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Short Review

RIFM fragrance ingredient safety assessment, butyl alcohol, CAS Registry Number 71-36-3

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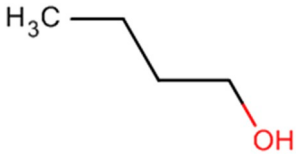
Version: 110218. This version replaces any previous versions.
Name: Butyl alcohol
CAS Registry Number: 71-36-3



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, 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

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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.

Butyl alcohol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that butyl alcohol is not genotoxic. Data on butyl alcohol provide a calculated MOE > 100 for the repeated dose toxicity and developmental and reproductive toxicity endpoints. Data from butyl alcohol and read-across analog propyl alcohol (CAS # 71-23-8) show that there are no safety concerns for butyl alcohol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; butyl alcohol 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 butyl alcohol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; butyl alcohol 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 genotoxic.	(ECHA Dossier: Butyl alcohol; ECHA, 2011)
Repeated Dose Toxicity: NOAEL = 41 mg/kg/day.	(ECHA Dossier: Butyl alcohol; ECHA, 2011)
Developmental and Reproductive Toxicity: NOAEL = 30 and 5503 mg/kg/day, respectively.	(Sitarek et al., 1994; Nelson et al., 1989a)
Skin Sensitization: Not a concern for skin sensitization under the current, declared levels of use.	(Gad et al., 1986; Ryan et al., 2000)
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: 3.5 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 3.2 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 1021 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: 1021 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 1.021 μg/L	
•**Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Butyl alcohol
2. **CAS Registry Number:** 71-36-3
3. **Synonyms:** 1-Butanol; Propyl carbinol; Eastman n-Butyl Alcohol; Butanol; Butyl hydroxide; n-Butanol; n-Butyl alcohol; 1-ブタノール; Butan-1-ol; Butyl alcohol
4. **Molecular Formula:** $C_4H_{10}O$
5. **Molecular Weight:** 74.12
6. **RIFM Number:** 734
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 117 °C (FMA Database), 113.91 °C (EPI Suite)
2. **Flash Point:** 85°F; CC (FMA Database), 35 °C (GHS)
3. **Log K_{OW}:** 0.88 (Patel et al., 2002), 0.84 (Abraham and Rafols, 1995), 0.84 (EPI Suite)
4. **Melting Point**: 62.33 °C (EPI Suite)
5. **Water Solubility:** 76700 mg/L (EPI Suite)
6. **Specific Gravity:** 0.80800 @ 25.00 °C*
7. **Vapor Pressure:** 4.4 mm Hg 20 °C (FMA Database), 7.78 mm Hg @ 25 °C (EPI Suite), 5.49 mm Hg @ 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Highly refractive, colorless volatile liquid with a mild, vinous, sweet, pungent odor

*http://www.thegoodscentscompany.com/data/rw1029131.html#tophyp, retrieved 10/27/15.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.000023% (RIFM, 2016)
3. **Inhalation Exposure*:** 0.000013 mg/kg/day or 0.00088 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0013 mg/kg/day (RIFM, 2016)

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

4. Derivation of systemic absorption

1. **Dermal:** Assumed 80%

Dermal penetration is estimated using Kroes approach (Kroes et al., 2007) using the RIFM SAM model. Based on a molecular weight of 74.12 Da and a measured log K_{OW} of 0.88 (Patel et al., 2002), dermal absorption is expected to be high. Hence, a conservative absorption value of 80% can be used for butyl alcohol.

J_{max} from the RIFM SAM model.

Name	Butyl alcohol
J_{max} ($\mu g/cm^2/h$)	1586[1]
Skin Absorption Class	80%

[1] J_{max} was calculated based on estimated log K_{OW} = 0.88 (consensus model) and Solubility = 63200 mg/L (consensus model).

