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RIFM fragrance ingredient safety assessment, 2-ethylbutyric acid, CAS Registry Number 88-09-5

A.M. Api [a], D. Belsito [b], S. Biserta [a], D. Botelho [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M. A. Cancellieri [a], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], S. Gadhia [a], L. Jones [a], K. Joshi [a], A. Lapczynski [a], M. Lavelle [a], D.C. Liebler [i], M. Na [a], D. O'Brien [a], A. Patel [a], T.M. Penning [j], G. Ritacco [a], F. Rodriguez-Ropero [a], J. Romine [a], N. Sadekar [a], D. Salvito [a], T. W. Schultz [k], F. Siddiqi [a], I.G. Sipes [l], G. Sullivan [a,*], Y. Thakkar [a], Y. Tokura [m], S. Tsang [a]

[a] *Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA*
[b] *Member Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA*
[c] *Member Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden*
[d] *Member Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 58109, USA*
[e] *Member Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany*
[f] *Member Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP 05508-900, Brazil*
[g] *Member Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany*
[h] *Member Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA*
[i] *Member Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA*
[j] *Member of Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA*
[k] *Member Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996- 4500, USA*
[l] *Member Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA*
[m] *Member Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

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* Corresponding author.
E-mail address: gsullivan@rifm.org (G. Sullivan).

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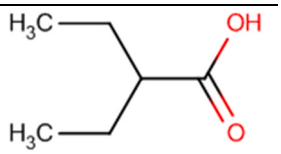

Abbreviation/Definition List:

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).

*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

(*continued on next column*)

(*continued*)

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-Ethylbutyric acid was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that 2-ethylbutyric acid is not genotoxic. Data on 2-ethylbutyric acid provide a calculated margin of exposure (MOE) > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the dermal sensitization threshold (DST) for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet (UV) spectra; 2-ethylbutyric acid is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the threshold of toxicological concern (TTC) for a Cramer Class I material, and the exposure to 2-ethylbutyric acid is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; 2-ethylbutyric acid 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 genotoxic. (ECHA REACH Dossier: 2-Ethylbutyric Acid; ECHA, 2018)

Repeated Dose Toxicity: NOAEL = 3 mg/kg/day. OECD (2006)

Reproductive Toxicity: Developmental toxicity: NOAEL = 50 mg/kg/day Fertility: NOAEL = 250 mg/kg/day. OECD (2006)

Skin Sensitization: No safety concerns for skin sensitization 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: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:

Persistence:
Critical Measured Value: 96% in 14 days (OECD 301 C) (ECHA REACH Dossier: 2-Ethylbutyric Acid; ECHA, 2018)

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

Ecotoxicity:
Screening-level: Fish LC50: 163.10 mg/L (RIFM Framework; Salvito, 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, 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 163.10 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.16310 μg/L

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

1. Identification

1. **Chemical Name:** 2-Ethylbutyric acid
2. **CAS Registry Number:** 88-09-5
3. **Synonyms:** Butanoic acid, 2-ethyl-; Diethylacetic acid; α-Ethylbutyric acid; アルカン酸（C = 4 ~ 3 0）; 2-Ethylbutanoic acid; 2-Ethylbutyric acid
4. **Molecular Formula:** $C_6H_{12}O_2$
5. **Molecular Weight:** 116.16
6. **RIFM Number:** 6084
7. **Stereochemistry:** Stereoisomer not specified. No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 195 °C (Fragrance Materials Association [FMA]), 195.8 °C (EPI Suite)
2. **Flash Point:** > 200 °F; CC (FMA), >93 °C (Globally Harmonized System)
3. **Log K_{OW}:** 1.98 (EPI Suite)
4. **Melting Point**: 15.24 °C (EPI Suite)
5. **Water Solubility:** 9456 mg/L (EPI Suite)
6. **Specific Gravity:** 0.920 (FMA)
7. **Vapor Pressure:** 0.332 mm Hg @ 20 °C (EPI Suite v4.0), 0.1 mm Hg 20 °C (FMA), 0.486 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless liquid that has an oily-fruity, acidulous odor, not as "rancid" as that of Caproic acid, and has a fruity-earthy, acid taste with a Nut-like undertone

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: 0.000018% (RIFM, 2017)
2. Inhalation Exposure*: <0.0001 mg/kg/day or 0.0000003 mg/day (RIFM, 2017)
3. Total Systemic Exposure**: 0.00048 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, 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, 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 v2.6	OECD QSAR Toolbox v3.2
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)

2-Ethylbutyric acid is reported to occur in the following foods by the VCF*:

Blue cheeses
Cheddar cheese
Cheese, various types
Guava and Feyoa
Wheaten bread

*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.

9. REACH dossier

Available; accessed 07/12/19.

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-ethylbutyric acid does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. The mutagenic activity of 2-ethylbutyric acid has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and according to OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, TA102, and *Escherichia coli* strain WP2uvrA were treated with 2-ethylbutyric acid in dimethyl sulfoxide (DMSO) 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, 2018). Under the conditions of the study, 2-ethylbutyric acid was not mutagenic in the Ames test.

The clastogenicity of 2-ethylbutyric acid was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Chinese hamster lung (CHL/IU) cells were treated with 2-ethylbutyric acid in DMSO at concentrations up to 1600 μg/mL in the presence and absence of metabolic activation. Polyploidy was not observed in any treatment group, but structural chromosomal aberrations were noted in Chinese hamster lung cells at 1200 and 1600 μg/mL without S9 metabolic activation (ECHA, 2018). Under the conditions of the study, 2-ethylbutyric acid was considered to be clastogenic in the *in vitro* chromosome aberration assay.

The clastogenic activity of 2-ethylbutyric acid 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 DMSO via the oral route of administration to groups of male BDF1 mice. 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, 2018). Under the conditions of the study, 2-ethylbutyric acid was considered to be not clastogenic in the *in vivo* micronucleus test.

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

Additional References: JECDB, 2001.

Literature Search and Risk Assessment Completed On: 08/15/19.

11.1.2. Repeated dose toxicity

The MOE for 2-ethylbutyric acid 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 for 2-ethylbutyric acid. In an OECD 422/GLP combined oral repeated dose and reproductive/developmental toxicity screening test, Sprague Dawley rats (13/sex/dose) were orally (via gavage) administered 2-ethylbutyric acid at doses of 0 (vehicle control, corn oil), 10, 50, and 250 mg/kg/day for 42 days (14 days before mating, 14 days during the mating period, and 14 days after the mating period) for males and for 41–53 days (14 days before mating, throughout the mating and gestation periods, and up to day 4 of lactation) for females. Hematological examination in males revealed statistically significant reductions in white blood cell counts (mid- and high-dose) and platelet counts (high-dose). There were no treatment-related effects on hematological parameters examined in female animals. Blood biochemistry analysis showed statistically significant increased γ-GT activity in females of the mid- and high-dose groups. However, the extent of this increase was minor, and no treatment-related effects were observed in liver weights and histopathology. Hence, this effect was not considered to be of toxicological significance. The kidney weights of males (relative weight) and females (absolute and relative weights) of the high-dose group were increased (statistically significant). However, there were no correlated adverse effects observed in blood biochemistry parameters for kidney function or in histopathology; hence, the cause of this effect was unknown. No alterations were observed in gross pathology and histopathology of treatment groups when compared to the controls. Based on the statistically significant decrease in white blood cell counts in mid- and high-dose group males, a NOAEL of 10 mg/kg/day was considered for males. Based on increases in the absolute and relative kidney weights in high-dose group females, a NOAEL of 50 mg/kg/day was considered for females (JECDB, 2001; also available at JECDB Study abstract, 2001; OECD, 2006).

In a 90-day dietary repeated dose toxicity study, male Sprague Dawley rats (6/dose) were fed diets (30% dextrose, 20% cornmeal, 20% soybean meal, 10% casein, 9% corn starch, 5% corn oil, 4% salt mixture, 2% mixture of vitamins) containing 2-ethylbutyric acid at concentrations of 0 (control) and 0.6% (equivalent to 300 mg/kg/day, as per EFSA report). No statistically significant, treatment-related alterations were reported in the parameters observed (food intake, weight gain, organ weights, tissue sections, urinalysis, hematology, biochemistry) in the study. Therefore, the NOAEL was considered to be 0.6% (equivalent to 300 mg/kg/day, as per the EFSA report), based on no adverse effects observed in the single tested dose group (Amoore, 1978; EFSA, 2012).

The most conservative NOAEL of 10 mg/kg/day from the OECD 422 study was considered for the risk assessment.

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity endpoint is 10/3 or 3.33 mg/kg/day.

Therefore, the 2-ethylbutyric acid MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-ethylbutyric acid NOAEL in mg/kg/day by the total systemic exposure to 2-ethylbutyric acid, 3.33/0.00048 or 6938.

In addition, the total systemic exposure to 2-ethylbutyric acid (0.48 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/07/19.

