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Short review

RIFM FRAGRANCE INGREDIENT SAFETY ASSESSMENT, 2-Methylbutanol, CAS Registry Number 137-32-6

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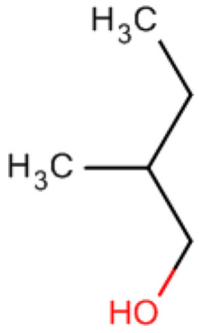

Abbreviation list:
2-Box Model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF- Assessment Factor
BCF- Bioconcentration Factor
DEREK- Derek nexus is an *in silico* tool used to identify structural alerts
DST- Dermal Sensitization Threshold
ECHA-European Chemicals Agency
EU – Europe/European Union
GLP- Good Laboratory Practice
IFRA- The International Fragrance Association
LOEL- Lowest Observable Effect Level
MOE- Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA – North America
NESIL- No Expected Sensitization Induction Level
NOAEC- No Observed Adverse Effect Concentration
NOAEL- No Observed Adverse Effect Level
NOEC- No Observed Effect Concentration
OECD- Organisation for Economic Co-operation and Development
OECD TG- Organisation for Economic Co-operation and Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- quantitative risk assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

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

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from the suitable read across analog butyl alcohol (CAS # 71-36-3) show that this material does not have skin sensitization potential. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (1.4 mg/day). The developmental and reproductive toxicity endpoints were completed using isoamyl alcohol (CAS # 123-51-3) as a suitable read across analog, which provided a MOE > 100. The repeated dose toxicity endpoint was completed using isoamyl alcohol (CAS # 123-51-3) as a suitable read across analog, which provided a MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoint was completed as described in the RIFM Framework.

Human Health Safety Assessment

Genotoxicity: Not genotoxic	(Kreja and Seidel, 2002)
Repeated Dose Toxicity: NOAEL = 1250 mg/kg/day	(Schilling et al., 1997)
Developmental and Reproductive Toxicity: NOAEL = 300 mg/kg/day	(ECHA REACH Dossier: 3-methylbutan-1-ol)
Skin Sensitization: Not a sensitization concern	(Ryan et al., 2000)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM DB)

(*continued on next page*)

(*continued*)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC	
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 93% (OECD 310)	(REACH Dossier; Accessed 10/9/14)
Bioaccumulation: Screening Level: 3.2 l/kg	(EpiSuite ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 523.6 mg/l	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-Level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 523.6 mg/l	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.5236 μg/L	
• Revised PEC/PNECs (2011 IFRA VoU): North America and Europe: Not Applicable; Cleared at Screening Level	

1. Identification

1. **Chemical Name:** 2-Methylbutanol
2. **CAS Registry Number:** 137-32-6
3. **Synonyms:** 1-Butanol, 2-methyl-; sec-Butylcarbinol; 2-Methylbutanol; (±) 2-Methyl-1-butanol; 2-Methylbutyl alcohol; Active amyl alcohol; アルカノール(C = 5~38); 2-Methylbutan-1-ol
4. **Molecular Formula:** $C_5H_{12}O$
5. **Molecular Weight:** 88.15
6. **RIFM Number:** 6275

2. Physical data

1. **Boiling Point:** 123.17 °C [EPI Suite]
2. **Flash Point:** 110.00 °F TCC (43.33 °C)*
3. **Log K_{OW}:** 1.26 [EPI Suite]
4. **Melting Point**: −61.49 °C [EPI Suite]
5. **Water Solubility:** 32200 mg/L [EPI Suite]
6. **Specific Gravity:** 0.81500 to 0.82000 @ 25.00 °C*
7. **Vapor Pressure:** 3.16 mmHg @ 20 °C [EPI Suite 4.0], 2.5 mm Hg 20C [FMA database], 4.54 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** No absorbance in the region 290–400 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A clear, colorless liquid with a medium roasted, wine, onion, fruity odor.*

*http://www.thegoodscentscompany.com/data/rw1059521.html, retrieved on 3/10/15.

