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Short Review

RIFM fragrance ingredient safety assessment, dimethyl adipate, CAS Registry Number 627-93-0

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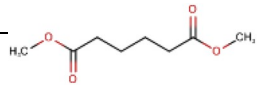
Version: 040319. This version replaces any previous versions.

Name: Dimethyl adipate
CAS Registry Number: 627-93-0



Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice

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IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use, but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api 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 existing information supports the use of this material as described in this safety assessment.

Dimethyl adipate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog dibutyl sebacate (CAS # 109-43-3) show that dimethyl adipate is not expected to be genotoxic. Data on read-across analog diisobutyl adipate (CAS # 141-04-8) provide a calculated MOE > 100 for the repeated dose toxicity and reproductive toxicity endpoints. The skin sensitization endpoint was completed using the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; dimethyl adipate is not expected to be phototoxic/photoallergenic. For the local respiratory endpoint, a calculated MOE > 100 was provided by the read-across analog dimethyl glutarate (CAS # 1119-40-0). The environmental endpoints were evaluated; dimethyl adipate 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. (Hachiya and Takizawa, 1994; ECHA REACH Dossier: Dimethyl Adipate; ECHA, 2012a)

Repeated Dose Toxicity: NOAEL = 100 mg/kg/day. (ECHA REACH Dossier: Diisobutyl Adipate; ECHA, 2018)

Reproductive Toxicity: Developmental toxicity: NOAEL = 300 mg/kg/day. Fertility: NOAEL = 1000 mg/kg/day. (ECHA REACH Dossier: Diisobutyl Adipate; ECHA, 2018)

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

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

Local Respiratory Toxicity: NOEC = 50 mg/m^3. (Bamberger et al., 2002; ECHA REACH Dossier: Dimethyl Glutarate; ECHA, 2012b)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 3.09 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)

Bioaccumulation: Screening-level: 2.221 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Critical Ecotoxicity Endpoint: 96-h Fish LC50: 53.11 mg/L (ECOSAR; US EPA, 2012b)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002)

Critical Ecotoxicity Endpoint:: 96-h Fish LC50: 53.11 mg/L (ECOSAR; US EPA, 2012b)

RIFM PNEC is: 5.311 μg/L

- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe < 1

1. Identification

1. **Chemical Name:** Dimethyl adipate
2. **CAS Registry Number:** 627-93-0
3. **Synonyms:** Dimethyl hexanedioate; Hexanedioic acid, dimethyl ester; Adipic acid, dimethyl ester; Dimethyl adipate
4. **Molecular Formula:** $C_8H_{14}O_4$
5. **Molecular Weight:** 174.19
6. **RIFM Number:** 39
7. **Stereochemistry:** No stereocenter present and no stereoisomer possible.

2. Physical data

1. **Boiling Point:** 186.96 °C (EPI Suite)
2. **Flash Point:** 116 °C (GHS)
3. **Log K_{OW}:** 1.39 (EPI Suite)
4. **Melting Point**: 71.54 °C (EPI Suite)
5. **Water Solubility:** 7749 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.687 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (worldwide band)

1. 100–1000 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in AirFresh Plugin:** 18.03% (RIFM, 2017)

(No reported use in hydroalcoholics).

2. **Inhalation Exposure*:** 0.0093 mg/kg/day or 0.66 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.011 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., 2015a; 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 V. It is derived from concentration survey data in the Creme RIFM Aggregate Exposure Model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015a; Safford et al., 2017; and Comiskey et al., 2017).

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** Dibutyl sebacate (CAS # 109-43-3)
   b. **Repeated Dose Toxicity:** Diisobutyl adipate (CAS # 141-04-8)
   c. **Reproductive Toxicity:** Diisobutyl adipate (CAS # 141-04-8)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** Dimethyl glutarate (CAS # 1119-40-0)
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

No relevant data available for inclusion in this safety assessment.
Additional References:
None.

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

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

Apple brandy (Calvados).

*VCF Volatile Compounds in Food: Database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH dossier

Available; accessed 04/03/19.

