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Short review



RIFM fragrance ingredient safety assessment, isobutylaldehyde, CAS Registry Number 78-84-2

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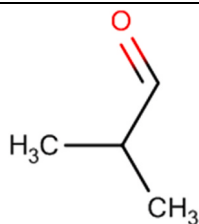
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**Abbreviation/Definition List:**

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

AF - Assessment Factor

BCF - Bioconcentration Factor

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

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, 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).

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*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.

Isobutyraldehyde was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that isobutyraldehyde is not genotoxic. Data on isobutyraldehyde provide a calculated margin of exposure (MOE) > 100 for the repeated dose, reproductive, and local respiratory toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for reactive materials (64 $\mu\text{g}/\text{cm}^2$); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; isobutyraldehyde is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; isobutyraldehyde 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.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (ECHA REACH Dossier: Isobutyraldehyde; ECHA, 2011; NTP, 1999)

Repeated Dose Toxicity: NOAEL = 1310 mg/kg/day. (NTP (1999))

Reproductive Toxicity: Developmental toxicity: 2937 mg/kg/day; Fertility: 2586 mg/kg/day. (ECHA REACH Dossier: Isobutyraldehyde; ECHA, 2011; NTP, 1999)

Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.

Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra; RIFM Database)

Local Respiratory Toxicity: NOAEC = 147.44 mg/m^3 (Abdo, 1998)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 80–90% (OECD 301 C) (ECHA REACH Dossier: Isobutyraldehyde; ECHA, 2011)

Bioaccumulation: Screening-level: 3.162 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 1214 mg/L (RIFM Framework; Salvido, 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvido, 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 1214 mg/L (RIFM Framework; Salvido, 2002)

RIFM PNEC is: 1.214 $\mu\text{g}/\text{L}$

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

1. Identification

- Chemical Name:** Isobutyraldehyde
- CAS Registry Number:** 78-84-2
- Synonyms:** Isobutyl aldehyde; Isobutyric aldehyde; 2-Methylpropanal; Propanal, 2-methyl-; Isobutanal; Isobutyraldehyde
- Molecular Formula:** $\text{C}_4\text{H}_8\text{O}$
- Molecular Weight:** 72.1
- RIFM Number:** 54
- Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

- Boiling Point:** 69.83 °C (EPI Suite)
- Flash Point:** < 40 °F; CC (FMA), -5 °C (GHS)

3. **Log K_{ow}**: 0.61 (Biobyte Corp.), 0.74 (EPI Suite)
4. **Melting Point**: 92.1 °C (EPI Suite)
5. **Water Solubility**: 31240 mg/L (EPI Suite)
6. **Specific Gravity**: 0.785 (FMA)
7. **Vapor Pressure**: 131 mm Hg at 20 °C (EPI Suite v4.0), 140 mm Hg at 20 °C (FMA), 164 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra**: No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol⁻¹ · cm⁻¹)
9. **Appearance/Organoleptic**: Clear, colorless, highly refractive liquid with a sharp, pungent odor

3. Volume of use (worldwide band)

1. 0.1–1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM Aggregate Exposure Model v1.0)

1. 95th Percentile Concentration in Hydroalcoholics: 0.000019% (RIFM, 2017)
2. Inhalation Exposure*: 0.000041 mg/kg/day or 0.0029 mg/day (RIFM, 2017)
3. Total Systemic Exposure**: 0.000068 mg/kg/day (RIFM, 2017)

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

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 v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:

- a. Genotoxicity: None
- b. Repeated Dose Toxicity: None
- c. Reproductive Toxicity: None
- d. Skin Sensitization: None
- e. Phototoxicity/Photoallergenicity: None
- f. Local Respiratory Toxicity: None
- g. Environmental Toxicity: None

3. Read-across Justification: None

7. Metabolism

No relevant data available for inclusion in this safety assessment.

Additional References: None.

