Food and Chemical Toxicology 134 (2019) 110904

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

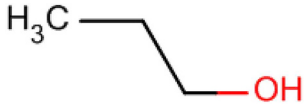
Short review

RIFM fragrance ingredient safety assessment, propyl alcohol, CAS Registry Number 71-23-8

A.M. Api[a], F. Belmonte[a], D. Belsito[b], S. Biserta[a], D. Botelho[a], M. Bruze[c], G.A. Burton Jr.[d], J. Buschmann[e], M.A. Cancellieri[a], M.L. Dagli[f], M. Date[a], W. Dekant[g], C. Deodhar[a], A.D. Fryer[h], S. Gadhia[a], L. Jones[a], K. Joshi[a], A. Lapczynski[a], M. Lavelle[a], D.C. Liebler[i], M. Na[a], D. O'Brien[a], A. Patel[a], T.M. Penning[j], G. Ritacco[a], F. Rodriguez-Ropero[a], J. Romine[a], N. Sadekar[a], D. Salvito[a], T.W. Schultz[k], I.G. Sipes[l], G. Sullivan[a,*], Y. Thakkar[a], Y. Tokura[m], S. Tsang[a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP, 05508-900, Brazil*
[g] *Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA*
[l] *Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

Version: 110218. This version replaces any previous versions.
Name: Propyl alcohol
CAS Registry Number: 71-23-8



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; Safford et al., 2015; Safford et al., 2017; Comiskey 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

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

https://doi.org/10.1016/j.fct.2019.110904
Received 13 May 2019; Received in revised form 18 October 2019; Accepted 22 October 2019
Available online 25 October 2019
0278-6915/

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.

Propyl 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 propyl alcohol is not genotoxic. Data on read-across material butyl alcohol (CAS # 71-36-3) provide a calculated MOE > 100 for the repeated dose toxicity endpoint. Data on propyl alcohol provide a calculated MOE > 100 for the developmental and reproductive toxicity endpoint. Data from read-across analog butyl alcohol (CAS # 71-36-3) show that there are no safety concerns for propyl alcohol for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; propyl 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 propyl alcohol is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; propyl 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: Propyl Alcohol; ECHA, (2011a)
Repeated Dose Toxicity: NOAEL = 41 mg/kg/day	ECHA Dossier: Butyl alcohol; ECHA (2011b)
Developmental and Reproductive Toxicity: NOAEL = 2602 mg/kg/day.	(Nelson et al., 1989)
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:	
Critical Measured Value: 81% (OECD 301D)	ECHA Dossier: Propyl Alcohol; ECHA (2011a)
Bioaccumulation:	
Screening-level: 3.16 L/kg (EPI Suite v4.11; US EPA, 2012a)	
Ecotoxicity:	
Screening-level: Fish LC50: 2209 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: 2209 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 2.209 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** Propyl alcohol
2. **CAS Registry Number:** 71-23-8
3. **Synonyms:** Albacol; Optal; 1-Propanol; Propan-1-ol; N-Propyl alcohol; Propyl alcohol
4. **Molecular Formula:** C_3H_8O
5. **Molecular Weight:** 60.09
6. **RIFM Number:** 7183
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 98 °C (FMA Database), 89.96 °C (EPI Suite)
2. **Flash Point:** 71 °F; CC (FMA Database), 24 °C (GHS)
3. **Log K_{OW}:** 0.25 (Abraham and Rafols, 1995), 0.25 (Patel et al., 2002), 0.35 (EPI Suite)
4. **Melting Point:** −74.95 °C (EPI Suite)
5. **Water Solubility:** 271500 mg/L (EPI Suite)
6. **Specific Gravity:** 0.80400 @ 25.00 °C*
7. **Vapor Pressure:** 15 mm Hg 20 °C (FMA Database), 23.2 mm Hg @ 25 °C (EPI Suite), 16.9 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:** Clear colorless volatile liquid with alcohol-like odor

*http://www.thegoodscentscompany.com/data/rw1009211.html#tophyp, retrieved 10/27/2015.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.00077% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.000015 mg/kg/day or 0.0011 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.0029 mg/kg/day (RIFM, 2014)

*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 80%

J_{max} from the RIFM SAM model.

