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Short review

RIFM fragrance ingredient safety assessment, 3-methyl-1-pentanol, CAS Registry Number 589-35-5

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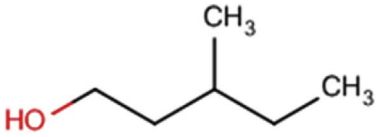
Version: 080717. This version replaces any previous versions.

Name: 3-Methyl-1-pentanol

CAS Registry Number: 589-35-5



Abbreviation list:

2-Box Model- a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration

AF- Assessment Factor

BCF- Bioconcentration Factor

Creme RIFM model- The Creme RIFM model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 2017) compared to a deterministic aggregate approach.

DEREK- Derek nexus is an *in silico* tool used to identify structural alerts

DST- Dermal Sensitization Threshold

ECHA- European Chemicals Agency

EU- Europe/European Union

GLP- Good Laboratory Practice

IFRA- The International Fragrance Association

LOEL- Lowest Observable Effect Level

MOE- Margin of Exposure

MPPD- Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition

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

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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
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- Ultra Violet/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 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 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 guidance relevant to human health and environmental protection.

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

The material (3-methyl-1-pentanol) was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from the read-across analog isoamyl alcohol (CAS # 123-51-3) show that 3-methyl-1-pentanol is not genotoxic and provided a MOE > 100 for the repeated dose toxicity endpoint. The developmental and reproductive toxicity endpoint was completed using isoamyl alcohol (CAS # 123-51-3) and 3,7-dimethyl-1-octanol (CAS # 106-21-8) as read-across analogs, which provided a MOE > 100. Data from the read-across analogs isononyl alcohol (isomer unspecified) (CAS # 27458-94-2) and isoamyl alcohol (CAS # 123-51-3) show that 3-methyl-1-pentanol 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 phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated, 3-methyl-1-pentanol was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (Kreja and Seidel, 2002; RIFM, 2007)

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 sensitizing. (ECHA REACH Dossier: Isononyl alcohol; Kern et al., 2010; RIFM, 1976; RIFM, 1973)

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)

Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening Level: 3.13 (BIOWIN 3) (US EPA, 2012a)

Bioaccumulation: Screening Level: 6.62 l/kg (US EPA, 2012a)

Ecotoxicity: Screening Level: LC50: 227.4 mg/l (RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-Level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint: 227.4 mg/l (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.2274 μg/L

- **Revised PEC/PNECs (2011 IFRA VoU)**: North America and Europe: Not Applicable; cleared at screening level

1. Identification

1. **Chemical Name**: 3-Methyl-1-pentanol
2. **CAS Registry Number**: 589-35-5
3. **Synonyms**: 2-Ethyl-4-butanol; 3-Methyl-1-pentanol; 1-Pentanol, 3-methyl-; Methyl Pentanol-3; 3-Methylpentan-1-ol
4. **Molecular Formula**: $C_6H_{14}O$
5. **Molecular Weight**: 102.18
6. **RIFM Number**: 6154

2. Physical data

1. **Boiling Point**: 145.86 °C (US EPA, 2012a)
2. **Flash Point**: 138.00 °F TCC (58.89 °C)*
3. **Log K_{OW}**: 1.75 (US EPA, 2012a)
4. **Melting Point**: −49.23 °C (US EPA, 2012a)
5. **Water Solubility**: 11950 mg/L (US EPA, 2012a)
6. **Specific Gravity**: 0.82300 @ 25.00 °C*
7. **Vapor Pressure**: 1.16 mmHg @ 20 °C [EPI Suite 4.0], 0.7 mm Hg 20C [FMA database], 1.7 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra**: No significant absorbance in the region 290–700 nm; molar absorption below the benchmark (1000 L mol^{-1} cm^{-1}).
9. **Appearance/Organoleptic**: Colorless liquid, vinous earthy green odor, giving a bitter odor impression sometimes referred to as "metallic" (Arctander, Volume II, 1969)

*http://www.thegoodscentscompany.com/data/rw1011821.html,

retrieved 2/25/15.