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

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

Coffee	Beer
Pepper (<i>Piper nigrum</i> L.)	Tea
Filbert, Hazelnut (<i>Corylus avellano</i>)	Grape brandy
Wheaten bread	Wine
Cocoa category	Whisky
Mentha oils	Honey
Truffle	

*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 10/02/20 (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, isobutyraldehyde does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of isobutyraldehyde has been evaluated in a bacterial reverse mutation assay conducted using the standard preincubation method. *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, TA104, and TA102 were treated with isobutyraldehyde in a solvent 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 (ECHA, 2011). Under the conditions of the study, isobutyraldehyde was not mutagenic in the Ames test. Isobutyraldehyde was also tested in mammalian cell line mutagenicity study, using mouse lymphoma cells L5178Y only in the absence of S9 condition and was concluded to be positive based on the increases observed. However, these increases were only observed at cytotoxic doses and hence may not be considered to be a biologically relevant response. Follow-up in vivo comet and micronucleus studies were negative, which can be considered to be the more biologically relevant outcome (ECHA, 2011). Taken together, isobutyraldehyde may not be considered to be mutagenic.

The clastogenicity of isobutyraldehyde was assessed in an *in vitro* chromosome aberration study. Chinese hamster ovary cells were treated with isobutyraldehyde in DMSO at concentrations up to 4000 µg/mL in the presence and absence of metabolic activation. Non-dose-responsive increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed without S9 metabolic activation (ECHA, 2011). Under the conditions of the study, isobutyraldehyde was considered to be positive (without S9) in the *in vitro* chromosome aberration study. This was an older study, and a newer *in vitro* chromosome aberration study conducted using CHO-K1 and HepG2 cells was negative when tested up to 1 mM in both with and without S9 test conditions (ECHA, 2011). The clastogenic activity of isobutyraldehyde was evaluated in an *in vivo* chromosomal aberration study. The test material was

administered in corn oil via the intraperitoneal (i.p.) route of administration to groups of male B6C3F1 mice. Doses of 1000, 1200, 1500, and 1750 mg/kg body weight were administered. Mice from each dose level were euthanized at 17 h, and the bone marrow was extracted and examined for chromosomal aberrations. Significant increases in the frequency of aberrant cells were observed only at the doses that produced notable clinical signs of toxicity (1500 and 1750 mg/kg). No details on clinical signs or mortality rates were provided. In a simultaneously performed study by NTP, the LD50 in a different mouse strain was 960 mg/kg (i.p.). Hence, the doses tested in the study exceeded the MTD. There was no increase in the number of aberrant cells in the absence of significant systemic toxicity. Hence, the results observed only at higher toxic doses may not be biologically relevant (ECHA, 2011). At the same time, NTP also conducted a mouse bone marrow micronucleus test. The test material was administered in corn oil via the intraperitoneal route of administration to groups of male B6C3F1 mice. Doses of 25, 39.06, 78.13, 156.5, 312.5, 652, and 1250 mg/kg body weight were administered. Mice from each dose level were euthanized at 72 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 (ECHA, 2011). Under the conditions of the study, the test material was considered to be not clastogenic in the *in vivo* micronucleus test. In a newer OECD guideline mouse micronucleus test, male Sprague Dawley rats were treated with isobutyraldehyde in corn oil by oral gavage. Doses of 500, 1000, or 2000 mg/kg were administered. Mice from each dose level were euthanized at 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 (ECHA, 2011). Under the conditions of the study, isobutyraldehyde was considered to be not clastogenic in the *in vivo* micronucleus test.

Considering all the genotoxicity data available along with negative carcinogenicity outcome observed in a 2-year carcinogenicity study (NTP, 1999), it can be concluded that isobutyraldehyde may not be a concern for genotoxicity.

Additional References: NTP, 1999.

Literature Search and Risk Assessment Completed On: 01/24/20.

