Food and Chemical Toxicology 159 (2022) 112689

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

RIFM fragrance ingredient safety assessment, myraldyl acetate, CAS Registry Number 72403-67-9

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ARTICLE INFO

Handling editor: Dr. Jose Luis Domingo

Version: 071621. Initial publication. All fragrance materials are evaluated on a five-year rotating basis. Revised safety

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assessments are published if new relevant data become available. Open access to all RIFM

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https://doi.org/10.1016/j.fct.2021.112689
Received 16 July 2021; Received in revised form 16 September 2021; Accepted 14 November 2021
Available online 17 November 2021

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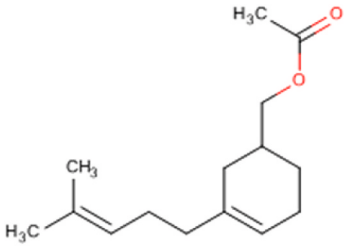
Fragrance Ingredient Safety Assessments is here: fragrance materialsafetyresource.elsevier.com.

Name: Myraldyl acetate
CAS Registry Number: 72403-67-9



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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2020)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

This safety assessment is based on the RIFM Criteria Document (Api, 2015), which should be referred to for clarifications. Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM Database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing

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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.

Myraldyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog nopyl acetate (CAS # 128-51-8) show that myraldyl acetate is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to myraldyl acetate is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across analog menthadiene-7-methyl formate (CAS # 68683-20-5) provided myraldyl acetate a No Expected Sensitization Induction Level (NESIL) of 1000 μg/cm^2 for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on data and ultraviolet/visible (UV/Vis) spectra; myraldyl acetate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; myraldyl acetate was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2003; RIFM, 2014)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: NESIL = 1000 μg/cm^2. RIFM (2007)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV/Vis Spectra, RIFM Database; RIFM, 1979c; RIFM, 1980)
Local Respiratory Toxicity: No NOAEC available. Exposure is above the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 67% (OECD 301F) RIFM (1995)
Bioaccumulation: Screening-level: 2946 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 96-h Algae LC50: 0.065 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) > (RIFM Framework; Salvito, 2002)
Critical Ecotoxicity Endpoint: 96-h Algae LC50: 0.065 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0065 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe <1

1. Identification

1. **Chemical Name:** Myraldyl acetate
2. **CAS Registry Number:** 72403-67-9
3. **Synonyms:** 3-Cyclohexene-1-methanol, 3 (or 4)-(4-pentenyl)-, acetate; 4 (or 3)-(4-Methyl-3-pentenyl)-3-cyclohexenylmethyl acetate & isomers; 3(Or 4)-(4-methylpenten-3-yl)cyclohex-3-ene-1-methyl acetate; Myraldyl acetate
4. **Molecular Formula:** $C_{15}H_{24}O_2$
5. **Molecular Weight:** 236.35
6. **RIFM Number:** 1309
7. **Stereochemistry:** No stereoisomer specified. One stereocenter present and 2 stereoisomers possible.

2. Physical data

1. **Boiling Point:** 304.21 °C (EPI Suite)
2. **Flash Point:** >110 °C at 99.96 kPa (RIFM, 2015e)
3. **Log K_{OW}:** 5.6 and 5.7 at 30 °C (RIFM, 1996), 5.76 (EPI Suite)
4. **Melting Point**: 38.19 °C (EPI Suite)
5. **Water Solubility:** 0.3369 mg/L (EPI Suite)
6. **Specific Gravity:** 0.947–0.957 (RIFM Database)
7. **Vapor Pressure:** 0.00119 mm Hg at 25 °C (EPI Suite), 0.00064 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No absorbance between 290 and 700 nm; the molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Organoleptic:** Colorless to pale yellow liquid with a floral, green, rosy odor

3. Volume of use (worldwide band)

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)

4. Exposure to fragrance ingredient (creme rifm aggregate exposure model v2.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.27% (RIFM, 2018)
2. **Inhalation Exposure*:** 0.00028 mg/kg/day or 0.020 mg/day (RIFM, 2018)
3. **Total Systemic Exposure**:** 0.0034 mg/kg/day (RIFM, 2018)