3. Exposure

1. **Volume of Use (worldwide band)**: < 0.1 metric tons (IFRA, 2011)
2. **95th Percentile Concentration in Hydroalcoholics**: 0.00015% (RIFM, 2016)
3. **Inhalation Exposure***: 0.00000010 mg/kg/day or 0.0000044 mg/day (RIFM, 2016)
4. **Total Systemic Exposure****: 0.000016 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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, 2017; 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

2. **Analogs Selected**:
   a. **Genotoxicity**: Isoamyl alcohol (CAS # 123-51-3)
   b. **Repeated Dose Toxicity**: Isoamyl alcohol (CAS # 123-51-3)
   c. **Developmental and Reproductive Toxicity**: Isoamyl alcohol (CAS # 123-51-3); 3,7-dimethyl-1-octanol (CAS # 106-21-8)
   d. **Skin Sensitization**: Isononyl alcohol (isomer unspecified) (CAS # 27458-94-2); isoamyl alcohol (CAS# 123-51-3)
   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)

3-Methyl-1-pentanol is reported to occur in the following foods*:
Allium species
Apple brandy (*Calvados*)
Apple fresh (*Malus* species)
Bilberry wine
Camomile
Cashew apple wine
Cheese, various types
Cider (apple wine)
Cocoa category
Dalieb, palmyra palm fruit (*Borassus aethiopum* L.)
Grape brandy
Guava wine
Lamb's lettuce (Valerianella locusta)
Litchi wine
Mangifera species
Pear brandy
Plum brandy
Potato (Solanum tuberosum L.)
Prickly pear (Opuntia ficus indica)
Sherry
Starfruit (Averrhoa carambola L.)
Strawberry wine
Tomato (Lycopersicon esculentum Mill.)
Vanilla
Walnut (*Juglans* species)
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

Pre-registered for 11/30/2010; No dossier available as of 08/07/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 3-methyl-1-pentanol does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 3-Methyl-1-pentanol was tested in the BlueScreen assay and was found to be negative for genotoxicity in the presence and the absence of metabolic activation (RIFM, 2013b). There are no studies assessing the mutagenic potential of 3-methyl-1-pentanol; however, read-across can be made to isoamyl alcohol (CAS # 123-51-3; see Section 5). The mutagenic activity of isoamyl alcohol was assessed in an *in vitro* mammalian cell gene mutation test conducted equivalent to OECD TG 476. Chinese hamster lung fibroblast cells (V79) were treated with isoamyl alcohol in DMSO (dimethyl sulfoxide) at concentrations up to 51.5 mM in the presence and absence of an exogenous, metabolically active microsomal mix (S9 mix). No increase in the number of spontaneous MN frequencies was observed at the concentrations tested (Kreja and Seidel, 2002). Under the conditions of the study, isoamyl alcohol was considered not mutagenic in the mammalian gene mutation test.

There are no studies assessing the clastogenicity of 3-methyl-1-pentanol; however, read-across can be made to isoamyl alcohol (CAS # 123-51-3). The clastogenic activity of isoamyl alcohol was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered in corn oil via oral route, to groups of male and female NMRI mice (5/sex/dose). Doses of 500, 1000, and 2000 mg/kg body weight were administered. Mice from each dose level were euthanized

at 24 or 48 h and the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (RIFM, 2007). Under the conditions of the study, isoamyl alcohol was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the available data, isoamyl alcohol does not present a concern for genotoxic potential and this can be extended to 3-methyl-1-pentanol.

Additional References: Chen et al., 1984; Kreja and Seidel, 2001; Seidel and Plappert, 1999; Nakajima et al., 2006; RIFM, 2007.

Literature Search and Risk Assessment Completed on: 09/28/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for 3-methyl-1-pentanol 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 3-methyl-1-pentanol. Read-across material, isoamyl alcohol (CAS # 123-51-3; See Section 5) has sufficient repeated dose toxicity data. A gavage OECD 422 combined repeated dose toxicity study was conducted on groups of 12 male and female Sprague-Dawley rats/group which 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 was 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 body weight gain in the males (ECHA REACH Dossier: 3-methylbutan-1-ol, accessed 07/09/14). In another study, an OECD/GLP 408, 13 week study conducted on groups of 10 SPF-Wistar, Chbb:THOM rats/sex/group. The animals 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; also available in RIFM, 1991). 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 as a result of test material administration up to the highest dose tested. Thus, the NOAEL was determined to be 1000 mg/kg/day (Carpanini et al., 1973). Since no adverse effects were reported among the animals during the 13 and 17 week studies, the NOAEL was determined to be 1250 mg/kg/day. Therefore, the 3-methyl-1-pentanol 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 3-methyl-1-pentanol, 1250/0.000016 or 78125000.

