Food and Chemical Toxicology 110 (2017) S299–S308

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Short review

RIFM fragrance ingredient safety assessment, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester, CAS Registry Number 25628-84-6

A.M. Api [a, *], D. Belsito [b], D. Botelho [a], D. Browne [a], M. Bruze [c], G.A. Burton Jr. [d], J. Buschmann [e], M.L. Dagli [f], M. Date [a], W. Dekant [g], C. Deodhar [a], A.D. Fryer [h], K. Joshi [a], S. La Cava [a], A. Lapczynski [a], D.C. Liebler [i], D. O'Brien [a], R. Parakhia [a], A. Patel [a], T.M. Penning [j], G. Ritacco [a], J. Romine [a], D. Salvito [a], T.W. Schultz [k], I.G. Sipes [l], Y. Thakkar [a], Y. Tokura [m], S. Tsang [a], J. Wahler [a]

[a] Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA
[b] Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA
[c] Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo SE-20502, Sweden
[d] Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI 58109, USA
[e] Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625 Hannover, Germany
[f] Member RIFM 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 RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078 Würzburg, Germany
[h] Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, USA
[i] Member RIFM 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 RIFM 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 RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN 37996- 4500, USA
[l] Member RIFM 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 RIFM 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

ARTICLE INFO

Article history:
Received 3 May 2017
Received in revised form
30 May 2017
Accepted 3 June 2017
Available online 6 June 2017

1. Identification

1. **Chemical Name:** Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester
2. CAS Registry Number: 25628-84-6
3. **Synonyms:** Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester
4. Molecular Formula: $C_{11}H_{13}NO_3$
5. Molecular Weight: 207.23
6. RIFM Number: 6954

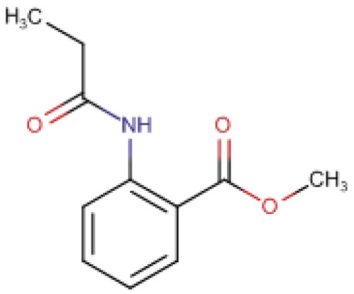
2. Physical data

1. **Boiling Point:** 366.92 °C [EPI Suite]
2. **Flash Point:** 369.00 °F. TCC (187.00 °C)*
3. **Log K_{OW}:** 2.22 [EPI Suite]
4. **Melting Point:** 134.33 °C [EPI Suite]
5. **Water Solubility:** 514.3 mg/L [EPI Suite]
6. Specific Gravity: Not Available
7. Vapor Pressure: 0.00000197 mmHg @ 20 °C [EPI Suite 4.0], 4.16e−006 mm Hg @ 25 °C [EPI Suite]
8. **UV Spectra:** Significant absorbance between 290 and 700 nm, with peak at 290–300 nm and gradually returning to baseline

* Corresponding author.
E-mail address: AApi@rifm.org (A.M. Api).

http://dx.doi.org/10.1016/j.fct.2017.06.002

Version: 042417. This version replaces any previous versions.
Name: Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester
CAS Registry Number: 25628-84-6



Abbreviation 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; Safford et al., 2015; Safford et al., 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
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
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
TTC - Threshold of Toxicological Concern
UV/Vis Spectra - Ultra Violet/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 reviews 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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (*i.e.*, 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 end-point 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current conditions is supported by existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data show that this material is not genotoxic. Data from the read across analogue methyl *N*-methylanthranilate (CAS# 85-91-6) show that this material does not have skin sensitization potential. Data on the read across analogs propionic acid (CAS# 79-09-4), methyl anthranilate (CAS# 134-20-3) and anthranilic acid (CAS# 118-92-3) provided a MOE > 100 for the repeated dose toxicity endpoint. The developmental and reproductive endpoints were completed using propionic acid (CAS# 79-09-4), methyl anthranilate (CAS# 134-20-3) as read across analogs, which provided a MOE > 100. The local respiratory toxicity endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class III material (0.47 mg/day). The phototoxicity endpoint was completed based on the highest dermal 95th percentile dermal concentration data, which is below the exposure benchmark for phototoxicity set in the Criteria Document (Api et al., 2015) The photoallergenicity endpoint was completed based on the read across analogue methyl *N*-methylanthranilate (CAS# 85-91-6) and the material is not photoallergenic. The environmental endpoints were evaluated and the material was not found to be a PBT; it was cleared at screening level.

