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Short review

# RIFM fragrance ingredient safety assessment, 2-ethyl-1-butanol, CAS Registry Number 97-95-0

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ABSTRACT

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

This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog 2-ethylhexanol (CAS # 104-76-7) show that this material is not genotoxic. Data from the suitable read across analog isopropyl alcohol (CAS # 67-63-0) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose toxicity endpoint was completed using 2-ethylhexanol (CAS # 104-76-7) and 1-heptanol, 2-propyl (CAS # 10042-59-8) as suitable read across analogs, which provided a MOE > 100. The developmental and reproductive toxicity endpoint was completed using 2-ethyl-hexanol (CAS # 104-76-7) and isobutyl alcohol (CAS # 78-83-1) as suitable read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.



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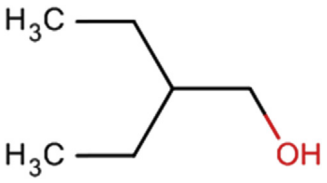


**Abbreviation list:**
**2-Box Model** – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**97.5th percentile**- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
**AF**- Assessment Factor
**BCF-** Bioconcentration Factor
**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
**OECD**- Organisation for Economic Co-operation and Development
**OECD TG**- Organisation for Economic Co-operation and Development Testing Guidelines
**PBT**- Persistent, Bioaccumulative, and Toxic
**PEC/PNEC**- Predicted Environmental Concentration/Predicted No Effect Concentration
**QRA-** quantitative risk assessment
**REACH**- Registration, Evaluation, Authorisation, and Restriction of Chemicals
**RIFM**- Research Institute for Fragrance Materials
**RQ**- Risk Quotient
**TTC**- Threshold of Toxicological Concern
**UV/Vis Spectra-** Ultra Violet/Visible spectra
**VCF**- Volatile Compounds in Food
**VoU**- Volume of Use
**vPvB**- (very) Persistent, (very) Bioaccumulative
**WOE** – Weight of Evidence

**RIFM's Expert Panel[a] concludes that this material is safe under the limits described in this safety assessment.**
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015) which should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).

**Summary: The use of this material under current conditions is supported by existing information.**
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the suitable read across analog 2-ethyl-hexanol (CAS # 104-76-7) show that this material is not genotoxic. Data from the suitable read across analog isopropyl alcohol (CAS # 67-63-0) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The repeated dose toxicity endpoint was completed using 2-ethyl-hexanol (CAS # 104-76-7) and 1-heptanol, 2-propyl (CAS # 10042-59-8) as suitable read across analogs, which provided a MOE > 100. The developmental and reproductive toxicity endpoint was completed using 2-ethyl-hexanol (CAS # 104-76-7) and isobutyl alcohol (CAS # 78-83-1) as suitable read across analogs, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

**Human Health Safety Assessment**
**Genotoxicity:** Not genotoxic. (Shimizu et al., 1985; NTP, 2007)
**Repeated Dose Toxicity:** NOAEL = 30 mg/kg/day (RIFM, 1996a)
**Developmental and Reproductive Toxicity:** NOAEL = 191 and 43.7 mg/kg/day respectively (RIFM, 1991; Tyl et al., 1992)
**Skin Sensitization:** Not sensitizing (Gerberick et al., 2004; RIFM, 1977)
**Phototoxicity/Photoallergenicity:** Not phototoxic/photoallergenic (UV Spectra, RIFM DB)
**Local Respiratory Toxicity:** No NOAEC available. Exposure is below the TTC.
**Environmental Safety Assessment**
**Hazard Assessment:**
**Persistence:** Screening Level: 3.13 (BIOWIN 3) (EpiSuite ver 4.1)
**Bioaccumulation**: Screening Level: 6.62 L/kg (EpiSuite ver 4.1)
**Ecotoxicity:** Screening Level: LC50: 227.4 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:** LC50: 227.4 mg/L (RIFM Framework; Salvito et al., 2002)
**RIFM PNEC is:** 0.2274 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not Applicable; Cleared at Screening level

[a] RIFM's Expert Panel is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM guidance relevant to human health and environmental protection.

