



ELSEVIER

Contents lists available at ScienceDirect

## Food and Chemical Toxicology

journal homepage: [www.elsevier.com/locate/foodchemtox](http://www.elsevier.com/locate/foodchemtox)

## Short Review

## RIFM fragrance ingredient safety assessment, 4-ethyloctanoic acid, CAS Registry Number 16493-80-4



A.M. Api<sup>a</sup>, D. Belsito<sup>b</sup>, D. Botelho<sup>a</sup>, M. Bruze<sup>c</sup>, G.A. Burton Jr.<sup>d</sup>, J. Buschmann<sup>e</sup>, M.L. Dagli<sup>f</sup>, M. Date<sup>a</sup>, W. Dekant<sup>g</sup>, C. Deodhar<sup>a</sup>, M. Francis<sup>a</sup>, A.D. Fryer<sup>h</sup>, L. Jones<sup>a</sup>, K. Joshi<sup>a</sup>, S. La Cava<sup>a</sup>, A. Lapczynski<sup>a</sup>, D.C. Liebler<sup>i</sup>, D. O'Brien<sup>a</sup>, A. Patel<sup>a</sup>, T.M. Penning<sup>j</sup>, G. Ritacco<sup>a</sup>, J. Romine<sup>a</sup>, N. Sadekar<sup>a</sup>, D. Salvito<sup>a</sup>, T.W. Schultz<sup>k</sup>, I.G. Sipes<sup>l</sup>, G. Sullivan<sup>a,\*</sup>, Y. Thakkar<sup>a</sup>, Y. Tokura<sup>m</sup>, S. Tsang<sup>a</sup>

<sup>a</sup> Research Institute for Fragrance Materials, Inc, 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA

<sup>b</sup> Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY, 10032, USA

<sup>c</sup> Malmö University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmö, SE-20502, Sweden

<sup>d</sup> School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St, Ann Arbor, MI, 48109, USA

<sup>e</sup> Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany

<sup>f</sup> 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

<sup>g</sup> University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany

<sup>h</sup> Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA

<sup>i</sup> Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA

<sup>j</sup> 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

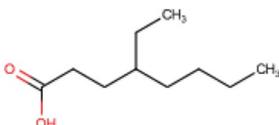
<sup>k</sup> The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

<sup>l</sup> Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

<sup>m</sup> The Journal of Dermatological Science (JDS), Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

Version: 040218. This version replaces any previous versions.

Name: 4-Ethyloctanoic acid CAS Registry Number: 16493-80-4

**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

**Crema RIFM Model** - The Crema 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) compared to a deterministic aggregate approach

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

**DST** - Dermal Sensitization Threshold

**ECHA** - European Chemicals Agency

**EU** - Europe/European Union

**GLP** - Good Laboratory Practice

**IFRA** - The International Fragrance Association

**LOEL** - Lowest Observable Effect Level

**MOE** - Margin of Exposure

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

**NA** - North America

**NESIL** - No Expected Sensitization Induction Level

**NOAEC** - No Observed Adverse Effect Concentration

**NOAEL** - No Observed Adverse Effect Level

**NOEC** - No Observed Effect Concentration

**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

**QRA** - Quantitative Risk Assessment

**REACH** - Registration, Evaluation, Authorisation, and Restriction of Chemicals

**RfD** - Reference Dose

**RIFM** - Research Institute for Fragrance Materials

**RQ** - Risk Quotient

\* Corresponding author.

E-mail address: [gsullivan@rifm.org](mailto:gsullivan@rifm.org) (G. Sullivan).

<https://doi.org/10.1016/j.fct.2019.03.022>

Received 17 April 2018; Received in revised form 4 October 2018; Accepted 11 March 2019

Available online 16 March 2019

0278-6915/© 2019 Elsevier Ltd. All rights reserved.