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

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

6.1. Cramer Classification

Class I, Low

Expert Judgment	Toxtree v3.1	OECD QSAR Toolbox v4.2
I	I	I

6.2. Analogs Selected

a. **Genotoxicity:** Nopyl acetate (CAS # 128-51-8)
b. **Repeated Dose Toxicity:** None
c. **Reproductive Toxicity:** None
d. **Skin Sensitization:** Menthadiene-7-methyl formate (CAS # 68683-20-5)
e. **Phototoxicity/Photoallergenicity:** None
f. **Local Respiratory Toxicity:** None
g. **Environmental Toxicity:** None

1. **Read-across Justification:** See Appendix below

7. Metabolism

Not relevant for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

8. Natural occurrence

Myraldyl acetate 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 containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

9. REACH Dossier

Available; accessed 07/16/21 (ECHA, 2016a).

10. Conclusion

The maximum acceptable concentrationsa in finished products for myraldyl acetate are detailed below.

IFRA Category[b]	Description of Product Type	Maximum Acceptable Concentrations[a] in Finished Products (%)[c]
1	Products applied to the lips (lipstick)	0.077
2	Products applied to the axillae	0.023
3	Products applied to the face/body using fingertips	0.46
4	Products related to fine fragrances	0.43
5A	Body lotion products applied to the face and body using the hands (palms), primarily leave-on	0.11
5B	Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on	0.11
5C	Hand cream products applied to the face and body using the hands (palms), primarily leave-on	0.11
5D	Baby cream, oil, talc	0.11
6	Products with oral and lip exposure	0.25
7	Products applied to the hair with some hand contact	0.88
8	Products with significant ano-genital exposure (tampon)	0.045
9	Products with body and hand exposure, primarily rinse-off (bar soap)	0.84
10A	Household care products with mostly hand contact (hand dishwashing detergent)	3.0
10B	Aerosol air freshener	3.0
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad)	1.7
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	No restriction

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For myraldyl acetate, the basis was a predicted skin absorption of 40% and a skin sensitization NESIL of 1000 μg/cm^2.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet

(https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf).

[c]Calculations by Creme RIFM Aggregate Exposure Model v3.0.5.

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data and use levels, myraldyl acetate does not present a concern for genetic toxicity.

11.1.1.1. Risk assessment. The mutagenic activity of myraldyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with myraldyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2003). Under the conditions of the study, myraldyl acetate was not mutagenic in the Ames test.

There are no data assessing the clastogenic activity of myraldyl acetate; however, read-across can be made to nopyl acetate (CAS # 128-51-8; see Section VI).

The clastogenic activity of nopyl acetate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with nopyl acetate in DMSO at concentrations up to 2083 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 376 μg/mL in the presence and absence of metabolic activation (S9) for 3 h and the absence of metabolic activation for 24 h. Nopyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either the presence or absence of an S9 activation system (RIFM, 2014). Under the conditions of the study, nopyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to myraldyl acetate.

Based on the data available, myraldyl acetate and read-across nopyl acetate do not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/01/21.

11.1.2. Repeated dose toxicity

There are no repeated dose toxicity data on myraldyl acetate or any read-across materials. The total systemic exposure to myraldyl acetate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on myraldyl acetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to myraldyl acetate (3.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/20/21.

11.1.3. Reproductive toxicity

There are no reproductive toxicity data on myraldyl acetate or any read-across materials. The total systemic exposure to myraldyl acetate is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on myraldyl acetate or on any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to myraldyl acetate (3.4 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/31/21.

11.1.4. Skin sensitization

Based on the existing data and read-across material menthadiene-7-methyl formate (CAS # 68683-20-5), myraldyl acetate is considered a skin sensitizer with a defined NESIL of 1000 μg/cm^2.