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## 1. Identification

1. **Chemical Name:** 2-Ethyl-1-butanol
2. **CAS Registry Number:** 97-95-0
3. **Synonyms:** 1-Butanol, 2-ethyl-; 2-Ethyl-1-butanol; 2-Ethylbutyl alcohol; 2-Ethylbutan-1-ol
4. **Molecular Formula:** $C_6H_{14}O$
5. **Molecular Weight:** 102.18
6. **RIFM Number:** 6096

## 2. Physical data

1. **Boiling Point:** 145.86 °C [EPI Suite]
2. **Flash Point:** 137.00 °F TCC (58.33 °C)*
3. **Log $K_{OW}$:** 1.75 [EPI Suite]
4. **Melting Point**: −49.23 °C [EPI Suite]
5. **Water Solubility:** 11950 mg/L [EPI Suite]
6. **Specific Gravity:** 0.82700 to 0.83900 @ 25.00 °C*
7. **Vapor Pressure:** 1.08 mmHg @ 20 °C [EPI Suite 4.0], 1.0 mm Hg 20C [FMA], 1.6 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Minor absorbance in the region 290–700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1}$ $cm^{-1}$).
9. **Appearance/Organoleptic:** A clear, colorless liquid with a medium sweet, musty, and alcoholic odor*

*http://www.thegoodscentscompany.com/data/rw1043501.html, retrieved 03/10/15.

## 3. Exposure

| | | |
|---|---|---|
| 1. | **Volume of Use (worldwide band):** <0.1 metric tons per year | (IFRA, 2011) |
| 2. | **Average Maximum Concentration in Hydroalcoholics:** 0.00041% | (IFRA, 2008) |
| 3. | **97.5th Percentile:** 0.0003% | (IFRA, 2008) |
| 4. | **Dermal Exposure**[a]**:** 0.00001 mg/kg/day | (IFRA, 2008) |
| 5. | **Oral Exposure:** Not Applicable | |
| 6. | **Inhalation Exposures**[b]**:** 0.00000046 mg/kg/day or 0.000028 mg/day | (IFRA, 2008) |
| 7. | **Total Systemic Exposure (Dermal + Inhalation):** (0.00001 mg/kg/day) + 0.00000046 mg/kg/day = 0.00001 mg/kg/day | |

[a] Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap) (Cadby et al., 2002; Ford et al., 2000).

[b] Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

## 4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Data not available — not considered.
3. Inhalation: Assumed 100%
4. **Total:** Dermal (Assume 100%) + Inhalation (assume 100%) absorbed = (0.00001 mg/kg/day) + 0.00000046 mg/kg/day = 0.00001 mg/kg/day

## 5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low

| Expert judgment | Toxtree v 2.6 | OECD QSAR toolbox v 3.2 |
|---|---|---|
| I | I | I |

## 6. Metabolism

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

2-Ethyl-1-butanol is reported to occur in the following foods*:

Mushroom
Sherry
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, contains information on published volatile compounds which have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

## 8. IFRA standard

None.

## 9. REACH dossier

Pre-registered for 2010; No dossier available as of 08/25/2016.

## 10. Summary

1. Human Health Endpoint Summaries:
   a. **Genotoxicity:** 2-Ethyl-hexanol (CAS # 104-76-7)
   b. **Repeated Dose Toxicity:** 2-Ethyl-hexanol (CAS # 104-76-7); 1-heptanol, 2-propyl (CAS # 10042-59-8)
   c. **Developmental and Reproductive Toxicity:** 2-Ethyl-hexanol (CAS # 104-76-7); isobutyl alcohol (CAS # 78-83-1)
   d. **Skin Sensitization:** Isopropyl alcohol (CAS # 67-63-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** 2-Ethyl-hexanol (CAS # 104-76-7)
   g. **Environmental Toxicity:** None
2. **Analogs Selected:**
   a. **Genotoxicity:** 2-Ethyl-hexanol (CAS # 104-76-7)
   b. **Repeated Dose Toxicity:** 2-Ethyl-hexanol (CAS # 104-76-7); 1-heptanol, 2-propyl (CAS # 10042-59-8)
   c. **Developmental and Reproductive Toxicity:** 2-Ethyl-hexanol (CAS # 104-76-7); isobutyl alcohol (CAS # 78-83-1)
   d. **Skin Sensitization:** Isopropyl alcohol (CAS # 67-63-0)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** 2-Ethyl-hexanol (CAS # 104-76-7)
   g. **Environmental Toxicity:** None
3. **Read-across Justification:** See Appendix below

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### 10.1. Genotoxicity

Based on the current existing data and use levels, 2-ethyl-1-butanol does not present a concern for genetic toxicity.

