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Short Review

RIFM fragrance ingredient safety assessment, Hexyl acetate, CAS Registry Number 142-92-7

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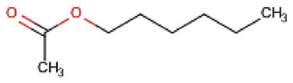
Version: 032118. This version replaces any previous versions.
Name: Hexyl acetate
CAS Registry Number: 142-92-7



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
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

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

Hexyl acetate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the target material and read-across analog hexyl propionate (CAS # 2445-76-3) show that this material is not genotoxic. Data from the target material hexyl acetate and read-across analog 2-butoxyethyl acetate (CAS# 112-07-2) show that this material does not have skin sensitization potential. The repeated dose and developmental endpoint was completed using data from read-across analog octyl acetate (CAS # 112-14-1), which provided an MOE > 100. The fertility endpoint was completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day). The local respiratory toxicity endpoint was completed using data from read-across analog n-butyl acetate (CAS # 123-86-4), which provided an MOE > 100. The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; hexyl 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	(RIFM, 1999b; RIFM, 2000b; RIFM, 2016)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day	(Daughtrey et al., 1989a; ECHA Dossier on Octyl acetate)
Reproductive Toxicity: Developmental: NOAEL = 500 mg/kg/day	Fertility: No NOAEL available. Exposure is below the TTC. (Daughtrey et al., 1989b)
Skin Sensitization: Not a concern for skin sensitization	(Kern et al., 2010)
Phototoxicity/ Photoallergenicity: Not phototoxic/photoallergenic	(UV Spectra, RIFM DB)

Local Respiratory Toxicity: NOAEC = 2375 mg/m^3. (ECHA REACH Dossier 08/03/17; data also available in David et al., 2001)

Environmental Safety Assessment

Hazard Assessment:

Persistence: Critical Measured Value: 85% (OECD 302C)	(RIFM, 1999a)
Bioaccumulation: Screening-level: 34.14 L/kg	(EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Critical Ecotoxicity Endpoint: 96-h fish LC50: 4.4 mg/L	(REACH dossier; accessed 8/2017)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	

Risk Assessment:

Screening-level: PEC/PNEC (North America and Europe) > 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: 96-h fish LC50: 4.4 mg/L	(REACH dossier; accessed 8/2017)

RIFM PNEC is: 4.4 µg/L

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

1. Identification

1 Chemical Name: Hexyl acetate
2 CAS Registry Number: 142-92-7
3 Synonyms: Acetate C-6; Acetic acid, hexyl ester; 酢酸ヘキシル; Hexyl acetate
4 Molecular Formula: $C_8H_{16}O_2$
5 Molecular Weight: 144.21
6 RIFM Number: 453
7 **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

1 **Boiling Point:** 168 °C (FMA), 170.05 °C (US EPA, 2012a)
2 **Flash Point:** 58 °C (GHS), 113 °F; CC (FMA)
3 **Log KOW:** 3.3 at 30 °C (RIFM, 1996a), 2.83 (US EPA, 2012a)
4 **Melting Point:** 32.64 °C (US EPA, 2012a)
5 **Water Solubility:** 308.7 mg/L (US EPA, 2012a)
6 **Specific Gravity:** 0.876 (FMA), .8700 (EOA, 1973 Sample 72–161)
7 **Vapor Pressure:** 1.02 mm Hg @ 20 °C (US EPA, 2012a), 1.0 mm Hg 20 °C (FMA), 1.45 mm Hg @ 25 °C (US EPA, 2012a)
8 **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L · mol-1

· cm-1)

9 **Appearance/Organoleptic:** Colorless clear oily liquid (est) with a fresh green and sweet, fruity, banana peel-like, apple-like, and pear-like odor.

* http://www.thegoodscentscompany.com/data/rw1003201.html, 08/17/17.