2. **Oral:** Assumed 100%

2. **Oral:** Assumed 100%

DiVincenzo and Hamilton, 1979**:** Butyl alcohol is readily absorbed from the oral mucosa and intestines and is expected to be completely absorbed from the gastrointestinal tract. In Sprague Dawley rats, when butyl alcohol was administered at a dose level of 450 mg/kg (vehicle: corn oil), it led to an excretion of 44.4% and 69.3% of the dose as CO_2 at 4 and 6 h, respectively. These results indicated rapid absorption of butyl alcohol through the oral route. In total, 83% was excreted as CO_2, 0.27%–0.56% was excreted as unchanged compound in exhaled air, 2.6%–5% was excreted in urine, 0.6%–1.1% was excreted in the feces, and 12.1%–16.3% remained in the carcass after 24 h. Total recovery in this study was reported as 97.5%–102.8%; these results suggested that absorption of butyl alcohol from the gastrointestinal tract is complete. The absorption of butyl alcohol was also studied *in vitro*, where butyl alcohol was transferred through the oral mucosa (lingual frenulum) of dogs and the mean permeability constant was reported to be 10^{-4} cm/s. In another study using rat jejunal preparations, it was reported that butyl alcohol is rapidly absorbed into the blood.

3. **Inhalation:** 48%

Butyl alcohol is readily absorbed from the respiratory tracts of rats, dogs, and humans. In rats, whole-body inhalation exposure to butyl alcohol at a concentration of 94 ± 9 ppm (290 ± 28 mg/m^3) for 7 h resulted in a mean steady state blood concentration of 173 ± 16 µg/L within 1 h. Dogs exposed by inhalation to butyl alcohol vapor at 53.9 mg/m^3 (50 ppm) over 6 h absorbed approximately 55% of the inhaled vapor (DiVincenzo and Hamilton, 1979). Human volunteers were exposed to butyl alcohol at dose levels of 300 or 600 mg/m^3 during rest and exercise for 2 h. At the highest dose, 48% (46%–48%) of the dose was absorbed at rest, and an average of 41% (37%–41%) was absorbed during exercise (ECETOC, 2003).

Additional References: Scheuplein (1966); Astrand I, 1976; Blank et al., 1967; Blank (1964); Akhter et al., 1984; Boman and Mellstrom, 1989a; Boman et al., 1989b; Cross et al., 2003; Bowman (1989); McAulife and Blank, 1991; Boman et al., 1995; Knutson et al., 1987.

5. Computational toxicology evaluation

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

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

2. Analogs Selected:

a. **Genotoxicity:** None
b. **Repeated Dose Toxicity:** None
c. **Developmental and Reproductive Toxicity:** None
d. **Skin Sensitization:** Propyl alcohol (CAS # 71-23-8)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

3. **Read-across Justification:** See Appendix below

6. Metabolism

DiVincenzo and Hamilton, 1979; US EPA, 2011: Butyl alcohol is expected to be readily absorbed from the skin, gastrointestinal tract, respiratory tract, and cornea. It can be distributed throughout the body, primarily to muscle, brain, kidney, liver, and fat. When administered orally in rats at a dose level of 450 mg/kg, systemic distribution was rapid, and peak blood concentration was achieved within 1 h. The distribution of butyl alcohol was observed throughout the body with the highest concentration reported in liver and blood. Butyl alcohol has the potential to cross the blood-brain barrier (BBB) and blood-tissue barriers in spleen, thyroid, and testes. In rats, butyl alcohol administered through the intracarotid artery resulted in observable brain concentrations within 1 min. Butyl alcohol is metabolized rapidly and completely in all animal species, including humans. Following oral administration of 450 mg/kg to rats, only 1.1% of the dose was excreted as unchanged compound in expired air, signifying complete metabolism of the compound. The metabolism of butyl alcohol follows a pattern similar to other aliphatic alcohols. Specifically, butyl alcohol undergoes oxidation by alcohol dehydrogenase (ADH) or other enzymes such as cytochrome P450 (to a minor extent) to form butyric aldehyde, which is then oxidized by aldehyde dehydrogenases (ALDH) to form butyric acid. Butyric acid is completely metabolized by fatty acid oxidation (β-oxidation) and tricarboxylic pathways and is excreted as carbon dioxide (CO_2) in exhaled air. Butyl alcohol is expected to be eliminated completely from the body without any accumulation potential in both animals and humans. There are several studies highlighting the metabolism and toxicokinetics of butyl alcohol (see additional references) (Fig. 1).

