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RIFM fragrance ingredient safety assessment, isodecyl acetate, CAS Registry Number 69103-24-8

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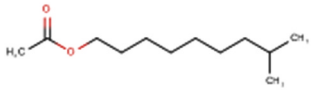

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Name: Isodecyl acetate
CAS Registry Number: 69103-24-8

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

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CNIH – Confirmation of No Induction in Humans test. A Confirmation of No Induction in Humans 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; Safford et al., 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 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.

Isodecyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog isononyl acetate (isomer unspecified) (CAS # 40379-24-6) show that isodecyl acetate is not expected to be genotoxic. Data on read-across analog 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7) provide a calculated MOE >100 for the repeated dose and reproductive toxicity endpoints. Data from read-across analog isoamyl acetate (CAS # 123-92-2) show that there are no safety concerns for isodecyl acetate for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; isodecyl acetate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material, and the exposure to isodecyl acetate is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; isodecyl acetate 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.

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Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.	(RIFM, 2016a; RIFM, 2016b)
Repeated Dose Toxicity: NOAEL = 20 mg/kg/day.	(ECHA REACH Dossier: 3,5,5-Trimethylhexyl acetate; ECHA, 2013)
Reproductive Toxicity: Developmental toxicity: 40 mg/kg/day. Fertility: 40 mg/kg/day.	(ECHA REACH Dossier: 3,5,5-Trimethylhexyl acetate; ECHA, 2013; RIFM, 2013a)
Skin Sensitization: Not a concern for skin sensitization at the current, declared use levels.	RIFM (1987)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV/Vis Spectra; RIFM Database)

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Screening-level: 2.90 (BIOWIN 3)	(EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 25.51 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 1.16 mg/L	(RIFM Framework; Salvito et al., 2002)

Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 1.16 mg/L	(RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.00116 μg/L

- **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** Isodecyl acetate
2. **CAS Registry Number:** 69103-24-8
3. **Synonyms:** Acetic acid, isodecyl ester; 2,6-Dimethyl octanylacetate; Isodecyl acetate
4. **Molecular Formula:** $C_{12}H_{24}O_2$
5. **Molecular Weight:** 200.32 g/mol
6. **RIFM Number:** 5953
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no isomer possible.

2. Physical data

1. **Boiling Point:** 236.95 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 4.72 (EPI Suite)
4. **Melting Point**: 1.93 °C (EPI Suite)
5. **Water Solubility:** 4.064 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0544 mm Hg at 25 °C (EPI Suite), 0.035 mm Hg at 20 °C (EPI Suite v4.0)
8. **UV Spectra:** No absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} • cm^{-1})
9. **Appearance/Organoleptic:** A colorless liquid that has a sweet floral-fruity, somewhat honey-waxy odor

3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v3.1.1)

1. **95**th **Percentile Concentration in Toothpaste:** 0.015% (RIFM, 2020b)
   (No Reported Use in Fine Fragrance)
2. **Inhalation Exposure*:** <0.0001 mg/kg/day or <0.0001 mg/day (RIFM, 2020b)
3. **Total Systemic Exposure**:** 0.000093 mg/kg/day (RIFM, 2020b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 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., 2015; 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 v3.1	OECD QSAR Toolbox v4.2
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2. Analogs Selected:
   a. **Genotoxicity:** Isononyl acetate (isomer unspecified) (CAS # 40379-24-6)
   b. **Repeated Dose Toxicity:** 3,5,5-Trimethylhexyl acetate (CAS # 58430-94-7); Weight of Evidence (WoE): 2-propylheptan-1-ol (CAS # 10042-59-8)
   c. **Reproductive Toxicity:** 3,5,5-Trimethylhexyl acetate (CAS # 58430-94-7); WoE: 2-propylheptan-1-ol (CAS # 10042-59-8)
   d. **Skin Sensitization:** Isoamyl acetate (CAS # 123-92-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   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

Isodecyl acetate is not reported to occur in foods 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

Isodecyl acetate has been pre-registered for 2010; no dossier available as of 02/07/22.