Name	Propyl alcohol
J_{max} (μg/cm^2/h)	12813[1]
Skin Absorption Class	80%

[1]J_{max} was calculated based on estimated log K_{OW} = 0.25 (consensus model) and Solubility = 1000000 mg/L (consensus model).

2. **Oral:** Assumed 100%
3. **Inhalation:** Assumed 100%

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:** Butyl alcohol (CAS # 71-36-3)
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** Butyl alcohol (CAS # 71-36-3)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

EU, 2008: Propyl alcohol is rapidly oxidized in the liver to propionaldehyde by alcohol dehydrogenase (ADH) and to a lesser extent, by the NADPH-dependent microsomal ethanol oxidizing system involving cytochrome P450 following a chronic exposure. Propionic acid forms from propionaldehyde followed by coenzyme A (CoA) conjugation and carboxylation to eventually form succinyl-CoA, which enters the tricarboxylic cycle for further biotransformation to carbon dioxide and water. Aside from the liver, propyl alcohol is known to undergo metabolism in the nasal mucosa. Studies using hamster homogenates and surgically isolated respiratory tracts demonstrate that metabolism in the nasal mucosa is also catalyzed by ADH, although the rate is dependent on the inspiratory flow rate.

Soelberg et al., 2009: Inhalation and intravenous (iv) exposure studies were conducted in rats to determine the blood pharmacokinetics of propanol and its major metabolite, propionic acid. Propanol was administered via inhalation at 500 or 3500 ppm for 2 h followed by measurement of blood concentrations of propanol and propionic acid. For propanol and propionic acid, C_{max} was achieved within 2 h with an immediate decline in blood concentrations at the end of the exposure. Following 3500 ppm inhalation exposure, peak propanol levels were several fold higher than those observed after 25 mg/kg iv dose. However, propionic acid levels were less than that reported following iv administration of propanol, suggesting saturable propanol metabolism. Following an iv administration of propionic acid, C_{max} and AUC for propionic acid were ~6 × higher following propionic acid administration compared to an equimolar dose of propanol. However, the rate of elimination following iv administration of propanol and propionic acid was the same. This study demonstrates that propyl alcohol is readily absorbed through inhalation and metabolized to propionic acid.

Additional References: EFSA, 2012; WHO, 1998 (accessed 08/23/18); Forsander, 1967; Auty and Branch, 1976; Abshagen and Rietbrock, 1970; Beauge et al., 1979; Fahelbum and Sybil, 1979; Kamil et al., 1953; ECHA, 2011a.

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Propyl alcohol is reported to occur in the following foods by the VCF* and in some natural complex substances (NCS):

Apple fresh (*Malus* species), Black currants (*Ribes nigrum* L.), Citrus fruits, Fish, Milk and milk products, Mushroom, Oats (*Avena sativa* L.), Olive (*Olea europaea*),Papaya (*Carica papaya* L.) Pork.

*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

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, propyl alcohol does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of propyl alcohol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using both the plate incorporation and the preincubation methods. *Salmonella typhimurium* strains TA 1535, TA 100, TA 1537, TA 98, and *E. coli* WP2 uvrA were treated with propyl alcohol in water at concentrations up to 5000 μg/plate with and without S9. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (ECHA Dossier: Propyl Alcohol; ECHA, 2011a). Under the conditions of the study, propyl alcohol was not mutagenic in the Ames test.

The clastogenicity of propyl alcohol was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung fibroblasts (V79) were treated with propyl alcohol in water at concentrations up to 600 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 dose of the test item, either with or without S9 metabolic activation (ECHA Dossier: Propyl Alcohol; ECHA, 2011a). Under the conditions of the study, propyl alcohol was considered to be non-clastogenic to mammalian cells.

Based on the available data, propyl 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 for propyl alcohol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on propyl alcohol, as the studies only include only 1 dose level in both oral and inhalation studies. Hence, these studies are included only as Weight of Evidence in the presented safety assessment. There are sufficient repeated dose toxicity data on the read-across material butyl alcohol (CAS # 71-36-3; see section V). A subchronic, 13-week repeated dose toxicity study was conducted (GLP compliant, non-guideline) using Sprague Dawley rats (20 rats/sex/group with an additional 10 rats/sex/group for interim sacrifice) 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 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 count (RBC), and packed cell volume (PCV) in females of the high-dose group during week 6; however, no changes were reported in males during week 6 or 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 Dossier: Butyl Alcohol; ECHA, 2011b; accessed 08/08/18).