Human Health Safety Assessment
Genotoxicity: Not genotoxic (RIFM, 2014a; RIFM, 2014b)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day (Hagan et al., 1967)
Reproductive Toxicity: Developmental toxicity: NOAEL = 400 mg/kg/day and **Fertility:** No NOAEL available. Exposure is below the TTC. (SIDS Dossier approved at SIAM25)

(*continued*)

Skin Sensitization: Not sensitizing (RIFM, 1993a; RIFM, 1993b; RIFM, 1982; RIFM, 1966)
Phototoxicity/Photoallergenicity: Not phototoxic at the current use levels; Not photoallergenic (RIFM, 1978a)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.
Environmental Safety Assessment
Hazard Assessment:
Persistence: Screening Level: 2.8 (Biowin 3) (EpiSuite ver 4.1)
Bioaccumulation: Screening Level: 13.47 L/kg (EpiSuite ver 4.1)
Ecotoxicity: Screening Level: Fish LC50: 179.9 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: 179.9 mg/L (Salvito et al., 2002)
RIFM PNEC is: 0.1799 μg/L

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: not applicable; cleared at screening level

by 380–390 nm; molar absorption coefficient is above the benchmark (1000 L mol^{-1} cm^{-1})
9. Appearance/Organoleptic: Not Available

* http://www.thegoodscentscompany.com/data/rw1687461.html#toorgano, accessed 10/3/2016.

3. Exposure

1.Volume of Use (worldwide band): <0.1 metric tons per year (IFRA, 2011)
2. 95th Percentile Concentration in Toothpaste (no reported use in hydroalcoholics):0.012% (RIFM, 2016)
3. Inhalation Exposure*: <0.0001 mg/kg/day or 0.00000050 mg/day (RIFM, 2016)
4. Total Systemic Exposure**: 0.00056 mg/kg/day (RIFM, 2016)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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 and Safford et al., 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. Cramer Classification: Class III, High (Expert Judgment)

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
III*	III	II

*See Appendix below for explanation.

2. Analogs Selected:
   a. **Genotoxicity**: None
   b. **Repeated Dose Toxicity:** Propionic acid (CAS# 79-09-4), methyl anthranilate (CAS# 134-20-3) and anthranilic acid (CAS# 118-92-3)
   c. **Reproductive Toxicity:** Propionic acid (CAS# 79-09-4), methyl anthranilate (CAS# 134-20-3)
   d. **Skin Sensitization:** Methyl n-acetylanthranilate (CAS# 2719-08-6)
   e. **Phototoxicity/Photoallergenicity:** None (phototoxicity); Methyl n-methylanthranilate (CAS# 85-91-6; photoallergenicity)
   f. Local Respiratory Toxicity: None
   g. Environmental Toxicity: None
3. Read-across Justification: See Appendix below

6. Metabolism

Metabolism was considered in this risk assessment for some endpoint evaluations.

7. Natural occurrence (discrete chemical) or composition (ncs)

Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester is not reported to occur in food by the VCF*.

*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, contains information on published volatile compounds which 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 2010, no dossier available as of 04/21/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester was assessed in the BlueScreen assay and found negative for genotoxicity with metabolic activation and positive for genotoxicity without metabolic activation however, genotoxicity occurred at cytotoxic concentrations (RIFM, 2013). The mutagenic activity of benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (CAS # 25628-84-6) 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 TA1535, TA1537, TA98, TA100 and *Escherichia coli* strains WP2uvrA were treated with benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2014a). Under the conditions of the study, benzoic acid, 2-[(1-oxopropyl) amino]-, methyl ester was not mutagenic in the Ames test.

The clastogenic activity of benzoic acid, 2-[(1-oxopropyl) amino]-, methyl ester 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 benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester in DMSO at concentrations up to 2080 μg/mL in the presence and absence of metabolic activation (S9) at the 3-h and 24-h time points. Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems at the 3-h time point and also in the 24-h non-activated test system (RIFM, 2014b). Under the conditions of the study, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the mutagenicity and clastogenicity data, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed on: 09/09/2016.