3. Exposure

1. **Volume of Use (worldwide band):** < 0.1 metric tons per year (IFRA, 2011)
2. **Average Maximum Concentration in Hydroalcoholics:** 0.001% (IFRA, 2007)
3. **97.5**th **Percentile:** 0.007% (IFRA, 2007)
4. **Dermal Exposure*:** 0.00018 mg/kg/day (IFRA, 2007)
5. **Oral Exposure:** Not applicable
6. **Inhalation Exposures**:** 0.000011 mg/kg/day or 0.00065 mg/day (IFRA, 2007)
7. **Total Systemic Exposure (Dermal + Inhalation):** (0.00018 mg/kg/day × 5.2%) + 0.000011 mg/kg/day = 0.000020 mg/kg/day

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

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

4. Derivation of systemic absorption

1. **Dermal:** 100%
2. **Oral:** Data not available — not considered.
3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Ramer classification:** Class I, Low

Expert judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
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2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** isoamyl alcohol (CAS # 123-51-3)
   c. **Developmental and Reproductive Toxicity:** isoamyl alcohol (CAS # 123-51-3)
   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

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

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

2-Methylbutanol is reported to occur in the following foods* and in some natural complex substances (NCS):

Acerola (Malpighia).
Anise brandy.
Apple brandy (Calvados).
Apple fresh (Malus species).
Apple processed (Malus species).
Apricot (Prunus armeniaca L.).
Arrack.
Artichoke.
Artocarpus species.
Banana (Musa sapientum L.).
Beans.
Beef.
Beer.
Bilberry wine.
Black currants (Ribes nigrum L.).
Blackberry brandy.
Blue cheeses.
Cabbage (*Brassica oleracea*).
Camomile.
Cape gooseberry (Physalis peruviana L.).
Capsicum species.
Cardamom (Ellettaria cardamomum Maton.).
Cheese, various types.
Cherry brandy.
Cider (apple wine).
Citrus fruits.
Cloudberry (Rubus chamaemorus L.).
Durian (Durio zibethinus).
Elderberry (Sambucus nigra L.).
Filbert, hazelnut (Corylus avellano).
Grape (Vitis species).
Grape brandy.
Guava and feyoa.
Guava wine.
Honey.
Hop (Humulus lupulus).
Katsuobushi (dried bonito).
Litchi (Litchi chinensis Sonn.).
Maize (Zea mays L.).
Malt.
Mangifera species.
Melon.
Mentha oils.
Mezcal (Agave salmiana).
Milk and milk products.
Mulberry spirit (Mouro).
Mushroom.
Nectarine.
Olive (Olea europaea).
Papaya (Carica papaya L.).
Passion fruit (passiflora species).
Passion fruit wine.
Peach (Prunus persica L.).
Peanut (*Arachis hypogaea* L.).
Pear (Pyrus communis L.).
Pear brandy.
Peas (Pisum sativum L.).
Pimento (allspice) (Pimenta dioica L. Merr.).
Pineapple (Ananas comosus).
Plum (Prunus species).
Plum brandy.
Pork.
Potato (Solanum tuberosum L.).
Prickly pear (Opuntia ficus indica).
Quince, marmelo (Cydonia oblonga Mill.).
Raspberry brandy.
Raspberry, blackberry and boysenberry.
Rooibos tea (Aspalathus linearis).
Rum.
Rye bread.
Sake.
Scallop.
Sherry.
Shoyu (fermented soya hydrolysate).
Shrimps.
Soybean (Glycine max. L. merr.).
Starfruit (Averrhoa carambola L.).
Strawberry (Fragaria species).
Strawberry wine.
Tapereba, caja fruit (Spondias lutea L.).
Tea.
Tequila (Agave tequilana).
Tomato (Lycopersicon esculentum Mill.).
Trassi (cooked).
Truffle.
Vaccinium species.
Vanilla.
Vinegar.
Walnut (Juglans species).
Wheaten bread.
Whisky.
Wine.

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

8. IFRA standard

None.

9. REACH dossier

Available, accessed on 09/16/14.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. The mutagenicity of 2-methylbutanol was assessed in an *in vitro* mammalian gene mutation assay conducted equivalent to OECD TG 476. The Chinese hamster lung fibroblast cell line V79 was exposed to 2-methylbutanol at concentrations of up to 46 mM in 10 ml of medium with and without metabolic activation. Cells were exposed for two hours before being split into parallel cultures to ensure growth of independent mutants in 6-thioguanine-containging medium for seven days. No concentration-dependent increase in spontaneous HPRT frequency was observed (Kreja and Seidel, 2002). Under the conditions of the study, 2-methylbutanol

was considered not mutagenic in mammalian cells. As a weight of evidence, read across material isobutyl alcohol (CAS # 78-83-1; see Section 5) was also found negative for mutagenicity in an Ames test conducted by the National Toxicology Program (NTP); this conclusion can be extended to 2-methylbutanol. 2-Methylbutanol does not present a concern for mutagenicity.