**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 under the limits described in this safety assessment.**

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

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

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

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

4-Ethyl octanoic acid was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs isovaleric acid (CAS # 503-74-2) and 2-methylheptanoic acid (CAS # 1188-02-9) show that 4-ethyl octanoic acid is not expected to be genotoxic. The skin sensitization endpoint was completed using DST for non-reactive materials (900  $\mu\text{g}/\text{cm}^2$ ); exposure is below the DST. Data provide a calculated MOE > 100 for the repeated dose and reproductive toxicity endpoints. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and exposure to 4-ethyl octanoic acid is below the TTC (1.4 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; 4-ethyl octanoic acid is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, 4-ethyl octanoic acid was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC) are < 1.

#### Human Health Safety Assessment

**Genotoxicity:** Not expected to be genotoxic. (RIFM, 1999; RIFM, 2014b)

**Repeated Dose Toxicity:** 3 mg/kg/day. (OECD, 2006)

**Reproductive Toxicity: Developmental Toxicity:** 50 mg/kg/day. **Fertility:** 250-mg/kg/day. (OECD, 2006)

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

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

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

#### Environmental Safety Assessment

##### Hazard Assessment:

**Persistence:** Screening-level: 3.5 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

**Bioaccumulation:** Screening-level: 3.16 L/kg (EPI Suite v4.11; US EPA, 2012a)

**Ecotoxicity:** Screening-level: Fish LC50: 4.768 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:** Fish LC50: 4.768 mg/L (Salvito et al., 2002)

RIFM PNEC is: 0.00477  $\mu\text{g}/\text{L}$

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

## 1. Identification

- Chemical Name:** 4-Ethyl octanoic acid
- CAS Registry Number:** 16493-80-4
- Synonyms:** Octanoic acid, 4-ethyl-; 4-Ethyl octanoic acid
- Molecular Formula:**  $\text{C}_{10}\text{H}_{20}\text{O}_2$
- Molecular Weight:** 172.27
- RIFM Number:** 5432

7. **Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers possible.

## 2. Physical data

- Boiling Point:** 268.98 °C (US EPA, 2012a)
- Flash Point:** 212.00 °F TCC (100.00 °C)\*
- Log  $K_{ow}$ :** 3.94 (US EPA, 2012a)
- Melting Point:** 59.15 °C (US EPA, 2012a)
- Water Solubility:** 64.05 mg/L (US EPA, 2012a)
- Specific Gravity:** 0.89800 to 0.90800 @ 25.00 °C\*
- Vapor Pressure:** 0.00266 mm Hg @ 20 °C (US EPA, 2012a), 0.0048 mm Hg @ 25 °C (US EPA, 2012a)
- UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark ( $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$ )
- Appearance/Organoleptic:** Colorless to pale yellow clear liquid (est); goaty lamb/mutton fatty\*

\*<http://www.thegoodscentcompany.com/data/rw1515051.html>.

## 3. Exposure to fragrance ingredient

- Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2015)
- 95th Percentile Concentration in Hydroalcohols:** 0.000020% (RIFM, 2017)
- Inhalation Exposure\*:** 0.0000004 mg/kg/day or 0.000023 mg/day (RIFM, 2017)
- Total Systemic Exposure\*\*:** 0.0000006 mg/kg/day (RIFM, 2017)

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

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

## 4. Derivation of systemic absorption

- Dermal:** Assumed 100%
- Oral:** Assumed 100%
- Inhalation:** Assumed 100%

## 5. Computational toxicology evaluation

- Cramer Classification:** Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

- Analogs Selected:
  - Genotoxicity:** Isovaleric acid (CAS # 503-74-2); 2-Methylheptanoic acid (CAS # 1188-02-9)
  - Repeated Dose Toxicity:** 2-Ethylbutyric acid (CAS # 88-09-5)
  - Reproductive Toxicity:** 2-Ethylbutyric acid (CAS # 88-09-5)
  - Skin Sensitization:** None
  - Phototoxicity/Photoallergenicity:** None
  - Local Respiratory Toxicity:** None

g. **Environmental Toxicity:** None

3. Read-across Justification: See Appendix below

## 6. Metabolism

No relevant data available for inclusion in this safety assessment.

