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Short review

RIFM fragrance ingredient safety assessment, amyl alcohol, CAS Registry Number 71-41-0

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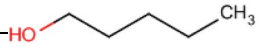

Name: Amyl alcohol
CAS Registry Number: 71-41-0

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
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level

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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.

The existing information supports the use of this material as described in this safety assessment.

Amyl alcohol was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog propyl alcohol (CAS # 71-23-8) show that amyl alcohol is not expected to be genotoxic. Data provide a calculated MOE > 100 for the repeated dose toxicity endpoint. Data on read-across analog isoamyl alcohol (CAS # 123-51-3) provide a calculated MOE > 100 for the developmental and reproductive toxicity endpoint. Data from read-across materials butyl alcohol (CAS # 71-36-3) and propyl alcohol (CAS # 71-23-8) show that there are no skin sensitization safety concerns for amyl alcohol under current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; amyl alcohol is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; amyl alcohol was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(ECHA Dossier: Propan-1-ol; ECHA, 2011b)
Repeated Dose Toxicity: 150 mg/kg/day.	(Butterworth et al., 1978)
Developmental and Reproductive Toxicity: NOAEL = 4324 and 300 mg/kg/day, respectively.	(Nelson et al., 1989; ECHA Dossier: 3-Methylbutan-1-ol; ECHA, 2011c)
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: 100% (Iso Method 9439 D)	RIFM (2001)
Bioaccumulation: Screening-level: 4.6 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 455.1 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: 455.1 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.4551 µg/L

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

1. Identification

1. **Chemical Name:** Amyl alcohol
2. **CAS Registry Number:** 71-41-0
3. **Synonyms:** *n*-Butyl carbinol; 1-Pentanol; Pentyl alcohol; アルカノール (C = 5 ~ 38); Pentan-1-ol; *n*-Pentanol; Amyl alcohol
4. **Molecular Formula:** $C_5H_{12}O$
5. **Molecular Weight:** 88.15
6. **RIFM Number:** 6077
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 136–138 °C (Aldrich), 136.95 °C (EPI Suite)
2. **Flash Point:** 120 °F; CC (FMA Database), 47 °C (GHS)
3. **Log K_{OW}:** 1.51 (Patel et al., 2002), 1.51 (Abraham and Rafols, 1995), 1.33 (EPI Suite)
4. **Melting Point**: 49.96 °C (EPI Suite)
5. **Water Solubility:** 20890 mg/L (EPI Suite)
6. **Specific Gravity:** 0.811 (Aldrich)
7. **Vapor Pressure:** 1.3 mm Hg 20 °C (FMA Database), 2.65 mm Hg @ 25 °C (EPI Suite), 1.82 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:** Colorless liquid with mild characteristic odor, sweet and pleasant odor, or fuse-like odor with a burning taste

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.0012% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.000012 mg/kg/day or 0.00086 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.00018 mg/kg/day (RIFM, 2015)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; and Comiskey et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

6. Analogs selected

a. **Genotoxicity:** Propyl alcohol (CAS # 71-23-8)
b. **Repeated Dose Toxicity:** None
c. **Developmental and Reproductive Toxicity:** Isoamyl alcohol (CAS # 123-51-3)
d. **Skin Sensitization:** Butyl alcohol (CAS # 71-36-3); 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

7. Metabolism

In rats, amyl alcohol is primarily oxidized by alcohol dehydrogenase to valeraldehyde followed by formation of valeric acid that is metabolized through fatty acid and tricarboxylic acid pathways, the products of which are excreted in the urine. Following inhalation exposure to amyl alcohol the metabolite valeraldehyde has been shown to have a negligible presence in blood but has been observed in the brain at an inhaled concentration of 600 ppm (see below).

Savolainen et al., 1985; ECHA REACH Dossier on Pentan-1-ol (ECHA, 2011a; **accessed 07/23/18):** In an *in vivo* metabolism and distribution study, male Wistar rats (10 rats/group) were exposed to amyl alcohol through inhalation (5 days/week for 6 h) at concentrations of 0, 100, 300, and 600 ppm (equivalent to 0, 0.36, 1.08, and 2.16 mg/L, respectively) for a period of 7–14 weeks. The amyl alcohol and valeraldehyde in the blood and brain were analyzed by gas chromatography with flame ionization detection. While amyl alcohol increased dose-dependently in both the blood and brain, valeraldehyde was not present in the blood. Blood concentrations of amyl alcohol were not significantly different between exposure weeks 7 and 14; however, amyl alcohol concentrations in the brain increased dose-dependently during both exposure weeks. At the 300 and 600 ppm doses, amyl alcohol in the brain statistically significantly decreased from week 7 to week 14, while blood levels did not significantly change for all doses between weeks 7 and 14. The formation of valeraldehyde was presumed to have occurred from an intracerebral reaction catalyzed by alcohol dehydrogenases in the brain.