10. Conclusion

The existing information supports the use of this material as described in this safety assessment.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, dimethyl adipate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no data assessing the mutagenic activity of dimethyl adipate; however, read-across can be made to dibutyl sebacate (CAS # 109-43-3; see Section VI).

The mutagenic activity of dibutyl sebacate 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 TA97, TA98, TA100, and TA102 and *Escherichia coli* strain WP2uvrA were treated with dibutyl sebacate in dimethyl sulfoxide (DMSO) or Tween 80 at concentrations up to 10000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (Hachiya and Takizawa, 1994). Under the conditions of the study, dibutyl sebacate was not mutagenic in the Ames test, and this can be extended to dimethyl adipate.

The clastogenic activity of dimethyl adipate was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. The test material was administered via inhalation to groups of male and female Fischer 344 mice. Doses of 0.5, 1, or 2.0 mg/L body weight were administered. Mice from each dose level were euthanized at 24 h. The bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow in any dose (ECHA, 2012a). Under the conditions of the study, dimethyl adipate was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, dimethyl adipate and read-across material dibutyl sebacate do not present a concern for genotoxic potential.

Additional References: Wild et al., 1983.

Literature Search and Risk Assessment Completed On: 04/19/19.

11.1.2. Repeated Dose Toxicity

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

11.1.2.1. Risk assessment. There are limited repeated dose toxicity data on dimethyl adipate, but the read-across material diisobutyl adipate (CAS # 141-04-8; see Section VI), has sufficient data to support the repeated dose toxicity endpoint.

In a GLP-compliant subchronic inhalational toxicity study (similar to OECD TG 413), 10 Crl:CD (SD)IGS BR rats/sex/dose were administered dimethyl adipate via whole-body inhalation at concentrations of 0 or 400 mg/m^3 (6 h/day, 5 days/week) for 90 days. Animals were allowed a recovery period of 4 weeks following the treatment. The tested parameters included body weights, food consumption, clinical signs, hepatic, lung, and nasal cell proliferation, clinical pathology, neurobehavioral assessments, and neuropathology. No treatment-related effects were reported for mortality, clinical signs, gross observations, ophthalmology, hematology, serum, chemistry, urinalysis, or neurobehavior in either sex at all tested doses. Treated males were reported to have decreased bodyweight gains and decreased body weights during the recovery period. No treatment-related effects on body weight or food efficiency were observed in treated females. Food efficiency was significantly decreased in treated males. Relative weights of the epididymides and spleen were statistically significantly increased in males treated with 400 mg/m^3 dose. However, the changes in relative organ weights were not accompanied by microscopic alterations. Treatment-related degeneration and atrophy of the olfactory mucosa were observed during the study as well as recovery in treated animals. Significantly increased nasal cell proliferation was reported in treated males. Since this is a single dose study with limited details on the study details including histopathology, a NOAEL could not be determined from the study (ECHA, 2012a).

In an OECD 421 and GLP-compliant subchronic toxicity study, 13 Sprague Dawley rats/sex/dose were administered diisobutyl adipate via oral gavage at doses of 0, 100, 300, or 1000 mg/kg/day. The treatment in females was initiated 2 weeks prior to mating and continued until lactation day 4; in males, treatment was initiated 2 weeks prior to mating until the end of the study duration for a total of 42 days. No treatment-related adverse effects were reported for mortality, clinical signs, food consumption, ophthalmology, hematology, gross pathology, neuropathology, or histopathology. In the high-dose group, male bodyweight gain was lower than the control animals throughout the study. In addition, kidney weight increased in both sexes in the high-dose group but was not accompanied by any histopathological findings. Based on the increased kidney weights and decreased male body weights at the highest tested dose, the NOAEL for repeated dose toxicity was considered to be 300 mg/kg/day (ECHA, 2018).