In addition, the total systemic exposure to 3-methyl-1-pentanol (0.016 μg/kg/day) is below the TTC (30 μg/kg bw/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: RIFM, 2010a; RIFM, 2010b; RIFM, 1988a; RIFM, 1991; Gibel et al., 1975; RIFM, 1992; RIFM, 1988b; Klimisch and Hellwig, 1995; RIFM, 1990b; RIFM, 1988c; RIFM, 1990a; RIFM, 2010c; Meyer, 1965; McLaughlin et al., 1964; ECHA REACH Dossier: Alcohols, C9-11-iso-, C10-rich; ECHA REACH Dossier: Alcohols, C7-9-iso-, C8-rich.

Literature Search and Risk Assessment Completed on: 02/14/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for 3-methyl-1-pentanol 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 toxicity data on 3-methyl-1-pentanol. Read-across material, isoamyl alcohol (CAS # 123-51-3; see section 5) has sufficient developmental toxicity data. 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 body weight parameters of New Zealand rabbits. The NOEL for developmental toxicity was determined to be 10 mg/l or 1365 mg/kg/day, the highest dose tested (RIFM, 1990a). 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 according to standard minute volume and body weight parameters of Wistar rats. The NOEL for developmental toxicity was determined to be 10 mg/l or 2695 mg/kg/day, the highest dose tested (RIFM, 1990b). 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 selected for the developmental toxicity endpoint.

There are no reproductive toxicity data on 3-methyl-1-pentanol. Read-across material, isoamyl alcohol (CAS # 123-51-3; see section 5) has sufficient reproductive toxicity data. An OECD 422 gavage combined repeated dose toxicity study with the reproduction/developmental toxicity screening test was 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 reproductive performance of the parental generation animals up to the highest dose tested (ECHA REACH Dossier: 3-methylbutan-1-ol). A 14-day screening study for reproductive toxicity in male rats was done on read-across material, 3,7-dimethyl-1-octanol (CAS # 106-21-8; See section 5). There were no adverse effects on male reproductive organs or sperm parameters at 1000 mg/kg/day, the only dose tested (RIFM, 2013a). The NOAEL of 1000 mg/kg/day supports the NOAEL for reproductive toxicity which was determined to be 300 mg/kg/day based on the OECD 422 study on isoamyl alcohol.

Therefore, the 3-methyl-1-pentanol MOE for the developmental and reproductive toxicity endpoints can be calculated by dividing the isoamyl alcohol NOAEL in mg/kg/day by the total systemic exposure to 3-methyl-1-pentanol, 300/0.000016 or 18750000.

In addition, the total systemic exposure to 3-methyl-1-pentanol (0.016 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007 and Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Additional References: RIFM, 2010a; RIFM, 2010b; RIFM, 1988a; Carpanini et al., 1973; Schilling et al., 1997; RIFM, 1991; Gibel et al., 1975; RIFM, 1992; RIFM, 1988b; Klimisch and Hellwig, 1995; RIFM, 1990b; RIFM, 1988c; RIFM, 1990a; RIFM, 2010c; Meyer, 1965; McLaughlin et al., 1964; ECHA REACH Dossier: Alcohols, C9-11-iso-, C10-rich; ECHA REACH Dossier: Alcohols, C7-9-iso-, C8-rich.

Literature Search and Risk Assessment Completed on: 02/14/2017.