Butyl alcohol was evaluated for systemic toxicity in a 90-day inhalation study (non-GLP compliant) only 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, 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) was 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 inhalational 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 inhalational study. NOAEL is derived from the subchronic oral toxicity study. Therefore, the NOAEL of 41 mg/kg/day was considered for the risk assessment for the repeated dose toxicity endpoint.

Therefore, the propyl 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 propyl alcohol (mg/kg/day), 41/0.0029 or 14138.

In addition, the total systemic exposure to propyl alcohol (2.9 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; for a Cramer Class I material) for the repeated dose toxicity endpoint at the current level of use.

Additional References: Gibel et al., 1975; EU, 2008; Wakabayashi et al., 1984; Hillbom, 1974; WHO, 1998 (accessed 08/23/18); US EPA, 2005; US EPA, 2011; NTRL, 1989 (accessed 08/08/18); ECETOC, 2003; US EPA, 1989; EMA, 1997; OECD, 2001; EFSA, 2013; ECHA, 2018; ECHA, 2011a (accessed on 08/23/18)

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

10.1.3. Developmental and reproductive toxicity

The margin of exposure for propyl 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 reproductive and developmental toxicity data on propyl alcohol.

A developmental and reproductive toxicity study (non-guideline and non-GLP compliant) was conducted in Sprague Dawley rats. Groups of 15 pregnant female rats/dose were exposed to propyl alcohol via inhalation (whole body) for 7 h/day at doses of 0, 3500, or 7000 ppm throughout the gestation period. Groups of 18 male Sprague Dawley rats/dose were also exposed to propyl alcohol for 6 weeks, which were mated with the non-exposed females and handled in the same manner as sham-exposed females. Infertility in 7000 ppm group males was observed; hence, the last 6 exposed males were retained (the others had been euthanized before infertility was noted) and re-mated at biweekly intervals to look for reversibility of infertility, which was observed in other males of the high-dose group. Infertility reported at 7000 ppm paternally-exposed male rats was found to be reversible by 13 weeks. No significant differences in the number of live pups per litter, length of gestation, birth weights, neonatal survival, behavioral and neurochemistry parameters were reported in any of the dose groups tested. Soon after birth, in the high-dose maternally-exposed group, external malformations (crooked tail) were reported in 2/15 litters and persisted throughout the study, which were considered to be treatment-related effects. The NOAEC for male and female reproductive toxicity was considered to be 3500 ppm and 7000 ppm, respectively, based on infertility observed among 7000 ppm dose group males. Using standard minute volume and body weight values for male and female Sprague Dawley rats, the calculated NOAEL for male and female reproductive toxicity was 2602 and 5204 mg/kg/day, respectively. The NOAEC for developmental toxicity was considered to be 3500 ppm or 2602 mg/kg/day, based on external malformations (crooked tail) among high-dose group pups. (Nelson et al., 1989). The more conservative NOAEL of 2602 mg/kg/day for male reproductive toxicity was selected for the risk assessment.

In a DRF study, groups of 15 pregnant female Sprague Dawley rats/dose were exposed to propyl alcohol via inhalation (whole body) for 7 h/day at doses of 0, 3500, 7000, or 10000 ppm from GDs 1–19. The NOAEC for both developmental and maternal toxicity was considered to be 3500 ppm or 2656 mg/kg/day (as per the standard minute volume and body weight values for female Sprague Dawley rats), based on decreased body weight in dams, increased skeletal malformations, and decreased weights of fetuses among higher dose group animals (Nelson et al., 1988). It was noted that propyl alcohol caused skeletal malformations (rudimentary cervical ribs) (Nelson et al., 1988) and external malformations (crooked tail-ectrodactyly) in the main study (Nelson et al., 1989). Therefore, the most conservative NOAEL of 2602 mg/kg/day for developmental toxicity was selected for the risk assessment.

