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Short Review

RIFM fragrance ingredient safety assessment, 2-pentanol, CAS Registry Number 6032-29-7

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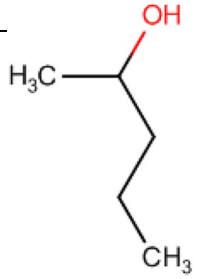
Version: 022219. This version replaces any previous versions.

Name: 2-Pentanol
CAS Registry Number: 6032-29-7



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015; Safford 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
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-Pentanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog 2-butanol (CAS # 78-92-2) show that 2-pentanol is not expected to be genotoxic. Data on read-across material 2-butanol (CAS # 78-92-2) provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints and show that there are no safety concerns for 2-pentanol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 2-pentanol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to 2-pentanol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2-pentanol was found not to be 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 expected to be genotoxic.	(ECHA REACH Dossier: Butan-2-ol; ECHA, 2011; https://tools.niehs.nih.gov/cebs3/ui/?study=002-01302-0001-0000-9 NTP, 2004)
Repeated Dose Toxicity: NOAEL = 1644 mg/kg/day.	(Union Carbide, 1992)
Reproductive Toxicity: Developmental toxicity: NOAEL = 1644 mg/kg/day. Fertility: NOAEL = 3122 mg/kg/day.	(Union Carbide, 1992)
Skin Sensitization: Not a sensitization concern under the current, declared levels of use.	(ECHA REACH Dossier: Butan-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: 3.2 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation:	
Screening-level: 2.83 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: Fish LC50: 523.6 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: 523.6 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.5236 µg/L	

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

1. Identification

1. **Chemical Name:** 2-Pentanol
2. **CAS Registry Number:** 6032-29-7
3. **Synonyms:** *sec-n*-Amyl alcohol; α-Methylbutanol; Methyl *n*-propyl carbinol; Propyl methyl carbinol; Pentan-2-ol; 2-Pentanol
4. **Molecular Formula:** $C_5H_{12}O$
5. **Molecular Weight:** 88.15
6. **RIFM Number:** 318
7. **Stereochemistry:** No isomer specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 115.64 °C (EPI Suite)
2. **Flash Point:** 34 °C (GHS)
3. **Log K_{OW}:** 1.25 (Abraham and Rafols, 1995), 1.26 (EPI Suite)
4. **Melting Point**: −63.68 °C (EPI Suite)
5. **Water Solubility:** 39190 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 3.9 mm Hg 20 °C (FMA), 7.26 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 500 nm; the molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Colorless liquid with winey-ethereal, rather choking odor.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric ton per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Shampoo:** 0.0008% (RIFM, 2017)
   No reported use in hydroalcoholics
3. **Inhalation Exposure*:** < 0.0001 mg/kg/day or < 0.0001 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00015 mg/kg/day (RIFM, 2017)

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

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)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	II	I

*Due to potential discrepancies between 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. See Appendix below.

2. Analogs Selected:
   a. **Genotoxicity:** 2-Butanol (CAS # 78-92-2)
   b. **Repeated Dose Toxicity:** 2-Butanol (CAS # 78-92-2)
   c. **Reproductive Toxicity:** 2-Butanol (CAS # 78-92-2)
   d. **Skin Sensitization:** 2-Butanol (CAS # 78-92-2)
   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 are available for inclusion in this safety assessment.

6.1. Additional References

None.

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

2-Pentanol is reported to occur in the following foods by the VCF*:
Apple, fresh (*Malus* species)
Cheese, various types.
Citrus fruits.
Filbert, hazelnut (*Corylus avellano*)
Guava and feyoa
Olive (*Olea europaea*)
Papaya (*Carica papaya* L.)
Strawberry (*Fragaria* species)
Tea.
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. Not a complete list.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 02/12/19.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 2-pentanol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. There are no data assessing the mutagenic and clastogenic activity of 2-pentanol; however, read-across can be made to 2-butanol (CAS # 78-92-2; see Section V).

The mutagenic activity of 2-butanol 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

preincubation method. *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA98, and TA 100 were treated with 2-butanol in dimethyl sulfoxide (DMSO) at concentrations up to 10000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2011). Under the conditions of the study, 2-butanol was not mutagenic in the Ames test (and this can be extended to 2-pentanol).

