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Short review

RIFM fragrance ingredient safety assessment, 2-ethylhexyl acetate, CAS Registry Number 103-09-3

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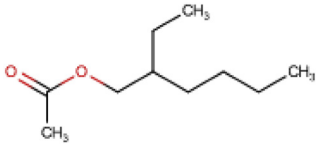
Version: 032818. This version replaces any previous versions.
Name: 2-Ethylhexyl acetate CAS Registry Number: 103-09-3



Abbreviation/Definition List:

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

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EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

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

2-Ethylhexyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from target material and read-across analogs 2-ethyl-1-hexanol (CAS# 104-76-7) and 1,5-dimethylhexyl acetate (CAS# 67952-57-2) show that 2-ethylhexyl acetate is not expected to be genotoxic. The repeated dose and developmental toxicity endpoints were completed using 2-ethyl-1-hexanol (CAS# 104-76-7) and acetic acid (CAS# 64-19-7) as read-across analogs, which provided an MOE > 100. Data from target material and read-across analog isoamyl acetate (CAS# 123-92-2) show that 2-ethylhexyl acetate is not a concern for skin sensitization. The fertility and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material (0.03 mg/kg/day and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; 2-ethylhexyl 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.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (Mee, 2016; RIFM, 2016; NTP, 2007)

Repeated Dose Toxicity: NOAEL = 50 mg/kg/day. (Astill, 1996)

Reproductive Toxicity: Developmental toxicity NOAEL = 191 mg/kg/day. No NOAEL available for fertility, exposure is below the TTC. (NTP, 1991)

Skin Sensitization: No safety concerns under the current, declared levels of use. (RIFM, 1987)

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

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

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 70% (OECD 301B) (ECHA Dossier)

Bioaccumulation: Screening-level: 135 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 7.7 mg/L (RIFM Framework; Salvito, 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, 2002)

Critical Ecotoxicity Endpoint: Fish LC50: 7.7 mg/L (RIFM Framework; Salvito, 2002)

RIFM PNEC is: 0.0077 µg/L

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

1. Identification

1 **Chemical Name:** 2-Ethylhexyl acetate
2 **CAS Registry Number:** 103-09-3
3 **Synonyms:** Acetic acid, 2-ethylhexyl ester; 2-Ethylhexyl acetate
4 **Molecular Formula:** $C_{10}H_{20}O_2$
5 **Molecular Weight:** 172.27
6 **RIFM Number:** 866
7. **Stereochemistry:** Isomer not specified. One stereocenter and 2 total stereoisomers possible.

2. Physical data

1 **Boiling Point**: 198.6 °C (Schmidt, 1969), 198.83 °C (US EPA, 2012a)
2 **Flash Point**: 71 °C (GHS)
3 **Log KOW**: 3.74 (US EPA, 2012a)
4 **Melting Point**: −20.47 °C (US EPA, 2012a)
5 **Water Solubility:** 38.59 mg/L (US EPA, 2012a)
6 **Specific Gravity:** 0.87000 to 0.87600 @ 25.00 °C*
7 **Vapor Pressure:** 0.257 mm Hg @ 20 °C (US EPA, 2012a), 0.4 mm Hg 20 °C (FMA database), 0.379 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption coefficient is below the benchmark (1000 $L \cdot mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless liquid that has a very pleasant, sweet-fruity odor reminiscent of raspberry juice

*The Good Scents Company, accessed 09/13/17.

3. Exposure

1 Volume of Use (Worldwide Band): 0.1–1 metric ton per year (IFRA, 2015)
2 95th Percentile Concentration in Hydroalcoholics: 0.010% (RIFM, 2015)
3 Inhalation Exposure*: 0.000025 mg/kg/day or 0.0018 mg/day (RIFM, 2015)
4 Total Systemic Exposure**: 0.00096 mg/kg/day (RIFM, 2015)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM 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 4. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral, and inhalation routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey, 2015, 2017; Safford, 2015, 2017).