Additional References: Iwersen and Schmoldt, 1995; Forsander (1967); Aasmoe et al., 1998; Strubelt et al., 1999, Gaillard and Derache, 1965; HSDB, 2018 (accessed 07/23/18).

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

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

Allium species	Brazil nut (*Bertholletia excelsa*)
Annatto (*Bixa orellana* L.)	Buckwheat
Apple brandy (Calvados)	Cabbage (*Brassica oleracea*)
Apple fresh (*Malus* species)	Camomile
Apple processed (*Malus* species)	Cape gooseberry (*Physalis peruviana* L.)
Apricot (*Prunus armeniaca* L.)	*Capsicum* species
Arrack	Cashew apple (*Anacardium occidentale*)
Asparagus (*Asparagus officinalis* L.)	Cashew apple wine
Avocado (*Persea americana* Mill.)	Cheddar cheese
Babaco fruit (*Carica pentagona* Heilborn)	Cheese, various types
Banana (*Musa sapientum* L.)	Cherimoya (*Annona cherimolia* Mill.)
Bantu beer	Cherry
Barley	Cherry brandy
Beans	Chicken
Beef	Chinese quince (*Pseudocydonia sinensis*
Beer	Schneid)
Bilberry wine	Cider (apple wine)
Black currants (*Ribes nigrum* L.)	Citrus fruits

Blue cheeses	Clam
Cloudberry (*Rubus chamaemorus* L.)	Kumazasa (*Sasa albo-marginata*)
Cocoa	Lamb and mutton
Coffee	Lamb's lettuce (*Valerianella locusta*)
Crayfish	Laurel (*Laurus nobilis* L.)
Crispbread	Lentils
Dalieb, Palmyra palm fruit (*Borassus aethiopum* L.)	Licorice (*Glycyrrhiza glabra* L.)
Date (*Phoenix dactylifera* L.)	Litchi wine
Dill (*Anethum* species)	Loganberry (*Rubus ursinus* var. *loganobaccus*)
Dwarf quince (*Chaenomeles japonica*)	Loquat (*Eriobotrya japonica* Lindl.)
Egg	Lovage (*Levisticum officinale* Koch)
Elderberry (*Sambucus nigra* L.)	Macadamia nut (*Macadamia integrifolia*)
Filbert, hazelnut (*Corylus avellano*)	Maize (*Zea mays* L.)
Fish	Malt
Ginger (*Zingiber* species)	*Mangifera* species
Grape (*Vitis* species)	Marula (*Sclerocarya birrea* subsp. *caffra*)
Grape brandy	Mate (*Ilex paraguayensis*)
Guava and feyoa	Matsutake (*Tricholoma matsutake*)
Guava wine	Melon
Guinea hen	Mentha oils
Honey	Milk and milk products
Hop (*Humulus lupulus*)	Mountain papaya (*C. candamarcensis, C. pubescens*)
Katsuobushi (dried bonito)	Mushroom
Kiwifruit (*Actinidia chinensis*, syn. *A. deliciosa*)	Mustard (*Brassica* species)
Naranjilla fruit (*Solanum quitoense* Lam.)	Pumpkin (*Cucurbita pepo* L.)
Nectarine	Quince, marmelo (*Cydonia oblonga* Mill.)
Oats (*Avena sativa* L.)	Rambutan (*Nephelium lappaceum* L.)
Olive (*Olea europaea*)	Raspberry brandy
Oysters	Raspberry, blackberry, and boysenberry
Papaya (*Carica papaya* L.)	Red currants (*Ribes rubrum* L.)
Parsnip root (*Pastinaca sativa* L.)	Rice (*Oryza sativa* L.)
Passion fruit (*Passiflora* species)	Rooibos tea (*Aspalathus linearis*)
Peach (*Prunus persica* L.)	Rum
Peanut (*Arachis hypogaea* L.)	Rye bread
Pear (*Pyrus communis* L.)	Sake
Pear brandy	Sauerkraut
Peas (*Pisum sativum* L.)	Scallop
Pecan (*Carya illinoensis* Koch)	Sesame seed (roasted)
Pimento (allspice) (*Pimenta dioica* L. Merr.)	Sherry
Pineapple (*Ananas comosus*)	Shoyu (fermented soya hydrolysate)
Plum (*Prunus* species)	Shrimps
Plum brandy	Southernpea (*Vinga unguiculata* L.)
Pork	Soybean (*Glycine max*. L. merr.)
Potato (*Solanum tuberosum* L.)	Starfruit (*Averrhoa carambola* L.)
Potato chips (American)	Strawberry (*Fragaria* species)
Prickly pear (*Opuntia ficus indica*)	Strawberry wine
Pulasan (*Nephelium ramboutan-ake* (Labill.) Leenh.)	Swiss cheeses
Tamarind (*Tamarindus indica* L.)	*Syzygium* species
Tea	Vanilla
Tequila (*Agave tequilana*)	Vinegar
Tomato (*Lycopersicon esculentum* Mill.)	Walnut (*Juglans* species)
Trassi (cooked)	Water yam (*Dioscorea alata*)
Truffle	Wheaten bread
Turkey	Whisky
Vaccinium species	Wild marjoram (*Origanum vulgare* L.)
	Wine