#### 10.1.1. Risk assessment

2-Ethyl-1-butanol was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2013). There are no studies assessing the mutagenicity of 2-ethyl-1-butanol. Read across material 2-ethyl-1-hexanol (CAS # 104-76-7; see Section 5) was assessed in an Ames study conducted in accordance with OECD TG 471 and 472. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and Escherichia Coli strain WP2uvrA were treated with 2-etyhl-1-hexanol in DMSO (dimethyl sulfoxide) at the concentrations 0, 1, 5, 10, 50, 100, 500, 1000 μg/plate in the presence and absence of metabolic activation. No increase in the number of revertant colonies was observed in the tester strains at any concentration (Shimizu et al., 1985). Under the conditions of the study, 2-ethyl-1-hexanol was considered not mutagenic in bacteria.

There are no studies assessing the clastogenic potential of 2-ethyl-1-butanol. Read across material 2-ethyl-1-hexanol was assessed in an in vitro chromosome aberration study conducted by the National Toxicology Program (NTP) equivalent to OECD TG 473. The Chinese hamster ovary (CHO) cell line was treated with 2-ethyl-1-hexanol in DMSO at the concentrations 0, 50, 108, 233 and 500 μg/ml in the presence and absence of metabolic activation. 2-Ethyl-1-hexanol did not increase chromosome aberrations in vitro with or without metabolic activation (NTP, 2007 study 463951). Under the conditions of the study, 2-ethyl-1-hexanol was considered did not cause structural aberrations in cultured mammalian cells.

Based on the available data, 2-ethyl-1-hexanol is not a concern for genotoxic potential and this can be extended to 2-ethyl-1-butanol.

**Additional References:** von Daniken et al., 1984; DiVincenzo et al., 1985; Agarwal et al., 1985; Seed, 1982; Shimizu et al., 1985; Phillips et al., 1982; Ward et al., 1986; Zeiger et al., 1985; Zeiger et al., 1982; Hodgson et al., 1982; Rushbrook et al., 1982; Kirby et al., 1983; Warren et al., 1982; Tomita et al., 1982; Barber et al., 1985; DiVincenzo et al., 1983; Putman et al., 1982, 1983; RIFM, 1983; Astill et al., 1986; Saido et al., 2003; RIFM, 1986.

**Literature Search and Risk Assessment Completed on:** 10/10/14.

### 10.2. Repeated dose toxicity

The margin of exposure for 2-ethyl-1-butanol is adequate for the repeated dose toxicity endpoint at the current level of use.

#### 10.2.1. Risk assessment

There are no repeated dose toxicity data on 2-ethyl-1-butanol. Read across material 1-heptanol, 2-propyl (CAS # 10042-59-8; see Section 5) has an OECD 408 gavage 90-day subchronic toxicity study conducted in rats. The NOAEL was determined to be 30 mg/kg/day, based on increased liver weights and diffuse hypertrophy of the hepatocytes in females (RIFM, 1996a). **Therefore, the MOE is equal to the 1-heptanol, 2-propyl NOAEL in mg/kg/day divided by the total systemic exposure, 30/0.00001 or 3,000,000.**

An additional read across material, 2-ethyl-1-hexanol (CAS # 104-76-7; see Section 5), has carcinogenicity data which were reviewed by RIFM's Expert Panel* (Belsito et al., 2010). 2-Ethyl-1-hexanol is a weak inducer of liver tumors in female mice (Astill, 1996b). Mechanistic studies showed that 2-ethyl-1-hexanol is an activator of PPAR-alpha (see Additional References Section below). These substances can contribute to liver carcinogenesis by promoting tumor cell proliferation. While the relevance of this mechanism for humans is still a matter of debate and cannot be completely discounted, it is reasonable to assume that humans are less sensitive than rodents. When correcting for skin absorption (see Section 4), the total systemic exposure to 2-ethyl-1-butanol is 0.00000098 mg/kg/day, which is more than 51020000 times lower than the 50 mg/kg/day NOAEL for liver carcinomas in mice from 2-ethyl-1-hexanol. This MOE is considered adequate for a non-genotoxic compound.

In addition, the total systemic exposure for 2-ethyl-1-butanol (0.01 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.

*RIFM's Expert Panel is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

**Additional References:** McGinty et al., 2010a, 2010b; Belsito et al., 2010; Kamil et al., 1953a; Haggard et al., 1945; Iwersen and Schmoldt, 1995; Forsander, 1967; Strubelt et al., 1999; Astill, 1996a; Li et al., 2000; Sjoberg et al., 1986; McGinty et al., 2010c; SIAM, 1995: 2-Ethylhexanol; Rhodes et al., 1984; RIFM, 1992e; RIFM, 1992b; RIFM, 1992c; RIFM, 1992f; Weaver et al., 1989; Keith et al., 1985; Lake et al., 1975; Barber and Topping, 1995; Klimisch et al., 1998; Yamada, 1974; Morton and Rubin, 1979; Putman et al., 1983; Wood and Bitman, 1984; Bojes and Thurman, 1994; Lundgren et al., 1988; Rhodes et al., 1984; Hodgson, 1987; Keith et al., 1988, 1992; Lapinskas et al., 2005; Maloney and Waxman, 1999; Law and Moody, 1989, 1991; Cornu et al., 1992; Rose et al., 1999; Mitchell et al., 1985; Gray et al., 1982, 1983; Keller et al., 1990, 1991, 1992; Badr et al., 1990; Warren et al., 1982; Hellwig and Jackh, 1997; Bui et al., 1998; Taubeneck et al., 1996; Nelson et al., 1988, 1989; Ritter et al., 1987; Hardin et al., 1987; Regnier et al., 2004; Sakagami et al., 1977; Gray and Gangolli, 1986; Gray and Beamand, 1984; Moss et al., 1988; Gangolli, 1982; Piche et al., 2012; Deisinger et al., 1993; Albro, 1975, 1982; Kamil et al., 1953b; Asano and Yamakawa, 1950; Carter et al., 1974; von Daniken et al., 1984; Fukuwatari et al., 2002; Schmidt et al., 1973; Akiya and Yamakawa, 1950; Barber et al., 1992; RIFM, 1988; Li et al., 1999; RIFM, 1996b; RIFM, 1996c; Kaempfe et al., 1997; Schilling et al., 1997; RIFM, 1992d; Hillbom et al., 1974a; Hillbom et al., 1974b; Gibel et al., 1975; RIFM, 1992a; Klimisch and Hellwig, 1995; Aarstad et al., 1986; Clegg, 1964; Dugard and Scott, 1986; Meyer, 1965; Martinez-Alfaro et al., 2009; Lyon et al., 1981; ECHA REACH Dossier: 2-Propylheptan-1-ol; OECD SIDS, 2006: OxoAlcohols; McGinty et al., 2010d.

**Literature Search and Risk Assessment Completed on:** 10/14/14.

### 10.3. Developmental and reproductive toxicity

The margin of exposure for 2-ethyl-1-butanol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

#### 10.3.1. Risk assessment

There are no developmental toxicity data on 2-ethyl-1-butanol. Read across material 2-ethyl-1-hexanol (CAS # 104-76-7; see Section 5) has a dietary developmental toxicity study conducted in mice. The NOAEL for developmental toxicity was determined to be 0.09%, or 191 mg/kg/day, the highest dosage tested (RIFM, 1991, data also available in Price et al., 1991). **Therefore, the MOE for developmental toxicity is equal to the 2-ethyl-1-hexanol NOAEL in mg/kg/day divided by the total systemic exposure, 191/0.00001 or 19,100,000.**

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The reproductive toxicity data of 2-ethyl-1-butanol are insufficient to determine a NOAEL for the reproductive toxicity endpoint. The developmental toxicity was extensively studied in rats and mice via several routes of exposure. In a dermal developmental toxicity study, the maternal toxicity NOAEL was determined to be 840 mg/kg/day, based on reduced maternal body weight gain (Tyl et al., 1992, data also available in Fisher et al., 1989). To account for bioavailability following dermal application, the data from a dermal absorption study conducted in rats (Deisinger et al., 1994, see Section 4) were used to revise the NOAEL of 840 mg/kg/day to reflect the systemic dose. At a dermal penetration of 5.2% of the applied dose, the revised maternal toxicity NOAEL from the dermal study is 43.7 mg/kg/day. Additionally, read across material isobutyl alcohol (CAS # 78-83-1; see Section 5) has an inhalation 2-generation reproductive toxicity study conducted in rats which determined the NOAEL for reproductive toxicity to be 2500 ppm, or 1965 mg/kg/day, the highest dosage tested (OECD SIDS, 2004: Isobutanol). The most conservative NOAEL was selected for this safety assessment. Therefore, the MOE for reproductive toxicity is equal to the 2-ethyl-1-hexanol NOAEL in mg/kg/day divided by the total systemic exposure, 43.7/0.00001 or 4,370,000.