11.1.4.1. Risk assessment. Limited skin sensitization studies are available for myraldyl acetate. Based on the existing data and read-across material menthadiene-7-methyl formate (CAS # 68683-20-5; see Section VI), myraldyl acetate is considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts, 2007; OECD Toolbox v4.2; Toxtree v3.1.0). Read-across material menthadiene-7-methyl formate was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA) and KeratinoSens test (RIFM, 2015b; RIFM, 2015a). However, in a murine local lymph node assay (LLNA), read-across material menthadiene-7-methyl formate was found to be non-sensitizing up to 10% (2500 μg/cm^2) (RIFM, 2008). In a guinea pig Open Epicutaneous Test (OET), myraldyl acetate did not present reactions indicative of sensitization (ECHA, 2016). In 3 human maximization tests, skin sensitization reactions were observed at 10% (6900 μg/cm^2) of read-across material menthadiene-7-methyl formate (RIFM, 1977a; RIFM, 1978a; RIFM, 1978b). However, in the follow up 2 human maximization tests, no reactions indicative of sensitization were observed at 1.5% (1035 μg/cm^2) and 1% (690 μg/cm^2) of read-across material menthadiene-7-methyl formate (RIFM, 1979b; RIFM, 1979a). Additionally, in 2 Confirmation of No Induction in Humans tests (CNIHs) with 10% in dimethyl phthalate (DMP) of myraldyl acetate and 0.9% (1063 μg/cm^2) in 3:1 diethyl phthalate:ethanol (DEP:EtOH) of read-across material menthadiene-7-methyl formate, no reactions indicative of sensitization was observed in any of the 52 and 101 volunteers, respectively (RIFM, 1977b; RIFM, 2007).

Based on the available data on read-across material menthadiene-7-methyl formate, summarized in Table 1, myraldyl acetate is considered to be a skin sensitizer with a defined NESIL of 1000 μg/cm^2. Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM,

Table 1
Data summary for menthadiene-7-methyl formate as read-across material for myraldyl acetate.

LLNA Weighted Mean EC3 Value μg/cm^2 (No. Studies)	Potency Classification Based on Animal Data[a]	Human Data			
		NOEL-CNIH (Induction) μg/cm^2	NOEL-HMT (Induction) μg/cm^2	LOEL[b] (Induction) μg/cm^2	WoE NESIL[c] μg/cm^2
>2500 [1]	Weak	1063	1035	6900	1000

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

2020).

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/27/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available data and UV/Vis absorption spectra, myraldyl acetate would not be considered to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). No evidence for phototoxicity or photoallergy was observed in guinea pigs at the maximum tested concentration of 3% (RIFM, 1979c; RIFM, 1980). Based on the lack of absorbance, and the available *in vivo* study data, myraldyl acetate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/19/21.

11.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to a lack of appropriate data. The exposure level for myraldyl acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

11.1.6.1. Risk assessment. There are insufficient inhalation data available on myraldyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.020 mg/day. This exposure is 70 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: Belsito (2008).

Literature Search and Risk Assessment Completed On: 05/28/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of myraldyl acetate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiers 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 (EPI Suite v4.11), 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, myraldyl acetate 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 myraldyl acetate as possibly persistent but bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥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). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

11.2.2. Risk assessment

Based on the current VoU (2015), myraldyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. **RIFM, 1995:** Biodegradability of the test material was evaluated by the manometric respirometry test according to OECD Guideline 301F. The degradation rate at 10 and 28 days was 53% and 67%, respectively.

11.2.2.1.2. Ecotoxicity. **RIFM, 2015c:** An algae growth inhibition test was conducted according to OECD 201 guidelines under static conditions. Under the conditions of the test, the 72-h growth rate EC50 value was reported to be greater than 1.2 mg/L.

RIFM, 2015d: A *Daphnia* acute immobilization test was conducted according to OECD 202 guidelines under semi-static conditions. Under the conditions of the test, in terms of the time-weighted mean measured concentration, the 48-h EC50 value was reported to be 1.01 mg/L (95% CI: 0.55–1.32 mg/L).

11.2.2.1.3. Other available data. Myraldyl acetate has been registered for REACH with no additional data at this time.

11.2.3. Risk assessment refinement

Myraldyl acetate 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 highlighted.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	5.7	5.7
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	<1
Risk Characterization: PEC/PNEC	**<1**	**<1**

Based on available data, the RQ for this material is > 1. Additional assessment is necessary.

The RIFM PNEC is 0.0065 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 volumes of use.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.192			1000000	0.00019	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.201	0.279	0.065	10000	0.0065	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.081	0.065	0.204			Neutral Organic SAR (Baseline toxicity)

Literature Search and Risk Assessment Completed On: 05/25/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://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 07/16/21.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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.2021.112689.

Appendix

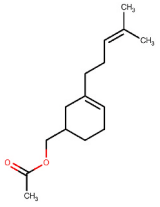
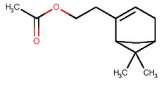
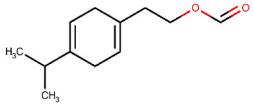
Read-across Justification

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, 2017).