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. IFRA standard

None.

10. REACH dossier

Available; accessed 10/31/18

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

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

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic activity of amyl alcohol; however, read-across can be made to propyl alcohol (CAS # 71-23-8); see Section V). 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, 2011b). Under the conditions of the study, propyl alcohol was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of amyl alcohol; however, read-across can be made to propyl alcohol (CAS # 71-23-8); see Section V). 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, 2011b). Under the conditions of the study, propyl alcohol was considered to be non-clastogenic to mammalian cells.

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

Additional References: None.

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

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on amyl alcohol. In a non-guideline and non-GLP subchronic toxicity study, ASH/CSE rats (15 rats/sex/group) were administered amyl alcohol via oral gavage at 0, 50, 150, and 1000 mg/kg/day doses for 13 weeks. Additionally, groups of 5 rats/sex/group were administered the test material at doses of 0, 150, and 1000 mg/kg/day, and euthanized after 2 or 6 weeks for hematological and urine analyses. During the study, body weights were measured on days 1, 2, and 6, and then at weekly intervals up to study day 91. At necropsy, organ weights and gross pathology were evaluated. Microscopic examination of the liver and kidneys was performed in all animals but, for all other tissues, it was performed only in half of the animals in the control and highest dose groups. Hematological examination was limited to the controls and highest dose groups, except for week 2, where leucocyte counts were also examined in the 150 mg/kg/day group. During weeks 2, 6, and 12, urinalyses were performed to test for renal concentration and dilution abilities. No treatment-related effects were observed in appearance, behavior, body weight, food and water consumption, or serum analysis. Organ weight examination (performed at weeks 2 and 13) revealed isolated differences at week 2, which recovered during the study duration. In males, relative stomach weight increased dose-dependently, while in females, there was a dose-

dependent decrease in relative spleen and kidney weights. In addition, the study reports an increase in absolute heart weight with no change in relative heart weight in females receiving the highest dose (no further details provided in the study). The hematological changes observed included a lower total WBC count at week 2 in males receiving 150 and 1000 mg/kg/day doses, and a lower hemoglobin concentration at week 13 in males receiving 50 and 1000 mg/kg/day doses. The changes in hemoglobin concentration were not considered to be treatment-related adverse events despite being indicative of mild anemia because the effects were sex-specific and lacked a dose-response. In addition, the highest dose triggered an increase (within historical limits) in percentage of reticulocytes during week 2 (males only) and week 13 (females only). In either sex, no change in differential WBC counts was reported except for a lower percentage of lymphocytes in females receiving the highest dose at week 6. Since observed hematological changes were sex-specific and not supported by other biological changes, these effects were considered to be incidental. During urinalysis, albumin concentration was reported to be similar in all groups including the control group. In males receiving 150 and 1000 mg/kg/day doses, urine cell counts were reportedly lower at week 6. At week 12 in females receiving the highest dose, increased urine specific gravity and lower urine volume were reported. Overall, no treatment-related histopathological changes were observed during the study. Protein casts and calcification were observed in male kidneys, but the frequency of incidence was similar in control and treated groups. Similarly, incidences of fatty change and inflammatory cell infiltration in the liver were comparable between control and treated animals (additional details are not available). Based on these results, the NOAEL was considered to be 150 mg/kg/day due to treatment-related effects that were reported for the highest dose tested.