10.1.2. Repeated dose toxicity

The margin of exposure is adequate at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester. Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester is expected to hydrolyze to propionic acid (CAS# 79-09-4; see Section 5), methyl anthranilate (CAS# 134-20-3; see Section 5) and anthranilic acid (CAS# 118-92-3; see Section 5). Metabolite, propionic acid, has sufficient repeated dose toxicity data. A 90-day diet study was conducted on groups of 20 Sprague Dawley rats/sex. The animals were treated with 0 or 0.62%, 1.25%, 2.5%, or 5% propionic acid. The concentrations are equal to 0, 312, 625, 1250 or 2500 mg/kg/day respectively (as per the conversion factors for old rats, available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives). There was a 12% decrease in relative kidney weights in high dose males. In high dose females, there was a 5% increase in relative heart weights and a 9% increase in the relative liver weights. Examination of tissues revealed no lesions except point-of-contact changes of the mucosa of the forestomach in rats in the 5% (2500 mg/kg/day) treatment group. The changes observed in the forestomach were not observed in the post-exposure recovery group, and there were no differences in relative or absolute organ weights. Forestomach is a species-specific organ and is not found among humans hence, the effects observed in the rat forestomach were considered to be of no relevance to humans. Also, since the alterations in the weights of the liver and kidneys were not associated with histopathological alterations, they were not considered to be adverse. The NOAEL for systemic effects was 2500 mg/kg/day (SIDS Dossier approved at SIAM25).

In another study, propionic acid was fed in the diet to groups of 8 male and female Beagle dogs for approximately 100 days. The dogs received a 0, 0.3, 1.0, or 3.0% (0, 225, 750 and 2250 mg/kg/day, respectively, conversion factors available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives) propionic acid in the diet. After the administration interval, eight high dose and control animals (4 of each sex) were maintained for an additional 6-week recovery interval. There were no effects of treatment on the dogs, except point-of-contact diffuse epithelial hyperplasia of the mucosa of the esophagus in three dogs in the high dose group. At the end of the recovery interval, the incidence of lesions of the esophagus were the same in control and high dose animals. The incidence of focal epithelial hyperplasia in lower dose (225 and 750 mg/kg/day) animals was comparable to controls. The NOAEL for systemic toxicity for this study is 1% (750 mg/kg/day) propionic acid in the diet or 660 mg/kg/day for male dogs, and 696 mg/kg/day for female dogs (SIDS Dossier approved at SIAM25). Metabolite methyl anthranilate was administered via diet to 10 weanling Osborne-Mendel rats/per sex/group for 90 days at doses of 0, 1000, and 10000 ppm equivalent to 0, 50, and 500 mg/kg/day (as per the conversion factors for old-rats available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives). There were no effects on growth or hematology and no macroscopic or microscopic histopathological lesions. The NOAEL for methyl anthranilate was determined to be 10000 ppm, equivalent to 500 mg/kg/day (Hagan et al., 1967).

In another study, Fischer 344 rats or B6C3F1 mice were treated with metabolite anthranilic acid administered via diet at doses up to 30,000 ppm and 50,000 ppm to rats and mice, respectively, for a period of 2 years. There was no evidence of carcinogenicity that could be related to treatment with anthranilic acid (RIFM, 1978b). The dietary dose in rats and mice was equivalent to 3000 mg/kg/day and 7500 mg/kg/day, respectively (as per the conversion factors for old-rats available in the JECFA guidelines for the preparation of toxicological working papers on Food Additives). The most conservative NOAEL for the repeated dose toxicity endpoint was determined to be 500 mg/kg/day from the studies conducted on rats (Hagan et al., 1967; data also available in Bar and Griepentrog, 1967). Therefore, the benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester MOE can be calculated by dividing the methyl anthranilate NOAEL by the total systemic exposure to benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester, 500/0.00056 or 892857.

In addition, the total systemic exposure to benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (0.56 μg/kg bw/day) is below the

TTC (1.5 μg/kg bw/day) for the repeated dose toxicity endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/29/2016.

10.1.3. Reproductive toxicity

The margin of exposure is adequate at the current level of use.

There are insufficient fertility data on benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester or any read across materials. The exposure is below the TTC.