## 7. Natural occurrence (discrete chemical) or composition (NCS)

4-Ethylheptanoic acid is reported to occur in the following foods by the VCF\*:

Blue cheeses  
Cheese, various types  
Lamb and mutton

\*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.

## 8. IFRA standard

None.

## 9. REACH dossier

Pre-registered for 05/31/2013; no dossier available as of 03/26/2018.

## 10. Summary

### 10.1. Human health endpoint summaries

#### 10.1.1. Genotoxicity

Based on the current existing data, 4-Ethylheptanoic acid does not present a concern for genotoxicity.

**10.1.1.1. Risk assessment.** 4-Ethylheptanoic acid was assessed in the BlueScreen assay and found negative for both cytotoxicity ( $\leq 30\%$  cell viability) and genotoxicity, with and without metabolic activation (RIFM, 2014a). There are no data assessing the mutagenic activity of 4-ethylheptanoic acid; however, read-across can be made to isovaleric acid (CAS # 503-74-2; see Section V). The mutagenic activity of isovaleric acid 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 method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with isovaleric acid in dimethyl sulfoxide (DMSO) at concentrations up to 5000  $\mu\text{g}/\text{plate}$ . No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 1999). Under the conditions of the study, isovaleric acid was not mutagenic in the Ames test, and this can be extended to 4-ethylheptanoic acid.

There are no data assessing the clastogenic activity of 4-ethylheptanoic acid; however, read-across can be made to 2-methylheptanoic acid (CAS # 1188-02-9; see Section V). The clastogenic activity of 2-methylheptanoic acid was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with 2-methylheptanoic acid in DMSO at concentrations up to 1440  $\mu\text{g}/\text{mL}$  in the presence and absence of metabolic activation (S9) for 4 and 24 h. 2-Methylheptanoic acid did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-

activated test systems (RIFM, 2014b). Under the conditions of the study, 2-methylheptanoic acid was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 4-ethylheptanoic acid.

Based on the data available, 4-ethylheptanoic acid does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 09/25/2017.

#### 10.1.2. Repeated dose toxicity

The margin of exposure for 4-ethylheptanoic acid is adequate for the repeated dose toxicity endpoint at the current level of use.

**10.1.2.1. Risk assessment.** There are insufficient repeated dose toxicity data on 4-ethylheptanoic acid. Read-across material 2-ethylbutyric acid (CAS # 88-09-5; see section V) has sufficient repeated dose toxicity data. 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  $\gamma$ -glutamyl transferase 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. Kidney weights of males (relative weight) and females (absolute and relative weights) of the high-dose group were statistically significantly increased. 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 Study report, 2001; also available at JECDB Study abstract, 2001 and OECD SIDS Initial Assessment Report for SIAM 23, 2006 [OECD, 2006]).

In a 90-day dietary repeated dose toxicity study, male Sprague Dawley rats (6/dose) were fed diet (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 parameters observed in the study. Therefore, the NOAEL was considered to be 0.6% (equivalent to 300 mg/kg/day, as per EFSA report), based on no adverse effects observed in the single tested dose group. (Amoore et al., 1978; EFSA, 2008).

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. 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 mg/kg/day.

Therefore, the 4-ethylheptanoic 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 4-ethyloctanoic acid, 3/0.0000006 or 5000000.

In addition, the total systemic exposure to 4-ethyloctanoic acid (0.0006 µg/kg bw/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

\*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:** 10/04/2017.

### 10.1.3. Reproductive toxicity

The margin of exposure for 4-ethyloctanoic acid is adequate for the reproductive toxicity endpoint at the current level of use.