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, isodecyl acetate does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. Isodecyl acetate was assessed in the BlueScreen assay and found positive for cytotoxicity (positive: <80% relative cell density) and negative for genotoxicity, with and without metabolic activation (RIFM, 2013b). BlueScreen is a human cell-based assay for measuring the genotoxicity and cytotoxicity of chemical compounds and mixtures. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic or clastogenic activity of isodecyl acetate; however, read-across can be made to isononyl acetate (isomer unspecified) (CAS # 40379-24-6; see Section VI).

The mutagenic activity of isononyl acetate (isomer unspecified) has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2uvrA were treated with isononyl acetate (isomer unspecified) 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, 2016a). Under the conditions of the study, isononyl acetate (isomer unspecified) was not mutagenic in the Ames test (and this can be extended to isodecyl acetate).

The clastogenic activity of isononyl acetate (isomer unspecified) was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with isononyl acetate (isomer unspecified) in DMSO at concentrations up to 1860 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 500 μg/mL in the presence and absence of metabolic activation. Isononyl acetate (isomer unspecified) did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation system (RIFM, 2016b). Under the conditions of the study, isononyl acetate (isomer unspecified) was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to isodecyl acetate.

Based on the data available, isononyl acetate (isomer unspecified) does not present a concern for genotoxic potential, and this can be extended to isodecyl acetate.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/04/21.

11.1.2. Repeated dose toxicity

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

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on isodecyl acetate. Read-across material 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7; see Section VI) has sufficient repeated dose toxicity data. In an OECD 422 gavage study in 10 rats/sex/group, 3,5,5-trimethylhexyl acetate was administered at dose levels of 0, 40, 125, and 400 mg/kg/day, the NOAEL was 40 mg/kg/day. Mortality occurred in females at the mid and high doses (RIFM, 2013a). There was an alteration in the hematology and clinical chemistry parameters among animals in the mid- and high-dose groups. Adaptive histopathological alterations were reported in the liver and thyroid in females in the mid- and high-dose groups and in males of all treatment groups. In addition, males were reported to exhibit hyaline droplet nephropathy in all treatment groups. No other parental toxicological alterations were reported. Thus, the NOAEL for males was considered to be 400 mg/kg/day, and in females, the NOAEL was reported to be 40 mg/kg/day.

In an OECD 408 and GLP compliant subchronic toxicity study, 10 Sprague Dawley rats/sex/dose were orally administered 3,5,5-trimethylhexyl acetate at doses of 0, 20, 80, and 300 mg/kg/day for 13 weeks. There were no treatment-related effects observed in both sexes for mortality, behavior, motor activity, and hematological parameters. At the mid and high doses, urine output in animals was increased, resulting in wet fur (urogenital area) and brown skin staining (tail region). A similar effect was observed in high-dose group males at the end of the recovery period. Increased food consumption was reported in both sexes at the highest dose without bodyweight alterations. Significant dose-dependent increases in absolute and relative liver weights and increased hepatocellular hypertrophy and vacuolation along with pale-looking livers were reported in mid- and high-dose group animals. However, increased female liver weights at the highest dose were reversed during recovery. In addition, females were reported to have dose-dependent increases in liver enzyme activity (ALAT, not statistically significant). In high-dose group females, hepatic microsomal enzyme UDP-glucuronosyl transferase increased while serum albumin/globulin ratio decreased at the mid and high doses. In males, serum triglycerides decreased at 300 mg/kg/day during the study and increased along with serum cholesterol, urea, glucose at the end of the recovery period. There was a treatment-related increase in hepatic microsomal enzymes in males at all tested doses. A dose-dependent increase in absolute and relative kidney weights was observed in males at all tested doses in conjunction with dose-dependent increases in tubular degeneration, necrosis, granular casts, interstitial inflammation, and hyaline droplets (confirmed by immunohistochemistry) in the tubular epithelium. Unlike hyaline droplet formation, renal tubular degeneration and necrosis persisted in high-dose group males. Since α-2u-globulin is a sex- and species-specific lesion, the male kidney lesions were not considered relevant to human health. Based on the liver effects that were observed in females at doses of 80 and 300 mg/kg/day, a NOAEL of 20 mg/kg/day was selected (ECHA, 2013). **The most conservative NOAEL for the repeated dose toxicity endpoint was selected from the 408 study, which was the NOAEL of 20 mg/kg/day.**

The isodecyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the 3,5,5-trimethylhexyl acetate NOAEL in mg/kg/day by the total systemic exposure to isodecyl acetate, 20/0.000093, or 215053.

In addition, the total systemic exposure to isodecyl acetate (0.093 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.

Data on 2-propylheptan-1-ol (CAS # 10042-59-8) can be used as WoE to support the safe use of isodecyl acetate for the repeated dose endpoint. In a GLP and OECD 408-compliant study, 10 Fischer 344 rats/sex/dose were administered 2-propylheptan-1-ol via gavage at doses of 0, 30, 150, and 600 mg/kg/day for 3 months. Based on increased mean liver weights in females (as well as diffuse hypertrophy of the liver cells in one female) at 150 mg/kg/day, the NOAEL for this study was considered to be 30 mg/kg/day (ECHA, 2011).

*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: 05/20/21.

11.1.3. Reproductive toxicity

The MOE for isodecyl acetate is adequate for the reproductive toxicity endpoint at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on isodecyl acetate. Read-across material 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7; see Section VI) has sufficient reproductive toxicity data.

In an OECD 422/GLP study conducted in Wistar rats (10/sex/group), 3,5,5-trimethylhexyl acetate was administered via oral gavage at doses of 0, 40, 125, or 400 mg/kg/day in corn oil to males for 28 days and to females for 14 days prior to pairing, and throughout the pairing and gestation periods until the F1 generation reached day 4 post-partum. Eight high-dose females and 2 mid-dose females were found dead at the end of the gestation period. Complications during the last days of pregnancy and/or difficult parturition were considered to be the possible cause of the deaths; therefore, this was considered to be treatment-related. At 400 mg/kg/day, the number of implantation sites calculated for females that died before giving birth was lower than the control value and below the historical control range. Due to mortality at the high-dose level, the remaining reproduction and breeding data were not evaluated at this dose level. At 125 mg/kg/day, increased post-implantation and postnatal loss were noted, which resulted in reduced litter size at this dose level. The mean number of postnatal losses per dam was 0.8 at 125 mg/kg/day compared to 0.2 in the control group. Consequently, a statistically significantly reduced viability index was noted: 89.1% at the mid-dose compared to 98.0% in the control group. No treatment-related findings were noted in pups at first litter check or during lactation at any dose level. Pup body weights on day 1 post-partum were not affected by the treatment at the 40 and 125 mg/kg/day dose groups. No treatment-related findings were noted during the necropsy of pups at any dose level. The NOAEL for male fertility was considered to be 400 mg/kg/day, the highest dose tested. The NOAEL for female fertility was considered to be 40 mg/kg/day, based on increased post-implantation loss at 125 mg/kg/day. The NOAEL for developmental toxicity was considered to be 40 mg/kg/day, based on increased postnatal loss at 125 mg/kg/day (RIFM, 2013a). The most conservative fertility NOAEL of 40 mg/kg/day was selected for this study.

In an OECD 408/GLP subchronic toxicity study, Sprague Dawley rats (10/sex/group) were administered 3,5,5-trimethylhexyl acetate via oral gavage at doses of 0, 20, 80, or 300 mg/kg/day in corn oil once daily for 13 weeks. In addition to systemic toxicity parameters, female estrous cycling and male sperm analysis were also evaluated. Females had a dose-dependent increase in prolonged estrous and the number of sequences of consecutive estrous days but without any associated histopathological changes in the ovaries and reproductive tract, or changes to thyroid hormone levels. However, the prolonged estrous and increased number of sequences of consecutive estrous days was most pronounced at the highest dose. There were no treatment-related effects in male reproduction, which included sperm motility, count, or morphology. Thus, the NOAEL for female fertility was considered to be 80 mg/kg/

day, based on treatment-related effects observed in female estrus at the highest dose group. The NOAEL for male fertility was considered to be 300 mg/kg/day, the highest dose tested (ECHA, 2013). The most conservative fertility NOAEL of 80 mg/kg/day was selected for this study.

