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Short Review

RIFM fragrance ingredient safety assessment,2-methyl-2-propanol, CAS registry number 75-65-0

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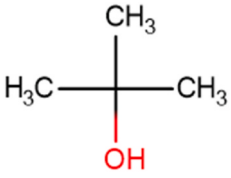
Name: 2-Methyl-2-propanol
CAS Registry Number: 75-65-0



Abbreviation/Definition List:

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2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic

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(*continued*)

estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach

DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).

*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

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

2-Methyl-2-propanol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization potential, and environmental safety. Data show that 2-methyl-2-propanol is not genotoxic and provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose, reproductive toxicity, and local respiratory endpoints. Data from read-across analog 2-methyl-2-butanol (CAS # 75-85-4) show that there are no safety concerns for 2-methyl-2-propanol for skin sensitization under the current, declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 2-methyl-2-propanol is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 2-methyl-2-propanol was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

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Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	NTP (1995)
Repeated Dose Toxicity: NOAEL = 195 mg/kg/day.	(Cirvello et al., 1995)
Reproductive Toxicity: Developmental toxicity: NOAEL = 187.2 mg/kg. Fertility: NOAEL = 160 mg/kg/day.	US EPA (2004)
Skin Sensitization: No concern for skin sensitization under the current, declared levels of use.	(ECHA REACH Dossier: 2-Methylpropan-2-ol; ECHA, 2011; ECHA REACH Dossier: 2-Methylbutan-2-ol; ECHA, 2013)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)	
Local Respiratory Toxicity: NOAEC = 40.6 mg/m^3.	NTP (1997)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence: Critical Measured Value: 99% (EU Method C.4-A)	(ECHA REACH Dossier: 2-Methylpropan-2-ol; ECHA, 2011)
Bioaccumulation: Screening-level: 3.162 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 2725 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: 2725 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 2.725 μg/L	
• **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level	

1. Identification

1. **Chemical Name:** 2-Methyl-2-propanol
2. **CAS Registry Number:** 75-65-0
3. **Synonyms:** *tert*-Butanol; t-Butyl alcohol; 1,1-Dimethylethanol; 2-Propanol, 2-methyl-; Trimethylcarbinol; Trimethylmethanol; Trimethyl carbinol; *Tert*-butyl alcohol; 2-Methylpropan-2-ol; 2-Methyl-2-propanol
4. **Molecular Formula:** $C_4H_{10}O$
5. **Molecular Weight:** 74.12 g/mol
6. **RIFM Number:** 6078
7. **Stereochemistry:** Stereoisomer not specified. Stereocenter not present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 70.42 °C (EPI Suite)
2. **Flash Point:** 15 °C (Globally Harmonized System)
3. **Log K_{OW}:** 0.35 (Abraham and Rafols, 1995), 0.73 (EPI Suite)
4. **Melting Point**: −73.81 °C (EPI Suite)
5. **Water Solubility:** 217,500 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 31 mm Hg at 20 °C (EPI Suite v4.0), 29 mm Hg at 20 °C (Fragrance Materials Association), 46.9 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with a camphoraceous and somewhat "minty" odor; the dryness being characteristic and different from the other isomers

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.019% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.000061 mg/kg/day or 0.0045 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.000062 mg/kg/day (RIFM, 2017)

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

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

5. Derivation of systemic absorption

1. **Dermal:** 1.5%

McGregor (2010): An in vivo dermal absorption study was conducted in male rats. At 72 h, less than 1.5% of ^{14}C-*t*-butyl alcohol (2-methyl-2-propanol) applied topically was absorbed. The absorbed material was rapidly cleared from the application site and excreted.

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

6. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low* (Expert Judgment)

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	III	III

*See the Appendix below for details.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** 2-Methyl-2-butanol (CAS # 75-85-4)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References:
None.

8. Natural occurrence

2-Methyl-2-propanol is reported to occur in the following foods by the VCF*:

Apple fresh (*Malus* species).
Beef.
Cheese, various types.
Chicken.
Coffee.
Grape (*Vitis* species).
Guava and feyoa
Mangifera species.
Walnut (*Juglans* species).
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. This is a partial list.