**10.1.3.1. Risk assessment.** There are insufficient reproductive toxicity data on 4-ethyloctanoic acid. Read-across material 2-ethylbutyric acid (CAS # 88-09-5; see section V) has sufficient reproductive toxicity data. 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 estrous cycle, reproductive performance (precoital interval, numbers of corpora lutea, copulation index, and fertility index), gestation length, ovulation, number of implantation, 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 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 at the highest dose

group (JECDB Study report, 2001; also available at JECDB Study abstract, 2001 and OECD SIDS Initial Assessment Report for SIAM 23, 2006 [OECD, 2006]).

Therefore, the 4-ethyloctanoic 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 4-ethyloctanoic acid, 50/0.0000006 or 83333333.

The 4-ethyloctanoic 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 4-ethyloctanoic acid, 250/0.0000006 or 416666666.

In addition, the total systemic exposure to 4-ethyloctanoic acid (0.0006 µg/kg bw/day) is below the TTC (30 µg/kg bw/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:** Narotsky et al., 1994.

**Literature Search and Risk Assessment Completed On:** 10/04/2017.

### 10.1.4. Skin sensitization

Based on the application of DST, 4-ethyloctanoic acid does not present a safety concern for skin sensitization under the current, declared levels of use.

**10.1.4.1. Risk assessment.** The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). No skin sensitization studies are available for 4-ethyloctanoic acid or read-across materials.

Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 µg/cm<sup>2</sup>. 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 acceptable concentrations for 4-ethyloctanoic acid, which presents no appreciable risk for skin sensitization based on the non-reactive DST.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 09/26/17.

### 10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 4-ethyloctanoic acid would not be expected to present a concern for phototoxicity or photoallergenicity.

**Table 1**

Acceptable concentration limits for 4-ethyloctanoic acid based on non-reactive DST.

IFRA Category <sup>a</sup>	Description of Product Type	Acceptable Concentrations in Finished products	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.07%	0.00%
2	Products applied to the axillae	0.02%	0.00% <sup>b</sup>
3	Products applied to the face using fingertips	0.41%	0.00%
4	Fine fragrance products	0.39%	0.00% <sup>b</sup>
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%
6	Products with oral and lip exposure	0.23%	0.00%
7	Products applied to the hair with some hand contact	0.79%	0.00%
8	Products with significant ano-genital exposure	0.04%	No Data
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.00%
10	Household care products with mostly hand contact	2.70%	0.00%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.00% <sup>b</sup>

Note.

<sup>a</sup> For a description of the categories, refer to the IFRA/RIFM Information Booklet.

<sup>b</sup> Negligible exposure (< 0.01%).

**10.1.5.1. Risk assessment.** There are no phototoxicity studies available for 4-ethyloctanoic acid 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 et al., 2009). Based on lack of absorbance, 4-ethyloctanoic acid does not present a concern for phototoxicity or photoallergenicity.

**10.1.5.2. 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,  $1000 \text{ L mol}^{-1} \cdot \text{cm}^{-1}$  (Henry et al., 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 09/20/17.

#### 10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 4-ethyloctanoic acid is below the Cramer Class I TTC value for inhalation exposure local effects.

**10.1.6.1. Risk assessment.** There are no inhalation data available on 4-ethyloctanoic acid. Based on the Creme RIFM Model, the inhalation exposure is 0.000023 mg/day. This exposure is 60870 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 10/05/17.

### 10.2. Environmental endpoint summary

#### 10.2.1. Screening-level assessment

A screening-level risk assessment of 4-ethyloctanoic acid 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

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, 4-ethyloctanoic 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) 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, 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  $\geq 2000 \text{ L/kg}$ . 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 1.

**10.2.1.1. Risk assessment.** Based on the current Volume of Use (2015), 4-ethyloctanoic acid does not present a risk to the aquatic compartment in the screening-level assessment.

**Biodegradation:** No data available.

**Ecotoxicity:** No data available.

**10.2.1.2. Other available data.** 4-Ethyloctanoic acid has been pre-registered for REACH with no additional data at this time.