Additionally, the mutagenic activity of 2-butanol has been evaluated in a bacterial reverse mutation assay conducted by the National Toxicology Program (NTP) using the standard preincubation method. *Salmonella typhimurium* strains TA98 and TA 100 and *Escherichia coli* strain pKM101 were treated with 2-butanol in dimethyl sulfoxide (DMSO) at concentrations up to 10000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (https://tools.niehs.nih.gov/cebs3/ntpViews/?studyNumber=002-01302-0001-0000-9 NTP, 2004). Under the conditions of the study, 2-butanol was not mutagenic in the Ames test (and this can be extended to 2-pentanol).

The clastogenicity of 2-butanol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster ovary or lung cells were treated with 2-pentanol in DMSO at concentrations up to 5000 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (https://echa.europa.eu/registration-dossier/-/registered-dossier/14353/7/7/2/?documentUUID=370c9601-28e4-4248-8c64-08a0592f4e15 ECHA, 2011). Under the conditions of the study, 2-butanol was considered to be non-clastogenic in the *in vitro* chromosome aberration assay (and this can be extended to 2-pentanol).

Based on the available data, 2-butanol is not considered to have genotoxic potential, and this can be extended to 2-pentanol.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/28/19.

10.1.2. Repeated dose toxicity

The margin of exposure for 2-pentanol 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 2-pentanol. Read-across material, 2-butanol (CAS 78-92-2; see section V) has sufficient repeated dose toxicity data. In a non-GLP, non-guideline, multigeneration toxicity study, 30 weanling Wistar rats/sex/dose were administered 2-butanol in drinking water (purity: not reported) at doses of 0 (control: water), 0.3%, 1%, and 3% (equivalent to 0, 538, 1644, and 5089 mg/kg/day [males] and 0, 594, 1771, 4571 mg/kg/day [females]) for F0 rats; and 0 (control: water), 0.3%, 1%, and 2% (538, 1644, 3384 mg/kg/day [males] and 594, 1771, 3122 mg/kg/day [females], respectively for F1A generation). No treatment-related mortalities were reported for F0 animals at any dose level. No treatment-related clinical signs were reported in both the generations at any dose level. In F1A rats, no changes were reported for hematology, clinical chemistry, urinalysis, and necropsy at any dose level. Decreased parental weight gain (F0) was reported in the high-dose animals prior to mating (15% and 16% for males and females, respectively). The reduced weight gain was associated with a decrease in food (21% and 20% for males and females, respectively) and water consumption (24% and 38% for males and females, respectively) during the premating period. Dose-dependent reductions in body weight were also reported for all treated F1A males. However, the difference was due to lower initial weights of the treatment group F1A males compared to controls. Similarly, a significant reduction in body weight in high-dose-treated F1A males was accompanied by decreased food (9%) and water consumption (16%). In F1A rats, high-dose male rats showed kidney lesions indicative of early stages of alpha2u-globulin-associated rat nephropathy. Since this condition is sex and species-specific to male rats, it was not considered a hazard to human health (Lehman-McKeeman and Caudill, 1992; Lehman-McKeeman et al., 1990). Based on the decreased body weight that was accompanied by decreased food and water consumption at the highest dose of 2-butanol in the F0 generation, combined with decreased body weight and increased mortality in the F1A generation the no observed adverse effect level (NOAEL) for repeated dose toxicity was considered to be 1% (equivalent to 1644 mg/kg/day) (Union Carbide, 1992; ECETOC, 2003; US EPA IRIS, 2003).

Therefore, the 2-pentanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-butanol NOAEL in mg/kg/day by the total systemic exposure to 2-pentanol, 1644/0.00015 or 10960000.

In addition, the total systemic exposure to 2-pentanol (0.15 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) 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: 02/04/19.

10.1.3. Reproductive toxicity

The margin of exposure for 2-pentanol is adequate for the reproductive toxicity endpoint at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 2-pentanol. Read-across material 2-butanol (CAS # 78-92-2; see Section V) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint.

A prenatal developmental toxicity study was conducted in pregnant female Sprague Dawley rats. Groups of 15 dams/dose were administered 2-butanol via inhalation exposure at concentrations of 0, 3500, 5000, or 7000 ppm for 7 h/day, through gestation days (GDs) 1–19. Dams were euthanized on GD 20, and one-half of the fetuses were examined for skeletal malformations, while the remaining half for soft-tissue malformation. Maternal weight gain and food consumption were decreased (statistical significance not mentioned) at all dose groups. Dams exhibited dose-dependent narcosis at the mid- and high-dose groups and impaired locomotor activity at the mid-dose group. At 7000 ppm, a significant reduction in the number of live fetuses and increased resorptions were reported. Fetal body weights were significantly decreased in the mid- and high-dose groups. No teratogenic effects were observed in any of the dose groups. Thus, the NOAEL for maternal toxicity could not be established since reduced body weight was observed at all dose levels; thus, the LOAEL for maternal toxicity was considered to be 3500 ppm or 3277 mg/kg/day (using standard minute volume [0.15 L/min] and bodyweight values [0/204 kg] for female Sprague Dawley rats; US EPA, 1998). The NOAEL for developmental toxicity was considered to be 3500 ppm or 3277 mg/kg/day (using standard minute volume and bodyweight values for female Sprague Dawley rats), based on reduced body weight of pups at ≥5000 ppm and decreased number of live fetuses at 7000 ppm (Brightwell et al., 1987).

