** 2-Octanol (CAS # 123-96-6)
   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)

3-Octanol is reported to occur in the following foods by the VCF*:

Acerola (Malpighia)	Mentha Oils
Brown Algae	Mushroom
Calamintha Nepeta Oil	Thyme (*Thymus* species)
Fish	Vanilla
Litchi (*Litchi chinensis* Sonn.)	Wine

*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. This is a partial list.

9. REACH dossier

Available; accessed 01/31/20 (ECHA, 2018)

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, 3-octanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Read-across analog 3-hexanol was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2014). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of 3-octanol; however, read-across can be made to 3-hexanol (CAS # 623-37-0; see Section VI).

The mutagenic activity of 3-hexanol 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 3-hexanol 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,

2017b). Under the conditions of the study, 3-hexanol was not mutagenic in the Ames test, and this can be extended to 3-octanol.

There are no studies assessing the clastogenic activity of 3-octanol; however, read-across can be made to 3-hexanol (CAS # 623-37-0; see Section VI).

The clastogenic activity of 3-hexanol 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 3-hexanol in DMSO at concentrations up to 10,000 μM in the presence and absence of S9 for 3 h and in the absence of S9 for 24 h 3-Hexanol did not induce binucleated cells with micronuclei when tested up to the maximum concentration in either the presence or absence of an S9 activation system (RIFM, 2017a). Under the conditions of the study, 3-hexanol was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 3-octanol.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/19/20.

11.1.2. Repeated dose toxicity

The MOE for 3-octanol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on 3-octanol.

In an OECD 408/non-GLP compliant subchronic toxicity study, 10 Wistar rats/sex/group were administered 3-octanol (purity: 99.7%) via gavage at doses of 0 (vehicle control: soybean oil), 25, 100, and 400 mg/kg/day for 90 days. At 100 mg/kg/day and 400 mg/kg/day, a significant increase in terminal body weight of females was reported. Overt treatment-related signs of toxicity were reported in the liver of both sexes and kidneys of male rats at 100 and 400 mg/kg/day (>50% frequency). Animals at 25 mg/kg/day exhibited liver lesions such as granulomas (6/20), bile duct proliferation (3/20), and kidney lesions such as protein droplets (6/10 males), but these lesions were minimal in severity. Animals at 100 mg/kg/day exhibited histological liver lesions such as granulomas (10/20), bile duct proliferation (4/20), kidney lesions such as protein droplets (6/10 males), tubular karyomegaly (4/10 males), and a significant increase in tubular epithelial cell desquamation (8/10 males), although the incidence of these effects was not significantly increased. Animals at 400 mg/kg/day exhibited liver lesions such as granulomas (12/20), significantly increased bile duct proliferation (12/20) in both sexes, and kidney lesions such as protein droplets (9/10 males), a significant increase in tubular karyomegaly (8/10 males), and tubular epithelial cell desquamation (7/10 males). Furthermore, fatty changes indicative of mild hepatic injury were noted in 3 males and 1 female at 400 mg/kg/day but not at 100 mg/kg/day. The bile duct proliferation seen in low- and high-dose animals consisted of minimal to mild proliferation of small bile ductules within portal areas and could have been a secondary response to chemically induced liver injury, although the lesions were mild and not associated with any related changes in liver enzymes. The liver and kidney lesions reported were minimal to mild in severity at both the mid and high doses, except for protein droplets which were mild in severity at the high dose. No similar changes were reported in the kidneys of females. However, at the mid and high doses, multiple changes were noted more frequently than in controls. Therefore, based on increased relative liver weight and microscopic evaluations of liver and kidney at the mid and high doses, the NOAEL was considered to be 25 mg/kg/day (Lindecrona et al., 2003; ECHA, 2018).

Therefore, the 3-octanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3-octanol NOAEL in mg/kg/day by the total systemic exposure to 3-octanol, 25/0.0003, or 83,333.

In addition, the total systemic exposure to 3-octanol (0.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/10/20.