In an OECD 414/GLP prenatal developmental toxicity study, pregnant female Sprague Dawley rats (24/group) were administered 3,5,5-trimethylhexyl acetate via oral gavage at doses of 0, 15, 50, or 250 mg/kg/day in corn oil from gestation days 5–20. Mortality was reported for 2 high-dose group dams. These deaths were considered to be treatment-related due to macroscopic findings that consisted of pale, discolored livers and dark foci observed in the stomach. Similar macroscopic changes in the liver and stomach were reported in surviving females from the high-dose group, as well as small spleen and gelatinous pancreas. Body weight, bodyweight gain, and food consumption were decreased in females treated at 250 mg/kg/day. No treatment-related effects were observed in the number of corpora lutea, implantation sites, live fetuses, sex ratio, resorptions, or post-implantations loss. Gravis uterus weight was significantly lower in dams treated with 250 mg/kg/day due to statistically significant decreases in fetal body weights. The NOAEL for maternal toxicity was considered to be 50 mg/kg/day, based on decreased body weight, and treatment-related gross pathology observed among high-dose group dams. No treatment-related effects were observed in external, internal, skeletal, or visceral malformations in fetuses for all dose groups. Secondary effects on maternal toxicity included increased incidences of incomplete ossification of the frontal, interparietal, pubis, and parietal bones for both litters and fetuses along with a significant increase in fetuses with incomplete ossification of the supraoccipital bones in the 250 mg/kg/day dose group. The authors of the study concluded the developmental toxicity NOAEL to be 250 mg/kg/day, the highest dose tested. However, since incomplete ossification of the skeletal bones and decreased fetal body weight were observed among the high-dose group, a conservative developmental toxicity NOAEL was considered to be 50 mg/kg/day (ECHA, 2013).

The most conservative developmental toxicity NOAEL of 40 mg/kg/day from the OECD 422 study was considered for the developmental toxicity endpoint. **The isodecyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the 3,5,5-trimethylhexyl acetate NOAEL in mg/kg/day by the total systemic exposure to isodecyl acetate, 40/0.000093 or 430107.**

The most conservative fertility NOAEL of 40 mg/kg/day from the OECD 422 study was considered for the fertility endpoint. **The isodecyl acetate MOE for the fertility endpoint can be calculated by dividing the 3,5,5-trimethylhexyl acetate NOAEL in mg/kg/day by the total systemic exposure to isodecyl acetate, 40/0.000093, or 430107.**

In addition, the total systemic exposure to isodecyl acetate (0.093 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.

Data on 2-propylheptan-1-ol (CAS # 10042-59-8) can be used as WoE to support the safe use of isodecyl acetate for the developmental and reproductive endpoints. In a GLP and OECD 416-compliant study, 25 Wistar rats/sex/dose were administered 2-propylheptan-1-ol via diet at doses of 0, 40, 200, and 600 mg/kg/day for 126 days (F0 generation) and 131 (F1 generation). No effects were observed on reproductive performance, estrous cycle, or sperm measures. Based on no effects seen up to the highest dose, the fertility NOAEL for this study was considered to be 600 mg/kg/day (ECHA, 2011).

In a GLP and OECD 414-compliant study, 25 Wistar rats/sex/dose were administered 2-propylheptan-1-ol via gavage at doses of 0, 50, 200, and 600 mg/kg/day for 20 days. No effects were observed on reproductive performance, estrous cycle, or sperm measures. Based on the delay of ossification and increased incidence of supernumerary thoracic vertebrae and supernumerary/wavy ribs at 600 mg/kg/day, the developmental NOAEL for this study was considered to be 200 mg/kg/day (ECHA, 2011).