- 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
Principal Name	Myraldyl acetate	Nopyl acetate	Menthadiene-7-methyl formate
CAS No.	72403-67-9	128-51-8	68683-20-5
Structure			
Similarity (Tanimoto Score)		0.64	0.45
Read-across Endpoint		• Genotoxicity	• Skin Sensitization
Molecular Formula	$C_{15}H_{24}O_2$	$C_{13}H_{20}O_2$	$C_{12}H_{18}O_2$
Molecular Weight	236.35	208.30	194.27
Melting Point (°C, EPI Suite)	38.19	54.20	33.96
Boiling Point (°C, EPI Suite)	304.21	259.16	253.24
Vapor Pressure (Pa @ 25°C, EPI Suite)	1.59E-01	1.19E+00	2.49E+00
Log K_{OW} (KOWWIN v1.68 in EPI Suite)	5.76	4.30	4.23
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.3369	8.429	11.35
J_{max} (μg/cm^2/h, SAM)	11.830	17.690	28.193
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.53E+02	6.10E+01	1.97E+02
Genotoxicity			
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	• AN2|AN2 ≫ Schiff base formation after aldehyde release after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters	• AN2|AN2 ≫ Schiff base formation after aldehyde release|AN2 ≫ Schiff base formation after aldehyde release ≫ Specific Acetate Esters|SN1|SN1 ≫ Nucleophilic attack after carbenium ion formation|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters|SN2|SN2 ≫ Acylation|SN2 ≫ Acylation ≫ Specific Acetate Esters|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters	
DNA Binding (OECD QSAR Toolbox v4.2)	• No alert found	• No alert found	
Carcinogenicity (ISS)	• No alert found	• No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found	
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found	
Oncologic Classification	• Not classified	• Not classified	
Skin Sensitization			
Protein Binding (OASIS v1.1)	• No alert found		• No alert found
Protein Binding (OECD)	• No alert found		• No alert found

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material
Protein Binding Potency	• Not possible to classify according to these rules (GSH)		• Not possible to classify according to these rules (GSH)
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• 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

Summary

There are insufficient toxicity data on myraldyl acetate (CAS # 72403-67-9). 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, nopyl acetate (CAS # 128-51-8) and menthadiene-7-methyl formate (CAS # 68683-20-5) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Nopyl acetate (CAS # 128-51-8) was used as a read-across analog for the target material myraldyl acetate (CAS # 72403-67-9) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of esters.
  - o The target material and the read-across analog share an acetate ester functionality.
  - o The key difference between the target material and the read-across analog is that the target material has a cyclic primary alcohol with a branched unsaturated alkyl substitution, while the read-across analog has a bridged cyclic primary alcohol. This structural difference is toxicologically insignificant.
  - o The 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog have an2, SN1, and SN2 Schiff base formation alert. This alert is due to the presence of acetate ester functionality. The data described in the genotoxicity section above confirm that the material poses no concern for genetic toxicity. The predictions are superseded by the data.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Menthadiene-7-methyl formate (CAS # 68683-20-5) was used as a read-across analog for the target material myraldyl acetate (CAS # 72403-67-9) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of esters.
  - o The target material and the read-across analog share a cyclic unsaturated primary alcohol moiety.
  - o The key difference between the target material and the read-across analog is that the target material has a cyclic primary alcohol with a branched unsaturated alkyl substitution, while the read-across analog has a cyclic unsaturated ring with a saturated alkyl substitution primary alcohol. Moreover, the target material is an acetate whereas the read-across analog is a formate. This structural difference is toxicologically insignificant.
  - o The 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.
  - o The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - o The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

References

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.

Belsito, D., Bickers, D., Bruze, M., Calow, P., Greim, H., Hanifin, J.M., Rogers, A.E., Saurat, J.H., Sipes, I.G., Tagami, H., 2008. A toxicologic and dermatologic assessment of cyclic acetates when used as fragrance ingredients. Food Chem. Toxicol. 46 (12S), S1–S27.

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. CAESAR models for developmental toxicity. In: Chemistry Central Journal, vol. 4. Springer International Publishing, p. S4.

Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regul. Toxicol. Pharmacol. 72 (3), 660–672.

Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S. H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices

data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul. Toxicol. Pharmacol. 88, 144–156.
ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. http://echa.europa.eu/.
ECHA, 2016. Myraldyl Acetate Registration Dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/17778/1.
ECHA, 2017. Read-across Assessment Framework (RAAF). Retrieved from. www.echa.europa.eu/documents/10162/13628/raaf_en.pdf.
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.
Na, M., Ritacco, G., O'Brien, D., Lavelle, M., Api, A., Basketter, D., 2020. Fragrance skin sensitization evaluation and human testing, dermatitis. https://doi.org/10.1097/DER.0000000000000684. November 16, 2020. Volume Publish Ahead of Print Issue. Retrieved from.
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. http://www.qsartoolbox.org/.
RIFM Research Institute for Fragrance Materials, Inc, 1977a. Report on Human Maximization studies. Report to RIFM. RIFM report number 1691. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1977b. Sensitization and Irritation Studies of Myraldyl Acetate in Human Subjects. Unpublished report from Givaudan-Roure Corporation. RIFM report number 17234. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1978a. Report on Human Maximization studies. Report to RIFM. RIFM report number 1698. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1978b. Report on Human Maximization Studies. Report to RIFM. RIFM report number 1787. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1979a. Report on human maximization studies. RIFM report number 1775 Report to RIFM. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1979b. The Appraisal of the Contact-Sensitizing Potential of Menthadiene-7-Methyl Formate (Isobergamate) by Means of the Maximization Study in Humans. Unpublished report from Dragoco, Inc. RIFM report number 3010 (RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1979c. Determination of Phototoxicity in guinea Pigs with Myraldyl Acetate. Unpublished report from Givaudan. RIFM report number 56054. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1980. A guinea Pig Assay of Photosensitizing Potential of Myraldyl Acetate. Unpublished report from Givaudan. RIFM report number 56055. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1995. Ready Biodegradability of Myraldyl Acetate. Unpublished report from Givaudan. RIFM report number 51507. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 1996. Partition Coefficient N-Octanol/water of Myraldyl Acetate. Unpublished report from Givaudan. RIFM report number 51508. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2003. Myraldyl Acetate: Reverse Mutation in Five Histidine-Requiring Strains of Salmonella typhimurium. Unpublished report from Givaudan. RIFM report number 42164. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2007. Repeated Insult Patch Test with Menthadiene-7-Methyl Formate. RIFM report number 53723. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2008. Local Lymph Node Assay with Menthadiene-7-Methyl Formate. RIFM report number 54429. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2014. Nopyl Acetate: in Vitro Micronucleus Assay in Human Peripheral Blood Lymphocytes. RIFM report number 67598. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2015a. Induction of Antioxidant-Response Element Dependent Gene Activity Cytotoxicity (Using MTT) in the Keratinocyte ARE- Reporter Cell Line Keratinosens. RIFM report number 69647. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2015b. Direct Peptide Reactivity Assay (DPRA) of Alpha-Amylcinnamyl Alcohol, Benzyl Cinnamate, Butyl Acrylate, P-Tert-Butyldihydrocinnamaldehyde, Carvone and 1-cyclohexylethyl 2-butenoate. RIFM report number 69649. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2015c. Myraldyl Acetate: Inhibition of Growth to the Alga Pseudokirchneriella Subcapitata. Unpublished report from RIFM report number 70953. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2015d. Myraldyl Acetate: Acute Toxicity to Daphnia Magna. Unpublished report from RIFM report number 70954. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2015e. Myraldyl Acetate: Evaluation of Selected Physical Chemical Properties. Unpublished report from RIFM report number 70957. RIFM, Woodcliff Lake, NJ, USA.
RIFM Research Institute for Fragrance Materials, Inc, 2018. Exposure Survey 21. September 2018.
RIFM Research Institute for Fragrance Materials, Inc, 2020. Updating Exposure Assessment for Skin Sensitization Quantitative Risk Assessment for Fragrance Materials. RIFM report number 76775. RIFM, Woodcliff Lake, NJ, USA.
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., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul. Toxicol. Pharmacol. 72, 673–682.
Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul. Toxicol. Pharmacol. 86, 148–156.
Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environ. Toxicol. Chem. 21 (6), 1301–1308.
Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., 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.
US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
US EPA, 2012b. The ECOSAR (ECOlogical Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.