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

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

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

2 Analogs Selected:
a **Genotoxicity:** 2-Ethyl-1-hexanol (CAS # 104-76-7); 1,5-dimethylhexyl acetate (CAS # 67952-57-2)
b **Repeated Dose Toxicity:** 2-Ethyl-1-hexanol (CAS # 104-76-7); acetic acid (CAS # 64-19-7)
c **Reproductive Toxicity:** 2-Ethyl-1-hexanol (CAS # 104-76-7); acetic acid (CAS # 64-19-7)
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

6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

2-Ethylhexyl acetate is reported to occur in the following foods by the VCF* and is not found in natural complex substances (NCS):
Elderberry (sambucus nigra l.)
Litchi wine.
Melon.
Vaccinium species.
*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

8. IFRA standard

None.

9. Reach Dossier

Dossier available, accessed 09/13/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on current existing data, 2-ethylhexyl acetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 2-Ethylhexyl acetate was assessed in the BlueScreen assay and was found to be negative for genotoxicity, with

and without metabolic activation (RIFM, 2013). The mutagenic activity of 2-ethylhexyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100, and *Escherichia coli* strain WP2uvrA were treated with 2-ethylhexyl 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 dose in the presence or absence of S9 (RIFM, 2016). Under the conditions of the study, 2-ethylhexyl acetate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of 2-ethylhexyl acetate. The OECD SIAM task force evaluated 2-ethylhexyl acetate, and it was stated that acetate esters of primary alcohols undergo rapid hydrolysis. The reaction is catalyzed by esterases and proteases found in mammalian tissue and gastric fluids (SIAM, 2010). The rapid and complete hydrolysis of 2-ethylhexyl acetate to 2-ethylhexan-1-ol (CAS # 104-76-7; see Section 5) as a primary metabolite has been demonstrated to occur *in vitro* within blood (half-life 2.3 min) and *in vivo*. The clastogenicity of read-across metabolite 2-ethylhexan-1-ol was assessed in an *in vitro* chromosome aberration study conducted by the National Toxicology Program (NTP) equivalent to OECD TG 473. The Chinese hamster ovary cell line was treated with 2-ethyl-1-hexanol in DMSO at the concentrations 0, 50, 108, 233, and 500 μg/mL in the presence and absence of metabolic activation. 2-Ethyl-1-hexanol did not increase chromosome aberrations *in vitro* with or without metabolic activation (ECHA Dossier: 2-ethylhexan-1-ol). Under the conditions of the study, 2-ethyl-1-hexanol was concluded to be negative for structural aberrations in cultured mammalian cells, and this can be applied to 2-ethylhexyl acetate. As an additional weight of evidence, the clastogenic activity of 1,5-dimethylhexyl acetate (CAS # 67952-57-2; see Section 5) 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 1,5-dimethylhexyl acetate in DMSO at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h 1,5-Dimethylhexyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2017). Under the conditions of the study, 1,5-dimethylhexyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 2-ethylhexyl acetate.

Based on the available data, 2-ethylhexyl acetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/03/17.

10.1.2. Repeated dose toxicity

The margin of exposure for 2-ethylhexyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on 2-ethylhexyl acetate. The target material 2-ethylhexyl acetate undergoes rapid hydrolysis in the gastrointestinal tract to acetic acid (CAS # 64-19-7; see section 5) and 2-ethyl-1-hexanol (CAS # 104-76-7; see section 5), which are absorbed into the systemic circulation. Read-across metabolite 2-ethyl-1-hexanol has sufficient repeated dose toxicity data for the risk assessment of 2-ethylhexyl acetate. This approach was supported by a report published by the European Commission's Joint Research Center (DG JRC, 2013). Furthermore, OECD has also used the repeated dose, reproductive and developmental toxicity, and carcinogenicity data on 2-ethyl-1-hexanol for the risk assessment of 2-ethylhexyl acetate (OECD, 2-ethylhexyl acetate; 2010).

A 90-day OECD 413/GLP repeated dose inhalation toxicity study was conducted in Wistar rats. Groups of 10 rats/sex/dose were exposed to 2-ethyl-1-hexanol vapors in a horizontal-flow whole-body inhalation chamber at dose levels of 0, 15, 40, or 120 ppm (equivalent to 0, 79.8, 212.3, or 638.4 mg/m^3) for 6 h/day, 5 times/week for 90 days (total of 65 exposures). There were no treatment-related effects during the study. Hence, the NOAEC was considered to be 120 ppm or 638.4 mg/m3, the highest dose tested (Klimisch, 1998; also available in ECHA Dossier: 2-Ethyl-1-hexanol).