The clastogenicity of 2-methylbutanol was assessed in an *in vitro* chromosome aberration assay conducted equivalent to OECD TG 476. Chinese hamster lung fibroblasts cells (V79) were treated with 2-methylbutanol at the concentrations of 23 and 45 mM in the presence and absence of metabolic activation. No increase in spontaneous micronuclei frequency was observed (Kreja and Seidel, 2002). Under the conditions of the study, 2-methylbutanol was considered not clastogenic in mammalian cells. As a WoE approach, read across material isoamyl alcohol (CAS # 123-51-3; See Section 5) was found negative for clastogenicity in a GLP compliant in vivo micronucleus assay conducted in accordance with OECD TG 474 further demonstrating the lack of clastogenic potential for 2-methylbutanol (RIFM, 2007).

Based on the available data, 2-methylbutanol does not present a concern for genotoxic potential.

Additional References: Nakajima et al., 2006.

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

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 2-methylbutanol. There are sufficient repeated dose toxicity data on read across material isoamyl alcohol (CAS# 123-51-3; see Section 5). A gavage OECD 422 combined repeated dose toxicity study was conducted on groups of 12 male and female Sprague-Dawley rats/group and they were administered test material isoamyl alcohol via gavage at doses of 0, 30, 100 and 300 mg/kg/day, an additional satellite recovery group of 5 animals/sex/group were administered test material at doses of 0 and 300 mg/kg/day. The NOAEL was determined to be 100 mg/kg/day, based on reduced bodyweight gain in the males (ECHA REACH Dossier: 3-methylbutan-1-ol). In another study, an OECD/GLP 408, 13-week study was conducted on groups of 10 SPF-Wistar, Chbb:THOM rats/sex/group and they were administered test material isoamyl alcohol via drinking water at concentrations of 0, 1000 ppm (about 80 mg/kg/day), 4000 ppm (about 340 mg/kg/day) and 16,000 ppm (about 1250 mg/kg/day). Although there were slight alterations in the hematological parameters, the NOAEL was determined to be 16000 ppm or 1250 mg/kg/day, the highest dose tested, since the effects were not considered to be treatment-related (Schilling et al., 1997; #32049). In another study, groups of 15 rats/sex/group were gavaged with test material isoamyl alcohol at doses of 0, 150, 500 and 1000 mg/kg/day for 17 weeks. There were no adverse effects reported due to the test material administration up to the highest dose tested. Thus, the NOAEL was determined to be 1000 mg/kg/day (Carpaninini, 1973). Since no adverse effects were reported among the animals during the longer duration 13 and 17 week studies, the NOAEL was considered to be 1250 mg/kg/day. **Therefore, the 2-methylbutanol MOE for the repeated dose toxicity endpoint can be calculated by dividing the isoamyl alcohol NOAEL in mg/kg/day by the total systemic exposure to 2-methylbutanol, 33/0.000019 or 1736842. In addition, the total systemic exposure for 2-methylbutanol (0.19 μg/kg/day) is below the TTC (30 μg/kg bw/day) for the repeated dose toxicity endpoint at the current level of use.**

Additional References: None.

Literature Search and Risk Assessment Completed on: 6/1/2017.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are no developmental and reproductive toxicity data on 2-methylbutanol. There are sufficient developmental and reproductive toxicity data on read across material isoamyl alcohol (CAS# 123-51-3; see Section 5).

There is an OECD 414 developmental toxicity study conducted on 15 pregnant female Himalayan rabbits/group. The animals were administered test material isoamyl alcohol via inhalation at doses of 0, 0.5, 2.5 and 10 mg/l, equivalent to 0, 68, 341 and 1365 mg/kg/day, respectively, according to standard minute volume and bodyweight parameters of New Zealand rabbits. The NOAEL for developmental toxicity was determined to be 10 mg/l or 1365 mg/kg/day, the highest dose tested (RIFM, 1990). In another study, an OECD 414 developmental toxicity study conducted on groups of 25 pregnant female Wistar rats/group were administered test material isoamyl alcohol at doses of 0, 0.5, 2.5 and 10 mg/l, equivalent to 0, 135, 674 and 2695 mg/kg/day, respectively, according to standard minute volume and bodyweight parameters of Wistar rats. The NOAEL for developmental toxicity was determined to be 10 mg/l or 2695 mg/kg/day, the highest dose tested (RIFM, 1990). Subsequently, an OECD 422 gavage combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted on groups of 12 Sprague-Dawley rats/sex/group were administered test material isoamyl alcohol at doses of 0, 30, 100 and 300 mg/kg/day. There were no signs of toxicity towards the development of the fetus up to the highest dose tested (ECHA REACH Dossier: 3-methylbutan-1-ol). Thus, the NOAEL was determined to be 300 mg/kg/day, the highest dose tested. Due to uncertainty involved in the dose conversion from inhalation studies, the most conservative NOAEL of 300 mg/kg/day from the OECD 422 gavage study was considered for the developmental toxicity endpoint.