3. Exposure

1 **Volume of Use (worldwide band):** > 1000 metric tons per year (IFRA, 2015)
2 **95th Percentile Concentration in Hydroalcoholics:** 0.085% (RIFM, 2015)
3 **Inhalation Exposure*:** 0.0011 mg/kg/day or 0.080 mg/day (RIFM, 2015)
4 **Total Systemic Exposure**:** 0.0053 mg/kg/day (RIFM, 2015)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 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 et al., 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:** Hexyl propionate (CAS # 2445-76-3)
b **Repeated Dose Toxicity:** Octyl acetate (CAS # 112-14-1)
c **Reproductive Toxicity:** Octyl acetate (CAS # 112-14-1)
d **Skin Sensitization:** 2-Butoxyethyl acetate (CAS # 112-07-2)
e **Phototoxicity/Photoallergenicity:** None
f **Local Respiratory Toxicity:** n-Butyl acetate (CAS # 123-86-4)
g **Environmental Toxicity:** None
3Read-across Justification: See Appendix below

6. Metabolism

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

7. NATURAL OCCURRENCE (discrete chemical) or COMPOSITION (NCS)

Hexyl acetate is reported to occur in the following foods* and in some natural complex substances (NCS):

Acerola (*Malpighia*)
Anise brandy
Apple brandy (*Calvados*)
Apple fresh (*Malus* species)
Apple processed (*Malus* species)
Apricot (*Prunus armeniaca L.*)
Babaco fruit (*Carica pentagona* Heilborn)
Banana (*Musa sapientum* L.)
Beans
Beer
Bilberry wine
Black currants (*Ribes nigrum* L.)
Blue cheeses
Cashew apple (*Anacardium occidentale*)
Cashew apple wine
Cauliflower and broccoli
Chamomile
Cheddar cheese
Cheese, various types
Cherimoya (*Annona cherimolia* Mill.)
Cherry
Chestnut (*Castanea* species)
Chicken
Chinese quince (*Pseudocydonia sinensis* Schneid)
Cider (apple wine)
Citrus fruits
Cocoa category
Coffee
Date (*Phoenix dactylifera* L.)
Dill (*Anethum* species)
Grape (*Vitis* species)
Grape brandy
Guava and feyoa
Guava wine
Honey
Lamb's lettuce (*Valerianella locusta*)
Litchi wine
Lovage (*Levisticum officinale* Koch)
Maize (*Zea mays* L.)
Mangifera species
Mangosteen (*Garcinia mangostana* L.)
Matsutake (*Tricholoma matsutake*)
Melon
Mountain papaya (*C. candamarcensis, C. pubescens*)
Naranjilla fruit (*Solanum quitoense* Lam.)
Nectarine
Olive (*Olea europaea*)
Origanum (Spanish) (*Coridothymus cap.*(L.) Rchb.)
Passion fruit (*Passiflora* species)
Peach (*Prunus persica* L.)
Pear (*Pyrus communis* L.)
Pear brandy
Peas (*Pisum sativum* L.)
Pepino fruit (*Solanum muricatum*)
Plum (*Prunus* species)
Plum brandy
Plum wine
Quince, marmelo (*Cydonia oblonga* Mill.)

Rambutan (*Nephelium lappaceum* L.)
Raspberry brandy
Raspberry, blackberry and boysenberry
Rooibos tea (*Aspalathus linearis*)
Rum
Rye bread
Salvia species
Sapodilla fruit (*Achras sapota* L.)
Sauerkraut
SherrySoybean (*Glycine max.* L. Merr.)
Starfruit (*Averrhoa carambola* L.)
Strawberry (*Fragaria* species)
Strawberry wine
Syzygium species
Tapereba, caja fruit (*Spondias lutea* L.)
Tea
Tomato (*Lycopersicon esculentum* Mill.)
Vaccinium species
Vanilla
Whisky
Wine

*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

Available, accessed 08/17/17.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, hexyl acetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of hexyl acetate was investigated in an Ames assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 were treated with hexyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate in the presence and absence of S9. Hexyl acetate induced an increase in the mutation frequency of the tester strain TA102 in the absence of metabolic activation in all 3 experiments; however, it was only statistically significant in one experiment (RIFM, 1999b). In a repeat study, hexyl acetate was tested at concentrations up to 5000 μg/plate in the presence and absence of metabolic activation in *Salmonella typhimurium* strain TA102. No increase in the mutation frequency of the tester strain was observed (RIFM, 2000b). It was concluded that hexyl acetate was not mutagenic in the Ames assay.