The effect of 2-ethyl-1-hexanol was studied in a subchronic 90-day oral gavage study in groups of 10 F344 rats/sex/dose administered at dose levels of 0, 25, 125, 250, or 500 mg/kg/day. The findings at 500 mg/kg/day included a statistically significant reduction in body-weight gain, increase in reticulocyte count (in both sexes), decrease in plasma protein and albumin concentration (in males), decrease in cholesterol (in females), increase in kidney, liver, brain, testes, and stomach weights, and slight increase in a single and multiple foci in the mucosa of the forestomach (both sexes) at necropsy. Microscopic changes were seen in the stomach (focal or multifocal acanthosis) and liver (moderate decrease in hepatic peripheral lobular fatty infiltration). Findings at 250 mg/kg/day were limited to increased weights of the kidney, liver, stomach, and focal or multifocal acanthosis of the forestomach mucosa. Test material-related increases in cyanide-insensitive palmitoyl-CoA oxidase activity in the liver was observed at ≥250 mg/kg/day. There were no test material attributable effects observed at 25 and 125 mg/kg/day. Hence, the NOEL for male and female rats was considered to be 125 mg/kg/day (Astill, 1996; also available in ECHA Dossier: 2-Ethyl-1-hexanol).

In another study, 2-ethyl-1-hexanol was administered via oral gavage to groups of 10 B6C3F1 mice/sex/dose for 90-days at dose levels of 0, 25, 125, 250, or 500 mg/kg/day. One female died at 250 mg/kg/day. There were no changes in body weight, hematology, or clinical chemistry parameters. Significant increases in the relative weight of the stomach and liver in males of the 250 and 500 mg/kg/day groups were observed. Dark red foci in the glandular stomach were observed in females at 500 mg/kg/day. Microscopic examination showed mild focal or multi focal acanthosis of the forestomach mucosa in both the sexes of the high-dose group. There were no statistically significant changes observed in cyanide-insensitive palmitoyl-CoA oxidase activity in any of the treatment groups. The NOEL in male and females was considered to be 125 and 250 mg/kg/day, respectively (Astill, 1996; also available in ECHA Dossier: 2-Ethyl-1-hexanol).

Results of carcinogenicity tests conducted in Fischer 344 rats (50/sex at doses of 0, 50, 150, or 500 mg/kg/day for 24 months) and B6C3F1 mice (50/sex at doses of 0, 50, 200, or 750 mg/kg/day for 18 months) showed reductions in body weight and increases in mortality and clinical symptoms. Mortality of the animals was not attributable to any of the other symptoms. Inflammation of the forestomach was reported in the chronic toxicity data of the same chemical but was not observed in the carcinogenicity studies for both rats and mice. 2-Ethyl-1-hexanol is considered a weak inducer of liver tumors in female mice. The mechanism in mice is considered to occur via activation of PPAR-alpha, the relevance of which to humans is still unclear (Rusyn, 2011). The NOAEL for rats and mice was considered to be 50 mg/kg/day, based on a reduction in body weights among higher dose group animals (Astill, 1996; also available in ECHA Dossier: 2-Ethyl-1-hexanol).

The EFSA panel reviewed the carcinogenicity study on 2-ethylhexanol and concluded that “2-ethylhexanol showed a very weak hepatocarcinogenic effect in female mice only and that this type of tumor in this mouse strain is generally considered not relevant for humans” (EFSA, 2008).

The Expert Panel for Fragrance Safety* also reviewed the carcinogenicity study on 2-ethylhexanol (Belsito, 2010; RIFM, 2010)and concluded that “2-ethyl-1-hexanol is a weak inducer of liver tumors in female mice. Mechanistic studies showed that 2-ethyl-1-hexanol is an activator of PPAR-alpha. These substances can contribute to liver carcinogenesis by promoting tumor cell proliferation.”

Overall, the NOAEL for 2-ethylhexanol was considered to be 50 mg/

kg/day based on a 2-year carcinogenicity study conducted on rats and mice (Astill, 1996; also available in ECHA Dossier: 2-Ethyl-1-hexanol).