Additional References: Saito (1975); Aarstad et al., 1986; Mikheev (1980); US EPA, 1989; EMA, 1997; US EPA, 2005; WHO 1998 (accessed 08/08/18); ECHA, 2018; OECD, 2001; Gaillard and Derache, 1965; Pardridge and Fierer, 1985; US EPA, 1989; WHO, 1987 (accessed 08/08/18); ECHA, 2011 (accessed 08/08/18); Kamil et al., 1953; CIR, 2008; Gaillard and Derache, 1965; ECETOC, 2003.

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

Butyl alcohol is reported to occur in the following foods by the VCF*:

Apple fresh (*Malus* species)BeansBeefCheese, various typesCitrus fruitsClamHoneyMilk and milk productsOlive (*Olea europaea*)Papaya (*Carica papaya* 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. This is a partial list.

8. IFRA standard

None.

9. REACH dossier

Available; accessed 10/31/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, butyl alcohol does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. A mammalian cell gene mutation assay (HPRT) was conducted according to OECD TG 476. Chinese hamster lung fibroblasts (V79) were treated with butyl alcohol in dimethyl sulfoxide (DMSO) at concentrations of 740 μg/mL for 4 h. Effects were evaluated both with and without metabolic activation. No statistically significant increases in the frequency of mutant colonies were observed with any concentration of the test item, either with or without metabolic activation (ECHA, 2011). Under the conditions of the

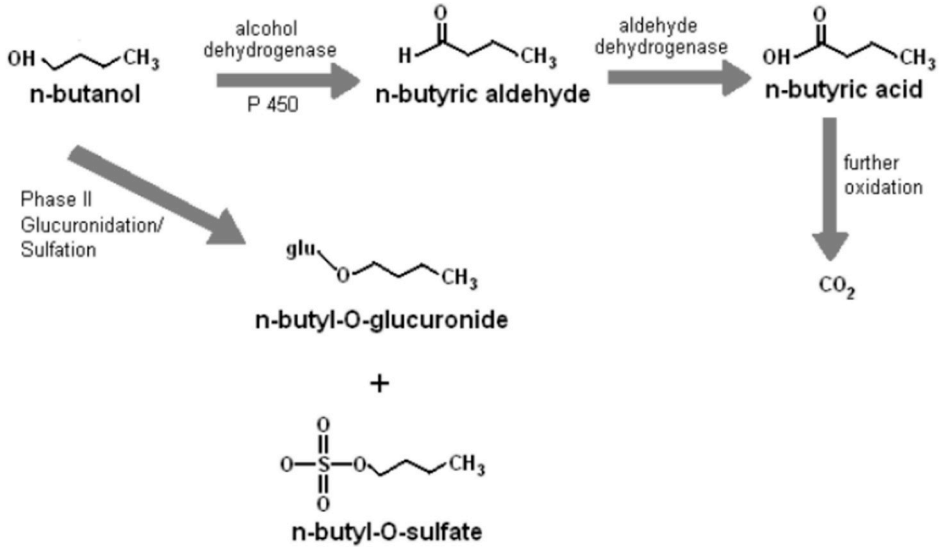


Fig. 1. Metabolism of butyl alcohol (adapted from US EPA, 2011).

study, butyl alcohol was not mutagenic to mammalian cells *in vitro*.

The clastogenic activity of butanol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. Butyl alcohol was administered in olive oil via the oral route to groups of male and female NMRI mice. Doses of 500, 1000, and 2000 mg/kg body weight were administered. Mice from each dose level were euthanized at 24 and 48 h, and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011). Under the conditions of the study, butyl alcohol was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, butyl alcohol does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/08/18.

