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Short Review

RIFM fragrance ingredient safety assessment, 2-hexanol, CAS Registry Number 626-93-7



A.M. Api^a, D. Belsito^b, S. Biserta^a, D. Botelho^a, M. Bruze^c, G.A. Burton Jr.^d, J. Buschmann^e, M. A. Cancellieri^a, M.L. Dagli^f, M. Date^a, W. Dekant^g, C. Deodhar^a, A.D. Fryer^h, S. Gadhia^a, L. Jones^a, K. Joshi^a, M. Kumar^a, A. Lapczynski^a, M. Lavelle^a, I. Lee^a, D.C. Lieblerⁱ, H. Moustakas^a, M. Na^a, T.M. Penning^j, G. Ritacco^a, J. Romine^a, N. Sadekar^a, T.W. Schultz^k, D. Selecknik^a, F. Siddiqi^a, I.G. Sipes^l, G. Sullivan^{a,*}, Y. Thakkar^a, Y. Tokura^m

^a Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA

^b Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA

^c Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden

^d School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 48109, USA

^e Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany

^f University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil

^g University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany

^h Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA

ⁱ Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA

^j University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA

^k The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

^l Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

^m The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

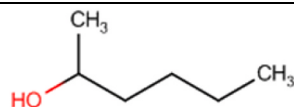
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Name: 2-Hexanol CAS Registry Number: 626-93-7



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

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AF - Assessment Factor

BCF - Bioconcentration Factor

Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach

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* Corresponding author.

E-mail address: gsullivan@rifm.org (G. Sullivan).

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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.

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

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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, 2017c; RIFM, 2017b)

Repeated Dose Toxicity: NOAEL = 100 mg/kg/day. (ECHA REACH Dossier: Octan-2-ol; ECHA, 2011)

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)

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

Bioaccumulation: Screening-level: 6.734 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 223 mg/L (RIFM Framework; Salvitto, 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvitto, 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 223 mg/L (RIFM Framework; Salvitto, 2002)

RIFM PNEC is: 0.223 µg/L

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

1. Identification

1. **Chemical Name:** 2-Hexanol
2. **CAS Registry Number:** 626-93-7
3. **Synonyms:** 2-Hydroxyhexane; Hexan-2-ol; 2-Hexanol
4. **Molecular Formula:** C₆H₁₄O
5. **Molecular Weight:** 102.17
6. **RIFM Number:** 6166
7. **Stereochemistry:** One chiral center and 2 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 138.62 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{ow}:** 1.76 (Abraham, 1995), 1.75 (EPI Suite)
4. **Melting Point:** -51.34 °C (EPI Suite)
5. **Water Solubility:** 11710 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 2.94 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ · cm⁻¹)
9. **Appearance/Organoleptic:** 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. **95th Percentile Concentration in Hydroalcoholics:** 0.0000021% (RIFM, 2017a)
2. **Inhalation Exposure*:** <0.00010 mg/kg/day or <0.00010 mg/day (RIFM, 2017a)
3. **Total Systemic Exposure**:** <0.0001 mg/kg/day (RIFM, 2017a)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 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, 2015, 2017; Safford, 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)

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:** 2-Octanol (CAS # 123-96-6)
 - 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.

7.1. Additional References

None.

8. Natural occurrence (Discrete chemical) or composition (NCS)

2-Hexanol is reported to occur in the following foods by the VCF*:

Apple brandy (<i>Cavados</i>)	<i>Artocarpus</i> species
Apple fresh (<i>Malus</i> species)	Banana (<i>Musa sapientum</i> L.)
Apricot (<i>Prunus armeniaca</i> L.)	

*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. REACHdossier

Pre-registered for 2020; no dossier available as of 08/12/20.

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, 2-hexanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic or clastogenic activity of 2-hexanol; 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, 2017c). Under the conditions of the study, 3-hexanol was not mutagenic in the Ames test, and this can be extended to 2-hexanol.

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 10000 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, 2017b). 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 2-hexanol.

Additional References: None.