Based on the available data (Human health Tier II assessment for Acetic acid; accessed 09/11/17; Scientific Opinion on the safety and efficacy of acetic acid, sodium diacetate and calcium acetate as preservatives for feed for all animal species, 2012; JECFA, 2006; FDA, 21CFR184.1005, Revised as of April 1, 2016), acetic acid does not show specific reproductive or developmental toxicity. Thus, as such, acetic acid does not pose any systemic (repeated dose), developmental, or reproductive toxicity to human health when used in fragrances.

Therefore, the 2-ethylhexyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the 2-ethylhexyl hexanol NOAEL in mg/kg/day by the total systemic exposure to 2-ethylhexyl acetate, 50/0.00096 or 52083.

In addition, the total systemic exposure to 2-ethylhexyl acetate (0.96 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

*The Expert Panel for Fragrance Safety is composed of scientific and technical experts in their respective fields. This group provides advice and guidance.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/11/17.

10.1.3. Reproductive toxicity

The margin of exposure for 2-ethylhexyl acetate is adequate for the developmental toxicity endpoint at the current level of use.

There are insufficient fertility data on 2-ethylhexyl acetate or any read-across materials. The total systemic exposure to 2-ethylhexyl acetate is below the TTC for the fertility endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are insufficient reproductive toxicity data on 2-ethylhexyl acetate. The target material 2-ethylhexyl acetate undergoes rapid hydrolysis in the gastrointestinal tract to acetic acid (CAS # 64-19-7; see section 5) and 2-ethyl-1-hexanol (CAS# 104-76-7; see section 5), which are absorbed into the systemic circulation. Read-across metabolite 2-ethyl-1-hexanol has sufficient developmental toxicity data for the risk assessment of 2-ethylhexyl acetate.

Based on available data on acetic acid (Human Health Tier II Assessment for Acetic acid; accessed 09/11/2017; Scientific Opinion on the safety and efficacy of acetic acid, sodium diacetate and calcium acetate as preservatives for feed for all animal species, 2012; JECFA, 2006; FDA, 21CFR184.1005, Revised as of April 1, 2016), acetic acid does not show specific reproductive or developmental toxicity. Thus, as such, acetic acid does not pose any systemic (repeated dose), developmental, or reproductive toxicity to human health when used in fragrances.

An OECD 414/GLP dietary prenatal developmental toxicity study was conducted on CD1 Swiss mice. Groups of 28 mice/sex/dose were fed *ad libitum* 0%, 0.009%, 0.03%, or 0.09% (calculated doses of 0, 17, 59, or 191 mg/kg/day, respectively) of test material 2-ethyl-1-hexanol microencapsulated for 17 days during gestation days 0–17. There were no effects attributable to the administration of test material. Thus the NOAEL for both maternal and developmental toxicity was considered to be 0.09% or 191 mg/kg/day, the highest dose tested (NTP, 1991; also available in Price, 1991; and ECHA Dossier: 2-Ethyl-1-hexanol).

An OECD 414 dermal prenatal developmental toxicity study was conducted in F344 rats with 2-ethyl-1-hexanol. The main study was conducted in groups of 25 pregnant rats with neat 2-ethyl-1-hexanol at dose levels of 0, 0.3, 1.0, or 3.0 mL/kg/day (equivalent to doses of 0, 252, 840, or 2520 mg/kg/day). The control animals received deionized water at 3 mL/kg/day, and the positive controls received undiluted 2-methoxyethanol at 1.0 mL/kg/day. Maternal bodyweight gain was reduced at 3 mL/kg/day (2520 mg/kg/day). Exfoliation, crusting, and erythema were observed at the application site at 1.0 and 3.0 mL/kg/day (840 and 2520 mg/kg/day, respectively). Thus, the NOAEL for maternal local toxicity was considered to be 0.3 mL/kg/day (252 mg/kg/day) based on local skin irritation, and the NOAEL for systemic toxicity was considered to be 1.0 mL/kg/day (840 mg/kg/day) based on reduced bodyweight gain. The developmental toxicity NOAEL was considered to be 3.0 mL/kg/day or 2520 mg/kg/day, the highest dose tested (Tyl, 1992; also available in ECHA Dossier: 2-Ethyl-1-hexanol).