9. REACH dossier

Available; accessed 04/12/21 (ECHA, 2011).

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, 2-methyl-2-propanol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2-methyl-2-propanol has been evaluated in a bacterial reverse mutation assay conducted in an equivalent manner to OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with 2-methyl-2-propanol in dimethyl sulfoxide (DMSO) at concentrations up to 10,000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (NTP, 1995). Under the conditions of the study, 2-methyl-2-propanol was not mutagenic in the Ames test.

The clastogenic activity of 2-methyl-2-propanol was evaluated in an in vivo micronucleus test conducted in an equivalent manner to OECD TG 474. The test material was administered in drinking water to groups of male and female B6C3F1 mice. Doses of 3000, 5000, 10,000, 20,000, and 40,000 ppm were administered. Mice from each dose level were euthanized after 13 weeks, the peripheral blood was extracted, and the percent micronucleated normochromatic erythrocytes (NCE) was assessed. The test material did not induce a statistically significant increase in the incidence of micronucleated normochromatic erythrocytes in the bone marrow (NTP, 1995). Under the conditions of the study, 2-methyl-2-propanol was considered to be not clastogenic in the in vivo micronucleus test.

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

Additional References: Zeiger et al., 1987; McGregor et al., 2005.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

The MOE for 2-methyl-2-propanol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. 2-Methyl-2-propanol has been extensively studied for repeated dose toxicity in rats and mice via several routes of exposure. A 2-year oral (drinking water) carcinogenicity study was conducted in F344/N rats. Groups of 60 male rats/dose were given 0%, 0.125%, 0.25%, or 0.5% 2-methyl-2-propanol in drinking water for 2 years, equivalent to an average daily dose of 0, 85, 195, or 420 mg/kg/day. Groups of 60 female rats/dose were given 0%, 0.25%, 0.5%, or 1% 2-methyl-2-propanol in drinking water for 2 years, equivalent to an average daily dose of 0, 175, 330, or 650 mg/kg/day. Survival was significantly reduced in 0.5% males and 1% females. The mean bodyweight gain of 0.5% males was lower at week 20, and the final mean bodyweight gain was reduced by 24% compared to controls. Mean body weights of males at 0.125% and 0.25% were similar to controls up to week 65 then decreased for the remainder of the study. A mean bodyweight gain of 1% in females was lower after week 29, and the final mean bodyweight gain was reduced by 21% compared to controls. Water consumption increased with the dose for males. Water consumption decreased with the dose for females, which was likely reflected in the increased urine specific gravity and decreased urine volumes noted at 0.5% and 1%. At doses of 0.5% or more, kidney inflammation, nephropathy, mineralization, or hyperplasia were significantly greater than that of controls. The NOAEL was determined to be 0.25%, or 195 mg/kg/day, based on reduced bodyweight gain and survival of male rats in an oral (drinking water) 2-year carcinogenicity study (Cirvello et al., 1995). Therefore, the MOE is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 195/0.000062, or 3,145,161.

In addition, the total systemic exposure to 2-methyl-2-propanol (0.062 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.

2-Methyl-2-propanol is a non-genotoxic carcinogen in rats and mice (reviewed in McGregor, 2010). In oral (drinking water) 2-year carcinogenicity studies conducted in rats and mice by the US NTP, there was some evidence of carcinogenic activity in male F344/N rats (renal tubule adenoma or carcinoma [combined]), some evidence in female B6C3F1 mice (follicular cell adenoma of the thyroid gland), and equivocal evidence in male B6C3F1 mice (follicular cell adenoma or carcinoma [combined] of the thyroid gland). There was no evidence of carcinogenic activity in female F344/N rats (Cirvello et al., 1995). The renal tumors in male rats were determined to be related to α-2u-globulin nephropathy (male rat-specific) and chronic progressive nephropathy (rat-specific), and therefore not relevant to human risk (Hard et al., 2011). Regarding the thyroid tumors in mice, the role of the chemical is not certain, although a strain-specific response cannot be ruled out. The induction of thyroid tumors in rodents, delivered either as 2-methyl-2--propanol or as an endogenously formed metabolite of methyl-tert-butyl ether (MTBE, CAS # 1634-04-4), has not been consistently shown. There are few data to support any of the known modes of action for thyroid follicular cell neoplasia, and there was no evidence that 2-methyl-2-propanol is directly toxic to the thyroid (reviewed in McGregor, 2010). In a carcinogenic risk assessment conducted on the thyroid tumors according to guidelines from the US EPA, the human Reference Dose (RfD)* was estimated to be 220 μg/kg/day (Shipp et al., 2006), which is 3500 times greater than the total systemic exposure from fragrances (0.062 μg/kg/day). This MOE is considered adequate.