10.1.3.1. Risk assessment. There are no developmental toxicity data on benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester. Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester is expected to hydrolyze to propionic acid (CAS# 79-09-4; see Section 5), methyl anthranilate (CAS# 134-20-3; see Section 5) and anthranilic acid (CAS# 118-92-3; see Section 5). There are sufficient developmental toxicity data on metabolite propionic acid. Calcium propionate the calcium salt of propionic acid was administered via gavage to 21–24 pregnant female Wistar rats per group on gestation days 6–15 at doses of 0, 3, 14, 65, 300 mg/kg/day. There were no treatment-related effects reported among the treated females or the development of the fetus up to the highest dose tested. Thus the NOAEL for maternal toxicity and the development of the fetus was determined to be 300 mg/kg/day the highest dose tested (SIDS Dossier approved at SIAM25). In another study, calcium propionate the calcium salt of propionic acid was administered via gavage to 21–22 pregnant female Syrian golden, outbred hamsters per dose group on gestation days 6–10 at doses of 0, 4, 19, 86, 400 mg/kg/day. There were no treatment-related effects reported among the treated females or the development of the fetus up to the highest dose tested. Thus the NOAEL for maternal toxicity and the development of the fetus was determined to be 400 mg/kg/day the highest dose tested (SIDS Dossier approved at SIAM25). In another study, calcium propionate, the calcium salt of propionic acid, was administered via gavage to 10–11 pregnant female Dutch-belted rabbits per dose group on gestation days 6–18 at doses of 0, 4, 19, 86, 400 mg/kg/day. There were no treatment-related effects reported among the treated females or the development of the fetus up to the highest dose tested. Thus the NOAEL for maternal toxicity and the development of the fetus was determined to be 400 mg/kg/day the highest dose tested (SIDS Dossier approved at SIAM25). Thus the propionic acid NOAEL for the developmental toxicity endpoint was determined to be 400 mg/kg/day the highest dose tested among all species treated. Metabolite, methyl anthranilate also has sufficient developmental toxicity data. Methyl anthranilate was administered via diet to a group of 25 presumed pregnant Crl:CD(SD) female rats/dose group. The rats were fed methyl anthranilate in the diet at dose levels of 0, 1000, 5000 and 10000 ppm (average daily consumption of 0, 80.4, 389.9 and 768.4 mg/kg/day) on Days 6 through 20 of presumed gestation. Exposure to methyl anthranilate in the diet at 1000, 5000 and 10000 ppm resulted in reduced body weight gains and food consumption at 5000 and 10000 ppm but did not produce any developmental toxicity at exposure levels as high as 10000 ppm. Even in the presence of slight maternal toxicity (reduced body weight gains), no effects were observed on any of the investigated developmental parameters of the fetus. Based on the results of this study, the NOAEL for developmental toxicity was greater than 10000 ppm, equivalent to 768.4 mg/kg/day (RIFM, 2012). There are no developmental toxicity data on metabolite anthranilic acid. Thus the most conservative NOAEL of 400 mg/kg/day derived from the data on propionic acid was determined for the developmental toxicity endpoint. Therefore, the benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester MOE can be calculated by dividing the propionic acid NOAEL by the total systemic exposure to benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester 400/0.00056 or 714285.

In addition, the total systemic exposure to benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (0.56 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day) for the developmental toxicity endpoint of a Cramer Class III material at the current level of use.

There are no fertility data on benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester. Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester is expected to hydrolyze to propionic acid (CAS# 79-09-4; see Section 5), methyl anthranilate (CAS# 134-20-3; see Section 5) and anthranilic acid (CAS# 118-92-3; see Section 5). A 90-day diet study was conducted on groups of 20 Sprague Dawley rats/sex. The animals were treated with 0 or 0.62%, 1.25%, 2.5%, or 5% propionic acid. The concentrations are equal to approximately 0, 312, 625, 1250 or 2500 mg/kg/day. There were no effects of propionic acid treatment on the male or female reproductive organ weights or histopathology up to the highest dose tested. Thus the NOAEL for the reproductive toxicity/fertility effects was determined to be 2500 mg/kg/day (SIDS Dossier approved at SIAM25). In another study, propionic acid was fed in the diet to groups of 8 male and female Beagle dogs for approximately 100 days. The dogs received a 0, 0.3, 1.0, or 3.0% propionic acid in the diet. There were no significant changes in the relative or absolute weight of the testes or ovaries in test group animals relative to controls, and there were no histologic changes in the male or female reproductive organs in animals fed propionic acid in the diet for 90 days. The NOAEL for reproductive toxicity/fertility effects for this study is 3% propionic acid in the diet or 1848 mg/kg for male dogs, and 1832 mg/kg for female dogs (SIDS Dossier approved at SIAM25). Thus the most conservative NOAEL of 1832 mg/kg/day from the female dogs was determined for the reproductive toxicity/fertility effects. There are no fertility data on benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester or its other metabolites, methyl anthranilate or anthranilic acid, thus a NOAEL could not be determined for the fertility effects of benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester. The total systemic exposure to benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (0.56 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day) for the fertility endpoint of a Cramer Class III material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed on: 11/29/2016.

10.1.3.2. Skin sensitization. Based on the existing data on read across analogue methyl *N*-acetylanthranilate (CAS# 2719-08-6), benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester does not present a concern for skin sensitization.