This NOAEL was obtained as follows:

- Obtain exposure in $mg/m^3$ from the ppm value, $mg/m^3$ = [ppm ($mL/m^3$)] [molecular weight (g/Mol)]/24.45 (L/Mol at RT)
- Convert $mg/m^3$ to mg/L, mg/L = ($mg/m^3$)(1 $m^3$/1000 L)
- Obtain NOAEL in mg/kg bw/day by using the following formula, mg/kg/day = [(mg/L/day)(UF)(MV)(min/day)]/BW, assuming an uncertainty factor (UF) of 1 for inhalation:inhalation exposure, a minute ventilation (MV) of 0.17 L/min for a Sprague-Dawley rat, duration of exposure of 360 min per day (min/day) (according to GLP study guidelines), and a body weight (BW) of 0.236 kg (average for male/female Sprague-Dawley rats).

In addition, the total systemic exposure to 2-ethyl-1-butanol (0.01 μg/kg/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the developmental and reproductive toxicity endpoint.

**Additional References:** McGinty et al., 2010a, 2010b; Belsito et al., 2010; Kamil et al., 1953a; Haggard et al., 1945; Iwersen and Schmoldt, 1995; Forsander, 1967; Strubelt et al., 1999; Astill, 1996a; Li et al., 2000; Sjoberg et al., 1986; McGinty et al., 2010c; SIAM, 1995: 2-Ethylhexanol; Rhodes et al., 1984; RIFM, 1992e; RIFM, 1992b; RIFM, 1992c; RIFM, 1992f; Weaver et al., 1989; Keith et al., 1985; Lake et al., 1975; Barber and Topping, 1995; Klimisch et al., 1998; Yamada, 1974; Morton and Rubin, 1979; Putman et al., 1983; Wood and Bitman, 1984; Bojes and Thurman, 1994; Lundgren et al., 1988; Rhodes et al., 1984; Hodgson, 1987; Keith et al., 1988, 1992; Lapinskas et al., 2005; Maloney and Waxman, 1999; Law and Moody, 1989, 1991; Cornu et al., 1992; Rose et al., 1999; Mitchell et al., 1985; Gray et al., 1982, 1983; Keller et al., 1990, 1991, 1992; Badr et al., 1990; Warren et al., 1982; Hellwig and Jackh, 1997; Bui et al., 1998; Taubeneck et al., 1996; Nelson et al., 1988, 1989; Ritter et al., 1987; Hardin et al., 1987; Regnier et al., 2004; Sakagami et al., 1977; Gray and Gangolli, 1986; Gray and Beamand, 1984; Moss et al., 1988; Gangolli, 1982; Piche et al., 2012; Deisinger et al., 1993; Albro, 1975, 1982; Kamil et al., 1953b; Asano and Yamakawa, 1950; Carter et al., 1974; von Daniken et al., 1984; Fukuwatari et al., 2002; Schmidt et al., 1973; Akiya and Yamakawa, 1950; Barber et al., 1992; RIFM, 1988; Li et al., 1999; RIFM, 1996b; RIFM, 1996c; Kaempfe et al., 1997; Schilling et al., 1997; RIFM, 1992d; Hillbom et al., 1974a; Hillbom et al., 1974b; Gibel et al., 1975; RIFM, 1992a; Klimisch and Hellwig, 1995; Aarstad et al., 1986; Clegg, 1964; Dugard and Scott, 1986; Meyer, 1965; Martinez-Alfaro et al., 2009; Lyon et al., 1981; ECHA REACH Dossier: 2-Propylheptan-1-ol; OECD SIDS, 2006: OxoAlcohols; McGinty et al., 2010d.

**Literature Search and Risk Assessment Completed on:** 10/14/14.

### 10.4. Skin sensitization

Based on existing data on read across isopropyl alcohol (CAS # 67-63-0), 2-ethyl-1-butanol does not present a concern for skin sensitization.