10.1.2. Repeated dose toxicity

The margin of exposure is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on butyl alcohol. A subchronic, 13-week repeated dose toxicity study was conducted (GLP-compliant, non-guideline) using Sprague Dawley rats (20 rats/sex/group) that were administered butyl alcohol via oral gavage at dose levels of 0, 30, 125, and 500 mg/kg/day. An additional group of 10 animals/sex/group were maintained for a period of 6 weeks as an interim terminal group. Parameters evaluated included: mortality, clinical signs, body weight (weekly), feed consumption (weekly), eye examination, hematology and urinalysis. During necropsy, organ weights (brain, heart, liver, spleen, kidneys, testes with epididymides, ovaries, adrenals, and thyroid) were determined for all terminal groups, while histopathology was performed only in control and high-dose animals. No treatment-related mortality or changes in body weight, feed consumption, ophthalmoscopic examination, clinical chemistry, urinalysis, organ weights, necropsy, and histopathology were reported. However, ataxia and hypoactivity occurred immediately after dosing and persisted for less than 1 h in both sexes in the high-dose group during the last 6 weeks of the study. These are commonly observed changes following high oral doses to alcohols. Hematological analysis revealed statistically significant decreases in hemoglobin (Hb), red blood cell (RBC), and packed cell volume (PCV) in females from the high-dose group during week 6; however, no changes were reported in males during week 6 and in either sex of the treatment groups during week 13. These hematological changes were considered to be transient rather than adverse. The no observed adverse effect level (NOAEL) was considered to be 125 mg/kg/day based on the transient effects of ataxia, hypoactivity, and Hb changes (in females) at the highest dose (ECHA, 2011).

Butyl alcohol was evaluated for systemic toxicity in a 90-day inhalation (non-GLP-compliant) only study on male Wistar rats (12 animals/treatment group and 24 in control group). The study lacked histopathological evaluation and included only 2 dose levels. Animals were exposed to butyl alcohol (purity: 99.61%) through inhalation at concentrations of 0 (control-dilution air), 50 ppm (154 mg/m^3; 41 mg/kg/day), and 100 ppm (308 mg/m^3; 82 mg/kg/day) for 6 h/day, 5 days/week, for 90 days. Parameters evaluated included: mortality, clinical signs, body weight (weekly), and hematology clinical chemistry. Rotarod test with additional learned avoidance behavior analysis was conducted prior to the study and at 30-day intervals for 90 days. In addition, a hot plate test was conducted at the termination of the study. At the end of the exposure period, organ weights were measured. Livers were analyzed for microsomal protein content, aniline *p*-hydroxylase activity, CYP-450 activity, lipid peroxidation, and triglyceride content. During the study, no treatment-related mortalities or changes of clinical signs, clinical chemistry, pain sensitivity, and organ weights were reported. However, a statistically significant increase in body weight was reported at both dose levels up to 60 days; but the body weight of all treatment groups was comparable to the control at termination. At 50 ppm, there was a significant decrease in Hb, while both Hb and RBC were significantly decreased at 100 ppm. However, the decrease in Hb at 50 ppm was not associated with decreases in other hematological parameters such as hematocrit and RBC. Therefore, the decreased Hb was not considered to be treatment-related. At 100 ppm, there was a significant increases in WBC, % eosinophils, and lipid peroxidation (also at 50 ppm) were reported. However, in absence of liver damage increase in lipid peroxidation was not considered biologically significant. Treatment-related motor disturbances were reported, as evidenced by the increased incidences of dose-dependent and duration-dependent failures in rotarod performance at both dose levels during the entire duration of the study. Furthermore, the motor effects were substantial and statistically significant at 100 ppm. The major effects observed from the inhalation exposure to 100 ppm (equivalent to 82 mg/kg/day) were hematological alterations (with a specific decrease in RBC and Hb) and motor disturbances. Using standard minute volume and body weight values for male Wistar rats, the calculated NOAEL for repeated dose toxicity is 41 mg/kg/day.

$$NOAEL\ (mg/kg/day) = \frac{NOAEC\ (mg/L) \times UF \times MV \times (T/day)}{Body\ weight\ (kg)} = \frac{0.154 \times 1 \times 0.16 \times 360}{0.217} = 41 mg/kg/day$$

Where: Uncertainty factor (UF) is 1;

Minute volume (MV) is 0.16 L/min for male Wistar rats (subchronic);
Exposure Time (T/day) is 360 min (6 h/day for 5 days in a week);
Body weight (BW) is 0.217 kg (average for male Wistar rats).

Since butanol and propanol are widely used as solvents, the inhalation route is considered more relevant for exposure to butanol, despite methodological deficiencies in the inhalation study. Therefore, the NOAEL of 41 mg/kg/day was considered for the risk assessment for the repeated dose toxicity endpoint.

Therefore, the butyl alcohol MOE for the repeated dose toxicity endpoint can be calculated by dividing the butyl alcohol NOAEL (mg/kg/day) by the total systemic exposure for butyl alcohol (mg/kg/day), 41/0.0013 or 31538.