10.1.3.3. Risk assessment. No skin sensitization studies are available for benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester. Based on the available data on read across analogue methyl *N*-acetylanthranilate (CAS# 2719-08-6; See Section 5), benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester does not present a concern for skin sensitization. The chemical structure of these materials

indicate that they could potentially be protein reactive (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). However, in guinea pig test methods no results indicative of sensitization were observed with methyl *N*-acetylanthranilate (RIFM, 1993a; RIFM, 1982). Additionally, no reactions indicative of skin sensitization were observed in human repeated insult patch tests methyl *N*-acetylanthranilate (RIFM, 1993b; RIFM, 1966).

Additional References: None.

Literature Search and Risk Assessment Completed on: 9/26/16.

10.1.4. Phototoxicity/photoallergenicity

Based on the highest dermal 95th percentile concentration data, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester does not present a concern for phototoxicity. Based on human data on read across analogue methyl *N*-methylanthranilate, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester does not present a risk for photoallergenicity.

10.1.4.1. Risk assessment. Based on the available UV/Vis spectra, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester has the potential for photoactivation with peak absorbance at 290–300 nm and returning to baseline by 380–390 nm. The molar absorption coefficient for peak absorbance between 290 and 700 nm is above the benchmark of concern for phototoxic effects (Henry et al., 2009). Suitable study data are not available for benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester. The 95th percentile concentration data across all applicable product categories were obtained using the Creme RIFM model for aggregate exposure. The highest 95th percentile dermal concentration among all phototoxicity-applicable product categories was 0.000018%, which is below the maximum limit for leave-on cosmetics (0.0005%). Based on the highest dermal 95th percentile concentration data, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester does not present a concern for phototoxicity. Suitable photoallergy study data are not available for benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester. The structural analogue, methyl *N*-methylanthranilate demonstrates an even greater degree of UV absorbance than the target material, and has sufficient study data to address photoallergenicity; as such, it is a suitable read across analogue for the photoallergenicity endpoint.

No photoallergic responses were reported with 5% methyl n-methylanthranilate in a photoallergenicity study conducted in human volunteers (RIFM, 1978a). Based on human data on read across analogue methyl *N*-methylanthranilate, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester does not present a risk for photoallergenicity.

Additional References: None.

Literature Search and Risk Assessment Completed on: 03/30/17.

10.1.5. Local respiratory toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The material, benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester, exposure level is below the Cramer Class III TTC value for inhalation exposure local effects.

10.1.5.1. Risk assessment. There are no inhalation data available on benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester. Based on the Creme RIFM model, the inhalation exposure is 0.00000050 mg/day. This exposure is 940000 times lower than the Cramer Class III TTC value of 0.47 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: 4/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this Safety Assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, benzoic acid, 2-[(1-oxopropyl)amino], methyl ester 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 EPISUITE ver 4.1 did not identify benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (*e.g.*, OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (*e.g.*, USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1).

10.2.2. Risk assessment

Based on current Volume of Use (2011), benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester does not present a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester has been pre-registered for REACH with no additional data at this time.

11. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	179.9 mg/L			1,000,000	0.1799 µg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.22	2.22
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 additional assessment is necessary.

The RIFM PNEC is 0.1799 µg/L. The revised PEC/PNECs for EU and NA: not applicable. Cleared at screening level and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 9/26/2016.

12. Literature search*

- RIFM database: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHA: http://echa.europa.eu/
- NTP: http://tools.niehs.nih.gov/ntp_tox/index.cfm
- 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/
- IARC: (http://monographs.iarc.fr)
- OECD SIDS: http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- EPA Actor: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- US EPA HPVIS: http://www.epa.gov/hpv/hpvis/index.html
- US EPA Robust Summary:http://cfpub.epa.gov/hpv-s/
- Japanese NITE: http://www.safe.nite.go.jp/english/db.html
- Japan Existing Chemical Data Base: http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- Google: https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.06.002.

Transparency document

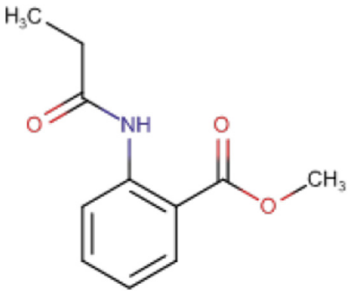
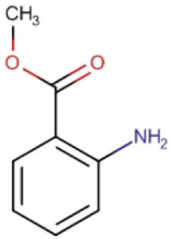
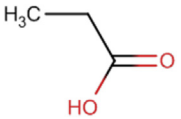
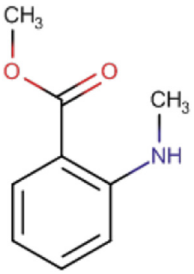
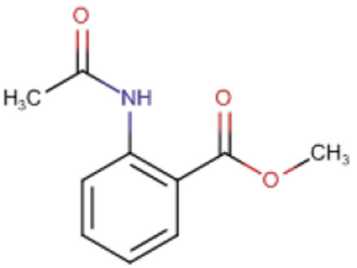
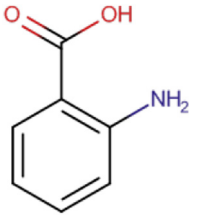
Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.06.002.