11.1.2. Repeated dose toxicity

The MOE for isobutyraldehyde is sufficient 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 isobutyraldehyde. Isobutyraldehyde was evaluated for repeated dose systemic toxicity in NTP 13-week and 105-week studies on groups of 10–50 F344N strain rats/sex/dose and 10–50 B6C3F1 mice strain mice/sex/dose. In the 13-week study, 10 animals/sex/dose of both species were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, 2000, 4000, and 8000 ppm (equivalent to 0, 655, 1310, 2621, 5242, and 10484 mg/kg/day, respectively) through inhalation (6 h and 12 min per day, 5 days per week). Mortality was observed in both sexes of both species at ≥ 4000 ppm when exposed for 13 weeks. No other systemic adverse effects were observed up to 2000 ppm in either sex of either species. Based on these results, in the carcinogenicity study, 50 animals/sex/dose of both species were exposed to isobutyraldehyde by whole-body inhalation at concentrations of 0, 500, 1000, or 2000 ppm (equivalent to 0, 655, 1310, and 2621 mg/kg/day) for 105 weeks (6 h and 12 min per day, 5 days per week). No systemic adverse effects were observed up to 2000 ppm in either sex of either species during the 105-week exposure period except decreased body weight in female mice at 2000 ppm. Hence, the mid dose (1000 ppm; 1310 mg/kg/day) from the 2-year carcinogenicity study in mice was considered to be the systemic

NOAEL based on decreased average body weight at the high dose (2000 ppm; 2620 mg/kg/day) (NTP, 1999).

The most conservative NOAEL of 1310 mg/kg/day, based on the 105-week study on mice, was considered for risk assessment of the repeated dose toxicity endpoint.

Therefore, the isobutyraldehyde MOE can be calculated by dividing the isobutyraldehyde NOAEL in mg/kg/day by the total systemic exposure to isobutyraldehyde, 1310/0.000068, or 19264706.

In addition, the total systemic exposure to isobutyraldehyde (0.068 $\mu\text{g}/\text{kg}/\text{day}$) is below the TTC (30 $\mu\text{g}/\text{kg}/\text{day}$; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Abdo (1998).

Literature Search and Risk Assessment Completed On: 01/22/20.

11.1.3. Reproductive toxicity

The MOE for isobutyraldehyde is sufficient for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are sufficient developmental toxicity and fertility data on isobutyraldehyde. In an OECD TG 414 and GLP-compliant prenatal developmental toxicity study, a group of 25 Wistar rats/sex/dose were exposed through inhalation (whole-body exposure) with isobutyraldehyde at concentrations of 0, 3, 7.6, and 12 mg/L (equivalent to 0, 734.4, 1860, and 2937 mg/kg/day, respectively) for 6 h/day through gestational days (GDs) 6–15. No treatment-related adverse effects were reported for conception rate, pre- and post-implantation loss, viability, number of corpora lutea, number of implantation sites, external examination, fetal weight, visceral observations, and skeletal observations in fetuses. Therefore, the NOAEL for developmental toxicity was considered to be 2937 mg/kg/day based on the absence of adverse developmental effects up to the highest tested dose (ECHA, 2011).

In an NTP 13-week repeated dose toxicity study, a group of 10 F344N strain rats/sex/dose were exposed with isobutyraldehyde at concentrations of 0, 500, 1000, 2000, and 4000 ppm through inhalation (equivalent to 433, 866, 1732, and 3464.2 mg/kg/day, respectively) 6 h and 12 min/day, 5 days/week, for 13 weeks. Three males and six females in the 4000 ppm group and 1 female in the 500 ppm group died before the end of the study. No treatment-related reproductive adverse effects were reported for sperm concentration, sperm motility, sperm density, sperm morphology, weights of right cauda epididymis, and right testis in males and estrous cycle evaluation (di-estrous, pro-estrous, estrous, and met-estrous) in females up to the highest tested dose. Therefore, the NOAEL for fertility was considered to be 3464.2 mg/kg/day (NTP, 1999).