There are no studies assessing the clastogenic activity of hexyl acetate; however, read-across can be made to hexyl propionate (CAS # 2445-76-3; see Section 5). The clastogenic activity of hexyl propionate 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 hexyl propionate in DMSO at concentrations up to 1580 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Hexyl propionate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2016).Under the conditions of the study, hexyl propionate was considered to be non-clastogenic in the *in vitro* micronucleus test and this can be extended to hexyl acetate.

Based on the available data hexyl acetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/28/2016.

10.1.2. Repeated dose toxicity

The margin of exposure for hexyl 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 hexyl acetate. Read-across material octyl acetate (CAS # 112-14-1; see Section 5) has sufficient repeated dose toxicity data. Groups of 20 SD rats/sex/dose were gavaged with octyl acetate 5 days per week for 13 weeks at doses of 0 (distilled water), 100, 500, or 1000 mg/kg/day. At week 13, relative liver weights among mid- and high-dose animals were statistically significantly increased compared to controls. The increase in liver weights was considered to be adaptive due to lack of histopathological evidence (necrosis, fibrosis, inflammation, and steatotic vacuolar degeneration) showing liver cell damage and associated clinical chemistry alterations (Hall et al., 2012). Relative kidney weights among high-dose animals were also statistically significantly increased compared to controls. Gross pathological examinations did not reveal any differences among treated and control group animals. At week 13, microscopic evaluation of the kidneys revealed evidence of mild tubular nephropathy only in the high-dose male rats. The specific findings consisted of an increased incidence of dilated renal tubules (cortical-medullary zone) containing granular casts and regenerative hyperplasia in proximal convoluted tubules. These histopathological findings were not observed in high-dose females or in either sex among mid- and low-dose group animals. Microscopic alterations in the kidneys of high-dose males were consistent with documented changes of α-2μ-globulin nephropathy, which is species-specific to male rats in response to treatment with some hydrocarbons. This effect is not considered a hazard to human health (Lehman-McKeeman, 1992; and Lehman-McKeeman et al., 1990). However, there were no reports of confirmatory staining during histopathological examinations. Thus, the NOAEL was considered to be 500 mg/kg/day based on the increased kidney weight among high-dose females (Daughtrey et al., 1989b; also available in ECHA Dossier: Octyl acetate). Therefore, the hexyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the octyl acetate NOAEL in mg/kg/day by the total systemic exposure to hexyl acetate, 500/0.0053 or 94340.

In addition, the total systemic exposure to hexyl acetate (5.3 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/16/17.

10.1.3. Reproductive toxicity

The margin of exposure for hexyl acetate is adequate for the

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

10.1.3.1. Risk assessment. There are insufficient developmental toxicity data on hexyl acetate. Read-across material octyl acetate (CAS # 112-14-1; see Section 5) has sufficient developmental toxicity data. A gavage developmental toxicity study was conducted in Sprague Dawley rats. Groups of 22 mated females/sex/group were gavaged on gestation days (GDs) 6–15 with test material octyl acetate at doses of 0, 100, 500, or 1000 mg/kg neat. Mortality was reported among 2 females from the high-dose group that expired on GD 10 and 12. Maternal animals in the high-dose group had increased incidence of alopecia, rales, red nasal discharge, and anal-genital staining. Additionally, mean body weights were decreased in high-dose treated maternal rats at GDs 9, 12, 16, and 20, when compared to the control group. Four fetuses from the high-dose group had different types of vertebral anomalies in the form of incomplete ossifications, but these were not statistically significantly different compared to controls. Visceral examination revealed dilated lateral cerebral ventricles in 2 fetuses in the high-dose group. These anatomical variations were within the historical controls and thus not considered to be toxicologically relevant. Various types of skeletal variations of incomplete ossifications were observed in all groups. The total number of fetuses (litters) with malformations in the control, low-dose, mid-dose, and high-dose groups were 1(1), 1(1), 1(1), and 6(6), respectively. Thus, the NOAEL for maternal toxicity was considered to be 500 mg/kg/day based on incidences of clinical observations and decrease in body weights among high-dose group females. The authors of the study determined the developmental toxicity NOAEL to be 1000 mg/kg/day (Daughtrey et al., 1989b). Since there were anomalies observed in fetuses of the highest dose group, a more conservative NOAEL of 500 mg/kg/day was considered for the developmental toxicity endpoint. