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Short Review

Update to RIFM fragrance ingredient safety assessment, isoamyl alcohol, CAS Registry Number 123-51-3

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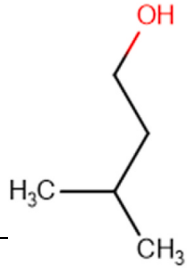


Name: Isoamyl alcohol
CAS Registry Number: 123-51-3

Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
CAESAR - Computer-Assisted Evaluation of industrial chemical Substances According to Regulations
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 estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017, 2024) 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; please note that the citation dates used for studies sourced from the ECHA website are the dates the dossiers were first published, not the dates that the studies were conducted
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
HESS - Hazard Evaluation Support System; a repeated dose profiler that is used to identify the toxicological profiler of chemicals
IFRA - The International Fragrance Association
IRB - Institutional Review Board
ISS - Istituto Superiore di Sanità (Italian National Institute of Health)
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
OASIS - OASIS Laboratory of Mathematical Chemistry (LMC)
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
Toxtree - an *in silico* tool that can estimate toxic hazard by applying a decision tree approach
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

(*continued on next column*)

(*continued*)

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 who 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.

Isoamyl alcohol was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, photoirritation/photoallergenicity, skin sensitization, and environmental safety. Data show that isoamyl alcohol is not genotoxic. Data on isoamyl alcohol provide a calculated Margin of Exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. Data show that there are no safety concerns for isoamyl alcohol for skin sensitization under the current declared levels of use. The photoirritation/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra; isoamyl alcohol is not expected to be photoirritating/photoallergenic. For the local respiratory endpoint, a calculated MOE >100 was provided by the read-across analog propyl alcohol (CAS # 71-23-8). The environmental endpoints were evaluated; isoamyl alcohol 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 (VoU) in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment	
Genotoxicity: Not genotoxic.	(ECHA, 2010a; RIFM, 2007)
Repeated Dose Toxicity: NOAEL = 1250 mg/kg/day.	RIFM (1991)
Reproductive Toxicity: NOAEL = 1221 mg/kg/day.	ECHA (2010a)
Skin Sensitization: No concern for skin sensitization.	(Kern et al., 2010)
Photoirritation/Photoallergenicity: Not expected to be photoirritating/photoallergenic.	(UV/Vis spectra, RIFM Database)
Local Respiratory Toxicity: NOAEC = 12779.88 mg/m^3.	(ECHA, 2010b)
Environmental Safety Assessment	
Hazard Assessment:	
Persistence:	
Critical Measured Value: Critical Measured Value: 84% (OECD 301F)	ECHA (2010a)
Bioaccumulation:	
Screening-level: 2.706 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity:	
Screening-level: LC50: 523.6 mg/L	(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	(Salvito et al., 2002)
Critical Ecotoxicity Endpoint: LC50: 523.6 mg/L	(Salvito et al., 2002)
RIFM PNEC is: 0.5236 µg/L	
• **Revised PEC/PNECs (2019 IFRA VoU):** North America and Europe: Not Applicable; cleared at the screening-level	

1. Identification

1. **Chemical Name:** Isoamyl alcohol
2. **CAS Registry Number:** 123-51-3
3. **Synonyms:** 1-Butanol, 3-methyl-; Isobutyl carbinol; Isopentyl alcohol; 3-Methyl-1-butanol; Isopentanol; 3-Methylbutan-1-ol; アルカノ-

⩾(C = 5–38); Isoamylol; iso-Pentanol; iso-Amyl alcohol; 3-Methylbutyl alcohol; 3-Methylbutane-1-ol; 2-Methyl-4-butanol; Isoamyl alcohol
4. **Molecular Formula:** $C_5H_{12}O$
5. **Molecular Weight:** 88.15 g/mol
6. **RIFM Number:** 803
7. **Stereochemistry:** No stereocenter is present, and no stereoisomer is possible.

2. Physical data

1. **Boiling Point:** 132 °C (Carpanini et al., 1973), 132 °C (Fragrance Materials Association [FMA]), 123.17 °C (EPI Suite v4.11)
2. **Flash Point:** 109 °F (closed cup) (FMA), 43 °C (Globally Harmonized System)
3. **Log K_{OW}:** 1.28 (Abraham and Rafols, 1995), 1.16 (Patel et al., 2002), 1.26 (EPI Suite v4.11)
4. **Melting Point**: 117.2 °C (Carpanini et al., 1973), −61.49 °C (EPI Suite v4.11)
5. **Water Solubility:** 41580 mg/L at 25 °C (EPI Suite v4.11)
6. **Specific Gravity:** 0.809–0.815 at 20 °C (Carpanini et al., 1973), 0.812 (FMA), 0.8149 (Essential Oils Association, 1976 Sample 76–151)
7. **Vapor Pressure:** 1.5 mm Hg at 20 °C (FMA), 3.84 mm Hg at 25 °C (EPI Suite v4.11)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** Colorless liquid with a disagreeable alcohol odor and a pungent, repulsive taste (Merck)

3. Volume of use (worldwide band)

1. 1–10 metric tons per year (IFRA, 2019)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.4.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0032% (RIFM, 2023)
2. **Inhalation Exposure*:** 0.000015 mg/kg/day or 0.0011 mg/day (RIFM, 2023)
3. **Total Systemic Exposure**:** 0.00036 mg/kg/day (RIFM, 2023)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017, 2024).

**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, 2017; Safford et al., 2015, 2017, 2024).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.6 (OECD, 2023)
I	I	I

2. Analogs Selected:
   a **Genotoxicity:** None
   b **Repeated Dose Toxicity:** None
   c **Reproductive Toxicity:** None
   d **Skin Sensitization:** None
   e **Photoirritation/Photoallergenicity:** None
   f **Local Respiratory Toxicity:** Propyl alcohol (CAS # 71-23-8)
   g **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

Kamil et al., 1953**:** The amount of glucuronide-conjugated isoamyl alcohol excreted was studied after administering a 25-mm/3-kg dose to large chinchilla rabbits. The animals were kept on a constant diet to obtain glucuronide levels 1 week prior to administration of isoamyl alcohol. Isoamyl alcohol was administered with water via gavage, and the glucuronide acid output collected from urine was determined on 3 animals. 9% of administered dose was excreted as the glucuronide-conjugate of isoamyl alcohol at the end of 24 h. The urine did not contain aldehydes or ketones.

Additional References: None.

8. Natural occurrence

Isoamyl alcohol is reported to occur in the following foods by the VCF*.

Anise brandy	Apple fresh (*Malus* species)
Apply brandy (non-categorized)	Banana (*Musa sapientum* L.)
Beer (non-categorized)	Cocoa category
Cheese, various types	Grape brandy
Citrus fruits	Whiskey

*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 on 10/25/24.

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, isoamyl alcohol does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Isoamyl alcohol was assessed in the BlueScreen assay and found negative for both cytotoxicity (positive: <80% relative cell density) and genotoxicity, with and without metabolic activation (RIFM, 2013). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and

mixtures (Thakkar et al., 2022). Additional assays were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

The mutagenic activity of isoamyl alcohol has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with isoamyl alcohol in dimethyl sulfoxide at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2010a). Under the conditions of the study, isoamyl alcohol was not mutagenic in the Ames test.

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 the oral route to groups of male and female NMRI mice. Doses of 500, 1000, and 2000 mg/kg 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 statistically 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 not to be clastogenic in the *in vivo* micronucleus test.

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

Additional References: Chen et al., 1984; Kreja and Seidel, 2001; Seidel and Plappert, 1999; Nakajima et al., 2006; Kreja and Seidel, 2002

Literature Search and Risk Assessment Completed On: 03/29/24.

11.1.2. Repeated dose toxicity

The MOE for isoamyl alcohol is adequate for the repeated dose toxicity endpoint at the current level of use.

11.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on isoamyl alcohol. A gavage OECD 422 combined repeated dose toxicity study was conducted on groups of 12 Sprague Dawley rats/sex/group, and they were administered the 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 test material 3-methylbutan-1-ol (isoamyl alcohol) in 1 w/v% carboxymethyl cellulose solution containing 1% Tween 80 in water was administered to male and female Sprague Dawley rats daily by oral gavage for 42 days for the males (14 days before mating, 14 days during the mating period and 14 days after the end of the mating period), 41–53 days for the females (14 days before mating, throughout the mating and gestation periods up to day 4 of lactation) and for 42 days in the satellite recovery group. Examinations included mortality, clinical signs, food consumption, body weight, hematology, clinical chemistry, organ weights, urinalysis, neurobehavioral examination, gross pathology, and histopathology. There was no treatment-related mortality throughout the study. In the 300 mg/kg/day group, bodyweight gain during day 39 of the administration period was transiently low in the males in the main group, and the difference was statistically significant. During the recovery period, the bodyweight gains of the males in the 300 mg/kg/day group tended to be higher than that of the control group, though they were not statistically significant. Otherwise, there was no treatment-related effect in the males or females in the main group or recovery group. The NOAEL was determined to be 100 mg/kg/day, based on reduced bodyweight gain in the high-dose group males (ECHA, 2010a).

In another study, an OECD/GLP 408, 13-week study was conducted on groups of 10 Wistar rats/sex/dose, and they were administered isoamyl alcohol via drinking water at concentrations of 0, 1000 ppm (approximately 80 mg/kg/day), 4000 ppm (approximately 340 mg/kg/day), and 16000 ppm (approximately 1250 mg/kg/day). Examinations included mortality, clinical signs, food/water consumption, body weight, hematology, clinical chemistry, organ weights, gross pathology, and histopathology. There was no treatment-related mortality throughout the study. There were slight alterations in the hematological parameters at the high dose (a marginal increase in the red blood cell count, as well as a slight decrease in the mean corpuscular volume and the mean corpuscular hemoglobin content was observed in the males only. 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 (RIFM, 1991).

In another 17-week subchronic toxicity study, groups of 15 Ash/CSE rats/sex/group were administered isoamyl alcohol via oral gavage at doses of 0, 150, 500, and 1000 mg/kg/day for 17 weeks. In addition, a group of 5 rats/sex/group was treated at doses of 0, 500, or 1000 mg/kg/day for 3 or 6 weeks. Examinations included mortality, clinical signs, food/water consumption, body weight, hematology, clinical chemistry, organ weights, urinalysis, gross pathology, and histopathology. No treatment-related mortality occurred throughout the study. However, two high-dose rats died due to complications with gavage, which was confirmed via histopathological examination. No adverse effects were reported due to the test material administration up to the highest dose tested. Thus, the NOAEL was determined to be 1000 mg/kg/day (Carpanini et al., 1973).

The only effects reported among treated animals during the OECD 422 gavage study were reduced bodyweight gains among males. Since no adverse effects were reported among the animals during the longer-duration 13-week (drinking water) and 17-week (gavage) studies, the NOAEL was determined to be 1250 mg/kg/day, the highest dose tested. **Therefore, the isoamyl alcohol 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 isoamyl alcohol, 1250/0.00036 or 3472222.**

In addition, the total systemic exposure to isoamyl alcohol (0.36 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Schilling (1997).

Literature Search and Risk Assessment Completed On: 03/26/24.

11.1.3. Reproductive toxicity

The MOE for isoamyl alcohol is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity data on isoamyl alcohol. 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. Examinations included mortality, clinical signs, body weight, food/water consumption, gross pathology, uterus weight, number of corpora lutea, number/distribution of implantations sites, early/late resorptions, dead fetuses, and pre- and post-implantation losses in parental animals. Examinations of fetuses included sex, body weight, soft tissue examinations, histopathology, and skeletal examinations. There was no treatment-related mortality throughout the study. Clinical signs included the presence of reddish eyes, eyelid closure, and discharge from the eyes at the high dose only. At the high dose, there was a significant but slight retardation in bodyweight gain of the females. However, there was a significant increase in body weight in the post-exposure observation period, but it

was interpreted as recovery towards the end of the exposure period, so this effect was not considered adverse. No effects were seen in the fetuses. The maternal NOAEL was considered to be 341 mg/kg/day, based on the clinical signs seen at the high dose. The NOAEL for developmental toxicity was determined to be 1365 mg/kg/day, the highest dose tested (RIFM, 1990c).

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. Examinations included mortality, clinical signs, body weight, food/water consumption, gross pathology, uterus weight, number of corpora lutea, number/distribution of implantations sites, early/late resorptions, dead fetuses, and pre- and post-implantation losses in parental animals. Examinations of fetuses included sex, body weight, soft tissue examinations, histopathology, and skeletal examinations. There was no treatment related-mortality throughout the study. However, one low-dose female was found dead on post-coitum day 12 and was found to not be pregnant. This was considered to be incidental because it lacked a dose-response relationship. Body weight among the animals of the high-dose group was significantly decreased as compared to the controls between days 6–9 post-coitum and increased from days 12–15 post-coitum. This effect was considered to be a slight indication of maternal toxicity only during the first phase of exposure to a very high concentration of 10 mg/L of the test material. No other treatment-related alterations were reported among the treated animals. Thus, it was concluded that apart from marginal and transient alterations in the body weights of the treated rats of the high-dose group, no other adverse effects were reported towards the females or their respective fetuses. The maternal NOAEL was considered to be 692.31 mg/kg/day based on the significant decrease in body weight. The developmental NOAEL was considered to be 2769.23 mg/kg/day, based on no adverse effects to the fetuses (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. The test material 3-methylbutan-1-ol (isoamyl alcohol) in 1 w/v% CMC solution containing 1% Tween 80 in water was administered to male and female Sprague Dawley rats daily by oral gavage for 42 days for the males (14 days before mating, 14 days during the mating period and 14 days after the end of the mating period), 41–53 days for the females (14 days before mating, throughout the mating and gestation periods up to day 4 of lactation) and 42 days in the satellite recovery group. Examinations included mortality, clinical signs, food consumption, body weight, estrous cyclicity, sperm parameters (i.e., testes and epididymis weight, sperm count in testes and epididymis, sperm motility, sperm morphology), gross pathology, histopathology, and reproductive indices (i.e., male/female mating index, male/female fertility index, gestation index, live birth index, and post-implantation loss). Offspring examinations included viability index, survival index, number of pups, pup sex, anogenital distance, presence of nipples in male pups, thyroid hormone concentrations, gross necropsy, and histopathology of thyroid/parathyroid glands. There was no treatment-related mortality throughout the study. There was no treatment-related mortality throughout the study. There were no signs of toxicity towards the development of the fetus up to the highest dose tested or the reproductive performance of the parental generation animals up to the highest dose tested. A NOAEL of 300 mg/kg/day from the study was considered for the developmental toxicity and fertility endpoints (ECHA, 2010a).

In an OECD 443/GLP Extended One-Generation Reproductive Toxicity study conducted in Wistar rats, groups of 25 rats/sex/dose were administered 3-methylbutan-1-ol in drinking water at 0, 1250, 3750 or 12500 ppm (equivalent to 131, 404, and 1221 mg/kg/day for males and 159, 520, and 1521 mg/kg/day for females). Males and females were treated for a minimum of 10 weeks, then males and females from the same dose group were mated overnight at a ratio of 1:1. Females were allowed to deliver pups until postnatal day (PND) 4 or PND 21 or PND 22 (depending on the cohort). Pups of the F1 litter (F1 rearing animals) were selected and assigned to 2 different cohorts, which were subjected to specific postweaning examinations. Examinations included mortality, clinical signs, body weight, food/water consumption, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, histopathology, estrous cyclicity, sperm parameters (i.e., sperm head count in testes and epididymis, sperm motility, sperm morphology), male/female mating index, male/female fertility index, gestation index, live birth index, and post-implantation loss in parental animals. Litter observations included number and sex of pups, viability, weight gain, gross anomalies, physical or behavioral abnormalities, anogenital distance, presence of nipples in male pups, and organ weights (no histopathology of pup organs, but tissues were preserved). There was no treatment-related mortality throughout the study. Two females in the control group, 2 females in the low-dose group, and 1 female in the mid-dose group did not deliver F1 pups. For parental animals, decreased body weights in the males from pre-mating day 28 onwards until the end of the study were observed, and the average final in-life weight was 7% below control. There was decreased bodyweight gain during pre-mating (9% below control). No treatment-related effects were observed in parental males and females for any general behavior, reproductive parameters, T4, and TSH levels. For the F1 generation, no treatment-related mortality was observed. When comparing the control group with the test groups, the mean relative weights of the liver in males for all test groups and thymus in females for low and high-dose groups were significantly changed. The relative liver weight in males was within historical control values. The weight of the thymus in the control group was above the historical control data, which led to the statistical significance. There was no dose-response relationship, and the absolute thymus weight of females was within historical control data. Hence, these weight changes were regarded to be incidental and unrelated to treatment. No treatment-related developmental toxicity effects were seen for either cohort or any dose group. Thus, the NOAEL for general toxicity was considered to be 3750 ppm (equivalent to 404 mg/kg/day in males and 520 mg/kg/day in females). The NOAEL for developmental toxicity and fertility was considered to be 12500 ppm (equivalent to 1221 mg/kg/day in males and 1521 mg/kg/day in females) (ECHA, 2010a).

Since no adverse effects were reported among the animals during the longer-duration OECD 443 studies, the NOAEL for developmental toxicity and fertility was considered to be 1221 mg/kg/day.

Therefore, the isoamyl alcohol MOE for the developmental toxicity and fertility endpoints can be calculated by dividing the isoamyl alcohol NOAEL in mg/kg/day by the total systemic exposure to isoamyl alcohol, 1221/0.00036 or 3391667.

In addition, the total systemic exposure to isoamyl alcohol (0.36 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: 03/24/24.

11.1.4. Skin sensitization

Based on the existing data, isoamyl alcohol presents no concern for skin sensitization.

11.1.4.1. Risk assessment. Based on the existing data, isoamyl alcohol is not considered a skin sensitizer. The data are summarized in Table 1. This material is predicted *in silico* to be non-reactive with skin proteins directly (Roberts et al., 2007a; Toxtree v3.1.0; OECD Toolbox v4.6).

Isoamyl alcohol was found to be negative in an *in vitro* direct peptide reactivity assay (DPRA) and LuSens assay (ECHA, 2010a). In a murine local lymph node assay (LLNA), isoamyl alcohol was found to be non-sensitizing when tested up to 50% (12500 μg/cm^2) (Kern et al., 2010). In a human maximization test, no skin sensitization reactions were observed when tested at 5520 μg/cm^2 (RIFM, 1976).

Based on the weight of evidence (WoE) from structural analysis, *in vitro* studies, an animal study, and a human study, isoamyl alcohol does not present a concern for skin sensitization.

Additional References: Roberts et al., 2007b; Enoch et al., 2008; Patlewicz et al., 2007.

Literature Search and Risk Assessment Completed On: 03/25/24.

11.1.5. Photoirritation/photoallergenicity

Based on the available UV/Vis absorption spectra, isoamyl alcohol would not be expected to present a concern for photoirritation or photoallergenicity.

11.1.5.1. Risk assessment. There are no photosafety studies available for isoamyl alcohol in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. Based on the lack of absorbance, isoamyl alcohol does not present a concern for photoirritation or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no absorbance in the range of 290–700 nm. Therefore, it is not a concern for photoirritating or photoallergenic effects (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 03/19/24.

Table 1
Summary of existing data on isoamyl alcohol.

WoE Skin Sensitization Potency Category[1]	Human Data				Animal Data		
	NOEL-CNIH (induction) μg/cm^2	NOEL-HMT (induction) μg/cm^2	LOEL (induction) μg/cm^2	WoE NESIL μg/cm^2	LLNA[2] Weighted Mean EC3 Value μg/cm^2	GPMT	Buehler
No evidence of sensitization[4]	N/A	5520	N/A	N/A	Negative up to 12500 (50%)	N/A	N/A
	In vitro Data[3]				*In silico* protein binding alerts (OECD Toolbox v4.6)		
	KE 1	KE 2	KE 3		Target Material	Autoxidation simulator	Metabolism simulator
	Negative	Negative [LuSens]	N/A		No alert found	No alert found	Schiff base formation

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans; HMT = Human Maximization Test; LOEL = lowest observed effect level; EC3 = concentration of test chemical required to induce a 3-fold increase in lymph node cell proliferation; GPMT = Guinea Pig Maximization Test; KE = Key Event; N/A = Not Available.

[1]WoE Skin Sensitization Potency Category is only applicable for identified sensitizers with sufficient data, based on collective consideration of all available data (Na et al., 2021).

[2]Based on animal data using classification defined in the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Technical Report No. 87 (ECETOC, 2003).

[3]Studies conducted according to the OECD TG 442, Cottrez et al. (2016), or Forreryd et al. (2016) are included in the table.

[4]Determined based on Criteria for the RIFM safety evaluation process for fragrance ingredients (Api et al., 2015).

11.1.6. Local respiratory toxicity

There are insufficient inhalation data available on isoamyl alcohol; however, in a two-week inhalation study for the analog propyl alcohol (CAS # 71-23-8; see section VI), a NOAEC of 12779.88 mg/m^3 was reported (ECHA, 2010b).

11.1.6.1. Risk assessment. The calculated chronic inhalation exposure was considered along with toxicological data from the scientific literature to estimate the MOE when used in perfumery. A NOAEC of 12779.88 mg/m^3 was identified in a 90-day inhalation exposure study in Fischer 344 rats (ECHA, 2010b). In an OECD 413 guideline study, 10 male and 10 female Fischer 344 rats were treated with vapors of propyl alcohol via whole-body inhalation exposure to 0, 1228.83, 3932.27, and 12779.88 mg/m^3 for 6 h a day, 5 days per week for 13 weeks. Standard examinations and observations were performed, which included clinical observations, body weights, food consumption, hematology, clinical chemistry, gross pathology, and histopathology. Microscopic examinations revealed the presence of mononuclear cell infiltration and alveolar macrophage aggregates in the lungs and pigmentation of the tracheobronchial lymph node in control and high-dose group animals. Some microscopic observations in the lungs that were not specified in the ECHA summary were considered incidental or spontaneous lesions commonly observed as background lesions in similar-aged rats. No other effects of respiratory tract irritation were observed after inhalation exposures. Therefore, the NOAEC for local respiratory toxicity was identified as 12779.88 mg/m^3, the highest exposure concentration.

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

- (12779.88 mg/m^3) × (1 m^3/1000 L) = 12.8 mg/L
- Minute ventilation of 0.17 L/min* for a Fischer rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (12.8 mg/L) × (61.2 L/d) = 783.36 mg/day
- (783.36 mg/day)/(0.0016 kg lung weight of rat**) = 489600 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.0011 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 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 0.0017 mg/kg lung weight/day, resulting in a MOE of 288000000 (i.e., [489600 mg/kg lung weight of rat/day]/[0.0017 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species (i.e., between different species) variation (× 10) and intra-species (i.e., within the same species) variation (× 10), the material exposure by inhalation at 0.0011 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Arms and Travis (1988).

** Phalen (2009).

Additional References: Smyth Jr et al., 1969; Kane et al., 1980; Frantik et al., 1994; Klimisch (1995); Kumagai et al., 1999; Korpi et al., 1999; RIFM, 1979; RIFM, 1990b; RIFM, 1990c; RIFM, 1988a; RIFM, 1988b.