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

11.1.2. Repeated dose toxicity

The MOE for 2-hexanol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are not sufficient repeated dose toxicity data on 2-hexanol. Read-across material 2-octanol (CAS # 123-96-6; see Section VI) can be used to evaluate the repeated dose 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. One female at 1000 mg/kg/day was euthanized for humane reasons on day 2 of the study (pre-mating phase); no clinical signs were observed in the animal after the first administration, and pathological examinations did not reveal the underlying cause of the moribund condition. In the remaining animals in the study, no effects were

observed in motor activity, grip strength, sensory reactivity, or urinalysis. Clinical signs such as piloerection, ataxia, decreased activity, and hunched posture/kyphosis were observed in males at the high dose (1000 mg/kg/day) across the treatment period; the same effects, in addition to semi-closed or fully closed eyes, prone posture, and lethargic appearance, were observed in females at the high dose during the pre-mating period. Piloerection, ataxia, decreased activity, and kyphosis persisted in high-dose females through the post-coitum period. Food consumption was significantly reduced (−17%) in high-dose females during the pre-mating period, while bodyweight gain was slightly increased in this group at the end of the pre-mating period; bodyweight gain was statistically significant but did not persist through the post-coitum or post-partum periods and thus was not considered toxicologically significant. Statistically significant decreases in body weight (6–8%) and food consumption (7%–13%) were observed in high-dose females during the post-coitum and post-partum periods but were only slight in magnitude. A significant increase of neutrophils was recorded in males dosed at 300 mg/kg/day (81%) and 1000 mg/kg/day (87%), but due to the low severity and lack of other associated changes, it was not considered to be adverse. Mean corpuscular volume changes were reported in males, and lymphocyte changes were seen in both sexes, but these effects were not dose-related and thus were not considered to be treatment-related. Sodium levels were significantly increased in males at all doses (1% in all groups). Calcium levels were significantly increased in males at 300 mg/kg/day (4%) and 1000 mg/kg/day (7%). Albumin (7%) and bile acid (178%) levels were significantly increased in males at 1000 mg/kg/day. Bilirubin levels were significantly increased in females at 300 mg/kg/day (8.6-fold), but this change was not dose-related and thus was not considered treatment-related; furthermore, the high mean was driven by 1 outlier individual and thus was considered to be incidental. Absolute and relative liver weights were increased in both sexes at the high dose. This increase was statistically significant and treatment-related. This change was accompanied by minimal centrilobular hepatocellular hypertrophy in half of the high-dose males. Hepatocyte hypertrophy could be associated with microsomal enzyme induction secondary to exposure to the test material. Thickening of the non-glandular region of the stomach was observed in most rats of both sexes at the high dose, in 1 of each sex at the mid dose, and 1 control male at necropsy. However, forestomach lesions are not considered toxicologically relevant to humans. Based on adverse clinical signs in both sexes, as well as body weight and food consumption fluctuations in females, the NOAEL for the repeated dose endpoint was considered to be 300 mg/kg/day.

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 300/3 or 100 mg/kg/day. Therefore, the 2-hexanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-Octanol NOAEL in mg/kg/day by the total systemic exposure to 2-hexanol, 100/0.0001, or 1000000.

In addition, the total systemic exposure to 2-hexanol (0.1 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes, 2007) for the repeated dose 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: 02/11/20.

11.1.3. Reproductive toxicity

The MOE for 2-hexanol 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 2-hexanol. Read-across material 2-octanol (CAS # 123-96-6; see Section VI) can be used to evaluate the reproductive 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 values, but this effect was not dose-dependent. Based on estrous effects at 1000 mg/kg/day, the NOAEL for the fertility 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 toxicity endpoint was considered to be 100 mg/kg/day (ECHA, 2011).

Therefore, the 2-hexanol MOE for the fertility endpoint can be calculated by dividing the 2-octanol NOAEL in mg/kg/day by the total systemic exposure to 2-hexanol, 300/0.0001, or 3000000. The 2-hexanol 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 2-Hexanol, 100/0.0001, or 1000000.

In addition, the total systemic exposure to 2-hexanol (0.1 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive 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), 2-hexanol does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. No skin sensitization studies are available for 2-hexanol. Based on read-across material 2-octanol (CAS # 123-96-6; see Section VI), 2-hexanol 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, 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 when tested up to 100% (ECHA, 2011; 001 Key study).