Therefore, the MOE for the repeated dose toxicity endpoint can be calculated by dividing the amyl alcohol NOAEL by the total systemic exposure for amyl alcohol, 150/0.00018 or 833333.

In addition, the total systemic exposure to amyl alcohol (0.18 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer class I material at the current level of use.

Additional References: Savolainen et al., 1985; ECHA, 2011a (accessed 07/27/18); HSDB, 2018; (accessed 07/27/18); WHO, 1998.

Literature Search and Risk Assessment Completed On: 11/13/18.

11.1.3. Developmental and reproductive toxicity

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

11.1.3.1. Risk assessment. There are limited developmental toxicity data on amyl alcohol. In a developmental toxicity study, groups of 15 female Sprague Dawley rats were exposed to amyl alcohol via inhalation (7 h/day) at 0 or 14000 mg/m^3 (14 mg/L, 3900 ppm) on gestation days (GDs) 1–19. Breeder males and females were kept together for mating, and sperm-positive females (sperm presence = day 0) were selected for exposure. On GD 20, pregnant females were weighed, euthanized, and assessed by gross pathology. The uterus (with ovaries) was removed, and the number of corpora lutea of pregnancy, implantations, resorption sites, and live fetuses was assessed. Fetuses were weighed, sexed, and examined for external malformations. One-half of the fetuses were randomly selected and examined for skeletal malformations, while the remaining fetuses were examined for visceral abnormalities. Overall bodyweight gain (not statistically significant) and feed consumption (statistically significant) were reduced for exposed dams. No treatment-related effects were observed in clinical signs, water intake, number of corpora lutea, number or fetal weights of either sex, implantations, and resorption sites. No malformations were reported. Exposure resulted in non-significant reversible delays in ossification of the caudal vertebrae, sternum (first sternal center and xiphoid), metacarpals, and hind paw phalanges. These variations are frequently seen with growth retardation. The NOAEC for maternal and developmental toxicity was considered to be 14000 mg/m^3 or 4324 mg/kg/day (using standard minute volume and bodyweight values for female Sprague Dawley rats) (Nelson et al., 1989).

Read-across material isoamyl alcohol (CAS # 123-51-3; see Section V) has sufficient developmental toxicity data. An OECD 414/GLP prenatal developmental toxicity study was conducted in pregnant female Wistar rats. Groups of 25 rats/dose were exposed to test material 3-methylbutan-1-ol (isoamyl alcohol) via inhalation, 6 h per day, at concentrations of 0, 0.5, 2.5, or 10 mg/L from days 6–15 p.c. All dams were euthanized, and their fetuses removed and examined on day 20 p.c. The NOAEL for developmental toxicity was considered to be 10 mg/L or 2769 mg/kg/day (using standard minute volume and bodyweight values for female Wistar rats), the highest dose tested (RIFM, 1990b). In another study, an OECD 414/GLP prenatal developmental toxicity study was conducted in pregnant female Himalayan rabbits. Groups of 15 rabbits/dose were exposed to test material 3-methylbutan-1-ol (isoamyl alcohol) via inhalation, 6 h per day, at concentrations of 0, 0.5, 2.5, or 10 mg/L from days 7–19 post insemination. All dams were euthanized, and their fetuses were removed and examined on day 29 post insemination. The NOAEL for developmental toxicity was considered to be 10 mg/L or 1359 mg/kg/day (using standard minute volume and body weight values for female New Zealand rabbits), the highest dose tested (RIFM, 1990c).