Literature Search and Risk Assessment Completed On: 03/26/24.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of isoamyl alcohol was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio of 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 VoU Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, isoamyl alcohol was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify isoamyl alcohol as possibly being 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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

11.2.1.1. Risk assessment. Based on the current VoU (IFRA, 2019), isoamyl alcohol 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. RIFM, 1989**:** An algae growth inhibition test was conducted according to the DIN 38412 part 9 method. The EbC50 values were 493 and 180 mg/L at 72 and 96 h, respectively. The ErC50 values were 573 mg/L and 273 mg/L at 72 and 96 h, respectively.

RIFM, 1990a**:** A *Daphnia magna* acute toxicity study was conducted according to the DIN 38412 L11 method. The 48-h EC50 was reported to be 255 mg/L.

11.2.1.2.3. Other available data. Isoamyl alcohol has been registered under REACH, and the following data are available (ECHA, 2010a):

A ready biodegradability test was conducted with isoamyl alcohol following the OECD 301F guidelines. Biodegradation of 84% was observed after 28 days.

A fish (*Oncorhynchus mykiss*) acute toxicity test was conducted according to the OECD 203 method. The 96-h LC50 was reported to be 700 mg/L.

11.2.1.3. Risk assessment refinement. **Since isoamyl alcohol passed the screening criteria, measured data, including REACH data, are**

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	523.6			1000000	0.5236	

reported in this document for completeness only and have 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 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 VoU Tonnage Band	<1	1–10
Risk Characterization: PEC/PNEC	**<1**	**<1**

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

The RIFM PNEC is 0.5236 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 VoU.

Literature Search and Risk Assessment Completed On: 03/28/24.

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 Technical Bulletin:** https://www.nlm.nih.gov/pubs/techbull/nd19/nd19_toxnet_new_locations.html
- **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://pubchem.ncbi.nlm.nih.gov/source/ChemIDplus

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 10/25/24.

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.2025.115240.

Appendix

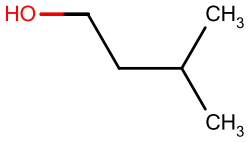
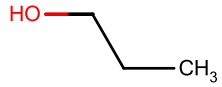
Read-across Justification:

Methods

The read-across analog was identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (Date et al., 2020). These criteria are in compliance with 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 Chemicals 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 (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, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.6 (OECD, 2023).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.6 (OECD, 2023).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.6 (OECD, 2023).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.6 (OECD, 2023).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.6 was selected as the alert system.

	Target Material	Read-across Material
Principal Name	Isoamyl alcohol	Propyl alcohol
CAS No.	123-51-3	71-23-8
Structure		
Similarity (Tanimoto Score)		0.58
SMILES	CC(C)CCO	CCCO
Endpoint		Local respiratory toxicity
Molecular Formula	$C_5H_{12}O$	C_3H_8O
Molecular Weight (g/mol)	88.15	60.096
Melting Point (°C, EPI Suite)	−117.20	−126.10
Boiling Point (°C, EPI Suite)	131.10	97.20
Vapor Pressure (Pa @ 25°C, EPI Suite)	3.16E+02	2.80E+03
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	2.67E+04	1.00E+06
Log K_{OW}	1.16	0.25
J_{max} (μg/cm^2/h, SAM)	733.51	12814.41
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.43E+00	7.51E-01
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.6)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on isoamyl alcohol (CAS # 123-51-3). 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, propyl alcohol (CAS # 71-23-8) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Propyl alcohol (CAS # 71-23-8) was used as a read-across analog for the target material, isoamyl alcohol (CAS # 123-51-3), for the local respiratory toxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the saturated alcohols group.
  - o The key difference between the target material and the read-across analog is the target material is a branched chain, whereas the read-across analog is a straight chain. This structural difference is toxicologically insignificant.
  - 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 v4.6, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o Neither the target material nor the read-across analog has alerts for local respiratory toxicity. The data on the read-across analog confirms that the material does not pose a concern for local respiratory toxicity. Therefore, based on the structural similarity between the target material and the read-across analog and the data on the read-across analog, the lack of *in silico* alerts and predictions is consistent with the 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.

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