11.1.3. Reproductive toxicity

The MOE for 3-octanol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are not sufficient fertility and developmental toxicity data on 3-octanol. Read-across material 2-octanol (CAS # 123-96-6; see Section VI) can be used to cover the fertility and developmental toxicity endpoint. In an OECD TG 422 study, 10 Sprague Dawley rats/sex/dose were administered 2-octanol via gavage at doses of 100, 300, and 1000 mg/kg/day. Males were dosed for 30–31 days and females were dosed for 7–8 weeks. No effects were observed in the parental generation on the reproductive function of sperm, the number of copulatory plugs, copulation index, or fertility index. Decreased numbers of non-sequential days in which females were in estrous were observed in all treatment groups; however, at the low and mid doses, the means remained within the historical control data. Vaginal smears were examined on the day of necropsy to determine the stage of the estrous cycle. Diestrous effects were recorded for the non-pregnant females of the control and low-dose groups. For the 2 non-pregnant females of the mid-dose group, diestrous and estrous effects were observed. Diestrous effects were recorded for all females euthanized on day 14 post-partum. Mean pre-coital intervals were significantly decreased at the high dose, but this effect was not considered toxicologically relevant because the high value in the control was due to 2 females that conceived after 12 and 14 days of pairing. No effects were seen in the F1 generation on pre-weaning clinical signs, male nipple retention, sex ratios, or gross pathological findings. Increased pup loss in the post-partum period was observed in females of the mid- and high-dose groups. Statistically significant decreases in litter weight and mean pup weight were observed in the post-partum period in the mid- and high-dose groups. A slight increase in the mean anogenital distance values was noted in high-dose female pups when compared to the control value, but this effect was not dose-dependent. Based on estrous effects at 1000 mg/kg/day, the NOAEL for the reproductive endpoint was considered to be 300 mg/kg/day. Based on increased pup loss and decreased litter weight and pup weight at 300 mg/kg/day and 1000 mg/kg/day, the NOAEL for the developmental endpoint was considered to be 100 mg/kg/day (ECHA, 2011).

Therefore, the 3-octanol MOE for the reproductive toxicity endpoint can be calculated by dividing the 2-octanol NOAEL in mg/kg/day by the total systemic exposure to 3-octanol, 300/0.0003, or 1,000,000. The 3-octanol MOE for the developmental toxicity endpoint can be calculated by dividing the 2-octanol NOAEL in mg/kg/day by the total systemic exposure to 3-octanol, 100/0.0003, or 333,333.

In addition, the total systemic exposure to 3-octanol (0.3 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive/developmental toxicity endpoint of a Cramer Class I material at the current level of use.

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

and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/19/20.

11.1.4. Skin sensitization

Based on read-across material 2-octanol (CAS # 123-96-6), 3-octanol does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 3-octanol. Based on the existing data and read-across material 2-octanol (CAS # 123-96-6; see Section VI), 3-octanol is not considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a murine local lymph node assay (LLNA), read-across material 2-octanol was not found to be sensitizing up to 100% (ECHA, 2011; 001 Key study). In a human maximization test, no skin sensitization reactions were observed with 3-octanol (RIFM, 1977).

Based on weight of evidence (WoE) from structural analysis, animal and human studies, and read-across material 2-octanol, 3-octanol 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: 02/21/20.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 3-octanol 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 3-octanol 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, 3-octanol 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: 02/18/20.

11.1.6. Local respiratory toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 3-octanol is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on 3-octanol. Based on the Creme RIFM Model, the inhalation exposure is 0.00090 mg/day. This exposure is 1555.6 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: Korpi et al., 1999.

Literature Search and Risk Assessment Completed On: 02/28/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 3-octanol 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, 3-octanol 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 3-octanol 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 $\geq$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).

11.2.2. Risk assessment

Based on the current Volume of Use (IFRA, 2015), 3-octanol presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.2.2. Ecotoxicity. No data available.

11.2.2.2. Other available data. 3-Octanol has been registered for REACH with no additional information available at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are 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)**	40.7			1000000	0.0470	

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	2.73	2.73
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 0.0470 μg/L. The revised PEC/PNECs for EU 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: 02/20/20.

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 05/31/20.

Declaration of competing interest

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

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111868.

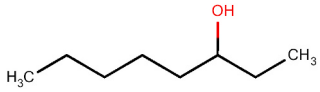
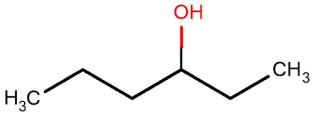
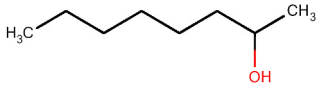
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). 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, 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), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- 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	Read-across Material
Principal Name	3-Octanol	3-Hexanol	2-Octanol
CAS No.	589-98-0	623-37-0	123-96-6
Structure			
Similarity (Tanimoto Score)		0.70	0.95
Endpoint		• Genotoxicity	• Skin Sensitization • Reproductive toxicity
Molecular Formula	$C_8H_{18}O$	$C_6H_{14}O$	$C_8H_{18}O$
Molecular Weight	130.23	102.18	130.23
Melting Point (°C, EPI Suite)	−16.00	−51.34	−31.60
Boiling Point (°C, EPI Suite)	195.00	134.75	180.00
Vapor Pressure (Pa @ 25°C, EPI Suite)	34.13	641.28	32.26
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	586.00	16100.00	1280.00
Log K_{OW}	2.73	1.65	2.90
J_{max} (μg/cm^2/h, SAM)	53.24	663.26	137.56
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.14	4.07	12.46
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found	No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found	No alert found
Carcinogenicity (ISS)	No alert found	No alert found	No alert found
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found	No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found	No alert found
Oncologic Classification	Not classified	Not classified	Not classified
Reproductive and Developmental Toxicity			
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)	Non-toxicant (low reliability)	Non-toxicant (low reliability)
Skin Sensitization			
Protein Binding (OASIS v1.1)	No alert found	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found	No alert found
Protein Binding Potency	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)	Not possible to classify according to these rules (GSH)