11.1.3. Reproductive toxicity

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

11.1.3.1. Risk assessment. There are sufficient reproductive toxicity data on 2-ethylbutyric acid. In an OECD 422/GLP combined oral repeated dose and reproductive/developmental toxicity screening test, Sprague Dawley rats (13/sex/dose) were orally (via gavage) administered 2-ethylbutyric acid at doses of 0 (vehicle control, corn oil), 10, 50, and 250 mg/kg/day for 42 days (14 days before mating, 14 days during the mating period, and 14 days after the end of the mating period) for males and for 41–53 days (14 days before mating, throughout the mating and gestation periods, and up to day 4 of lactation) for females. There were no treatment-related effects observed in the estrous cycle, reproductive performance (precoital interval, numbers of corpora lutea, copulation index, and fertility index), gestation length, ovulation, number of implantations, and implantation index. In the mid- and high-dose treatment groups, abnormalities in behavior (e.g., to collect pups after birth) and prolonged delivery were reported; however, no dose-dependency was found. Statistically significant decreases in the number of live newborns, birth index, live birth index (day 0 of lactation), and the number of live pups (day 4 of lactation) were reported in the high-dose group. No treatment-related effects were reported for pup viability (day 4 of lactation) and body weights of pups (both at days 0 and 4 of lactation). Furthermore, no treatment-related morphological alterations (external and visceral) were observed. Therefore, the fertility NOAEL was considered to be 250 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity was considered to be 50 mg/kg/day, based on a reduction in the number of live pups in the highest-dose group (OECD, 2006).

The 2-ethylbutyric acid MOE for the developmental toxicity endpoint can be calculated by dividing the 2-ethylbutyric acid NOAEL in mg/kg/day by the total systemic exposure to 2-ethylbutyric acid, 50/0.00048, or 104167.

The 2-ethylbutyric acid MOE for the fertility endpoint can be calculated by dividing the 2-ethylbutyric acid NOAEL in mg/kg/day by the total systemic exposure to 2-ethylbutyric acid, 250/0.00048, or 520833.

In addition, the total systemic exposure to 2-ethylbutyric acid (0.48 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: Narotsky (1989).

Literature Search and Risk Assessment Completed On: 08/16/19.

11.1.4. Skin sensitization

Based on the application of DST, 2-ethylbutyric acid does not present

a concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.3). No predictive skin sensitization studies are available for 2-ethylbutyric acid. Due to the absence of data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008, 2011, 2015b; Roberts, 2015). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for 2-ethylbutyric acid that present no appreciable risk for skin sensitization based on the non-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: 08/07/19.

Table 1
Maximum acceptable concentrations for 2-ethylbutyric acid that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU[b]
2	Products applied to the axillae	0.021%	0.0021%
3	Products applied to the face using fingertips	0.41%	NRU[b]
4	Fine fragrance products	0.39%	1.8×10^{-5}%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	2.6×10^{-7}%
6	Products with oral and lip exposure	0.23%	0.015%
7	Products applied to the hair with some hand contact	0.79%	NRU[b]
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	4.3×10^{-7}%
10	Household care products with mostly hand contact	2.7%	6.9×10^{-6}%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	1.5×10^{-7}%

Note:
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] No reported use.
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 2-ethylbutyric acid 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-ethylbutyric acid in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 2-ethylbutyric acid 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: 07/22/19.

11.1.6. Local Respiratory Toxicity

The MOE could not be calculated due to a lack of appropriate data. The exposure level for 2-ethylbutyric acid is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on 2-ethylbutyric acid. Based on the Creme RIFM Model, the inhalation exposure is 0.0000003 mg/day. This exposure is 4666667 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Smyth (1954); Smyth (1951); Stasenkova (1962); Hoffman (1991); Silver (1992); Hubbs (2002); VandenBergh (1999); NIOSH, 2006; Morris (2009).

Literature Search and Risk Assessment Completed On: 08/07/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of 2-ethylbutyric acid 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, 2-Ethylbutyric acid 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-ethylbutyric acid as possibly being persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	163.10			1000000	0.16310	

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 ≥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), 2-ethylbutyric acid presents no risk to the aquatic compartment in the screening-level assessment.

11.2.3. Key studies

11.2.3.1. Biodegradation. No data available.

11.2.3.2. Ecotoxicity. No data available.

11.2.4. Other available data

2-Ethylbutyric acid 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 (based on TOC) of 96% was observed after 14 days.

The 96-h acute fish (*Oryzias latipes*) toxicity test was conducted according to the OECD 203 guideline under semi-static conditions. The 96-h LC50 value, based on nominal concentrations, was reported to be > 50 - <100 mg/L.

The *Daphnia magna* acute immobilization test was conducted according to the OECD 202 guideline. The 48-h LC50 value was reported to be 70 mg/L.

The 21-day *Daphnia magna* reproduction test was conducted according to the OECD 211 guideline. The 48-h LC50 value was reported to be 70 mg/L. The 21-day NOEC value based on reproduction and mortality was reported to be 48.9 mg/L.

The algae growth inhibition test was conducted according to the OECD 201 guideline. The 72-h EC50 value based on growth rate was reported to be > 63 mg/L (ECHA, 2018).

11.2.5. Risk assessment refinement

Since 2-ethylbutyric acid 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 μg/L).

Endpoints used to calculate PNEC are highlighted.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	1.98	1.98
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. Additional assessment is necessary.

The RIFM PNEC is 0.16310 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: 08/08/19.

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**
- **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://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/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 09/30/19.

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.

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