Since the developmental toxicity study on the target material amyl alcohol was a single-dose study, data on the read-across material isoamyl alcohol (CAS # 123-51-3) was used as a weight of evidence (WoE) to support the single-dose study. **Therefore, the amyl alcohol MOE for the developmental toxicity endpoint can be calculated by dividing the amyl alcohol NOAEL in mg/kg/day by the total systemic exposure to amyl alcohol, 4324/0.00018 or 24022222.**

There are insufficient reproductive toxicity data on amyl alcohol. In a subchronic toxicity study, groups of 15 ASH/CSE rats/sex/dose were administered amyl alcohol via oral gavage at doses of 0, 50, 150, or 1000 mg/kg/day in corn oil for 13 weeks. In addition to systemic toxicity parameters, reproductive organs (organ weight analysis, macroscopic and microscopic examination) of both sexes were also assessed. No treatment-related adverse effects were observed for the reproductive organs. The NOAEL for reproductive toxicity was considered to be 1000 mg/kg/day, the highest dose tested (Butterworth et al., 1978).

Since insufficient data was available on estrous cycle or spermatology in the subchronic toxicity study conducted on amyl alcohol, read-across material isoamyl alcohol (CAS # 123-51-3; see Section V) has sufficient reproductive toxicity data that can be used to support the reproductive toxicity endpoint. An OECD 422/GLP combined repeated dose toxicity with reproduction/development toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were administered isoamyl alcohol via oral gavage at doses of 0, 30, 100, or 300 mg/kg/day in 1% w/v CMC solution containing 1% Tween 80 in water. Additional satellite groups of 5 rats/sex/dose were administered isoamyl alcohol at doses of 0 or 300 mg/kg/day to serve as the 14-day treatment-free recovery groups. Males were treated for 42 days (14 days before mating, 14 days during the mating period, and 14 days after the end of the mating period), while females were treated for 41–53 days (14 days before mating, throughout mating and gestation periods, up to day 4 of lactation). Females in the recovery group were not subjected to mating. In addition to systemic toxicity, the reproductive toxicity parameters were also assessed. No treatment-related adverse effects were observed on fertility or the development of the fetuses up to the highest dose tested. The NOAEL for reproductive and developmental toxicity was considered to be 300 mg/kg/day, the highest dose tested (ECHA, 2011c; accessed 08/09/18). **Therefore, the**

amyl alcohol MOE for the reproductive toxicity endpoint can be calculated by dividing the isoamyl alcohol NOAEL in mg/kg/day by the total systemic exposure to amyl alcohol, 300/0.00018 or 1666667.

In addition, the total systemic exposure to amyl alcohol (0.18 μg/kg/day) is below the TTC (30 μg/kg/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.

$$\text{NOAEL (mg/kg/day)} = \frac{\text{NOAEC (mg/L)}\times\text{UF}\times\text{MV}\times\text{(T/day)}}{\text{Body Weight (kg)}} = \frac{2.5\times1\times1.17\times360}{310} = 340\ \text{mg/kg/day}$$

$$\text{NOAEL (mg/kg/day)} = \frac{\text{NOAEC (mg/L)}\times\text{UF}\times\text{MV}\times\text{(T/day)}}{\text{Body Weight(kg)}} = \frac{10\times1\times1.17\times360}{3.10} = 1359\ \text{mg/kg/day}$$

Where: Uncertainty factor (UF) is 1 (ECHA, 2012).

Minute volume (MV) is 1.17 L/min for female New Zealand rabbits (US EPA, 1998)
Exposure Time (T/day) is 360 min (6 h/day)
Body weight (BW) is 3.10 kg (average for female New Zealand rabbits) (US EPA, 1998)

Additional References: ECHA, 2011a (accessed 07/27/18); Api et al., 2015

Literature Search and Risk Assessment Completed On: 10/09/18.

11.1.4. Skin sensitization

Based on the existing data and read-across materials butyl alcohol (CAS # 71-36-3) and propyl alcohol (CAS # 71-23-8), amyl alcohol does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. Insufficient skin sensitization studies are available for amyl alcohol. Based on the existing data and read-across materials butyl alcohol (CAS # 71-36-3; see Section V) and propyl alcohol (CAS # 71-23-8; see Section V), amyl 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 v4.1). Amyl alcohol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens assay (ECHA, 2011a; accessed 10/11/18). Read-across material butyl alcohol was found to be negative in an *in vitro* 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, 2011d; accessed 07/24/18). 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 with read-across material butyl alcohol 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 read-across material 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 and Gfeller, 2008; Wass and Belin, 1990; Natsch and Haupt, 2013; McKim et al., 2010; Roberts et al., 2007.

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

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, amyl alcohol would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for amyl 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, amyl alcohol does not present a concern for phototoxicity or photoallergenicity.

11.1.6. 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.