A study was conducted in which 15 female Sprague Dawley rats were exposed to vapors of 2-ethyl-1-hexanol at a dose of 850 mg/m^3 for 7 h per day for the whole gestation period. Dams were euthanized on gestation day 20. Observations included maternal body weight, food intake, and fetal examinations. Reduced maternal food intake was observed. No other treatment-related alterations were observed. At the stated concentration, although limited maternal toxicity was evidenced, no teratogenic effects were observed (Nelson, 1988; also available in Nelson, 1989; and ECHA Dossier: 2-Ethyl-1-hexanol).

The most conservative NOAEL of 191 mg/kg/day from the dietary developmental toxicity study was considered for the developmental toxicity endpoint. Therefore, the 2-ethylhexyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the 2-ethylhexyl hexanol NOAEL in mg/kg/day by the total systemic exposure to 2-ethylhexyl acetate, 191/0.00096 or 198958.

There are insufficient fertility data on 2-ethylhexyl acetate or any read-across materials. The total systemic exposure to 2-ethylhexyl acetate (0.96 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes, 2007; Laufersweiler, 2012) for the fertility endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/13/17.

10.1.4. Skin sensitization

Based on the existing data and read-across material isoamyl acetate, 2-ethylhexyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Limited studies are available for 2-ethylhexyl acetate. Based on the read-across material isoamyl acetate (CAS # 123-92-2; See Section 5), 2-ethylhexyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structures of these material indicate that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree 2.6.13; OECD toolbox v3.4). In a guinea pig maximization test, a mixture of primary amyl acetates did not result in reactions indicative of sensitization (Ballantyne, 1986). Similarly, read-across material isoamyl acetate was found to be negative in a guinea pig Open Epicutaneous Test (OET) (Klecak, 1979, 1985). In a human maximization test, no skin sensitization reactions were observed with 4% 2-ethylhexyl acetate or 8% of read-across material isoamyl acetate (RIFM, 1976; RIFM, 1973). Additionally, in a confirmatory human repeat insult patch test (HRIPT) with 20% or 23622 μg/cm^2 of read-across material isoamyl acetate in 75:25 ethanol:DEP, no reactions indicative of sensitization were observed in any of the 197 volunteers (RIFM, 1987).

Based on human data and the read-across material isoamyl acetate, 2-ethylhexyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/23/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV spectra, 2-ethylhexyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for 2-ethylhexyl acetate in experimental models. UV absorption spectra indicate no absorption between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, 2-ethylhexyl acetate does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available spectra indicate no absorbance in the range of 290–400 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/26/17.

10.1.6. Local respiratory toxicity

The margin of exposure could not be calculated due to the lack of appropriate data. The exposure level of 2-ethylhexyl acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

10.1.6.1. Risk assessment. There are no inhalation data available on 2-ethylhexyl acetate. Based on the Creme RIFM model, the inhalation exposure is 0.0018 mg/day. This exposure is 778 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: Smyth, 1944; Schmidt, 1969.

Literature Search and Risk Assessment Completed On: 09/11/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 2-ethylhexyl acetate was performed following the RIFM Environmental Framework (Salvito, 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, 2-ethylhexyl 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 2-ethylhexyl 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, 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.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), 2-ethylhexyl acetate does not present a risk to the aquatic compartment in the screening-level assessment.

Biodegradation: No data available.

Ecotoxicity: No data available.

10.2.2.1. Other available data. 2-Ethylhexyl acetate has been registered under REACH and the following data is available.

Biodegradation of 2-ethylhexyl acetate has been evaluated according to the OECD 301B method. After 28 days, biodegradation of 70% was observed.

A fish (*Oncorhynchus mykiss*) acute toxicity study was conducted according to the OECD 203 method under semi-static conditions, and the 96-h LC50 was reported to be 8.27 mg/L.

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under semi-static conditions. The 48-h EC50 was reported to be 22.9 mg/L.

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 based on measured concentration was reported to be greater than 21.9 mg/L for biomass and growth rate.

10.2.3. Risk assessment refinement

Since 2-ethylhexyl acetate has passed the screening criteria, measured data is included for completeness only and has not been used in PNEC derivation.

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

Endpoints used to calculate PNEC are underlined.