#### 10.2.2. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in  $\mu\text{g/L}$ ).

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 ( <i>Daphnia</i> ) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC ( $\mu\text{g/L}$ )	Chemical Class
RIFM Framework Screening-level (Tier 1)	<u>4.768</u>			1,000,000	0.00477	

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

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

Exposure	Europe (EU)	North America (NA)
Log $K_{ow}$ used	3.94	3.94
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
<b>Risk Characterization: PEC/PNEC</b>	<b>&lt; 1</b>	<b>&lt; 1</b>

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

The RIFM PNEC is 0.00477  $\mu\text{g/L}$ . The revised PEC/PNECs for EU and NA: not applicable, cleared at the screening-level, and therefore the material does not present a risk to the aquatic environment at the current reported volumes of use.

**Literature Search and Risk Assessment Completed On:** 09/26/2017.

## 11. Literature Search\*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** <http://echa.europa.eu/>
- **NTP:** <https://ntp.niehs.nih.gov/>
- **OECD Toolbox**
- **SciFinder:** <https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf>
- **PubMed:** <http://www.ncbi.nlm.nih.gov/pubmed>
- **TOXNET:** <http://toxnet.nlm.nih.gov/>

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2019.03.022>.

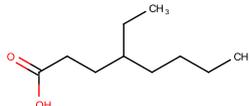
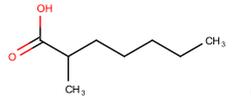
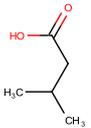
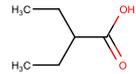
## Appendix

### Read-across Justification

#### Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity described in [Schultz et al. \(2015\)](#). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment ([OECD, 2015](#)) and the European Chemical Agency read-across assessment framework ([ECHA, 2016](#)).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was 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 substance and the read-across analogs were calculated using EPI Suite v4.11 ([US EPA, 2012a](#)).
- $J_{\text{max}}$  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 v3.4 ([OECD, 2012](#)).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 ([OECD, 2012](#)).
- Developmental toxicity was predicted using CAESAR v2.1.7 ([Cassano et al., 2010](#)), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 ([OECD, 2012](#)).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 ([OECD, 2012](#)).

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	4-Ethylheptanoic acid	2-Methylheptanoic acid	Isovaleric acid	2-Ethylbutyric acid
CAS No.	16493-80-4	1188-02-9	503-74-2	88-09-5
Structure				
Similarity (Tanimoto Score)		0.83	0.50	0.63
Read-across Endpoint		• Genotoxicity	• Genotoxicity	• Repeated dose • Reproductive toxicity
Molecular Formula	$\text{C}_{10}\text{H}_{20}\text{O}_2$	$\text{C}_8\text{H}_{16}\text{O}_2$	$\text{C}_5\text{H}_{10}\text{O}_2$	$\text{C}_6\text{H}_{12}\text{O}_2$
Molecular Weight	172.27	144.22	102.13	116.16
Melting Point ( $^{\circ}\text{C}$ , EPI Suite)	59.15	37.72	3.61	15.24
Boiling Point ( $^{\circ}\text{C}$ , EPI Suite)	268.98	234.20	175.25	195.80
Vapor Pressure (Pa @ 25 $^{\circ}\text{C}$ , EPI Suite)	0.0048	6.1	152	64.8
Log Kow (KOWWIN v1.68 in EPI Suite)	3.94	2.96	1.16	1.68
Water Solubility (mg/L, @ 25 $^{\circ}\text{C}$ , WSKOW v1.42 in EPI Suite)	64.05	592.1	40700	18000
$J_{\text{max}}$ (mg/cm <sup>2</sup> /h, SAM)	80.494	268.894	785.313	555.023

- **IARC:** <http://monographs.iarc.fr>
- **OECD SIDS:** <http://webnet.oecd.org/hpv/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](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:** <http://www.safe.nite.go.jp/english/db.html>
- **Japan Existing Chemical Data Base (JECDB):** [http://dra4.nihs.go.jp/mhlw\\_data/jsp/SearchPageENG.jsp](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.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