Appendix

Read across justification

Methods

- The identified read-across analogs were confirmed by using expert judgment.
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012).
- The Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.4) (OECD, 2012).
- Developmental toxicity and skin sensitization were estimated using CAESAR (v2.1.6) (Cassano et al., 2010).
- Protein binding were estimated 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)
- The strategies for find and using read across are outlined in Schultz et al. (2015).

	Target material	Read across material				
Principal Name	Benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester	Methyl anthranilate	Propionic acid	Methyl *N*-methylanthranilate	Methyl *N*-acetylanthranilate	Anthranilic acid
CAS No.	25628-84-6	134-20-3	79-09-4	85-91-6	2719-08-6	118-92-3
Structure						
Similarity (Tanimoto score)[1]		NA	NA	0.844	0.933	NA
Read across endpoint		• Repeated dose • Developmental and Reproductive	• Repeated dose • Developmental and Reproductive	• Phototoxicity	• Skin Sensitization	• Repeated dose
Molecular Formula	$C_{11}H_{13}NO_3$	$C_8H_9NO_2$	$C_3H_6O_2$	$C_9H_{11}NO_2$	$C_{10}H_{11}NO_3$	$C_7H_7NO_2$
Molecular Weight	207.23	151.16	74.08	165.19	193.2	139.15
Melting Point (°C, EPISUITE)	134.33	55.76	−8.99	42.10	126.43	94.08
Boiling Point (°C, EPISUITE)	366.92	263.57	145.02	249.86	355.32	307.7
Vapor Pressure (Pa @ 25 °C, EPISUITE)	0.000555	2.63	806	2.78	0.00128	0.0105
Log Kow (KOWWIN v1.68 in EPISUITE)	2.22	1.88	0.33[1]	2.81	1.65	1.21
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	514.3	2850	1,000,000	257	1847	3500
J_{max} (mg/cm^2/h, SAM)	14.671	50.57	10127	74.151	34.28	29.603
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	5.28E-011	1.23E-008	7.27E-007	2.69E-008	3.98E-011	3.83E-011
Repeated dose toxicity						
Repeated Dose (HESS)	• Not categorized	• Not categorized	• Carboxylic acids (Hepatotoxicity) No rank			• Not categorized
Reproductive and developmental toxicity						
ER Binding by OECD QSAR Tool Box (3.4)	• Non binder without OH or NH_2 group	• Weak binder NH_2 group	• Non binder non cyclic structure			
Developmental Toxicity Model by CAESAR v2.1.6	• Toxicant (low reliability)	• Toxicant (low reliability)	• Toxicant (low reliability)			
Skin Sensitization						
Protein binding by OASIS v1.1	• Acylation • AN2 • Michael type addition				• Acylation • AN2 • Michael type addition	
Protein binding by OECD	• Acylation				• Acylation	
Protein binding potency	• Not possible to classify				• Not possible to classify	
Protein binding alerts for skin sensitization by OASIS v1.1	• No alert found				• No alert found	
Skin Sensitization model (CAESAR) (version 2.1.6)	• Sensitizer (low reliability)				• Non sensitizer (moderate reliability)	
Metabolism						
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3	• See Supplemental Data 4	• See Supplemental Data 5	• No metabolites

1. Patel et al., 2002.

Summary

There are insufficient toxicity data on benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (CAS # 25628-84-6). Hence *in-silico* evaluation was conducted by determining suitable read across analogs for this material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, suitable analogs methyl *N*-methylanthranilate (CAS # 85-91-6) and methyl *N*-acetylanthranilate (CAS # 2719-08-6) were identified as read across materials with data for their respective toxicity end points.