10.1.4. Skin sensitization

Based on the available data and read-across materials isononyl alcohol (isomer unspecified) (CAS # 27458-94-2) and isoamyl alcohol (CAS # 123-51-3), 3-methyl-1-pentanol does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for 3-methyl-1-pentanol. Based on the existing data and read-across materials isoamyl alcohol (CAS # 123-51-3; see Section 5) and isononyl alcohol (isomer unspecified) (CAS # 27458-94-2; see Section 5), 3-methyl-1-pentanol does not present a concern for skin sensitization. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). In a Buehler test, read-across material isononyl alcohol (isomer unspecified) did not present reactions indicative of sensitization (ECHA REACH Dossier, accessed 9/30/2016). In a murine local lymph node assay (LLNA), read across material isoamyl alcohol was found to be non-sensitizing up to 50% (12500 μg/cm2) (Kern et al., 2010). In a confirmatory human repeated insult patch test (HRIPT), no sensitization reactions were reported to 0.5% 3-methyl-1-pentanol in alcohol in 31 subjects (RIFM, 1973). In a human maximization test, no reactions indicative of sensitization were observed with 8% of read-across material isoamyl alcohol (5520 μg/cm^2) (RIFM, 1976). Based on weight of evidence from structural analysis, human data and read-across materials isoamyl alcohol and isononyl alcohol (isomer unspecified), 3-methyl-1-pentanol does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed on: 10/28/2016.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, 3-methyl-1-pentanol does not present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 3-methyl-1-pentanol in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of absorbance, 3-methyl-1-pentanol does not present a concern for phototoxicity or photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/13/16.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, 3-methyl-1-pentanol, exposure level is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 3-methyl-1-pentanol. Based on the Creme RIFM model, the inhalation exposure is 0.0000044 mg/day. This exposure is 318182 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: None.

Literature Search and Risk Assessment Completed on: 10/2016.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of 3-methyl-1-pentanol 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; US EPA, 2012b) 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, 3-methyl-1-pentanol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening level PEC/PNEC < 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify 3-methyl-1-pentanol 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 EPI Suite v4.11).

10.2.2. Risk assessment

Based on current Volume of Use (2011), 3-methyl-1-pentanol 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.

Other available data:

3-Methyl-1-pentanol has been pre-registered for REACH with no additional data at this time.

10.2.4. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

		(Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	227.4 mg/L					

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	1.75	1.75
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

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

Literature Search and Risk Assessment Completed on: 8/13/14.

11. Literature search*

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

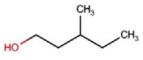
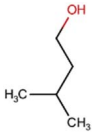
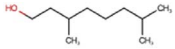
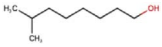
This is not an exhaustive list.

Appendix

Read-across justification

Methods:

- The identified read-across analogs were confirmed by using expert judgment.
- The physical-chemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (US EPA, 2012a).
- The J_{max} were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v.2.1.6) (Cassano et al., 2010).
- Protein binding were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.4) (OECD, 2012)

	Target material	Read-across material		
Principal Name	3-Methyl-1-pentanol	Isoamyl alcohol	3,7-Dimethyl-1-octanol	Isononyl alcohol (isomer unspecified)
CAS No.	589-35-5	123-51-3	106-21-8	27458-94-2
Structure				
Similarity (Tanimoto score)		0.79	0.58	0.54
Read-across endpoint		• Developmental and Reproductive • Repeated dose • Genotoxicity • Skin sensitization	• Developmental and reproductive	• Skin sensitization
Molecular Formula	$C_6H_{14}O$	$C_5H_{12}O$	$C_{10}H_{22}O$	$C_9H_{20}O$
Molecular Weight	102.18	88.15	158.29	144.58
Melting Point (°C, EPISUITE)	−49.23	−61.49	−13.66	−14.04
Boiling Point (°C, EPISUITE)	154.86	123.17	216.17	208.49
Vapor Pressure (Pa @ 25°C, EPISUITE)	227	512	4.74	2.63
	1.75	1.16[a]	3.9[b]	3.22