Additional References: None.

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

11.1.4. Skin sensitization

Based on read-across material isoamyl acetate (CAS # 123-92-2), isodecyl acetate is not considered a skin sensitizer under the current, declared levels of use.

11.1.4.1. Risk assessment. No skin sensitization studies are available for isodecyl acetate. Based on read-across material isoamyl acetate (CAS # 123-92-2; see Section VI), isodecyl acetate is not considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig maximization test, read-across material isoamyl acetate in a mixture of primary amyl acetates did not result in reactions indicative of sensitization (Ballantyne et al., 1986). Similarly, read-across material isoamyl acetate was found to be negative in a guinea pig open epicutaneous test (Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed with 8% or 5520 μg/cm^2 read-across material isoamyl acetate (RIFM, 1973). Additionally, in a Confirmation of No Induction in Humans test (CNIH) with 20% or 23622 μg/cm^2 of read-across material isoamyl acetate in 3:1 ethanol:diethyl phthalate, no reactions indicative of sensitization was observed in any of the 197 volunteers (RIFM, 1987).

Based on WoE from structural analysis, animal and human studies, and read-across material isoamyl acetate, isodecyl acetate does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/02/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, isodecyl acetate 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 isodecyl acetate in experimental models. UV/Vis absorption spectra indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, isodecyl 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 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: 06/01/21.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on isodecyl acetate. Based on the Creme RIFM Model, the inhalation exposure is $<$ 0.0001 mg/day. This exposure is at least 14000 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/03/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of isodecyl acetate 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, isodecyl acetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify isodecyl acetate 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, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), isodecyl acetate presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. Isodecyl acetate has been pre-registered for REACH with no additional information available at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	4.72	4.72
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	No VoU
Risk Characterization: PEC/PNEC	**<1**	**NA**

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

The RIFM PNEC is 0.00116 μg/L. The revised PEC/PNECs for EU and NA (No VoU) are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 05/12/21.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	1.16			1000000	0.00116	

- **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 02/07/22.

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.2022.113194.

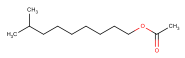
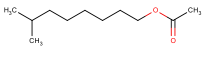
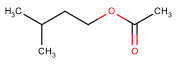
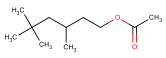
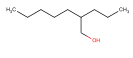
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 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, oncologic classification, ER binding, and repeat dose categorization predictions 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).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material	WoE Material
Principal Name	Isodecyl acetate	Isononyl acetate (isomer unspecified)	Isoamyl acetate	3,5,5-Trimethylhexyl acetate	1-Heptanol, 2-propyl
CAS No.	69103-24-8	40379-24-6	123-92-2	58430-94-7	10042-59-8
Structure					
Similarity (Tanimoto Score)		1.00	0.63	0.83	0.49
Endpoint		• Genotoxicity	• Skin sensitization	• Reproductive toxicity • Repeated dose toxicity	• Reproductive toxicity • Repeated dose toxicity
Molecular Formula	$C_{12}H_{24}O_2$	$C_{11}H_{22}O_2$	$C_7H_{14}O_2$	$C_{11}H_{22}O_2$	$C_{10}H_{22}O$
Molecular Weight (g/mol)	200.32	186.29	130.19	186.29	158.28
Melting Point (°C, EPI Suite)	1.93	−9.14	−78.50	−13.62	−2.83
Boiling Point (°C, EPI Suite)	236.95	218.34	142.50	198.85	217.50
Vapor Pressure (Pa @ 25°C, EPI Suite)	7.25	19.07	746.60	50.93	3.37
	4.06	12.56	2000.00	15.62	151.80