In addition, the total systemic exposure to butyl alcohol (1.3 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; of a Cramer Class I material) for the repeated dose toxicity endpoint at the current level of use.

Additional References: US EPA, 1989(accessed on 08/11/2018); EMA, 1997; ECHA, 2011 (accessed on 08/10/2018); Sinitsyna, 2003; ECHA, 2018; Munoz et al., 1991; WHO, 1998 (accessed 08/10/18); Wakabayashi et al., 1984; US EPA, 2011; CIR, 2008; NTRL, 1989 (accessed 08/08/18); ECETOC, 2003; US EPA, 2011(accessed 08/08/18); OECD, 2001; EFSA, 2013

Literature Search and Risk Assessment Completed On: 08/17/18.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for butyl alcohol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental and reproductive toxicity data on butyl alcohol, which has been extensively reviewed by ECHA, OECD, the US EPA, and other agencies.

A reproduction and prenatal developmental toxicity study (non-GLP and non-guideline) was conducted in pregnant female Imp: DAK rats (strain belonged to their own laboratory). Groups of 11–17 female rats/dose were administered butyl alcohol via drinking water at doses of 0%, 0.24%, 0.8%, or 4% (equivalent to 0, 300, 1000, and 5000 mg/kg/day, respectively, as per report) in tap water for 8 weeks during the pre-mating period, 3 weeks during the mating period, and throughout the gestation. All dams were euthanized on gestation day (GD) 20. No treatment-related effects were reported in fetal parameters such as body weight, intrauterine mortality, and live fetuses per litter. At 4%, the fetuses were significantly smaller than the controls, which resulted in a significant decrease in crown-rump length by 5% when compared to the controls. There was a dose-dependent increase in the percentage of fetuses with skeletal variations, such as delayed ossification of the sternum at all dose levels: 15%, 16%, 24%, and 33% at the 0%, 0.24%, 0.8%, or 4% dose groups, respectively; moreover, the incidence of skeletal variations at the highest dose achieved statistical significance. There was a significant increase in litter incidences with dilation of the subarachnoid space and dilation of cerebral ventricles (lateral and/or third ventricles of the brain) reported at all dose levels in a dose-dependent manner. The most frequently reported congenital defect was internal hydrocephalus observed at both mid- and high-dose groups, and external hydrocephalus was also reported for the mid-dose (17%) group. The NOAEL for female reproductive toxicity was considered to be 5000 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity could not be derived based on treatment-related pathological changes reported in microscopic examination of the brain even at the lowest dose group; therefore, a LOAEL was derived for developmental toxicity, which was considered to be 300 mg/kg/day, based on a significant increase in the incidence of pathological lesions in the brain at ≥ 300 mg/kg/day dose group fetuses (Sitarek et al., 1994).

An inhalation behavioral teratology study was conducted in Sprague Dawley rats. Groups of male and female rats (males: 18 rats/group, females: 15 rats/group) were exposed to butyl alcohol via inhalation (whole-body exposure) for 7 h/day at concentrations of 0, 3010, or 6000 ppm. Males were treated for 6 weeks during the pre-mating period and mated to non-exposed females (paternal exposure), and females were impregnated with non-exposed males and treated during GDs 1–20 (maternal exposure). On post-natal day (PND) 10, 1 rat/sex/litter was assigned to 1 of 4 treatment groups and evaluated during PNDs 10–90 for neurotoxicity. No treatment-related changes were reported in fertility at any dose levels. Statistically significant changes for neuromotor coordination and neurochemical analysis were reported in the different regions of the brain at low- and high-dose groups; however, these changes were not dose-dependent and fell within the historical control range. Therefore, the NOAEC for both male and female reproductive toxicity and developmental neurotoxicity was considered to be 6000 ppm or 5503 mg/kg/day (using standard minute volume and body weight values for male and female Sprague Dawley rats), the highest dose tested (Nelson et al., 1989a).

Additional studies are available that support the developmental toxicity study. In summary, butyl alcohol produced malformations such as rudimentary cervical ribs at a dose level of 8000 ppm (Nelson et al., 1989b); however, the study results could not be replicated in subsequent studies using the same strain. Moreover, the rudimentary cervical ribs were considered variations rather than malformations by the European Chemicals Agency (ECHA, 2011). Butyl alcohol is considered a developmental toxicant that tends to produce skeletal variations, such as delayed ossification of the sternum associated with decreased fetal weight in several studies (Nelson et al., 1989b; Sitarek et al., 1994; Ema et al., 2005a). For instance, the skeletal variations primarily occurred in the presence of maternal toxicity, with the exception of 1 study (Sitarek et al., 1994). Butyl alcohol produced developmental abnormalities in the brain such as dilation of subarachnoid space, dilation of cerebral ventricles, and internal hydrocephalus in Imp:DAK rats; however, the results were not reproducible in Sprague Dawley rats (Nelson et al., 1989a). A possible reason for the variable responses could be due to differences in study design and animal strain. For example, in Sitarek et al. (1994), female Imp:DAK rats were treated for 8 weeks prior to mating, whereas in Sprague Dawley rats, both sexes were treated and mated with their non-exposed counterparts (Nelson et al., 1989a). The background incidence of the cerebral lesions in Imp:DAK rats was higher as compared to other strains. The US EPA IRIS considered these effects in the brain as relevant to humans and thus considered the toxicological findings for an RfD calculation. In ECETOC, 2003 and OECD, 2001, it was reported that dilation of the brain ventricles/spaces, internal hydrocephalus, and wavy or extra ribs were considered variations or delayed development in commonly used historical databases. These variations are commonly described for several rat strains frequently used in the United States. In fact, Nelson et al. (1989a) described some lesions such as enlarged brain ventricles as variations and not malformations, suggesting that these lesions were developmental variations instead of malformations.

The US EPA considers that effects in the brain were relevant to humans; therefore, the most conservative approach was taken for this risk assessment for developmental toxicity, and a LOAEL of 300 mg/kg/day was considered, based on a significant increase in pathological lesions in the brain (Sitarek et al., 1994). Despite significant shortcomings of the Sitarek et al., 1994 study, the study was considered pivotal in determining a point of departure for the developmental toxicity endpoint since the study presents a very conservative LOAEL based on the brain lesions observed at doses ≥300 mg/kg/day. A default safety factor of 10 was used when deriving a NOAEL from LOAEL. The safety factor has been approved by the Expert Panel for Fragrance Safety*.

The derived NOAEL for the developmental toxicity data is 300/10 or 30 mg/kg/day.

Therefore, the butyl alcohol MOE for the developmental toxicity endpoint can be calculated by dividing the butyl alcohol NOAEL in mg/kg/day by the total systemic exposure to butyl alcohol, 30/0.0013 or 23077.

A NOAEL of 5503 mg/kg/day was considered for both male and female reproductive toxicity, based on the absence of treatment-related effects in any of the reproductive parameters evaluated in both sexes (Nelson et al., 1989a). This was supported by a 13-week subchronic study in which necropsy, organ weights, and histopathology of selected reproductive organs (e.g., testes with epididymides, ovaries, uterus, cervix, and mammary gland) were conducted in groups of 20 rats/sex/dose administered butyl alcohol via oral gavage at doses of 0, 30, 125, or 500 mg/kg/day. No effects were reported (see the Repeated Dose Toxicity section for study details; ECHA Dossier: Butyl alcohol; ECHA, 2011). **Therefore, the butyl alcohol MOE for the reproductive toxicity endpoint can be calculated by dividing the butyl alcohol**

NOAEL in mg/kg/day by the total systemic exposure to butyl alcohol, 5503/0.0013 or 4233077.