In an NTP 13-week repeated dose toxicity study, a group of 10 B6C3F1 strain mice/sex/group were exposed with isobutyraldehyde at concentrations of 0, 500, 1000, 2000, and 4000 ppm through inhalation (equivalent to 646.5, 1293, 2586, and 5172 mg/kg/day, respectively) for 6 h and 12 min/day, 5 days/week, for 13 weeks. No treatment-related reproductive adverse effects were reported for sperm concentration, sperm motility, sperm density, sperm morphology, weights of right cauda epididymis, and right testis in males and estrous cycle evaluation (di-estrous, pro-estrous, estrous, and met-estrous) in females up to the highest tested dose. Mortality was reported in 9 males and all females at 4000 ppm. Therefore, the NOAEL for fertility was considered to be 2586 mg/kg/day (NTP, 1999).

The NOAEL of 2937 mg/kg/day was considered for the risk assessment of the developmental toxicity endpoint. The NOAEL of 2586 mg/kg/day in rats was considered for the risk assessment of the fertility endpoint.

The isobutyraldehyde MOE for developmental toxicity endpoint can be calculated by dividing the isobutyraldehyde NOAEL in mg/kg/day by

the total systemic exposure to isobutyraldehyde, 2937/0.000068, or 43191177.

The isobutyraldehyde MOE for fertility endpoint can be calculated by dividing the isobutyraldehyde NOAEL in mg/kg/day by the total systemic exposure to isobutyraldehyde, 2586/0.000068, or 37764706.

In addition, the total systemic exposure to isobutyraldehyde (0.068 µg/kg/day) is below the TTC (30 µg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Abdo (1998).

Literature Search and Risk Assessment Completed On: 01/27/20.

11.1.4. Skin sensitization

Based on the existing data and the application of DST, isobutyraldehyde does not present a concern for skin sensitization.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for isobutyraldehyde. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD toolbox v4.2). In a mouse ear swelling test (MEST), no reactions indicative of skin sensitization were found (ECHA, 2011). In a human maximization test, no skin sensitization reactions were observed with isobutyraldehyde at 1% (690 µg/cm²) in petrolatum (RIFM, 1978). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the reactive DST of 64 µg/cm² (Safford, 2008; Safford et al., 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for isobutyraldehyde that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/26/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, isobutyraldehyde 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 isobutyraldehyde in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, isobutyraldehyde does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L mol⁻¹ · cm⁻¹ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/13/20.

11.1.6. Local respiratory toxicity

The MOE for isobutyraldehyde is adequate for the local respiratory toxicity 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

Table 1

Maximum acceptable concentrations for isobutyraldehyde that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category ^a	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.0049%	5.0 × 10 ⁻⁵ %
2	Products applied to the axillae	0.0015%	2.7 × 10 ⁻⁴ %
3	Products applied to the face using fingertips	0.029%	2.3 × 10 ⁻⁵ %
4	Fine fragrance products	0.027%	1.9 × 10 ⁻⁵ %
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	0.0012%
6	Products with oral and lip exposure	0.016%	4.5 × 10 ⁻⁴ %
7	Products applied to the hair with some hand contact	0.056%	1.2 × 10 ⁻⁴ %
8	Products with significant anogenital exposure	0.0029%	No Data ^c
9	Products with body and hand exposure, primarily rinse-off	0.054%	7.7 × 10 ⁻⁴ %
10	Household care products with mostly hand contact	0.19%	0.010%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No Data ^c
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not restricted	0.25%

Note:^aFor a description of the categories, refer to the IFRA/RIFM Information Booklet.

^bNo reported use.

^cFragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. A 2-year carcinogenicity study was carried out in 50 F344/N rats/sex/group (Abdo, 1998; also available in NTP, 1999). The animals were exposed to isobutyraldehyde via inhalation at 0, 1474.44, 2948.88, and 5897.75 mg/m³ for 6 h/day, 5 days/week. Test material-related non-neoplastic lesions were limited to the nose and consisted of respiratory epithelium squamous metaplasia, olfactory epithelium degeneration, and suppurative inflammation. Females were more susceptible to the test material-related effects pertaining to minimal to mild squamous metaplasia, which was observed to be significantly greater in males and females from the 2948.88 and 5897.75 mg/m³ groups and in females from the 1474.44 mg/m³ group as compared to chamber controls. All other local effects were observed in the animals from mid- and high-exposure groups. Considering the local respiratory effects observed, a LOAEC was identified at 1474.44 mg/m³. Therefore, by using a safety factor of 10, the NOAEC is estimated to be 147.44 mg/m³.

This NOAEC expressed in mg/kg lung weight/day is:
(147.44 mg/m³) × (1 m³/1000 L) = 0.14744 mg/L.

Minute ventilation (MV) of 0.17 L/min for a F344/N rat \times duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day.

$$(0.14744 \text{ mg/L}) \times (61.2 \text{ L/d}) = 9.023 \text{ mg/day.}$$

$$(9.023 \text{ mg/day}) / (0.0016 \text{ kg lung weight of rat}^*) = 5639.4 \text{ mg/kg lung weight/day.}$$

The 95th percentile calculated exposure was reported to be 0.0029 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey, 2015; Safford et al., 2015a). 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, 2009) to give 0.0045 mg/kg lung weight/day resulting in an MOE of 1,253,200 (i.e., [5639.4 mg/kg lung weight of rat/day] / [0.0045 mg/kg lung weight of human/day]) (Abdo, 1998; NTP, 1999).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.0029 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: "Comparative Physiology and Anatomy," subsection, "Comparative Airway Anatomy."

Additional References: Steinhagen (1984); Salem (1960); Smyth (1954); Gage (1970); Sim (1957).

Literature Search and Risk Assessment Completed On: 01/24/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of isobutyraldehyde was performed following the RIFM Environmental Framework (Salvito, 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, isobutyraldehyde 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 isobutyraldehyde 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, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF \geq 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).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), isobutyraldehyde presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. *Biodegradation.* No data available.

11.2.2.2. *Ecotoxicity.* No data available.

11.2.2.3. *Other available data.* Isobutyraldehyde has been registered for REACH with the following additional data available at this time:

The ready biodegradability of the test material was evaluated using the Modified MITI test (I) according to the OECD 301 C guideline. Biodegradation of 80%–90% was observed after 28 days.

The acute fish (Fathead minnows) toxicity test was conducted by following Standard Methods for the Examination of Water and Wastewater, under static conditions. The 96-h LC50 value based on nominal concentrations was reported to be 23 mg/L.

The acute toxicity test for *Daphnia* was conducted according to the EU method C.2, under static conditions. The 48-h EC50 value based on nominal test concentrations was reported to be 277 mg/L.

The acute toxicity test for algae was conducted according to the DIN 38412 Part 9 guideline, under static conditions. The 72-h EC50 value based on nominal test concentrations for growth rate was reported to be 83.7 mg/L.

11.2.3. Risk assessment refinement

Since isobutyraldehyde has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (<i>Daphnia</i>) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μ g/L)	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>1214</u>			1000000	1.214	

Exposure information and PEC calculation (following RIFM Environmental Framework: [Salvito, 2002](#))

Exposure	Europe (EU)	North America (NA)
Log Kow Used	0.74	0.74
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	<1
Risk Characterization: PEC/PNEC	<1	<1

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

The RIFM PNEC is 1.214 µg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at 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: 01/14/20.

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>
- **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://hvpchemicals.oecd.org/ui/Default.aspx>
- **EPA ACToR:** <https://actor.epa.gov/actor/home.xhtml>
- **US EPA HPVIS:** https://ofmpub.epa.gov/opthpv/public_search_publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **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/>

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 05/31/20.

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.

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