	5.35E-001	3.04E-001	1.30E-001	1.72E-001
Henry's Law (Pa·m <sup>3</sup> /mol, Bond Method, EPI Suite)				
<b>Genotoxicity</b>				
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	● No alert found	● No alert found	● No alert found	
DNA Binding (OECD QSAR Toolbox v3.4)	● No alert found	● No alert found	● No alert found	
Carcinogenicity (ISS)	● Non-carcinogen (low reliability)	● Carcinogen (low reliability)	● Non-carcinogen (low reliability)	
DNA Binding (Ames, MN, CA, OASIS v1.1)	● No alert found	● No alert found	● No alert found	
<i>In Vitro</i> Mutagenicity (Ames, ISS)	● No alert found	● No alert found	● No alert found	
<i>In Vivo</i> Mutagenicity (Micronucleus, ISS)	● No alert found	● No alert found	● No alert found	
Oncologic Classification	● Not classified	● Not classified	● Not classified	
<b>Repeated Dose Toxicity</b>				
Repeated Dose (HESS)	● Carboxylic acids (Hepatotoxicity) No rank			● Carboxylic acids (Hepatotoxicity) No rank
<b>Reproductive and Developmental Toxicity</b>				
ER Binding (OECD QSAR Toolbox v3.4)	● Non binder, non cyclic structure			● Non binder, non cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	● Non-toxicant (low reliability)			● Toxicant (good reliability)
<b>Metabolism</b>				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

## Summary

There are insufficient toxicity data on 4-ethyloctanoic acid (CAS # 16493-80-4). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 2-methylheptanoic acid (CAS # 1188-02-9), isovaleric acid (CAS # 503-74-2), and 2-ethylbutyric acid (CAS # 88-09-5) were identified as read-across materials with sufficient data for toxicological evaluation.

## Conclusions

- 2-Methylheptanoic acid (CAS # 1188-02-9) and isovaleric acid (CAS # 503-74-2) were used as a read-across analogs for the target material 4-ethyloctanoic acid (CAS # 16493-80-4) for the genotoxicity endpoint.
  - The target substance and the read-across analogs are structurally similar and belong to the class of branched chain aliphatic carboxylic acids.
  - The target substance and the read-across analogs share similar branched chain carboxylic acid structures.
  - The key structural difference between the target substance and the read-across analogs are that the read-across analog 2-methylheptanoic acid (CAS # 1188-02-9) has a C8 chain with an alpha-methyl substituent, whereas the target substance has a C6 chain with a gamma-ethyl substituent. The read-across analog isovaleric acid (CAS # 503-74-2) has a C4 chain with a beta-methyl substituent. These structural differences are insignificant for the genotoxicity end point.
  - Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score reflects similarity of these branched carboxylic acid structures. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The read-across analog 2-methylheptanoic acid (CAS # 1188-02-9) is predicted to be a carcinogen by the ISS model while the target substance does not have such an alert. This shows that the read-across analog is more reactive than the target substance. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genetic toxicity. Therefore, the alert will be superseded by the availability of the data.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-Ethylbutyric acid (CAS # 88-09-5) was used as a read-across analog for the target material 4-ethyloctanoic acid (CAS # 16493-80-4) for the repeated dose and reproductive toxicity endpoints.
  - The target substance and the read-across analog are structurally similar and belong to the class of branched chain aliphatic carboxylic acids.
  - The target substance and the read-across analog share similar branched chain carboxylic acid structures.
  - The key structural difference between the target substance and the read-across analog is that the target substance has a C8 chain with a gamma-methyl substituent, whereas the read-across analog has a C4 chain with a beta-ethyl substituent. These structural differences are toxicologically insignificant.
  - Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the carboxylic acid moiety. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - The read-across analog and the target substance are categorized as carboxylic acid substances with hepatotoxicity alerts for repeated dose toxicity by the HESS categorization scheme. It has been shown by numerous literature that carboxylic acids are excreted out from human body