In another subchronic study compliant with OECD TG 407 and GLP guidelines, 6 Sprague Dawley rats/sex/dose were administered diisobutyl adipate via oral gavage at doses of 0, 20, 140, and 1000 mg/kg/day for 28 days. No treatment-related effects were observed for mortality, clinical signs, body weight, food consumption, ophthalmology, hematology, clinical biochemistry, urinalysis, behavior, immunology, organ weight, gross pathology, neuropathology, or histopathology for both sexes at all tested doses. Based on the absence of treatment-related toxicity up to the highest tested dose, the NOAEL for repeated dose toxicity was considered to be 1000 mg/kg/day (ECHA, 2018).

The most conservative NOAEL of 300 mg/kg/day was derived from the 421 study for the repeated dose toxicity endpoint. A default safety factor of 3 was used when deriving a NOAEL from the 421 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 300/3 or 100 mg/kg/day.

The dimethyl adipate MOE for the repeated dose toxicity endpoint can be calculated by dividing the diisobutyl adipate NOAEL in mg/kg/day by the total systemic exposure for dimethyl adipate, 100/0.011 or 9091.

In addition, the total systemic exposure to dimethyl adipate (11 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*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: 04/10/19.

11.1.3. Reproductive Toxicity

The MOE for dimethyl adipate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are limited fertility data and no developmental toxicity data on dimethyl adipate.

A GLP subchronic inhalation toxicity study (similar to OECD 413) was conducted in Crl:CD (SD)IGS BR rats. Groups of 10 rats/sex/dose were administered dimethyl adipate via whole-body inhalation at concentrations of 0 or 400 mg/m^3 for 6 h per day, 5 days per week, over a period of 90 days. After the cessation of treatment, the animals were kept for 4 weeks of recovery. Reproductive parameters evaluated consisted of the estrous cycle in females (last 21 days of treatment) and sperm motility, sperm number, and sperm morphology for males. Serum luteinizing hormone, follicle-stimulating hormone, and testosterone in males and serum estradiol and progesterone for females were also measured. An increase in epididymal sperm counts and statistically significantly increased epididymal weight were reported in the treatment group. However, statistical significance was not attained for sperm count, and no correlated histopathological changes in the epididymis for increased sperm counts were observed; hence, this finding was not considered to be treatment-related. Therefore, the NOAEC for reproductive toxicity was considered to be 400 mg/m^3, the only dose tested. Using standard minute volume and body weight values for male and female Sprague Dawley rats, the calculated NOAEL for fertility effects is 103.7 mg/kg/day (ECHA, 2012a).

Since the fertility data on dimethyl adipate is from a single-dose

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

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.069%	NRU[b]
2	Products applied to the axillae	0.021%	NRU[b]
3	Products applied to the face using fingertips	0.41%	NRU[b]
4	Fine fragrance products	0.39%	NRU[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	NRU[b]
6	Products with oral and lip exposure	0.23%	NRU[b]
7	Products applied to the hair with some hand contact	0.79%	NRU[b]
8	Products with significant ano-genital exposure	0.041%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.32%
10	Household care products with mostly hand contact	2.7%	0.79%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.5%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	18%

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

study, data on read-across material diisobutyl adipate (CAS # 141-04-8; see Section VI) is used to support the fertility and developmental toxicity endpoints.

An OECD 421/GLP reproduction and developmental toxicity study was conducted in Sprague Dawley rats. Groups of 13 rats/sex/dose were administered diisobutyl adipate via oral gavage at doses of 0, 100, 300, or 1000 mg/kg/day during pre-mating (14 days), mating, throughout gestation, and early lactation (4 days) for females and 42 days for males. No treatment-related adverse effects were reported for sexual maturation, estrous cycle, sperm analysis, and reproductive performance for both males and females up to the highest dose tested. No treatment-related effects were observed for gestation length, number of corpora lutea, implantations and resorption, litter size, and sex ratio at any dose levels. High-dose group pups exhibited a decrease in pup body weight on postnatal days 0 and 4 in addition to a decrease in viability index on postnatal day 4. There were no treatment-related maternal signs of toxicity. Thus, the NOAEL for effects on fertility was considered to be 1000 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity was considered to be 300 mg/kg/day, based on decreases in pup viability and body weight among high-dose group pups (ECHA, 2018).