The propyl alcohol MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the propyl alcohol NOAEL in mg/kg/day by the total systemic exposure to propyl alcohol, 2602/0.0029 or 897241.

In addition, the total systemic exposure to propyl alcohol (2.9 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 toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: Nelson et al., 1985; EU, 2008; SCHER, 2008; OECD, 2008; EFSA, 2012; US EPA, 2005; Mankes et al., 1985.

Literature Search and Risk Assessment Completed On: 09/26/18.

10.1.4. Skin sensitization

Based on the existing data and read-across material butyl alcohol (CAS # 71-36-3), propyl alcohol does not present a concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for propyl alcohol. Based on the existing data and read-across material butyl alcohol (CAS # 71-36-3, see section V), propyl alcohol 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 2.6.13; OECD toolbox v4.1). Read-across material butyl alcohol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, human Cell Line Activation Test (h-CLAT), 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), read-across material butyl alcohol was found to be non-sensitizing up to 20% (Ryan et al., 2000; ECHA, 2011b; accessed 07/24/18). In a guinea pig maximization test (GPMT) and a Buehler test, 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). In a human maximization test, no skin sensitization reactions were observed with read-across material butyl alcohol at 4% (2760 μg/cm^2) (RIFM, 1976). Additionally, in a confirmatory human repeat insult patch test (HRIPT) on 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 propyl alcohol in the GPMT and with read-across material butyl alcohol in the LLNA, based on expert judgment and the weight of evidence (WoE), propyl alcohol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: Gollhausen and Kligman, 1985; Natsch and Gfeller, 2008; Wass and Belin, 1990; Natsch and Haupt, 2013; McKim et al., 2010; Piroird et al., 2015; Roberts et al., 2007.

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

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, propyl 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 propyl 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, propyl 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} · 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 propyl 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 (REACH Dossier on Butyl alcohol; ECHA, 2011b; Korsak et al., 1994; Nelson et al., 1988; Nelson et al., 1989) 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 propyl alcohol for the local respiratory toxicity endpoint. Based on the Creme RIFM Model, the inhalation exposure is 0.0012 mg/day. This exposure is 1166.7 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: Gerarde and Ahlstrom, 1966; Smyth et al., 1954; Kane et al., 1980; Edelfors and Ravn-Jonsen, 1985; Nelson et al., 1988; Lorber, 1972; Nelson et al., 1989; Nelson et al., 1985; Frantik et al., 1994; Rinehart et al., 1967; Silver, 1992; Soelberg et al., 2009.

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 propyl 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, propyl 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 propyl 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.1.1. Risk assessment. Based on the current VoU (2015), propyl alcohol does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2. Key studies

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Propyl alcohol has been registered under REACH and the following additional data is available.

A ready biodegradability study was conducted according to the OECD 301D method, and biodegradation of 81% was observed after 15 days.

A 96-h fish (Fathead minnow) acute study was conducted according to the OECD 203 method under flow-through conditions, and the LC50 was reported to be 4555 mg/L.

A *Daphnia magna* acute toxicity study was conducted according to the DIN 38412 part II method under static conditions, and the 48-h EC50 was reported to be 3644 mg/L.

An algae acute toxicity study was conducted under static conditions and the 48 h EC50 (growth rate) was reported to be 9170 mg/L.

A *Daphnia magna* Reproduction Test was conducted according to the OECD 211 method under semi-static conditions. Based on reproduction, The 21 days NOEC was reported to be greater than 100 mg/L.

10.2.3. Risk assessment refinement

Since propyl 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)**	2209			1,000,000	2.209	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	0.35	0.35
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 2.209 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: 09/24/18.

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.2019.110904.

Appendix

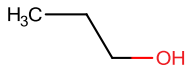
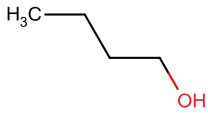
Read-across Justification

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, 2016).