11.1.7. Local respiratory toxicity

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

11.1.7.1. Risk assessment. The inhalation exposure studies used in the reproductive toxicity endpoint section (Nelson et al., 1989; ECHA Dossier: 3-methylbutan-1-ol (ECHA, 2011c; RIFM, 1990b; RIFM, 1990c); 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 amyl alcohol. Based on the Creme RIFM Model, the inhalation exposure is 0.00086 mg/day. This exposure is 1628 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; Scala and Burtis, 1973; Kane et al., 1980; Nelson et al., 1989; Savolainen et al., 1985; Hansen and Nielsen, 1994; Frantik et al., 1994; Silver (1992); RIFM, 1973.

Literature Search and Risk Assessment Completed On: 03/01/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of amyl 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, amyl 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).

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	455.1			1,000,000	0.4551	

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify amyl 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.

11.2.2. Risk assessment

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

11.2.3. Key studies

11.2.3.1. Biodegradation. RIFM, 2001: The biodegradability of the test material was evaluated according to ISO Method 9439 D. Under the conditions of this study, biodegradation of 100% was observed after 28 days.

11.2.3.2. Ecotoxicity. RIFM, 1990a: A *Daphnia magna* acute toxicity study was conducted according to the C2 Annex V 79/831 EEC method. The 48-h EC50 was reported to be 341.2 mg/L.

11.2.4. Other available data

Amyl alcohol has been registered under REACH with no additional data available at this time.

11.2.5. Risk assessment refinement

Since amyl alcohol has passed the screening criteria (Tier 1), 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.3	1.3
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 0.4551 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.

12. 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.2019.110892.

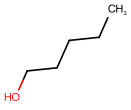
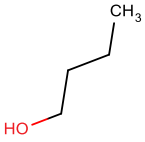
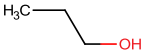
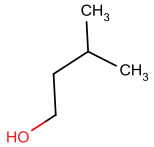
Appendix

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	Read-across Material	Read-across Material
Principal Name	Amyl alcohol	Butyl alcohol	Propyl alcohol	Isoamyl alcohol
CAS No.	71-41-0	71-36-3	71-23-8	123-51-3
Structure				
Similarity (Tanimoto Score)		0.70	0.45	0.74
Read-across Endpoint		• Skin Sensitization	• Skin Sensitization • Genotoxicity	• Repeated dose
Molecular Formula	$C_5H_{12}O$	$C_4H_{10}O$	C_3H_8O	$C_5H_{12}O$
Molecular Weight	88.15	74.12	60.10	88.15
Melting Point (°C, EPI Suite)	−49.96	−62.33	−74.95	−61.49
Boiling Point (°C, EPI Suite)	136.95	113.91	89.96	123.17
Vapor Pressure (Pa @ 25 °C, EPI Suite)	353	893	3.09E+003	512
Log Kow (KOWWIN v1.68 in EPI Suite)	1.51	0.88	0.25	1.16
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	2.2E+004	6.32E+004	1E+006	2.67E+004
J_{max} (μg/cm^2/h, SAM)	1028.17	1586.14	12813.05	733.512
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.34E+000	1.01E+000	7.62E-001	1.34E+000
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found		• No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found		• No alert found	
Carcinogenicity (ISS)	• Non-Carcinogen (low reliability)		• Non-Carcinogen (low reliability)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found		• No alert found	
In Vitro Mutagenicity (Ames, ISS)	• No alert found		• No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found		• No alert found	
Oncologic Classification	• Not classified		• Not classified	
Repeated Dose Toxicity				
Repeated dose (HESS)	• Not categorized			• Not categorized
Skin Sensitization				
Protein Binding (OASIS v1.1)	• No alert found	• No alert found	• No alert found	
Protein binding (OECD)	• No alert found	• No alert found	• No alert found	
Protein Binding Potency				