Based on weight of evidence (WoE) from structural analysis, animal

studies, and read-across material 2-octanol, 2-hexanol 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, 2-hexanol 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 2-hexanol 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, 2009). Based on the lack of absorbance, 2-hexanol 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, $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/21/20.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-hexanol 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 2-hexanol. Based on the Creme RIFM Model, the inhalation exposure is $< 0.0001 \text{ mg/day}$. This exposure is at least 14000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

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 2-hexanol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW} , and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, 2-hexanol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 2-hexanol 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 $\geq 2000 \text{ L/kg}$. 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 (2015), 2-hexanol presents no risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

2-Hexanol has been pre-registered for REACH with no additional information available at this time.

11.2.4.1. Risk assessment refinement. Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$).

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	1.76	1.76
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 further assessment is necessary.

The RIFM PNEC is $\mu\text{g/L}$. 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: 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>

	LC50 (Fish)	EC50	EC50	AF	PNEC (µg/L)	Chemical Class
	(mg/L)	(<i>Daphnia</i>) (mg/L)	(Algae) (mg/L)			
RIFM Framework Screening-level (Tier 1)	<u>223</u>	X	X	1000000	0.223	X

- **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/opthpv/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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2020.111894>.

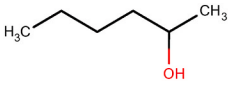
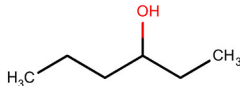
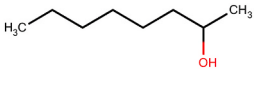
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date, 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	2-Hexanol	3-Hexanol	2-Octanol
CAS No.	626-93-7	623-37-0	123-96-6
Structure			
Similarity (Tanimoto Score)		0.88	0.76
Endpoint		<ul style="list-style-type: none"> • Genotoxicity 	<ul style="list-style-type: none"> • Skin sensitization • Repeated dose toxicity • Reproductive toxicity
Molecular Formula	C ₆ H ₁₄ O	C ₆ H ₁₄ O	C ₈ H ₁₈ O
Molecular Weight	102.18	102.18	130.23
Melting Point (°C, EPI Suite)	-51.34	-51.34	-31.60
Boiling Point (°C, EPI Suite)	136.00	134.75	180.00
Vapor Pressure (Pa @ 25 °C, EPI Suite)	331.97	641.28	32.26
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	13700.00	16100.00	1280.00
Log K _{ow}	1.76	1.65	2.90
J _{max} (µg/cm ² /h, SAM)	661.56	663.26	137.56
Henry's Law (Pa·m ³ /mol, Bond Method, EPI Suite)	2.47	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
<i>In Vitro</i> Mutagenicity (Ames, ISS)	No alert found	No alert found	No alert found
<i>In Vivo</i> Mutagenicity (Micronucleus, ISS)	No alert found	No alert found	No alert found
Oncologic Classification	Not classified	Not classified	Not classified
Repeated Dose Toxicity			
Repeated Dose (HESS)	Propylene glycol (Renal toxicity) Alert	Not categorized	Not categorized
Reproductive 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)
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 2-hexanol (CAS # 626-93-7). 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 2-hexanol (CAS # 626-93-7) for the genotoxicity endpoint.
- The target material and the read-across analog are structurally similar and belong to a class of aliphatic secondary alcohols.
- The target material and the read-across analog share a secondary hydroxyl group.
- 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 2 position whereas the read-across analog has the hydroxyl group on the 3 position. This structural difference is toxicologically insignificant.
- 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.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- 2-Octanol (CAS # 123-96-6) was used as a read-across analog for the target material 2-hexanol (CAS # 626-93-7) for the skin sensitization, reproductive, and repeated dose toxicity endpoints.
 - The target material and the read-across analog are structurally similar and belong to a class of secondary aliphatic alcohols.
 - The target material and the read-across analog share a secondary hydroxyl group.
 - The key difference between the target material and the read-across analog is that the target material has a longer aliphatic chain by 2 carbons compared to the read-across. This structural difference is toxicologically insignificant.
 - 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.
 - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
 - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
 - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
 - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

- Q1. 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)

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