The dimethyl adipate MOE for the fertility endpoint can be calculated by dividing the diisobutyl adipate NOAEL in mg/kg/day by the total systemic exposure for dimethyl adipate, 1000/0.011 or 90909.

The dimethyl adipate MOE for the developmental toxicity endpoint can be calculated by dividing the diisobutyl adipate NOAEL in mg/kg/day by the total systemic exposure for dimethyl adipate, 300/0.011 or 27273.

In addition, the total systemic exposure to dimethyl adipate (11 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/02/19.

11.1.4. Skin Sensitization

Based on the application of DST, dimethyl adipate does not present a safety concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 3.1.0; OECD Toolbox v4.2). No predictive skin sensitization studies are available for dimethyl adipate. Acting conservatively, due to the lack of data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for dimethyl adipate that present no appreciable risk for skin sensitization based on the non-reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/12/19.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, dimethyl adipate would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for dimethyl adipate 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 the lack of absorbance, dimethyl adipate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/03/19.

11.1.6. Local Respiratory Toxicity

There are insufficient inhalation data available on dimethyl adipate; however, in a subchronic inhalation exposure study for the read-across analog dimethyl glutarate (CAS # 1119-40-0; see section VI), a NOEC of

50 mg/m^3 was reported (Bamberger et al., 2002; also in ECHA, 2012b).

11.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a GLP-compliant and OECD 413 guideline inhalation study, Crl:CD (SD)IGS BR rats, 36/sex/group, were subjected to whole-body aerosol exposure of dimethyl glutarate at 0, 10, 50, and 400 mg/m^3 concentrations for 6 h/day, 5 days/week, for 13 weeks (90 days) (Bamberger et al., 2002). Bodyweight changes, changes in the clinical biochemistry, gross pathological, and histopathological changes were determined to be treatment-related. Nasal regions II and III, as well as the lungs, were analyzed for local respiratory effects by histopathology. While no effects were reported in the lungs, male and female rats exposed to the highest concentration showed degeneration or atrophy of the olfactory mucosa of the dorsal meatus and of the dorsomedial aspect of the dorsal endoturbinate. Focal respiratory metaplasia was observed as a less common incident. Minimal to mild severity lesions were also observed in the olfactory mucosa of the dorsal meatus. Significantly greater nasal level II and III CP was observed in the male and female rats from the highest exposure group. Therefore, the NOEC for local respiratory effects was considered at 50 mg/m^3.

This NOEC expressed in mg/kg lung weight/day is:

- (50 mg/m^3) × (1 m^3/1000 L) = 0.05 mg/L
- Minute ventilation volume of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.05 mg/L) × (61.2 L/day) = 3.06 mg/day
- (3.06 mg/day)/(0.0016 kg lung weight of rat*) = 1912.5 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.66 mg/day; this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; Safford et al., 2015a). To compare this estimated exposure with the NOEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 1.015 mg/kg lung weight/day resulting in a MOE of 1884 (i.e., [1912.5 mg/kg lung weight of rat/day]/[1.015 mg/kg lung weight of human/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.66 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 04/09/19.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of dimethyl adipate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class-specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, dimethyl adipate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify dimethyl adipate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012c). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.1.1. Risk assessment. Based on the current Volume of Use (2015), dimethyl adipate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.1.2. Key studies

11.2.1.2.1. Biodegradation. No data available.

11.2.1.2.2. Ecotoxicity. No data available.

11.2.1.2.3. Other available data. Dimethyl adipate has been registered for REACH with following additional data available:

A *Daphnia magna* acute immobilization study was conducted according to the OECD 202 guideline under static conditions. The 48-h EC50 based on mean measured concentrations was reported to be 72 mg/L (95% CI: 61–88 mg/L).

An algae growth inhibition test was conducted according to the OECD 201 guideline under static conditions. The 72-h EC50 was reported to be > 100 mg/L (ECHA, 2012a).

11.2.2. Risk assessment refinement

Dimethyl adipate has passed the screening criteria; measured data is included for completeness and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	797.5			1000000	0.7975	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	53.11	117.88	55.29	10000	5.311	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	508.37	272.77	160.79			Neutral Organics SAR (Baseline toxicity)

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	1.39	1.39
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	10–100	100–1000
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 5.311 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported VoU.