Duration in Detail	GLP/Guideline	No. of Animals/Dose (Species, Strain, Sex)	Route (Vehicle)	Doses (in mg/kg/day; Purity)	NOAEL/LOAEL/NOEL	Justification of NOAEL/LOAEL/NOEL	Reference
GD 1–19; 7 h/day	GLP-compliant (similar to OECD 414)	Pregnant female Sprague Dawley rats (15 rats/dose)	inhalation via whole-body exposure	0, 3500, 6000, or 8000 ppm (≥99% purity)	Maternal toxicity NOAEL = 6000 ppm or 5617 mg/kg/day (using standard minute volume and body weight values for female Sprague Dawley rats) Developmental toxicity NOAEL = 3500 ppm or 3277 mg/kg/day (using standard minute volume and body weight values for female Sprague Dawley rats)	Decreased bodyweight gain among high-dose group dams Decreased fetal body weights at both the mid- and high-dose group and dose-dependent increase in skeletal variations among high-dose group fetuses	Nelson et al., 1989b
GD 0–20	GLP-compliant (similar to OECD 414)	Pregnant female Sprague Dawley rats (20 rats/dose)	Oral via drinking water	0%, 0.2%, 1%, or 5% (equivalent to 0, 316, 1454, and 5654 mg/kg/day, respectively, as per report); (99.9% purity)	Maternal toxicity NOAEL = 1454 mg/kg/day Developmental toxicity NOAEL = 1454 mg/kg/day	Decreased bodyweight gain and feed and water consumption among high-dose group dams Increased incidence of skeletal variations and decreased body weight among high-dose group fetuses	Ema et al., 2005a
GDs 6–20; 6 h/day	Similar to OECD 414	Pregnant Sprague Dawley rats (19–21/group)	Inhalation via whole-body exposure	0, 500, 1000, 2000, 3000 ppm (equivalent to 371, 742, 1483, 2225 mg/kg/day)	Maternal toxicity NOAEL = 371 mg/kg/day Developmental toxicity NOAEL = 1483 mg/kg/day Teratogenicity NOAEL = 2225 mg/kg/day	Significant decrease in bodyweight gain and feed consumption at the mid- and high-doses. Decrease in fetal weights at the high-dose. No treatment-related malformations were reported up to the highest dose tested.	ECHA, 2011 (accessed 08/09/18)

In addition, the total systemic exposure to butyl alcohol (1.3 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive endpoints 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: Brightwell et al., 1987; US EPA, 2005; US EPA, 1989; CIR, 2008; EMA, 1997; OECD, 2001; ECETOC, 2003; ECHA, 2011; US EPA, 2011(all accessed 08/08/18); Mankes et al., 1985; Cater et al., 1977; Korsak et al., 1994; Ema et al., 2005b.

Literature Search and Risk Assessment Completed On: 10/11/18.

10.1.4. Skin sensitization

Based on the existing data and read-across material propyl alcohol (CAS # 71-23-8), butyl alcohol does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for butyl alcohol. Based on the existing data and read-across material propyl alcohol (CAS # 71-23-8), butyl alcohol does not present a concern for skin sensitization under the current, declared levels of use. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v 4.1). Butyl alcohol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens assay, human Cell Line Activation Test (h-CLAT) test, and U937-CD86 test (Aleksic et al., 2009; Natsch and Haupt, 2013; Johansson et al., 2011; Piroird et al., 2015). In a murine local lymph node assay (LLNA), butyl alcohol was found to be non-sensitizing up to 20% (Ryan et al., 2000; ECHA, 2011; accessed 10/11/18). In a guinea pig maximization test (GPMT) and a Buehler test, read-across material propyl alcohol did not present reactions indicative of sensitization at 100% (Gad et al., 1986). Similarly, in a mouse ear swelling test (MEST), propyl alcohol did not induce any contact sensitization at 100% (Gad et al., 1986). Additionally, in a human maximization test, no skin sensitization reactions were observed at 4% (2760 μg/cm^2) (RIFM, 1976). In addition, in a confirmatory human repeat insult patch test (HRIPT) on read-across material propyl alcohol, no reactions indicative of sensitization were observed in any of the 50 volunteers (Gad et al., 1986).

Although there were deviations from *in vivo* guidelines with butyl alcohol in the LLNA and with read-across material propyl alcohol in the GPMT, based on expert judgment and the weight of evidence (WoE), butyl alcohol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: Gollhausen and Kligman, 1985; Natsch (2008); Wass and Belin, 1990; Natsch and Haupt, 2013; McKim et al., 2010.

Literature Search and Risk Assessment Completed On: 10/11/18.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, butyl alcohol 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 butyl alcohol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, butyl alcohol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/16/18.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for butyl alcohol is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. The inhalation studies cited in the repeated dose and reproductive toxicity endpoint sections (ECHA REACH Dossier on Butyl alcohol; ECHA, 2011; Korsak et al., 1994; Sitarek et al., 1994; Nelson et al., 1989a) are lacking specific and standardized toxicologic evaluations of the respiratory tract, which are important for the local respiratory toxicity endpoint assessment. As such, there are insufficient inhalation data available on butyl alcohol. Based on the Creme RIFM Model, the inhalation exposure is 0.00088 mg/day. This exposure is 1591 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.