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material	WoE Material
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)					
Log K_{OW}	4.72	4.23	2.25	4.12	3.71
J_{max} (μg/cm^2/h, SAM)	0.60	1.68	101.63	1.97	20.52
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	227.98	171.24	59.48	171.24	5.54
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff 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	AN2|AN2 ≫ Shiff base formation after aldehyde release|AN2 ≫ Shiff 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 skin sensitization reactivity domains alerts identified.	No skin sensitization reactivity domains alerts identified.			
Oncologic Classification	Not classified	Not classified			
Repeated Dose Toxicity					
Repeated Dose (HESS)	Not categorized			Not categorized	Sodium valproate (Renal toxicity) Alert|Valproic acid (Hepatotoxicity) Alert
Reproductive Toxicity					
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure			Non-binder, non-cyclic structure	Non-binder, non-cyclic structure
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (low reliability)			Non-toxicant (low reliability)	Non-toxicant (low reliability)
Skin Sensitization					
Protein Binding (OASIS v1.1)	No alert found		No alert found		
Protein Binding (OECD)	No alert found		No alert found		
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 skin sensitization reactivity domains alerts identified.		No skin sensitization reactivity domains alerts identified.		
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	See Supplemental Data 5

Summary

There are insufficient toxicity data on isodecyl acetate (CAS # 69103-24-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, [metabolism data], physical–chemical properties, and expert judgment,

isononyl acetate (isomer unspecified) (CAS # 40379-24-6), isoamyl acetate (CAS # 123-92-2), 3,5,5-trimethylhexyl acetate (CAS # 58430-94-7) and 1-heptanol, 2-propyl (CAS # 10042-59-8) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Isononyl acetate (isomer unspecified) (CAS # 40379-24-6) was used as a read-across analog for the target material isodecyl acetate (CAS # 69103-24-8) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to the class of simple branched saturated esters of terpene alcohols.
  - 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 is one carbon longer in a saturated aliphatic chain compared to the read-across analog. However, this structural difference is toxicologically insignificant.
  - o The Tanimoto score indicates the similarity between the target material and the read-across analog. 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 a comparison of their toxicological properties.
    - oAccording 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 an alert for AN2, Schiff base formation, SN1, and SN2 nucleophilic substitution at the sp3 carbon. This alert is due to the acetate portion of the ester. By comparing the structures of these materials, it is confirmed that it is completely out of the structural domain from the training set used for the alert. Furthermore, the data for the read-across analog confirm that the material poses no concern for genetic toxicity**.** Therefore, 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.
- Isoamyl acetate (CAS # 123-92-2) was used as a read-across analog for the target material isodecyl acetate (CAS # 69103-24-8) for the skin sensitization endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of aliphatic ester of terpene alcohols.
  - o The target material and the read-across analog share an ester functionality.
  - o The key difference between the target material and the read-across analog is that the target material has a longer carbon chain in the saturated branched alcohol portion compared to the read-across analog. The read-across analog contains the structural features of the target material that are relevant to this endpoint and is expected to have equal or greater potential for toxicity as compared to the target.
  - 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 a 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 There are no alerts for the skin sensitization endpoint. The data on the read-across analog confirms that the MOE is adequate at the current level of use. Therefore, the *in silico* alerts are consistent with 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.
- 3,5,5-Trimethylhexyl acetate (CAS # 58430-94-7) was used as a read-across analog for the target material isodecyl acetate (CAS # 69103-24-8) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material and the read-across analog are structurally similar and belong to simple saturated aliphatic esters of terpene alcohols.
  - o The target material and the read-across analog share an ester functionality.
  - o The key difference between the target material and the read-across analog is that the alcohol portion in the target material has methyl substitution on the chain, whereas the read-across analog has tert. butyl substitution on the aliphatic chain of the alcohol portion. 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 a 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 There are no alerts for the repeated dose and reproductive toxicity endpoints. The data on the read-across analog confirms that the MOE is adequate at the current level of use. Therefore, the *in silico* alerts are consistent with 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.
- 1-Heptanol, 2-propyl (CAS # 10042-59-8) was used as a WoE material for the target material isodecyl acetate (CAS # 69103-24-8) for the repeated dose toxicity and reproductive toxicity endpoints.
  - o The target material belongs to the class of branched saturated esters while the WoE analog belongs to the class of branched saturated alcohols.
  - o The key structural difference between the target material and the read-across analog is that the target material is an ester whereas the WoE analog is a primary alcohol. The WoE analog is used here because it covers the longer carbon chain in the saturated branched alcohol portion of the target material. This structural difference is toxicologically insignificant.
  - o Structural similarity between the target material and the WoE analog is indicated by the Tanimoto score. The Tanimoto score reflects the near identity of these branched ethyl ester structures. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