Literature Search and Risk Assessment Completed On: 04/01/19.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 09/30/19.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111174.

Appendix

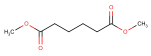
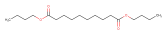
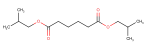
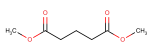
Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as 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 Chemicals 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 were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	Dimethyl adipate	Dibutyl sebacate	Diisobutyl adipate	Dimethyl glutarate (Pentanedioic acid, 1,5-dimethyl ester)
CAS No.	627-93-0	109-43-3	141-04-8	1119-40-0
Structure				
Similarity (Tanimoto Score)		0.65	0.69	0.65
Read-across Endpoint		• Genotoxicity	• Reproductive Toxicity • Repeated Dose Toxicity	• Local Respiratory Toxicity
Molecular Formula	$C_8H_{14}O_4$	$C_{18}H_{34}O_4$	$C_{14}H_{26}O_4$	$C_7H_{12}O_4$
Molecular Weight	174.19	314.46	258.35	160.16
Melting Point (°C, EPI Suite)	10.3	−10	−20	−42.5
Boiling Point (°C, EPI Suite)	186.96	344.5	279	214
Vapor Pressure (Pa @ 25 °C, EPI Suite)	8.05E+000	3.84E-004	0.75	2.40E+001
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	1.03	6.30	4.19	0.62
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	7749	0.04224	5.649	5.9e+004
J_{max} (μg/cm^2/h, SAM)	17.97	2.941	26.842	98.151
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.34E-001	4.91E-003	5.42E-001	7.45E-002
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• No alert found	• No alert found	• No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found	• No alert found	
Carcinogenicity (ISS)	• Phthalate (or butyl) diesters and monoesters (Nongenotox) • Structural alert for nongenotoxic carcinogenicity	• No alert found	• Phthalate (or butyl) diesters and monoesters (Nongenotox) • Structural alert for nongenotoxic carcinogenicity	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	• No alert found	
In Vitro Mutagenicity (Ames, ISS)	• No alert found	• No alert found	• No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	• No alert found	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	• Not classified	
Repeated Dose Toxicity				
Repeated Dose (HESS)	• Not categorized		• Not categorized	
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	• Non-binder, non-cyclic structure		• Non-binder, non-cyclic structure	
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (moderate reliability)		• Toxicant (low reliability)	
Local Respiratory Toxicity				
Respiratory Sensitization (OECD QSAR Toolbox v4.2)	• No alert found			• No alert found
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	• See Supplemental Data 1	• See Supplemental Data 2	• See Supplemental Data 3	• See Supplemental Data 4

Summary

There are insufficient toxicity data on dimethyl adipate (CAS # 627-93-0). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, dibutyl sebacate (CAS # 109-43-3), diisobutyl adipate (CAS # 141-04-8), and pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Dibutyl sebacate (CAS # 109-43-3) was used as a read-across analog for the target material dimethyl adipate (CAS # 627-93-0) for the

genotoxicity endpoint.

- ○ The target material and the read-across analog are structurally similar and belong to a class of straight-chain aliphatic diesters.
- ○ The target material and the read-across analog share a saturated diester functionality.
- ○ The key difference between the target material and the read-across analog is the target material is a dimethyl ester of a C6 dicarboxylic acid, whereas the read-across is a dibutyl ester of a C10 dicarboxylic acid. This structural difference is toxicologically insignificant.
- ○ Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
- ○ Differences are predicted for J_{max}, which estimates skin absorption. J_{max} for the target material corresponds to skin absorption $\leq 80\%$, and J_{max} for the read-across analog corresponds to skin absorption $\leq 40\%$. While percentage skin absorption estimated from J_{max} indicates exposure to the substance, it does not represent hazard or toxicity. This parameter provides context to assess the impact of bioavailability on toxicity comparisons between the materials evaluated.
- ○ According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
- ○ The target is predicted to have an alert under the Carcinogenicity (ISS) categorization scheme. However, the target structure does not match any of the reactive training set structures used in the Carcinogenicity (ISS) categorization scheme. The predictions are superseded by data.
- ○ The target material 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.

- Diisobutyl adipate (CAS # 141-04-8) was used as a read-across analog for the target material dimethyl adipate (CAS # 627-93-0) for the reproductive toxicity and repeated dose toxicity endpoints.
  - ○ The target material and the read-across analog are structurally similar and belong to a class of saturated aliphatic diesters.
  - ○ The target material and the read-across analog share an adipate diester functionality.
  - ○ The key difference between the target material and the read-across analog is that the target material is a dimethyl ester whereas the read-across analog is a diisobutyl ester. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - ○ Both target and read-across compounds are predicted to have an alert under the Carcinogenicity (ISS) categorization scheme. However, the target structure does not match any of the reactive training set structures used in the Carcinogenicity (ISS) categorization scheme. The predictions are superseded by data.
  - ○ Both the target and read-across materials have a toxicant alert for Developmental Toxicity (CAESAR v2.1.6). The data described in the reproductive toxicity section shows that the MOE is adequate at the current level of use. The predictions are superseded by data.
  - ○ The target material 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.
- Pentanedioic acid, 1,5-dimethyl ester (CAS # 1119-40-0) was used as a read-across analog for the target material dimethyl adipate (CAS # 627-93-0) for the local respiratory toxicity endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to a class of straight-chain aliphatic diesters.
  - ○ The target material and the read-across analog share a saturated dimethyl ester.
  - ○ The key difference between the target material and the read-across analog is that the target material has a C6 dicarboxylic acid whereas the read-across analog has a C5 dicarboxylic acid. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - ○ The target material 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.

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., 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.

Bamberger, J.R., Malley, L.A., Mylchreest, E., O'Connor, J.C., Kennedy, G.L., 2002. Dimethyl glutarate (DMG), dimethyl succinate (DMS), and dimethyl adipate (DMA): 90-Day inhalation toxicity study in rats. Toxicologist 66 (1-S), 193.

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. Dimethyl Adipate Registration Dossier. Retrieved from. https://www.echa.europa.eu/lv/web/guest/registration-dossier/-/registered-dossier/14132.

ECHA, 2012. Dimethyl Glutarate Registration Dossier. Retrieved from. https://www.echa.europa.eu/lv/web/guest/registration-dossier/-/registered-dossier/5377.

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.
ECHA, 2018. Diisobutyl Adipate Registration Dossier. Retrieved from: https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/23508/1.
Hachiya, N., Takizawa, Y., 1994. Mutagenicity of plastics additives. Japanese Journal of Mutagenicity Tests on Chemicals 3 (3), 147–154.
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.
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/.
OECD, 2018. The OECD QSAR Toolbox, v3.2–4.2. Retrieved from. http://www.qsartoolbox.org/.
RIFM (Research Institute for Fragrance Materials, Inc.), 2017. Exposure Survey 17, August 2017.
Roberts, D.W., Api, A.M., Safford, R.J., Lalko, J.F., 2015. Principles for identification of high potency category chemicals for which the dermal sensitization threshold (DST) approach should not be applied. Regul. Toxicol. Pharmacol. 72 (3), 683–693.
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.
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., 2015b. 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.
Safford, R.J., 2008. The dermal sensitisation threshold–A TTC approach for allergic contact dermatitis. Regul. Toxicol. Pharmacol. 51 (2), 195–200.
Safford, R.J., Api, A.M., Roberts, D.W., Lalko, J.F., 2015a. Extension of the dermal sensitization threshold (DST) approach to incorporate chemicals classified as reactive. Regul. Toxicol. Pharmacol. 72 (3), 694–701.
Safford, R.J., Aptula, A.O., Gilmour, N., 2011. Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul. Toxicol. Pharmacol. 60 (2), 218–224.
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., 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, 164–176.
US EPA, 2012. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.
Wild, D., King, M.T., Gocke, E., Eckhardt, K., 1983. Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, Basc and micronucleus tests. Food Chem. Toxicol. 21 (6), 707–719.