Metabolism

Metabolism of the target material was predicted using the rat liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4) (See table above). Target material is metabolized to methyl anthranilate (CAS 134-20-3) and propionic acid (CAS 79-09-4) in the first step with 0.95 intrinsic probability and 0.35 pre-calculated probability. Methyl *N*-methylanthranilate (CAS 85-91-6) is structurally similar read across analogue to methyl anthranilate. Hence methyl *N*-methylanthranilate can be use as read across for target material. Methyl *N*-methylanthranilate was out of domain for *in vivo* and *in vitro* rat S9 simulator (OASIS TIMES v2.27.19). However, based on expert judgement, the model's domain exclusion was overridden and a justification is provided.

Conclusion/Rationale

- Methyl *N*-methylanthranilate (CAS 85-91-6) and methyl anthranilate (CAS 134-20-3) is used as a structurally similar read across analogue for benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (CAS # 25628-84-6) for phototoxicity and repeated dose toxicity end points.
  - o The read across material methyl *N*-methylanthranilate is an analogue of the major metabolite methyl anthranilate of the target.
  - o The target substance has a propionamide group with metabolic cleavage point at the amide bond, yielding propionic acid and methyl anthranilate. The read across analogue is structurally similar to methyl anthranilate, which is a metabolite of the target substance.
  - o The structural difference in the target and the read across can be mitigated by the fact that the target could be metabolically oxidized to analogue of the read across used here. Therefore, toxicity profile of the target is expected to be that of its metabolites.
  - o The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the benzoate fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxicological perspective.
  - o The target substance and the read across analogue have similar physical chemical properties. Any differences in the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for phototoxicity and repeated dose toxicity endpoints are consistent between the target substance and the read across analogue.
  - o The target substance and the read across analogue are expected to metabolize differently. Since the read across analogue is a secondary amine, it will be a substrate for MAO (monoamine oxidase), yielding a primary amine target substance and formaldehyde.
  - o The read across analogue for repeated dose toxicity are categorized as carboxylic acid substances with hepatotoxicity alerts while the target substance is not categorized by HESS categorization scheme. It has been shown in the literature that carboxylic acids are excreted out from human body relatively quickly with no toxic effects. The data described in repeated dose section shows that the margin of exposure of the read across analogue is adequate at the current level of use. Therefore, the alert was superseded by availability of the data.
  - o The read across analogue methyl anthranilate is shown to have ER binding alert while no such alert is given for the target substance. ER Binding is molecular initiating event. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - o According to the CAESAR model for developmental toxicity, the target substance and the read across analogs are predicted to be toxicants. The data described in the developmental toxicity section above shows that the margin of exposure for these read across analogs is adequate at the current level of use. Therefore, the alert will be superseded by the availability of the data.
  - o The structural alerts for phototoxicity and repeated dose toxicity endpoints are consistent between the metabolites of the read across analogue and the target substance.
  - o The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.
- Methyl *N*-acetylanthranilate (CAS # 2719-08-6) could be used as structurally similar read across analogue for target material benzoic acid, 2-[(1-oxopropyl)amino]-, methyl ester (CAS # 25628-84-6) for the skin senzitization endpoint.
  - o The target substance and the read across analogue are structurally similar and belong to the structural class of amino benzoates.
  - o The target substance and the read across analogue have an amino benzoate fragment common among them.
  - o The key difference between the target substance and the read across analogue is that the target is ethyl ester while the read across is methyl ester. This structure difference between the target substance and the read across analogue do not raise additional structural alerts so the structure differences are not relevant from a toxic endpoint perspective.
  - o The target substance and the read across analogue have a Tanimoto score as mentioned in the above table. The Tanimoto score is mainly driven by the amino benzoate fragment. The differences in the structure which are responsible for Tanimoto score <1 are not relevent from a toxic endpoint perspective.
  - o The target substance and the read across analogue have similar physical chemical properties. Any differences in some of the physical chemical properties of the target substance and the read across analogue are estimated to be toxicologically insignificant for the skin senzitization endpoint.
  - o According to the QSAR OECD Toolbox (V3.4), structural alerts for the skin senzitization endpoint are consistent between the target substance and the read across analogue.
  - o The read across analogs are shows alerts for protein binding by OASIS model for skin sensitization. There are no other alerts for protein binding potency and DNA binding for skin sensitization. The data described in the skin sensitization

section shows that the read across analogs does not pose a concern for the skin sensitization endpoint. Therefore, the alert will be superseded by the availability of the data.

- o The target substance and the read across analogue are expected to be metabolized similarly as shown by metabolism simulator.
- o The structural alerts for the skin senzitization endpoint are consistent between the metabolites of the read across analogue and the target substance.
- o The structural differences between the target substance and the read across analogue are deemed to be toxicologically insignificant.