	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	• Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found	• No alert found	• No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found	• 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	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on amyl alcohol (CAS # 71-41-0). 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), isoamyl alcohol (CAS # 123-51-3), and propyl alcohol (CAS # 71-23-8) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Butyl alcohol (CAS # 71-36-3) was used as a read-across analog for the target material amyl alcohol (CAS # 71-41-0) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of saturated straight chain alcohols.
  - o The target substance and the read-across analog share a hydroxyl group attached to the saturated straight carbon chain.
  - o The key difference between the target substance and the read-across analog is that in the target substance, the hydroxyl group is attached to the C5 carbon chain, whereas in the read-across material it is attached to the C4 carbon chain. 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 structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Isoamyl alcohol (CAS # 123-51-3) was used as a read-across analog for the target material amyl alcohol (CAS # 71-41-0) for the repeated dose toxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of 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 branched aliphatic chain while the target substance has a straight chain. 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 structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Propyl alcohol (CAS # 71-23-8) was used as a read-across analog for the target material amyl alcohol (CAS # 71-41-0) for the skin sensitization and genotoxicity endpoints.
  - o The target substance and the read-across analog are structurally similar and belong to the class of 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 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 C5 carbon chain. 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 structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

Aasmoe, L., Winberg, J.-O., Aarbakke, J., 1998. The role of liver alcohol dehydrogenase isoenzymes in the oxidation of glycolethers in male and female rats. Toxicol. Appl. Pharmacol. 150 (1), 86–90.

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

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.

Butterworth, K.R., Gaunt, I.F., Heading, C.E., Grasso, P., Gangolli, S.D., 1978. Short-term toxicity of n-amyl alcohol in rats. Food Cosmet. Toxicol. 16 (3), 203–207.

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.

ECHA, 2011a. Registration dossier: pentan-1-ol. Retrieved from: https://echa.europa.eu/en/registration-dossier/-/registered-dossier/2115.

ECHA, 2011b. Registration dossier: propan-1-ol. Retrieved from: https://echa.europa.eu/registration-dossier/-/registered-dossier/14586/1.

ECHA, 2011c. Registration dossier: 3-Methylbutan-1-ol. Retrieved from: https://echa.europa.eu/lt/registration-dossier/-/registered-dossier/13936/1 .

ECHA, 2011d. Registration dossier: butan-1-ol. 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. Read-across assessment framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.

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.

Gaillard, D., Derache, R., 1965. Metabolism of different alcohols, present in alcoholic beverages, in the rat. Trav. Soc. Pharm. Montpellier. 25 (1), 51–62.

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

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.

Hansen, L.F., Nielsen, G.D., 1994. Sensory irritation, pulmonary irritation and structure-activity relationships of alcohols. Toxicology 88 (1–3), 81–99.

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.

HSDB, 2018. Hazardous Substances Data Base. Retrieved at: https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+111.

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

Iwersen, S., Schmoldt, A., 1995. ADH Independent metabolism of aliphatic alcohols: comparison of oxidation and glucuronidation. In: Advances in Forensic Science. 13, vol 4. pp. 19–22.

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.

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

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.

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., Khan, A., Krieg Jr., E.F., Hoberman, A.M., 1989. Developmental toxicology evaluation of 1-pentanol, 1-hexanol, and 2-ethyl-1-hexanol administered by inhalation to rats. J. Am. Coll. Toxicol. 8 (2), 405–410.

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), 1973. Result of the trade-toxicological preliminary test on amyl alcohol (n-pentanol). Unpublished report from BASF. RIFM report number 55310. RIFM, Woodcliff Lake, NJ, USA.

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), 1990. Determination of the Acute Effect of Amyl Alcohol on Daphnia Magna. Unpublished report from BASF. RIFM report number 55309. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1990. Prenatal Toxicity of Isoamyl Alcohol in Wistar Rats after Inhalation. Unpublished report from BASF. RIFM report number 55360. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 1990. Prenatal Toxicity of Isoamyl Alcohol in Rabbits after Inhalation. Unpublished report from BASF. RIFM report number 55361. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2001. Biodegradation of Amyl Alcohol. Unpublished report from BASF. RIFM report number 55308. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc), 2015. Exposure Survey 06, February 2015.

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.

Savolainen, H., Pfaffli, P., Elovaara, E., 1985. Blood and brain n-pentanol in inhalation exposure. Acta Pharmacol. Toxicol. 56, 260–264.

Scala, R.A., Burtis, E.G., 1973. Acute toxicity of a homologous series of branched-chain primary alcohols. Am. Ind. Hyg. Assoc. J. 34 (11), 493–499.

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.

Strubelt, O., Deters, M., Pentz, R., Siegers, C.-P., Younes, M., 1999. The toxic and metabolic effects of 23 aliphatic alcohols in the isolated perfused rat liver. Toxicol. Sci. 49 (1), 133–142.

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.

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.