In a 2-generation reproductive toxicity study, groups of 30 Wistar rats/sex/dose were administered 2-butanol in drinking water at doses of 0%, 0.3%, 1%, or 3% (equivalent to 0, 538, 1644, and 5089 mg/kg/day for males and 0, 594, 1771, and 4571 mg/kg/day for females, respectively [values taken from EPA IRIS report]) for F0 generation. Additionally, a separate group of 30/sex were treated with isopropanol (3% for F0 and 2% for F1A) which were used as a positive control for comparison of results. After 8 weeks of treatment, F0 male and female animals were mated to produce F1A litters, which were delivered and nursed through day 21 of lactation. 3% 2-butanol caused decreased parental body weight during premating, increased pup mortality, and

decreased pup body weight at postnatal days 4 and 21 for F1A litters. Consequently, all high-dose parents and F1A pups were given drinking water without 2-butanol for 2 weeks to allow for recovery and the highest dose was then lowered to 2% (estimated daily intakes of 3384 mg/kg/day in males and 3122 mg/kg/day in females). After a 2-week post-lactation period, F0 females were re-mated to produce F1B litters for teratologic evaluation. The F1B pregnancies of 20 pregnant rats/group were cesarean-sectioned on GD 20. F1B litters exhibited reduced body weight when compared with controls, with evidence of retarded skeletal maturation. Similar changes were observed in the positive control group. No significant soft-tissue findings were reported in any of the 2-butanol treated pups. Selected male and female F1A rats (30/sex/group) continued on their respective treatment protocols at 0%, 0.3%, 1%, or 2% 2-butanol and mated at 12 weeks of age to produce F2 litters that were delivered and nursed through day 21 of lactation. Reduced average pup body weight at postnatal days 4 and 21 was reported in the F2 pups of the high-dose group. Thus, the NOAEL for parental toxicity was considered to be 1% (1644 mg/kg/day for males and 1771 mg/kg/day for females), based on decreased body weight at 3% in the F0 generation, and decreased body weight and mortality at 2% in the F1A generation. Since the highest dose was lowered to 2% for 2 subsequent matings (F1B and F2), and no effect on fertility or reproduction was observed, the fertility NOAEL was considered to be 2% (3384 mg/kg/day for males and 3122 mg/kg/day for females). The NOAEL for developmental toxicity was considered to be 1% (1644 mg/kg/day for males and 1771 mg/kg/day for females), based on decreased body weight of weanling rats at 2% (F1A and F1B rats) and decreased average pup body weight and retarded skeletal maturation observed among the F2 generation, which resulted from the 2% F1A generation (Union Carbide, 1992). The most conservative NOAEL of 3122 mg/kg/day for female rats was selected for the fertility endpoint. **Therefore, the 2-pentanol MOE for the fertility endpoint can be calculated by dividing the 2-butanol NOAEL in mg/kg/day by the total systemic exposure to 2-pentanol, 3122/0.00015 or 20813333.**

The most conservative NOAEL of 1644 mg/kg/day from the 2-generation study for male rats was selected for the developmental toxicity endpoint. **Therefore, the 2-pentanol MOE for the developmental toxicity endpoint can be calculated by dividing the 2-butanol NOAEL in mg/kg/day by the total systemic exposure to 2-pentanol, 1644/0.00015 or 10960000.**

In addition, the total systemic exposure to 2-pentanol (0.15 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 02/01/19.

10.1.4. Skin sensitization

Based on the existing data and read-across material 2-butanol (CAS # 78-92-2), 2-pentanol does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for 2-pentanol. Based on the read-across material 2-butanol (CAS # 78-92-2; see Section V), 2-pentanol does not present a concern for skin sensitization under the current, declared levels of use. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test and Freund's complete adjuvant test (FCAT), read-across material 2-butanol did not present reactions indicative of sensitization at 100% and 50%, respectively (https://echa.europa.eu/registration-dossier/-/registered-dossier/14353/7/5/2 ECHA, 2011; accessed 01/04/19; OECD, 2008).