Explanation of Cramer classification

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

Q1. Normal constituent of the body? No
Q2. Contains functional groups associated with enhanced toxicity? No
Q3. Contains elements other than C, H, O, N, and divalent S? No
Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No
Q6. Benzene derivative with certain substituents? No
Q7. Heterocyclic? No
Q16. Common terpene? (see Cramer et al., 1978 for detailed explanation) No
Q17. Readily hydrolyzed to a common terpene? No
Q19. Open chain? No
Q23. Aromatic? Yes
Q27. Rings with substituents? Yes
Q28. More than one aromatic ring? No
Q30. Aromatic ring with complex substituents? Yes
Q31. Is the substance an acyclic acetal or ester of substances defined in Q30? No
Q32. Contains only the functional groups listed in Q30 or Q31 and either a) a single fused non-aromatic carbocyclic ring or b) aliphatic substituent chains longer than 5 carbon atoms or c) a polyoxyethylene ($n \geq 4$) on the aromatic or aliphatic side chain? No
Q22. Common component of food? No Class High (Class III)

References

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., Renkers, 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.

Bar, V.F., Griepentrog, F., 1967. Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel fur Lebensmittel. (Where we stand concerning the evaluation of flavoring substances from the viewpoint of health). Med. Ernahr. 8, 244–251.

Bhatia, S., Schultz, T., Roberts, D., Shen, J., Kromidas, L., Api, A.M., 2015. Comparison of Cramer classification between Toxtree, the OECD QSAR toolbox and expert judgment. Regul. Toxicol. Pharmacol. 71 (1), 52–62.

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., et al., 2010, July. CAESAR models for developmental toxicity. Chem. Central J. 4 (S1), S4 (Springer International Publishing).

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.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Cosmet. Toxicol. 16 (3), 255–276.

Essential Estimation Programs Interface (EPI) SuiteTM (version 4.1) [Software]. (Copyright 2000-2011). US Environmental Protection Agency's Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Retrieved from http://www.epa.gov/opptintr/exposure/pubs/episuite.htm Research, 20(6), 482–487.

Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.M., Brouwer, J.B., 1967. Food flavorings and compounds of related structure. II. Subacute and chronic toxicity. Food Cosmet. Toxicol. 5 (2), 141–157.

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), 2011. Volume of Use Survey. February 2011.

OECD, 2012. The OECD QSAR Toolbox, 3.1. http://www.qsartoolbox.org/.

Patel, H., ten Berge, W., Cronin, M.T.D., 2002. Quantitative structure-activity relationships (QSARs) for the prediction of skin permeation of exogenous chemicals. Chemosphere 48 (6), 603–613.

RIFM (Research Institute for Fragrance Materials, Inc.), 1966. Repeated Insult Patch Test with Methyl N-acetylanthranilate. Unpublished Report from IFF Incorporated. RIFM report number 47649 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 1978a. Phototoxicity and Contact Photoallergy Testing in Human Subjects. Report to RIFM. RIFM report number 1788 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 1978b. Bioassay of Anthranilic Acid (Benzoic Acid, 2-amino-) for Possible Carcinogenicity. NCI-CG-TR-36. Unpublished report from the National Cancer Institute. RIFM report number (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Klecak Open Epicutaneous Test Determination of the Contact Sensitization Potential of Methyl N-acetylanthranilate (N-acetyl Methyl Anthranilate) in the Guinea Pig. Unpublished report from Haarmann & Reimer GmbH. RIFM report number 17788 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 1993a. Delayed Contact Hypersensitivity Study of Methyl N-acetyl Anthranilate in Guinea Pigs (Buehler Technique). Report to RIFM. RIFM report number 20352 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 1993b. Repeated Insult Patch Test of Methyl N-acetyl-anthranilate on Human Subjects. RIFM report number 25758 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 2012. An Embryo-fetal Development Study of Methyl Anthranilate by Diet in Rats. RIFM report number 62729 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Benzoic Acid, 2-[(1-oxopropyl)amino]-, Methyl Ester in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65154 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Benzoic Acid, 2-[(1-oxopropyl)amino]-, Methyl Ester: in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM report number 67356 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. Benzoic Acid, 2-[(1-oxopropyl)amino]-, Methyl Ester (CAS# 25628-84-6): Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM report number 69952 (RIFM, Woodcliff Lake, NJ, USA.).

RIFM (Research Institute for Fragrance Materials), 2016. Use Level Survey, November 2016.

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. Chem. Res. Toxicol. 20 (7), 1019–1030.

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., et al., 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., et al., 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.

USEPA, 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, 4.11. United States Environmental Protection Agency, Washington, DC, USA.