#### 10.4.1. Risk assessment

No skin sensitization studies are available for 2-ethyl-1-butanol. The chemical structures of 2-ethyl-1-butanol and read across material isopropyl alcohol (CAS # 67-63-0; see Section 5) indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). However, read across material isopropyl alcohol was evaluated in a local lymph node assay (LLNA) and was found to be a non-sensitizer up to maximum tested levels of 50% (Gerberick et al., 2004). Moreover, in a confirmatory human maximization test, no reactions were observed with isopropyl alcohol at 10% (6900 $\mu g/cm^2$) (RIFM, 1977). Further support for the non-sensitizing classification of 2-ethyl-1-butanol is provided by lack of effects of read across isopropyl alcohol in in vitro sensitization tests (Natsch, 2013a).

**Additional References:** Basketter et al., 2003; Basketter et al., 2002; Roberts et al., 2007; Natsch and Haupt, 2013b; Emter et al., 2010.

**Literature Search and Risk Assessment Completed on:** 11/06/15.

### 10.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-ethyl-1-butanol would not be expected to present a concern for phototoxicity or photoallergenicity.

#### 10.5.1. Risk assessment

There are no phototoxicity studies available for 2-ethyl-1-butanol. UV/Vis spectra were obtained for 2-ethyl-1-butanol, and indicate minor absorbance between 290 and 700 nm. Molar absorption coefficient for the same range is below the benchmark of concern for phototoxicity, (1000 L $mol^{-1}$ $cm^{-1}$) (Henry et al., 2009). Based on the lack of significant absorbance in the critical range, 2-ethyl-1-butanol would not be expected to present a concern for phototoxicity or photoallergenicity.

**Additional References:** None.

**Literature Search and Risk Assessment Completed on:** 07/19/16.

### 10.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 2-ethyl-1-butanol, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

#### 10.6.1. Risk assessment

There is limited inhalation data available on 2-ethyl-1-butanol. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.0003%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.000028 mg/day, as calculated by RIFM's 2-Box Model

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and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value.

This value is 50,000 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:** Smyth et al., 1954.

**Literature Search and Risk Assessment Completed on:** 7/20/2016.

2. Environmental Endpoint Summary:

*10.7. Screening-level assessment*

A screening level risk assessment of 2-ethyl-1-butanol was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log $K_{ow}$ and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al., 2002. At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 2-ethyl-1-butanol 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 EPISUITE ver.4.1 did not identify 2-ethyl-1-butanol as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

*10.8. Risk assessment*

Based on current Volume of Use (2011), 2-ethyl-1-butanol does not present a risk to the aquatic compartment in the screening level assessment.

*10.9. Key studies*

*10.9.1. Biodegradation*

No data available.

*10.10. Ecotoxicity*

No data available.

*10.11. Other available data*

2-Ethyl-1-butanol has been pre-registered for REACH but no additional data is available at this time.

*10.12. Risk assessment refinement*

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

Endpoints used to calculate PNEC are underlined.

| | LC50 (Fish) | EC50 (Daphnia) | EC50 (Algae) | AF | PNEC | Chemical Class |
|---|---|---|---|---|---|---|
| RIFM Framework Screening Level **(Tier 1)** | 227.4 mg/l | | | 1,000,000 | 0.2274 μg/L | |

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

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ used | 1.75 | 1.75 |
| 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 these material is < 1. No further assessment is necessary.

**The RIFM PNEC is 0.2274 μg/L. The revised PEC/PNECs for EU and NA: Not Applicable; Cleared at Screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.**

**Literature Search and Risk Assessment Completed on:** 10/9/14.

## 11. Literature Search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf

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- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** (http://monographs.iarc.fr)
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

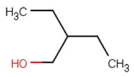
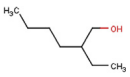
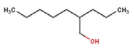
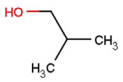
## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2016.09.022.

## Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2016.09.022.