- First, the 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	Propyl alcohol	Butyl alcohol
CAS No.	71-23-8	71-36-3
Structure		
Similarity (Tanimoto Score)		0.64
Read-across Endpoint		• Skin Sensitization • Repeated Dose Toxicity
Molecular Formula	C_3H_8O	$C_4H_{10}O$
Molecular Weight	60.09	74.12
Melting Point (°C, EPI Suite)	−74.95	−62.33
Boiling Point (°C, EPI Suite)	89.96	113.91
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.09E+003	1.04E+003
Log Kow (KOWWIN v1.68 in EPI Suite)	0.25	0.88
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1E+006	6.32E+004
J_{max} (μg/cm^2/h, SAM)	12813.05	1586.14
Henry's Law (Pa·m3/mol, Bond Method, EPI Suite)	7.62E-001	1.01E+000
Repeated Dose		
Repeated Dose (HESS)	Ethanol (hepatotoxicity) alert	Ethanol (hepatotoxicity) alert
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 propyl alcohol (CAS # 71-23-8). 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, butyl alcohol (CAS # 71-36-3) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Butyl alcohol (CAS # 71-36-3) was used as a read-across analog for the target material propyl alcohol (CAS # 71-23-8) for the repeated dose and skin sensitization endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the class of straight chain saturated aliphatic alcohols.
  - 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 the read-across analog has a 1 carbon longer aliphatic chain compared to the target substance. This structural difference is toxicologically insignificant.
  - o The 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 target substance as well as the read-across analog has an ethanol (hepatotoxicity) alert by HESS categorization. The margin of exposure for propyl alcohol is adequate for the repeated dose toxicity endpoint at the current level of use. Therefore, based on data for the read-across analog, the alert is superseded by the data.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

Abraham, M.H., Rafols, C., 1995. Factors that influence tadpole narcosis. An LFER analysis. J. Chem. Soc., Perkin Trans. 2 (10), 1843–1851.

Abshagen, U., Rietbrock, N., 1970. Interference tests with low aliphatic alcohols in vivo and in the isolated perfused rat liver. Naunyn Schmiedeberg's Arch. Pharmacol. 265, 411–424.

Aleksic, M., Thain, E., Roger, D., Saib, O., Davies, M., Li, J., Aptula, A., Zazzeroni, R., 2009. Reactivity profiling: covalent modification of single nucleophile peptides for skin sensitization risk assessment. Toxicol. Sci. 108 (2), 401–411.

Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G.,

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

Auty, R.M., Branch, R.A., 1976. The elimination of ethyl, n-propyl, n-butyl and iso-amyl alcohols by the isolated perfused rat liver. J. Pharmacol. Exp. Ther. 197 (3), 669–674.

Beauge, F., Clement, M., Nordmann, J., Nordmann, R., 1979. Comparative effects of ethanol, n-propanol and isopropanol on lipid disposal by rat liver. Chem. Biol. Interact. 26, 155–166.

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

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

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

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

ECETOC, 2003. European Centre for Ecotoxicology and Toxicology of Chemicals: N-Butanol. Retrieved from: http://www.ecetoc.org/wp-content/uploads/2014/08/JACC-041.pdf.

ECHA, 2011a. Registration Dossier Propyl Alcohol. Retrieved from: https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/14586/1.

ECHA, 2011b. Registration Dossier Butyl Alcohol. Retrieved from: https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/15322/1.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.

ECHA, 2016. European Chemical Agency Read-Across Assessment Framework. ECHA Read-across Assessment Framework. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

ECHA, 2018. Substance Evaluation Conclusion for Butan-1-Ol. Retrieved from: https://echa.europa.eu/documents/10162/92e909fd-1391-324f-6ff4-ce5f0695bc42.

Edelfors, S., Ravn-Jonsen, A., 1985. Calcium uptake in rat brain synaptosomes after short-term exposure to organic solvents: a pilot study. Acta Pharmacol. Toxicol. 56 (5), 431–434.

EFSA, 2012. European Food Safety Authority's Scientific Opinion on the Evaluation of the Substances Currently on the List in the Annex to Commission Directive 96/3/EC as Acceptable Previous Cargoes for Edible Fats and Oils. Retrieved from: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2012.2703.

EMA, 1997. Committee for Veterinary Medicinal Products: N-Butanol Summary Report. Retrieved from: https://www.ema.europa.eu/documents/mrl-report/n-butanol-summary-report-committee-veterinary-medicinal-products_en.pdf.