There are sufficient reproductive toxicity data on isoamyl alcohol. An OECD 422 gavage study (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test) was conducted on groups of 12 Sprague-Dawley rats/sex/group which were administered the test material isoamyl alcohol at doses of 0, 30, 100 and 300 mg/kg/day. There were no signs of toxicity towards the reproductive performance of the parental generation animals up to the highest dose tested (ECHA REACH Dossier: 3-methylbutan-1-ol). Thus the NOAEL for reproductive toxicity endpoint was considered to be 300 mg/kg/day, the highest dose tested. T**herefore, the MOE for 2-methylbutanol for the developmental and reproductive toxicity endpoint is equal to the isoamyl alcohol NOAEL in mg/kg/day divided by the total systemic exposure to 2-methylbutanol, 300/0.00019 or 1578947.**

In addition, the total systemic exposure to 2-methylbutanol (0.19 μg/kg/day) is below the TTC (30 μg/kg bw/day) at the current level of use for the developmental and reproductive toxicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 6/1/2017.

10.1.4. Skin sensitization

Based on read across to butyl alcohol (CAS # 71-36-3), 2-methylbutanol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. No skin sensitization studies are available for 2-methylbutanol. Based on read across to butyl alcohol (CAS # 71-36-3), 2-methylbutanol does not present a concern for skin sensitization. The chemical structures of these materials indicate that they would not be expected to react with skin proteins

(Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). Butyl alcohol was found to be negative in *in vitro* Direct Peptide Reactivity Assay (DPRA), KeratinoSens™ and U937-CD86 test (Natsch et al., 2013). Moreover, in a murine local lymph node assay (LLNA), butyl alcohol was found to be negative at maximum tested levels of 20% or 5000 μg/cm^2 (Ryan et al., 2000). Additionally, human maximization test with 4% or 2760 μg/cm^2 butyl alcohol did not show any positive reactions (RIFM, 1976). Based on the weight of evidence from the negative results of read across butyl alcohol in experiments representing each key event of the Adverse Outcome Pathway (AOP) for skin sensitization (OECD, 2012), 2-methylbutanol does not present a concern for skin sensitization.

Additional References: None.

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

10.1.5. Phototoxicity/photoallergenicity

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

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-methylbutanol in experimental models. UV absorption spectra for 2-methylbutanol indicate no absorbance between 290 and 400 nm; the corresponding molar absorption coefficient is well below the benchmark of concern for phototoxic effects, 1000 L mol^{-1} · cm^{-1} (Henry et al., 2009). Based on the lack of absorbance, 2-methylbutanol would not be expected to present a concern for phototoxicity or photoallergenicity.

Additional References: None.

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

10.1.6. Local respiratory toxicity

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

10.1.6.1. Risk assessment. There are limited inhalation data available on 2-methylbutanol. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.007%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the combined inhalation exposure would be 0.00065 mg/day, as calculated by RIFM's 2-Box Model and further refined using the Multiple Path Particle Deposition Model, using the 97.5th percentile IFRA survey hydroalcoholic use value.

This value is 2154 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Smyth et al., 1962; RIFM, 1979.

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

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 2-methylbutanol was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 2-methylbutanol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC <1).

A screening-level hazard assessment using EPISUITE ver 4.1 did not identify 2-methylbutanol as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

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

10.2.3. Key studies

10.2.3.1. Biodegradation. No data available.

10.2.3.2. Ecotoxicity. No data available.

10.2.3.3. Other available data. 2-methylbutanol has been registered under REACH and additional data is available (ECHA REACH Dossier: 2-Methylbutanol):

Ready biodegradability of 2-methylbutanol was evaluated according to the OECD 310 method. Biodegradation of 93% was observed after 28 days.

A 96 h acute fish (*Danio rerio*) study was conducted according to the OECD 203 method under semi-static conditions and the LC50 was reported to be > 120 mg/l.

An acute *Daphnia magna* study was conducted according to the OECD 202 method under static conditions. The 48 h EC50 was reported to be > 173 mg/l.

An algae inhibition test was conducted according to the OECD 201 method. The 72 h EC50 based on yield was reported to be 113 mg/l.