## Appendix

| | Target material | Read across material | | |
|---|---|---|---|---|
| **Principal Name** | 2-Ethyl-1-butanol | 2-Ethyl-1-hexanol | 1-Heptanol, 2-propyl | Isobutyl alcohol |
| **CAS No.** | 97-95-0 | 104-76-7 | 10042-59-8 | 78-83-1 |
| **Structure** |  |  |  |  |
| **3D Structure** | http://www.thegoodscentscompany.com/opl/97-95-0.html | http://www.thegoodscentscompany.com/opl/104-76-7.html | http://www.thegoodscentscompany.com/opl/10042-59-8.html | http://www.thegoodscentscompany.com/opl/78-83-1.html |
| **Read-across endpoint** | | • Genotoxicity<br>• Repeated Dose<br>• Devel/Repro | • Repeated Dose | • Devel/Repro |
| **Molecular Formula** | C6H14O | C8H18O | C10H22O | C4H10O |
| **Molecular Weight** | 102.18 | 130.23 | 158.29 | 74.12 |
| **Melting Point (°C, EPISUITE)** | −49.23 | −25.50 | −2.83 | −74.01 |
| **Boiling Point (°C, EPISUITE)** | 145.86 | 188.52 | 227.56 | 99.58 |
| **Vapor Pressure (Pa @ 25°C, EPISUITE)** | 213.3 | 24.66 | 3.373 | 1787 |
| **Log Kow (KOWWIN v1.68 in EPISUITE)** | 1.75 | 2.73 | 3.71 | 0.77 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)** | 1.195e+004 | 1379 | 151.8 | 9.712e+004 |
| **$J_{max}$ (mg/cm$^2$/h, SAM)** | 557.8466639 | 181.5455582 | 63.341116367 | 2014.159895 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPISUITE)** | 1.78332 | 3.143101 | 5.538425 | 1.011831 |
| **Similarity (Tanimoto score)**[a] | | 76% | 69% | 54% |
| ***Genotoxicity*** | | | | |
| ***DNA binding (OASIS v1.1)*** | • No alert found | • No alert found | | |
| ***DNA binding (OECD)*** | • No alert found | • No alert found | | |
| ***Carcinogenicity (genotox and non-genotox) alerts (ISS)*** | • Structural alert for nongenotoxic carcinogenicity<br>• Substituted *n*-alkylcarboxylic acids (Nongenotox) | • Structural alert for nongenotoxic carcinogenicity<br>• Substituted *n*-alkylcarboxylic acids (Nongenotox) | | |
| ***DNA alerts for Ames, MN, CA (OASIS v1.1)*** | • No alert found | • No alert found | | |
| ***In vitro mutagenicity (Ames test) alerts (ISS)*** | • No alert found | • No alert found | | |
| ***In vivo mutagenicity (Micronucleus) alerts (ISS)*** | • No alert found | • No alert found | | |
| ***Oncologic classification (OECD)*** | • Not classified | • Not classified | | |
| ***Repeated Dose Toxicity*** | | | | |
| ***Repeated dose (HESS)*** | Not categorized | Not categorized | Not categorized | |
| ***Developmental and Reproductive Toxicity*** | | | | |
| ***ER binding (OECD)*** | Non binder, non cyclic structure | Non binder, non cyclic structure | | Non binder, non cyclic structure |
| ***Developmental toxicity model (CAESAR v2.1.6)*** | Toxicant (good reliability) | Toxicant (good reliability) | | Toxicant (low reliability) |
| ***Metabolism*** | | | | |
| ***Rat liver S9 metabolism simulator (OECD)*** | See Supplemental Data 1 | See Supplemental Data 2 | See Supplemental Data 3 | See Supplemental Data 4 |

[a] Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).

*Summary:*

There are insufficient toxicity data on 2-ethyl-1-butanol (RIFM # 6096, CAS # 97-95-0). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

*Methods:*

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The $J_{max}$ were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

*Conclusion/Rationale*

- 2-Ethyl-1-hexanol (analog) was used as a read-across analog for 2-ethyl-1-butanol (target) based on:
  - o The target and analog belong to the generic class of alcohols, specifically, alcohol/branched chain/saturated/primary subclass.
  - o The key difference is the chain length. The target has a short chain length than the analog. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - o The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - o The target and analog show similar alerts for Repeated Dose (HESS) Categorization. The target and analog show similar alerts for ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - o The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.
- 1-Heptanol, 2-propyl (analog) was used as a read-across analog for 2-ethyl-1-butanol (target) based on:
  - o The target and analog belong to the generic class of alcohols, specifically, alcohol/branched chain/saturated/primary subclass.
  - o The key difference is the chain length. The target has a short chain length than the analog. The analog has a longer chain length than the target. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - o The target and analog show similar alerts for Repeated Dose (HESS) Categorization.
  - o The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.
- Isobutyl alcohol (analog) was used as a read-across analog for 2-ethyl-1-butanol (target) based on:
  - o The target and analog belong to the generic class of alcohols.
  - o The target and analog are primary alcohols with a saturated branch.
  - o The key difference is that the analog has a shorter branch chain than the target. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - o The target and analog show similar alerts for ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - o The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

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