10.1.6.2. Additional references. DiVincenzo and Hamilton, 1979; Gerarde and Ahlstrom, 1966; Smyth et al., 1951; Smyth and Smyth, 1928; Haglund et al., 1980; De Ceaurriz et al., 1981; Kane et al., 1980; DeCeaurriz et al., 1983; Nelson et al., 1943; Goodrich et al., 1981; Schumacher et al., 1962; Angerer and Wulf, 1985; Aarstad et al., 1986; Astrand et al., 1976; McOmie and Anderson, 1949; Tabershaw et al., 1944; Nelson et al., 1989b; Nelson et al., 1989a; Korsak et al., 1993; Frantik et al., 1994; Korsak et al., 1994; Bittersohl (1975); Velazquez et al., 1969; Kawai et al., 1997; Silver (1992); Major and Silver, 1999; Smeets and Dalton, 2002; Brightwell et al., 1987; Wise et al., 2007; Cain et al., 2010.

Literature Search and Risk Assessment Completed On: 03/01/2019.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of butyl alcohol 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, butyl alcohol 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 butyl alcohol 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 ≥ 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 VoU (2015), butyl alcohol does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.1.2. Key studies

10.2.1.2.1. Biodegradation. No data available.

10.2.1.2.2. Ecotoxicity. No data available.

10.2.2. Other available data

Butyl alcohol has been registered under REACH and the following additional data is available:

A 96-h fish (Fathead minnow) acute toxicity study was conducted according to the OECD 203 method, and the LC50 was reported to be 1376 mg/L.

A *Daphnia magna* immobilization study was conducted according to the OECD 202 method, and the 48-h EC50 was reported to be 1328 mg/L.

A *Daphnia magna* reproduction study was conducted according to the OECD 211 method. The 21-day NOEC (reproduction) was reported to be 4.1 mg/L.

An algae inhibition study was conducted according to the OECD 201 method, and the 96-h EC50 (growth rate) was reported to be 225 mg/L.

10.2.3. Risk assessment refinement

Since butyl alcohol has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1021			1,000,000	1.021	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	0.84	0.84
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	1–10
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 1.021 μg/L. The revised PEC/PNECs for EU and NA are: not applicable. The material was 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: 9/25/18.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/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:** http://www.safe.nite.go.jp/english/db.html
- **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 01/31/19.

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.2019.111000.

Appendix

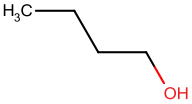
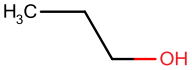
Read-across Justification

Methods

The read-across analogs were 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, 2018).

- 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 substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM).

- 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 and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material
Principal Name	Butyl alcohol	Propyl alcohol
CAS No.	71-36-3	71-23-8
Structure		
Similarity (Tanimoto Score)		0.78
Read-across Endpoint		• Skin sensitization
Molecular Formula	$C_4H_{10}O$	C_3H_8O
Molecular Weight	74.12	60.09
Melting Point (°C, EPI Suite)	−89.8	−126.1
Boiling Point (°C, EPI Suite)	118	97.2
Vapor Pressure (Pa @ 25 °C, EPI Suite)	8.93E+002	2.80E+003
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	0.88	0.25
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	6.32e+004	1e+006
J_{max} (μg/cm^2/h, SAM)	1586.14	12813.1
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	8.93E-001	7.51E-001
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 butyl alcohol (CAS # 71-36-3). 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, propyl alcohol (CAS # 71-23-8) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Propyl alcohol (CAS # 71-23-8) was used as a read-across analog for the target material butyl alcohol (CAS # 71-36-3) for the skin senzitization endpoint.
  - o The target substance and the read-across analog share a primary hydroxyl group attached to the straight chain saturated carbon chain.
  - o The key difference between the target substance and the read-across analog is that in the read-across analog the hydroxyl group is attached to the C3 carbon chain, whereas in the target substance it is attached to the C4 carbon chain. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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