11. Risk assessment refinement

Since 2-Methylbutanol has passed the screening criteria, measured data is included in this document 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)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	523.6 mg/l			1,000,000	0.5236 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.26	1.26
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.5236 µg/L. The revised PEC/PNECs for EU and NA: Not Applicable; Cleared at Screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

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

12. Literature Search*

- **RIFM database:** target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov/ntp_tox/index.cfm
- OECD Toolbox
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC** (http://monographs.iarc.fr):
- **OECD SIDS:** http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor:** http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS:** http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary:** http://cfpub.epa.gov/hpv-s/
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base:** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

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

This is not an exhaustive list.

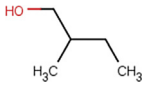
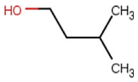
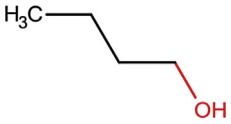
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.06.018.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.06.018.

Appendix

	Target Material	Read across Materials	
Principal Name	2-Methylbutanol	Isoamyl alcohol	Butyl alcohol
CAS No.	137-32-6	123-51-3	71-36-3
Structure			
3D Structure	http://www.thegoodscentscompany.com/opl/137-32-6.html	http://www.thegoodscentscompany.com/opl/123-51-3.html	http://www.thegoodscentscompany.com/opl/71-36-3.html
Read-across endpoint		• Repeated Dose • Devel/Repro • Genotoxicity (as weight of evidence)	•Skin Sensitization
Molecular Formula	C5H12O	C5H12O	C4H10O
Molecular Weight	88.15	88.15	74.12
Melting Point (°C, EPISUITE)	−61.49	−61.49	−62.33
Boiling Point (°C, EPISUITE)	123.17	123.17	113.91
Vapor Pressure (Pa @ 25°C, EPISUITE)	605.3	512	104.3

(*continued*)

	Target Material	Read across Materials	
Log Kow (KOWWIN v1.68 in EPISUITE)	1.26	1.26	0.88
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	3.22e+004	4.158e+004	7.67e+004
J_{max} (mg/cm^2/h, SAM)	1026.435936	1094.357328	1586.140
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.34357	1.34357	9.99
Similarity (Tanimoto score)[a]		53%	40%
Genotoxicity			
DNA binding (OASIS v 1.1 QSAR Toolbox 3.4)	No alert found	No alert found	
DNA binding by OECD QSAR Toolbox (3.4)	No alert found	No alert found	
Carcinogenicity (genotox and non-genotox) alerts (ISS)	Carcinogen (Low reliability)	Non carcinogen (Low reliability)	
DNA alerts for Ames, MN, CA by OASIS v 1.1	No alert found	No alert found	
In-vitro Mutagenicity (Ames test) alerts by ISS	No alert found	No alert found	
In-vivo mutagenicity (Micronucleus) alerts by ISS	No alert found	No alert found	
Oncologic Classification	Not classified	Not classified	
Repeated Dose Toxicity			
Repeated dose (HESS)	Not categorized	Not categorized	
Developmental and Reproductive Toxicity			
***ER binding* (*OECD*)**	Non binder, non-cyclic structure	Non binder, non-cyclic structure	
Developmental toxicity model (CAESAR v2.1.6)	Toxicant (good reliability)	Toxicant (good reliability)	
Skin Sensitization			
Protein binding by OASIS v1.1	No alert found		No alert found
Protein binding by OECD	No alert found		No alert found
Protein binding potency	Not possible to classify		Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	No alert found		No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	Non Sensitizer (Good reliability)		Non Sensitizer (Experimental value)
Metabolism			
***Rat liver S9 metabolism simulator* (*OECD*)**	See Supplemental Data 1	See Supplemental Data 2	No metabolites found

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

Summary:

There are insufficient toxicity data on 2-methylbutanol (RIFM # 6275, CAS # 137-32-6). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

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

Conclusion/Rationale

- Isoamyl alcohol (analog) was used as a read-across analog for 2-methylbutanol (target) based on:
  - The target and analog are structural isomers. They both belong to the generic class of alcohols, specifically, alcohols branched chain saturated.
  - The target and analog are primary alcohols with a branch.
  - The key difference is in the position of the methyl group. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER binding. ER binding is molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.
- Butyl alcohol (analog) was used as a read-across analog for 2-methylbutanol (target) based on:
  - The target and analog are structural isomers. They both belong to the generic class of alcohols, specifically, alcohols branched chain saturated.

- The target is primary alcohols with a branch while analog is straight chain primary alcohol.
- The key difference is in the position of the methyl group. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
- The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER binding. ER binding is molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
- The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

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