Log Kow (KOWWIN v1.68 in EPISUITE)				
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	4300	26700	175.4	461
J_{max} (mg/cm^2/h, SAM)	194.299	733.512	65.909	50.676
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	1.76E-005	1.33E-005	5.47E-005	4.12E-005
Genotoxicity				
DNA binding (OASIS v 1.4 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)	• Non-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		
Reproductive and developmental toxicity				
ER Binding by OECD QSAR Tool Box (3.4)	• Non-binder, non-cyclic structure	• Non-binder, non-cyclic structure	• Non binder, non-cyclic structure	
Developmental Toxicity Model by CAESAR v2.1.6	• toxicant (good reliability)	• toxicant (good reliability)	• Non-toxicant (low reliability)	
Skin Sensitization				
Protein binding by OASIS v1.1	• No alert found	• No alert found		• No alert found
Protein binding by OECD	• No alert found	• No alert found		• No alert found
Protein binding potency	• Not possible to classify	• Not possible to classify		• Not possible to classify
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found	• No alert found		• No alert found
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (moderate reliability)	• Non sensitizer (good reliability)		• Non sensitizer (moderate reliability)
Metabolism				
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

[a] Patel et al., 2002.
[b] RIFM, 1999.

Summary:

There are insufficient toxicity data on 3-methyl-1-pentanol (CAS # 589-35-5). Hence, *in silico* evaluation was conducted by determining suitable read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, suitable analogs isoamyl alcohol (CAS # 123-51-3), 3,7-dimethyl-1-octanol (CAS # 106-21-8), isononyl alcohol (CAS # 27458-94-2) and isononyl alcohol (CAS # 27458-94-2) were identified as proper read-across materials with data for their respective toxicological endpoints.

Conclusion/Rationale:

- For target material 3-methyl-1-pentanol (CAS # 589-35-5), the following materials can be used as structurally similar read-across analogs for said toxicological endpoints. Read across analog isoamyl alcohol (CAS # 123-51-3) was used for skin sensitization, genotoxicity, reproductive and developmental toxicity, and repeated dose toxicity, 3,7-dimethyl-1-octanol (CAS # 106-21-8) for reproductive and developmental toxicity and isononyl alcohol (CAS # 27458-94-2) for the skin sensitization endpoint.
  - o The target substance and the read-across analogs are structurally similar and belong to a class of saturated branched chain aliphatic primary alcohols.
  - o The key difference between the target substance and the read-across analogs is that they have different aliphatic carbon chain lengths. This structural difference between the target substance and read across analogs is not relevant from an endpoint toxicity perspective.
  - o The target substance and the read-across analogs have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the five carbon long branched aliphatic chain fragment. The differences in the structure which are responsible for a Tanimoto score < 1 are not relevant from a toxicological endpoint perspective.
  - o The target substance and the read-across analogs have similar physical-chemical properties. The J_{max} value of the target and the read-across analogs appear to be different, but with the calculated J_{max}, the read-across analog substances, as well as the target, are predicted to have skin

absorption up to 80%. Other differences in some of the physical-chemical properties of the target substance and the read across analogs are estimated to be toxicologically insignificant for genotoxicity, skin sensitization, developmental and reproductive toxicity and repeated dose toxicity endpoints.

- o According to the QSAR OECD Toolbox (V3.4), structural alerts for the toxicological endpoints are consistent between the target substance and the read across analogs.
- o The CAESAR model for skin sensitization predicts the target substance to be a sensitizer while the read across analogs isoamyl alcohol and isononyl alcohol (isomer unspecified) are predicted to be non-sensitizers. All other skin sensitization protein binding alerts for the target substance and the read across analogs are negative. The data described in the skin sensitization section show that the read-across analogs pose no concern for the skin sensitization endpoint. Based on a comparison of structural similarity, physical-chemical properties and reactivity predictions between the read across analogs and the target substance, the alert for the target will be superseded by availability of data for the read across analog. In addition, according to the CAESAR model, the target and read across analog isoamyl alcohol is predicted to be a toxicant with good reliability for the developmental and reproductive endpoint. The data described above in the developmental toxicity section for read-across show that the margin of exposure for the read across substance is adequate at the current level of use. So in this case, the *in silico* prediction will be superseded.
- 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 respective toxicological endpoints as mentioned above are consistent between the metabolites of the read across analogs and the target substance.
- o The structural differences between the target substance and the read across analogs are deemed to be toxicologically insignificant for the respective toxicological endpoints.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.11.036.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.11.036.

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