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

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>7.7</u>			1,000,000	0.0077	

Exposure	Europe	North America
Log K_{ow} used	3.74	3.74
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.0077 μg/L. The revised PEC/PNECs for EU and NA: not applicable; cleared at the screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 08/09/17.

11. Literature Search*

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

Search keywords: CAS number and/or material names.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.08.048.

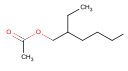
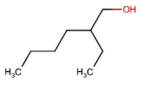
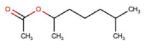
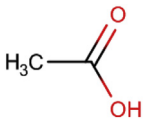
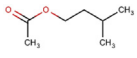
Appendix

Read-across justification

Methods

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

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster 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 substance 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 v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	2-Ethylhexyl acetate	2-Ethyl-1-hexanol	1,5-Dimethylhexyl acetate	Acetic acid	Isoamyl acetate
CAS No.	103-09-3	104-76-7	67952-57-2	64-19-7	123-92-2
Structure					
Similarity (Tanimoto Score)		NA	0.78	NA	0.73
Read-across Endpoint		• Genotoxicity	• Genotoxicity	• Repeated dose	

		• Repeated dose • Developmental		• Developmental	• Skin sensitization
Molecular Formula	$C_{10}H_{20}O_2$	$C_8H_{18}O$	$C_{10}H_{20}O_2$	$C_2H_4O_2$	$C_7H_{14}O_2$
Molecular Weight	172.27	130.23	172.27	60.05	130.19
Melting Point (°C, EPI Suite)	−20.47	−25.50	−31.53	−21.26	−56.05
Boiling Point (°C, EPI Suite)	198.83	188.52	186.63	122.30	134.87
Vapor Pressure(Pa @ 25°C, EPI Suite)	50.6	24.6	91.5	2.29e+003	756
Log Kow (KOWWIN v1.68 in EPI Suite)	3.74	2.73	3.66	−0.17	2.25
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	38.59	880	44.59	1,000,000	2000
J_{max} (mg/cm^2/h, SAM)	51.71	76.459	43.408	6283.004	101.618
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.27E-003	3.10E-005	1.27E-003	5.48E-007	5.45E-004
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• AN2, Schiff base formation • SN1, Nucleophilic attack • SN2, Acylation	• AN2, Schiff base formation • SN1, Nucleophilic attack • SN2, Acylation	• AN2, Schiff base formation • SN1, Nucleophilic attack • SN2, Acylation		
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found	• No alert found		
Carcinogenicity (ISS)	• Carcinogen (low reliability)	• Carcinogen (low reliability)	• Non-carcinogen (low reliability)		
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	• No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found	• No alert found		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found	• No alert found		
Oncologic Classification	• Not classified	• Not classified	• Not classified		
Repeated Dose Toxicity					
Repeated Dose (HESS)	• Not categorized	• Not categorized		• Carboxylic acid (Hepatotoxicity)	
Developmental Toxicity					
ER Binding (OECD QSAR Toolbox v3.4)	• 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)	• toxicant (good reliability)		• 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				• Not possible to classify
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 v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	No metabolites	See Supplemental Data 4

Summary

There are insufficient toxicity data on 2-ethylhexyl acetate (CAS # 103-09-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 2-ethyl-1-hexanol (CAS # 104-76-7), 1,5-dimethylhexyl acetate (CAS # 67952-57-2), acetic acid (CAS # 64-19-7), and isoamyl acetate (CAS # 123-92-2) were identified as read-across materials with sufficient data for toxicological evaluation.

Metabolism

Metabolism of the read-across material 2-ethylhexyl acetate (CAS # 103-09-3) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). The target material is predicted to be metabolized to 2-ethyl-1-hexanol (CAS # 104-76-7) and acetic acid (CAS # 64-19-7) in the first step with 0.95 probability. Hence, 2-ethyl-1-hexanol (CAS # 104-76-7) and acetic acid (CAS # 64-19-7) can be used as read-across analogs for the target material. Read-across analogs 2-ethyl-1-hexanol (CAS # 104-76-7) and acetic acid (CAS # 64-19-7) were out of domain for the *in vivo* rat and out of domain for the *in vitro* rat S9 simulators (OASIS TIMES v2.27.19). However, based on expert judgment, the model's domain exclusion was overridden and a justification is provided.