EU, 2008. European Union Risk Assessment Report: Propan-1-Ol. Retrieved from: https://echa.europa.eu/documents/10162/3fd81f2f-b48d-4123-88ea-12e88b53850f.

Fahelbum, I.M.S., Sybil, P.J., 1979. Absorption, distribution and metabolism of propyl anthranilate. Toxicology 12 (1), 75–87.

Forsander, O.A., 1967. Influence of some aliphatic alcohols on the metabolism of rat liver slices. Biochem. J. 105, 93–97.

Frantik, E., Hornychova, M., Horvath, M., 1994. Relative acute neurotoxicity of solvents: isoeffective air concentrations of 48 compounds evaluated in rats and mice. Environ. Res. 66 (2), 173–185.

Gad, S.C., Dunn, B.J., Dobbs, D.W., Reilly, C., Walsh, R.D., 1986. Development and validation of an alternative dermal sensitization test: the mouse ear swelling test (MEST). Toxicol. Appl. Pharmacol. 84 (1), 93–114.

Gerarde, H.W., Ahlstrom, D.B., 1966. The aspiration hazard and toxicity of homologous series of alcohols. Arch. Environ. Health 13 (4), 457–461.

Gibel, V.W., Lohs, K.H., Wildner, G.P., 1975. Experimental study on carcinogenic activity of propanol-1, 2-methylpropanol-1, and 3-methylbutanol-1. Arch. Geschwulstforsch. 45 (1), 19–24.

Gollhausen, R., Kligman, A.M., 1985. Human assay for identifying substances which induce non-allergic contact urticaria: the NICU-test. Contact Dermatitis 13, 98–106.

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

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

Johansson, H., Lindstedt, M., Albrekt, A.-S., Borrebaeck, C.A., 2011. A Genomic Biomarker Signature Can Predict Skin Sensitizers Using a Cell-Based in Vitro Alternative to Animal Tests, vol.12. Online Publication: BMC Genomics, pp. 399. http://www.biomedcentral.com/1471-2164/12/399.

Kamil, I.A., Smith, J.N., Williams, R.T., 1953. Studies in detoxication. 46. The metabolism of aliphatic alcohols. The glucuronic acid conjugation of acyclic aliphatic alcohols. Biochem. J. 53, 129–136.

Kane, L.E., Dombroske, R., Alarie, Y., 1980. Evaluation of sensory irritation from some common industrial solvents. Am. Ind. Hyg. Assoc. J. 41 (6), 451–455.

Korsak, Z., Wisniewska-Knypl, J., Swiercz, R., 1994. Toxic effects of subchronic combined exposure to n-butyl alcohol and m-xylene in rats. Int. J. Occup. Med. Environ. Health 7 (2), 155–166.

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

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

Lorber, M., 1972. Hematoxicity of synergized pyrethrin insecticides and related chemicals in intact, totally and subtotally splenectomized dogs. Acta Hepato-Gastroenterol. 19 (1), 66–78.

Mankes, R.F., LeFevre, R., Renak, V., Fiesher, J., Abraham, R., 1985. Reproductive effects of some solvent alcohols with differing partition coefficients. Teratology 31 (3), 67A.

McKim Jr., J.M., Keller III, D.J., Gorski, J.R., 2010. A new in vitro method for identifying chemical sensitizers combining peptide binding with ARE/EpRE-medicated gene expression in human skin cells. Cutan. Ocul. Toxicol. 29 (3), 171–192.

Natsch, A., Gfeller, H., 2008. LC-MS-Based characterization of the peptide reactivity of chemicals to improve the in vitro prediction of the skin sensitization potential. Toxicol. Sci. 106 (2), 464–478.

Natsch, A., Haupt, T., 2013. Utility of rat liver S9 fractions to study skin-sensitizing prohaptens in a modified keratinoSens assay. Toxicol. Sci. 135 (2), 356–368.

Nelson, B.K., Brightwell, W.S., Burg, J.R., 1985. Comparison of behavioral teratogenic effects of ethanol and n-propanol administered by inhalation to rats. Neurobehav. Toxicol. Teratol. 7, 779–783.

Nelson, B.K., Brightwell, W.S., MacKenzie-Taylor, D.R., Burg, J.R., Weigel, W.W., 1988. Teratogenicity of n-propanol and isopropanol administered at high inhalation concentrations to rats. Food Chem. Toxicol. 26 (1), 247–254.