- The physical–chemical properties of the target material and the WoE analog are sufficiently similar to enable a comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v4.2, structural alerts for the toxicological endpoint are consistent between the target material and the WoE analog.
- The WoE analog has a renal alert (Repeated Dose [HESS]). However, the data on the WoE analog confirms that the MOE is adequate at the current level of use. Therefore, the *in silico* alert is superseded.
- The target material and the WoE analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoint evaluated are consistent between the metabolites of the WoE 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 and Chemical Toxicology 82, S1–S19.

Ballantyne, B., Tyler, T.R., Auletta, C.S., 1986. The sensitizing potential of primary amyl acetate in the Guinea pig. Veterinary and Human Toxicology 28 (3), 213–215.

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 and Chemical Toxicology 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. Chemistry Central Journal (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. Regulatory Toxicology and Pharmacology 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. Regulatory Toxicology and Pharmacology 88, 144–156.

ECHA, 2011. 2-Propylheptan-1-ol registration dossier. Retrieved from. https://echa.europa.eu/lv/registration-dossier/-/registered-dossier/13788/1/2.

ECHA, 2012. Guidance on information requirements and chemical safety assessment. November 2012 v2.1. http://echa.europa.eu/.

ECHA, 2013. 3,5,5-Trimethylhexyl acetate registration dossier. Retrieved from. https://echa.europa.eu/registration-dossier/-/registered-dossier/13930/1.

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? Journal of Photochemistry and Photobiology B: Biology 96 (1), 57–62.

IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.

Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. Current Problems in Dermatology 14, 152–171.

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 and Chemical Toxicology 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. Regulatory Toxicology and Pharmacology 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. Retrieved from. http://www.qsartoolbox.org/.

RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Report on Human Maximization Studies. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 1802.

RIFM (Research Institute for Fragrance Materials, Inc.), 1987. Report on Human Repeated Insult Patch Test. RIFM, Woodcliff Lake, NJ, USA. Report to RIFM. RIFM report number 7973.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013a. 3,5,5-Trimethylhexyl Acetate (Neononyl Acetate): Combined Repeated Dose Toxicity Study with the Reproduction/developmental Toxicity Screening Test in the Han Wistar Rat. RIFM, Woodcliff Lake, NJ, USA. Unpublished report from Symrise. RIFM report number 65248.

RIFM (Research Institute for Fragrance Materials, Inc.), 2013b. Report on the Testing of Isodecyl Acetate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 66706.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. Isononyl Acetate: Bacterial Reverse Mutation Assay. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 69833.

RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Isononyl Acetate (Isomer Unspecified): in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM, Woodcliff Lake, NJ, USA. RIFM report number 70091.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020a. Clustering a Chemical Inventory for Safety Assessment of Fragrance Ingredients: Identifying Read-Across Analogs to Address Data Gaps. RIFM, Woodcliff Lake, NJ, USA. RIFM report number 76272.

RIFM (Research Institute for Fragrance Materials, Inc.), 2020b. Exposure Survey 27, May 2020.

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. Chemical Research in Toxicology 20 (7), 1019–1030.

Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. Journal of Chemical Information and Modeling 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. Regulatory Toxicology and Pharmacology 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. Regulatory Toxicology and Pharmacology 86, 148–156.

Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. Environmental Toxicology and Chemistry 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. Regulatory Toxicology and Pharmacology 72 (3), 586–601.

Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. Food and Chemical Toxicology 74, 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.