- relatively quickly with no toxic effects. The data described in repeated dose section above show that the margin of exposure of the read-across analog is adequate at the current level of use. Therefore, the alert is superseded by availability of the data.
- o The read-across analog is predicted to be a toxicant by the CAESAR model for developmental toxicity while the target substance is predicted to be a non-toxicant. The data described in the developmental toxicity section above show that the read-across analog has an adequate margin of exposure at the current level of use. Therefore, the alert is superseded by the availability of the data. The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

## References

- Amoore, J.E., Gumbmann, M.R., Booth, A.N., Gould, D.H., 1978. Synthetic flavors: efficiency and safety factors for sweaty and fishy odorants. *Chem. Senses Flavor* 3 (3), 307–317.
- Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the research Institute for fragrance materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. *Food Chem. Toxicol.* 82, S1–S19.
- Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. *Food Chem. Toxicol.* 47 (6), 1287–1295.
- Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. *Chem. Cent. J.* 4 (Suppl. 1), S4.
- Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. *Regul. Toxicol. Pharmacol.* 72 (3), 660–672.
- Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. *Regul. Toxicol. Pharmacol.* 88, 144–156.
- ECHA, 2012. Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment, November 2012 v1.1. <http://echa.europa.eu/>.
- ECHA, 2016. Read-across assessment framework (RAAF). Retrieved from. [www.echa.europa.eu/documents/10162/13628/raaf\\_en.pdf](http://www.echa.europa.eu/documents/10162/13628/raaf_en.pdf).
- EFSA (European Food Safety Authority), 2008. Flavouring Group Evaluation 6, Revision 1 (FGE.06Rev1): straight- and branched-chain aliphatic unsaturated primary alcohols, aldehydes, carboxylic acids, and esters from chemical groups 1 and 4 (Commission Regulation (EC) No 1565/2000 of 18 July 2000). *The EFSA J.* 616–675 2008.
- Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? *J. Photochem. Photobiol. B Biol.* 96 (1), 57–62.
- IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.
- Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. *Food Chem. Toxicol.* 45 (12), 2533–2562.
- Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. *Regul. Toxicol. Pharmacol.* 62 (1), 160–182.
- Narotsky, M.G., Francis, E.Z., Kavlock, R.J., 1994. Developmental toxicity and structure-activity relationships of aliphatic acids, including dose-response assessment of valproic acid in mice and rats. *Fundam. Appl. Toxicol.* 22 (2), 251–265.
- OECD, 2006. 2-Ethylbutyric acid SIDS initial assessment profile. *SIAM* 23 17–20 October 2006. <http://hpvchemicals.oecd.org/ui/handler.axd?id=10e057bc-024e-4993-ac8d-db92a6864b83/>, Accessed date: 27 September 2017.
- OECD, 2012. The OECD QSAR Toolbox, v3.4. Retrieved from. <http://www.qsartoolbox.org/>.
- OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment. IATA ENV/JM/HA(2015)7. Retrieved from. <http://www.oecd.org/>.
- RIFM (Research Institute for Fragrance Materials, Inc.), 1999. Isovaleric Acid: Reverse Mutation Assay "Ames Test" Using *Salmonella typhimurium*. Unpublished report from Symrise. RIFM report number 61910. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Report on the testing of 4-ethylctanoic acid in the BlueScreen HC Assay (-/+ S9 metabolic activation). RIFM report number 67157. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. 2-Methylheptanoic Acid: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM report number 67578. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Exposure Survey 16, May 2017.
- Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. *J. Chem. Inf. Model.* 50 (5), 742–754.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. *Regul. Toxicol. Pharmacol.* 72, 673–682.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. *Regul. Toxicol. Pharmacol.* 86, 148–156.
- Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. *Environ. Toxicol. Chem.* 21 (6), 1301–1308.
- Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T.D., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. *Regul. Toxicol. Pharmacol.* 72 (3), 586–601.
- Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. *Food Chem. Toxicol.* 74 (12), 164–176.
- US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
- US EPA, 2012b. The ECOSAR (ECOLOGICAL Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.