Nelson, B.K., Brightwell, W.S., Taylor, B.J., Khan, A., Burg, J.R., Krieg Jr., E.F., Massari, V.J., 1989. Behavioral teratology investigation of 1-propanol administered by inhalation to rats. Neurotoxicol. Teratol. 11 (2), 153–159.

NTRL, 1989. National Technical Reports Library's Health and Environmental Effects Document for 1-Butanol. Retrieved from: https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB91216465.xhtml.

OECD, 2001. SIDS Initial Assessment Report for SIAM 13: N-Butyl Alcohol. Retrieved from: https://hpvchemicals.oecd.org/UI/handler.axd?id=71542012-bd67-42b6-b0c0-89eaf4dc13c4.

OECD, 2015. *Guidance Document On the Reporting Of Integrated Approaches To Testing And Assessment (IATA)*. ENV/JM/HA(2015)7. Retrieved from: http://www.oecd.org/.

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

Patel, H., ten Berge, W., Cronin, M.T.D., 2002. Quantitative structure-activity relationships (QSARs) for the prediction of skin permeation of exogenous chemicals. Chemosphere 48 (6), 603–613.

Piroird, C., Ovigne, J.-M., Rousset, F., Martinozzi-Teissier, S., Gomes, C., Cotovio, J., Alepee, N., 2015. The Myeloid U937 Skin Sensitization Test (U-SENS) addresses the activation of dendritic cell event in the adverse outcome pathway for skin sensitization. Toxicol. In Vitro 29 (5), 901–916.

RIFM (Research Institute for Fragrance Materials, Inc), 1976. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1796. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2014. Exposure Survey 04. July 2014.

Rinehart, W.E., Kaschak, M., Pfitzer, E.A., 1967. Range-finding toxicity data for 43 compounds. Ind. Hyg. Foundation. Am. Chem. Toxicol. Ser. Bull. 6, 1–8.

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

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

Ryan, C.A., Gerberick, G.F., Cruse, L.W., Basketter, D.A., Lea, L., Blaikie, L., Dearman, R.J., Warbrick, E.V., Kimber, I., 2000. Activity of human contact allergens in the murine local lymph node assay. Contact Dermatitis 43 (2), 95–102.

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

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

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

SCHER, 2008. Risk Assessment Report on Propan-1-Ol. Retrieved from: http://ec.europa.eu/health/ph_risk/committees/04_scher/docs/scher_o_105.pdf.

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

Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. In: Annals of the New York Academy of Sciences, vol.641. pp. 152–163.

Smyth Jr., H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., 1954. Range-finding toxicity data. List V. Archives of Ind. Hyg. Archives of Ind. Hyg. 10, 61–68.

Soelberg, J.J., Poet, T.S., Busby, A.L., Sweeney, L.M., Faber, W., 2009. Intravenous- and inhalation-route pharmacokinetics of propanol and its metabolite propionic acid. Toxicologist 108 (1), 307.

US EPA, 1989. Health and Environmental Effects for N-Butanol. Retrieved from: https://nepis.epa.gov/Exe/ZyPDF.cgi/900R0B00.PDF?Dockey=900R0B00.PDF.

US EPA, 2005. Inert Reassessment *N*-Butanol. Retrieved from: https://www.epa.gov/

sites/production/files/2015-04/documents/butanol.pdf.
US EPA, 2011. Integrated Risk Information System: N-Butanol. Retrieved from: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0140_summary.pdf.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
Wakabayashi, T., Horiuchik, M., Sakaguchi, M., Onda, H., Iljima, M., 1984. Induction of megamitochondria in the rat liver by n-propyl alcohol and n-butyl alcohol. Acta path. jap. 34 (3), 471–480.
Wass, U., Belin, L., 1990. An in vitro method for predicting sensitizing properties of inhaled chemicals. Scand. J. Work Environ. Health 16 (3), 208–214.
WHO, 1998. World Health Organization, Safety Evaluation of Certain Food Additives and Contaminants, Who Food Additives Series 40. Retrieved from: http://www.inchem.org/documents/jecfa/jecmono/v040je10.htm.