*An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect the limitations of the data used (http://www.epa.gov/risk_assessment/glossary.htm).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

11.1.3. Reproductive toxicity

The MOE for 2-methyl-2-propanol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. The data on 2-methyl-2-propanol are sufficient for the developmental toxicity endpoint. An inhalation developmental toxicity study was conducted using Sprague Dawley rats. Groups of 15 pregnant rats/dose were exposed to 2000, 3500, or 5000 ppm t-butanol (equivalent to 1872, 3277, or 4681 mg/kg/day) for 7 h/day on gestation days 1–19. An equal number of controls were sham-exposed throughout gestation. Dams were euthanized on gestation day 20, and the uterus and ovaries were removed and examined. The high-dose level was maternally toxic; narcosis, reduced feed intake, and significantly reduced weight gain were observed. An unsteady gait was observed after exposure for all 3 concentrations. Fetal body weights were significantly reduced in all treated groups. The LOAEL for developmental toxicity was determined to be 2000 ppm, or 1872 mg/kg/day, based on reduced fetal body weights (Nelson et al., 1989a; data also available in Brightwell et al., 1987). These effects occurred at maternally toxic dosages, and no teratogenicity was observed up to the high dosage of 5000 ppm. The NOAEL was derived by dividing the LOAEL by a safety factor of 10, which is equal to 187.2 mg/kg/day. Therefore, the MOE for developmental toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 187.2/0.000062, or 3019355.

The fertility data on 2-methyl-2-propanol are sufficient for the fertility endpoint. An enhanced OECD 421 gavage reproduction and developmental toxicity screening test was conducted in Sprague Dawley rats. Groups of 12 rats/sex/dose were gavaged with 0, 64, 160, 400, or 1000 mg/kg/day 2-methyl-2-propanol for 4 weeks premating, mating, gestation, and lactation. Males were dosed for a total of 9 weeks. Females were treated up to postnatal day 21. Selected offspring were dosed beginning on postnatal day 21 for 7 days, at the same dosages as their parents. Reduced body weight was observed in males at 1000 mg/kg/day. In females at 1000 mg/kg/day, reduced bodyweight gain was observed at the end of gestation, after which food consumption was reduced, though body weight was increased at the end of lactation. There were no effects on mating performance, fertility, sperm motility, sperm morphology, or the number of implantation sites per pregnancy. An increase in gestation length was noted at 400 and 1000 mg/kg/day; while all females delivered within the normal range of 21–23 days, increased numbers of dams from these groups delivered on day 23. A significant reduction in the number of live-born pups and an increase in the number of stillborn pups was observed at 1000 mg/kg/day. Mean litter sizes on postnatal days 1 and 21 were significantly reduced. Significant perinatal mortality was observed at 1000 mg/kg/day. On postnatal day 4, survival at 1000 mg/kg/day was 80% due to total litter loss for 1 litter and 50% survival in 3/10 remaining litters. After postnatal day 4, no further survival effects were noted. F1 offspring at 1000 mg/kg/day had lower body weight on postnatal day 1, which continued throughout lactation. Direct exposure of pups (1 male, 1 female/litter) for 1 week after weaning did not exhibit further toxicity. The NOAEL for fertility was determined to be 160 mg/kg/day, based on an increase in gestation length in mid and high-dose groups (US EPA, 2004). Therefore, the MOE for reproductive toxicity is equal to the NOAEL in mg/kg/day divided by the total systemic exposure, 160/0.000062, or 2580645.

In addition, the total systemic exposure to 2-methyl-2-propanol (0.062 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

11.1.4. Skin sensitization

Based on existing data and read-across material 2-methyl-2-butanol (CAS # 75-85-4), 2-methyl-2-propanol does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for 2-methyl-2-propanol. Based on read-across material 2-methyl-2-butanol (CAS # 75-85-4; see Section VI), 2-methyl-2-propanol does not present a concern for skin sensitization. The chemical structure of these materials indicates that they would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, no reactions were observed with 2-methyl-2-propanol (ECHA, 2011). Additionally, in the murine local lymph node assay (LLNA), read-across material 2-methyl-2-butanol was reported to be a non-sensitizer up to the maximum tested concentration of 100% (ECHA, 2013).

Based on the weight of evidence (WoE) from structural analysis, animal study, and read-across 2-methyl-2-butanol 2-methyl-2-propanol does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV absorption spectra, 2-methyl-2-propanol 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 2-methyl-2-propanol in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, 2-Methyl-2-propanol does not present a concern for phototoxicity or photoallergenicity.

11.1.6. UV spectra analysis

The available spectra indicate no absorbance in the range of 290–400 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: 06/02/21.

11.1.7. Local Respiratory Toxicity

The MOE for 2-methyl-2-propanol is adequate for the respiratory endpoint at the current level of use.

11.1.7.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. A US NTP study was conducted on both rats and mice in a 13-week study (NTP, 1997). Groups of 10 male and 10 female rats were exposed to 2-methyl-2-propanol at concentrations 0, 409.25, 818.5, 1637.01, 3274.01, and 6366.13 mg/m3 for 6 h per day, 5 days per week for 13 weeks by whole-body exposures. Standard observations included mortality, body weights, clinical observations, and complete necropsy and histopathology. There were no treatment-related gross pathology or microscopic findings in the respiratory tissues of the animals from all exposure groups. Therefore, the local respiratory effects NOAEC was identified at 6366.13 mg/m3.

This NOAEC expressed in mg/kg lung weight/day is:

- (6366.13 mg/m^3) × (1 m^3/1000 L) = 6.37 mg/L
- MV of 0.17 L/min for a Sprague Dawley rat* × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (6.37 mg/L) × (61.2 L/d) = 389.8 mg/day
- (389.8 mg/day)/(0.0016 kg lung weight of rat**) = 243,625 mg/kg/day

The 95th percentile calculated exposure was reported to be 0.0045 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015 and Safford, 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.0069 mg/kg lung weight/day resulting in a MOE of 3,531,159 (i.e., [243,625 mg/kg lung weight of rat/day]/[0.0069 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.0045 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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Additional References: Nelson et al., 1989b; Borghoff et al., 2001; Olajos et al., 1998; Brightwell et al., 1987; Leavens and Borghoff, 2009

Literature Search and Risk Assessment Completed On: 06/03/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-methyl-2-propanol 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, 2-methyl-2-propanol 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 2-methyl-2-propanol 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, 2017a). 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).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), 2-methyl-2-propanol does not present a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.3. Other available data. 2-Methyl-2-propanol has been registered under REACH, and the following data is available:

A biodegradation study was conducted according to the OECD 302D method. After 56 days, biodegradation of 66% was reported.

A 28-day biodegradation study was conducted according to the OECD 301B method. Biodegradation of 5.1% was observed.

Biodegradation of 99% was observed after 28 days in a study conducted according to EU Method C.4-A.

A 96-h acute fish (fathead minnow) study was conducted according to OECD Guideline 203 under flow-through conditions. The 96-h LC50 value time-weighted average was reported to be > 961 mg/L.

The acute fish (*Danio rerio*) toxicity test was conducted according to the EU C.1 method, under semi-static conditions. The 96-h LC50 value based on mean measured concentration was reported to be > 856 mg/L.

The effect of short-term exposure to 2-methyl-2-propanol on the hatch rate and development of *Clarias gariepinus* was evaluated. After 120 h of exposure, the NOEC for fish (based on egg mortality) was determined to be 332 mg/L.

A 48-h *Daphnia magna* acute toxicity test was conducted according to the EU Method C.2, under static conditions.The EC50 was reported to be 933 mg/L based on nominal concentration.

A 48-h *Daphnia magna* acute toxicity test was conducted according to the DIN 38412, Part II method, under static conditions. The EC50 was reported to be 5504 mg/L.

A *Daphnia magna* reproduction test was conducted according to the OECD 211 guidelines under semi-static conditions. The 21-day NOEC value based on nominal test concentration for immobilization and reproduction was reported to be 100 mg/L.

A 96-h algae acute toxicity test was conducted according to the OECD Guideline 201, under static conditions. The EC50 value based on measured concentration for biomass and growth was reported to be > 976 mg/L.

A 72-h algae acute toxicity test was conducted according to the EU Method C.3, under static conditions. The 72-h EC50 value based on nominal test concentration for biomass and growth rate was reported to be > 1000 mg/L.

11.2.1.4. Risk assessment refinement. Since 2-methyl-2-propanol 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.

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	0.35	0.35
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 2.725 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 06/01/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
  - **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
  - **PubChem:** https://pubchem.ncbi.nlm.nih.gov/
  - **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
  - **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
  - **IARC:** https://monographs.iarc.fr
  - **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
  - **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
  - **US EPA ChemView:** https://chemview.epa.gov/chemview/
  - **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **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/

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	2725			1000000	2.725	

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 01/17/22.

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.2022.113512.

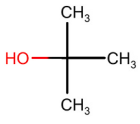
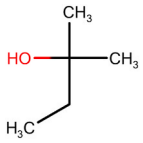
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (Date et al., 2020). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017b).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material 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). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, oncologic classification, ER binding, and repeat dose categorization predictions 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 material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the choice of the alert system.

	Target Material	Read-across Material
Principal Name	2-Methyl-2-propanol	*tert*-amylalcohol; 2-methyl-2-butanol; 2-butanol, 2-methyl-;2-methylbutan-2-ol;*tert*-pentyl alcohol
CAS No.	75-65-0	75-85-4
Structure		
Similarity (Tanimoto Score)		0.67
SMILES	CC(C)(C)O	CCC(C)(C)O
Endpoint		Skin sensitization
Molecular Formula	$C_4H_{10}O$	$C_5H_{12}O$
Molecular Weight (g/mol)	74.123	88.15
Melting Point (°C, EPI Suite)	25.81	−9.10
Boiling Point (°C, EPI Suite)	82.30	102.40
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.43E+03	2.23E+03
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.00E+06	1.10E+05
Log K_{OW}	0.35	0.89
J_{max} (μg/cm^2/h, SAM)	10463.67	1958.28
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	9.17E-01	1.40E+00
Skin Sensitization		
Protein Binding (OASIS v1.1)	No alert found	No alert found
Protein Binding (OECD)	No alert found	No alert found
Protein Binding Potency		Not possible to classify according to these rules (GSH)

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material
	Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found	No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domain alerts identified.	No skin sensitization reactivity domain alerts identified.
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 2-methyl-2-propanol (CAS # 75-65-0). 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, 2-methyl-2-butanol (CAS # 75-85-4) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- 2-Methyl-2-butanol (CAS # 75-85-4) was used as a read-across analog for the target material 2-methyl-2-propanol (CAS # 75-65-0) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to saturated aliphatic alcohols.
  - o The key difference between the target material and the read-across analog is that the read-across analog has one carbon longer chain compared to the target material. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - o The similarity between the target material 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 material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o There are no alerts for the target material and the read-across analog. The absence of i*n silico* alerts is consistent with data.
  - o The target material 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.

Explanation of Cramer Classification

Due to potential discrepancies with the current *in silico* tools (Bhatia et al., 2015), the Cramer class of the target material was determined using expert judgment based on the Cramer decision tree (Cramer et al., 1978).

Q1. A normal constituent of the body? No.
Q2. Contains functional groups associated with enhanced toxicity? No.
Q3. Contains elements other than C, H, O, N, and divalent S? No.
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.
Q6. Benzene derivative with certain substituents? No.
Q7. Heterocyclic? No.
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation). No.
Q17. Readily hydrolyzed to a common terpene? No.
Q19. Open chain? No.
Q20. Aliphatic with some functional groups (see Cramer et al., 1978 for detailed explanation)? No.
Q18. One of the list? (see Cramer et al., 1978 for a detailed explanation on the list of categories). No. Class I (Class low)

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