Based on the weight of evidence (WoE) from structural analysis and animal studies, and read-across material 2-butanol, 2-pentanol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?id=C8F7F728-A33F-4453-A4F7-342618F6AB9E OECD, 2008.

Literature Research and Risk Assessment Completed On: 01/30/19.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra, 2-pentanol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-pentanol in experimental models. UV absorption spectra indicate no absorption between 290 and 500 nm. As such, it is not a concern for phototoxicity or photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-pentanol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available spectra indicate no absorbance in the range of 290–500 nm. As the material does not absorb in the range of interest, it is not a concern for phototoxicity or photoallergenicity (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/11/19.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 2-pentanol 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 2-pentanol. Based on the Creme RIFM Model, the inhalation exposure is < 0.0001 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 et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: James et al., 1987.

Literature Search and Risk Assessment Completed On: 01/28/19.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-pentanol 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-pentanol 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-pentanol as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

10.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 2-pentanol presents no risk to the aquatic compartment in the screening-level assessment.

10.2.1.1.1. Biodegradation. No data available.

10.2.1.1.2. Ecotoxicity. No data available.

10.2.1.1.3. Other available data. 2-Pentanol has been pre-registered for REACH with no additional data available at this time.

10.2.2. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	523.6			1000000	0.5236	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	2.4	2.4
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	NA
Risk Characterization: PEC/PNEC	**< 1**	**NA**

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

The RIFM PNEC is 0.5236 μg/L. The revised PEC/PNECs for EU and North America are: not applicable. The material was cleared at the 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: 01/22/19.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** 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 05/31/19.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111175.

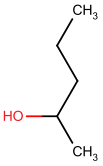
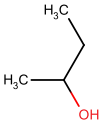
Appendix

Read-across Justification

Methods

The read-across analog was identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European 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 were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018) and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	2-Pentanol	2-Butanol
CAS No.	6032-29-7	78-92-2
Structure		
Similarity (Tanimoto Score)		0.77
Read-across Endpoint		• Genotoxicity • Skin Sensitization • Reproductive Toxicity • Repeated Dose Toxicity
Molecular Formula	$C_5H_{12}O$	$C_4H_{10}O$
Molecular Weight	88.15	74.12
Melting Point (°C, EPI Suite)	−73	−114.7
Boiling Point (°C, EPI Suite)	119.3	99.5
Vapor Pressure (Pa @ 25 °C, EPI Suite)	8.15E+002	8.93E+002
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	1.19	0.61
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	4.46e+004	1.81e+005
J_{max} (μg/cm^2/h, SAM)	1284.4	2020.2
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.50E+000	9.18E-001
Genotoxicity		
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Repeated Dose Toxicity		
Repeated Dose (HESS)	• Propylene glycol (Renal toxicity) Alert	• Propylene glycol (Renal toxicity) Alert
Reproductive Toxicity		
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	• Non-toxicant (low reliability)	• Non-toxicant (low reliability)
Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found	• No alert found
Protein Binding (OECD)	• No alert found	• No alert found
Protein Binding Potency	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• No alert found
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-pentanol (CAS # 6032-29-7). 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, 2-butanol (CAS # 78-92-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 2-Butanol (CAS # 78-92-2) was used as a read-across analog for the target material 2-pentanol (CAS # 6032-29-7) for the genotoxicity, skin sensitization, repeated dose toxicity, and reproductive toxicity endpoints.
  - ○ The target material and the read-across analog are structurally similar and belong to a class of saturated straight chain secondary alcohols.
  - ○ The target material and the read-across analog share a hydroxyl group branched into a saturated straight chain.
  - ○ The key difference between the target material and the read-across analog is that the target material is a C5 secondary alcohol while the read-across analog is a C4 secondary alcohol. This structural difference is toxicologically insignificant.
  - ○ The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable 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.
  - ○ Both materials present a Repeated Dose (HESS) alert for propylene glycol renal toxicity due to structural similarities of 54.5% with the target material and 60% with the read-across analog using the Dice score. Propylene glycol is a diol that is metabolized in the human body into pyruvic acid, acetic acid, lactic acid, and propionaldehyde leading to renal injuries. Since the target material, as well as the read-across analog, has only one alcohol group this alert can be ignored. The predictions are superseded by data.
  - ○ 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 between 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.

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q16. Common terpene? (see Cramer et al., 1978 for a 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 a detailed explanation)? Yes.
Q21. 3 or more different functional groups? No.
Q18. One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories) No, Low (Class I)

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