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified.	No skin sensitization reactivity domain alerts identified.	No skin sensitization reactivity domain alerts identified.
Metabolism			
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3

Summary

There are insufficient toxicity data on 3-octanol (CAS # 589-98-0). 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, 3-hexanol (CAS # 623-37-0) and 2-octanol (CAS # 123-96-6) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 3-Hexanol (CAS # 623-37-0) was used as a read-across analog for the target material 3-octanol (CAS # 589-98-0) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of secondary aliphatic alcohols.
  - o The target material and the read-across analog share a secondary hydroxyl group.
  - o The key difference between the target material and the read-across analog is that the target material has the longer aliphatic chain by 2 carbons compared to the read-across analog. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-Octanol (CAS # 123-96-6) was used as a read-across analog for the target material 3-octanol (CAS # 589-98-0) for the skin sensitization and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to a class of secondary aliphatic alcohols.
  - o The target material and the read-across analog share a secondary hydroxyl group.
  - o The key difference between the target material and the read-across analog is the location of the hydroxyl group. The target material has the hydroxyl group on the C3 atom whereas the read-across analog has the hydroxyl group on the C2 atom. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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. 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)? No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? Yes
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? Yes
Q21.3 or more different functional groups? No
Q18. One of the list (see Cramer et al., 1978 for detailed explanation on list of categories)? No, Class Low (Class I)

References

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the Research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. Food Chem. Toxicol. 82, S1–S19.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of cramer classification between toxtree, the OECD QSAR Toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food Chem. Toxicol. 47 (6), 1287–1295.

Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. Chem. Cent. J. (4 Suppl. 1), S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Chem. Toxicol. 16 (3), 255–276.

Date, M.S., O'Brien, D., Botelho, D., Schultz, T.W., Liebler, D.C., Penning, T.M., Salvito, D., 2020. Clustering a chemical inventory for safety assessment of fragrance ingredients: identifying read-across analogs to address data gaps. Chem. Res. Toxicol. (Ahead of print).

Echa, 2011. Octan-2-ol registration dossier. Retrieved from. https://echa.europa.eu/lt/registration-dossier/-/registered-dossier/14450/1.

Echa, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

Echa, 2017. Read-across assessment framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

Echa, 2018. Octan-3-ol registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/22691.

Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? J. Photochem. Photobiol. B Biol. 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Korpi, A., Kasanen, J.-P., Alarie, Y., Kosma, V.-M., Pasanen, A.L., 1999. Sensory irritating potency of some microbial volatile organic compounds (MVOCs) and a mixture of five MVOCs. Archives of Environmental Health 54 (5), 347–352.

Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. Food Chem. Toxicol. 45 (12), 2533–2562.

Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. Regul. Toxicol. Pharmacol. 62 (1), 160–182.

Lindecrona, R.H., Molck, A.-M., Gry, J., Poulsen, M., Andersen, R., Thorup, I., 2003. Subchronic oral toxicity study on the flavouring substances: Octan-3-ol, 2-methyl-crotonic acid and oct-3-yl 2-methylcrotonate in Wistar rat. Food Chem. Toxicol. 41 (5), 647–654.

OECD, 2015. Guidance document on the reporting of integrated Approaches to testing and assessment (IATA). ENV/JM/HA(2015)7. Retrieved from. http://www.oecd.org/.

OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc), 1977. Report on Human Maximization Studies. Report to RIFM. RIFM Report Number 1691. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2014. Report on the Testing of 3-hexanol in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM Report Number 67149. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2017a. Ells. RIFM Report Number 72406. In: 3-Hexanol: Genetic Toxicity Evaluation Using a Micronucleus Test in Human Lymphocyte C. RIFM, Woodcliff Lake, NJ, USA report.

RIFM (Research Institute for Fragrance Materials, Inc), 2017b. 3-Hexanol: Genetic Toxicity Evaluation Using Bacterial Reverse Mutation Test in Salmonella typhimurium TA1535, TA1537, TA98 and TA100, and Escherichia coli WP2 uvrA/pKM101. RIFM Report Number 74383. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2019. Exposure Survey 23, January 2019.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C. A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. J. Chem. Inf. Model. 50 (5), 742–754.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.

Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.

Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. Regul. Toxicol. Pharmacol. 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food Chem. Toxicol. 74, 164–176.

Us EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.

Us EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.