Conclusions

- Read-across alcohol 2-ethyl-1-hexanol (CAS # 104-76-7) is used as a read-across analog for the target ester, 2-ethylhexyl acetate (CAS # 103-09-3) for the genotoxicity, repeated dose, and developmental toxicity endpoints. Acetic acid (CAS # 64-19-7) is used as a read-across analog for the target ester 2-ethylhexyl acetate (CAS # 103-09-3) for the repeated dose and developmental toxicity endpoints.
  - o The products of ester hydrolysis (corresponding alcohol and acid) are used as read-across analogs for the target ester for the endpoints indicated in the table.
  - o The read-across materials are major metabolites or analogs of the major metabolites of the target.
  - o Structural differences between the target material and the read-across analog are mitigated by the fact that the target could be metabolically hydrolyzed to the read-across analogs. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
  - o The target material and the read-across analog have similar physical–chemical properties. Any differences in the physical–chemical properties of the target material and the read-across analogs are toxicologically insignificant.
  - o According to the QSAR OECD Toolbox v3.4, structural alerts for the endpoints evaluated are consistent between the target material and the read-across analog.
  - o The read-across analogs are predicted to be toxicants by the CAESAR model for developmental toxicity. All other alerts are negative. According to these predictions, the read-across analog is expected to be more reactive when compared to the target material. The data described in the developmental toxicity section above shows that the read-across analog has adequate margin of exposure at the current level of use. Therefore, the predictions are superseded by data.
  - o The read-across analog acetic acid (CAS # 64-19-7) for the repeated dose toxicity is categorized as a carboxylic acid material with hepatotoxicity alert while the target material is not categorized by HESS categorization scheme. It has been shown by numerus literature that carboxylic acids are excreted out from human body relatively quickly with no toxic effects. The data described in the repeated dose section above shows that the margin of exposure for the read-across analog is adequate at the current level of use. Therefore, the alert will supersede by the availability of the data.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 1,5-Dimethylhexyl acetate (CAS # 67952-57-2) was used as a read-across analog for the target material 2-ethylhexyl acetate (CAS # 103-09-3) 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 a common acid portion on the ester and a saturated branched aliphatic fragment on the alcohol portion of the ester.
  - o The key difference between the target material and the read-across analog is that the target and the read-across material have differences in branching on the alcohol portion of the ester. This structural difference is toxicologically insignificant.
  - o Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the common acid portion on the ester and the saturated branched aliphatic fragment on the alcohol portion of the ester. 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 v3.4, structural alerts for the toxicological endpoint are consistent between the target material and the read-across analog.
  - o The read-across analog and target material are predicted to have DNA binding alerts by OASIS for genotoxicity. In addition, the target is also predicted to be a non-genotoxic carcinogen by the ISS model while the read-across analog does not have such an alert. According to the ISS model within the OECD QSAR Toolbox, this structural alert is due to branching at the beta carbon of carboxylic acids or esters. Substances belonging to this class are potentially reactive peroxisome proliferators (PPs) via peroxisome proliferator-activated receptor alpha (PPAR a) with a tumor forming mechanism not fully understood yet. The detailed explanation can be found within the ISS models. Formation of carboxylic acid would happen in the second phase metabolism by liver enzymes. The concentration of this second phase metabolic product (carboxylic acid) is expected to be below the threshold. Also, the molecule is predicted to be a non-genotoxic carcinogen with low reliability. All the other genotoxicity alerts are negative. Therefore, the alert can be ignored. Data for read-across superseded predictions in this case.
  - 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 endpoint 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 2-ethylhexyl acetate (CAS # 103-09-3) 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 common acid portion on the ester and a saturated branched aliphatic fragment on the alcohol portion of the ester.

- The key difference between the target material and the read-across analog is that the target has a C8 branched aliphatic chain on the alcohol portion while the read-across analog has a C5 branched aliphatic chain on the alcohol portion of the ester. This structural difference is toxicologically insignificant.
- Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the common acid portion on the ester and the saturated branched aliphatic fragment on the alcohol portion of the ester. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- According to the OECD QSAR Toolbox v3.4, structural alerts for the toxicological endpoint are consistent between the target material and the read-across analog.
- The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoint evaluated are consistent between the metabolites of the read-across analog and the target material.

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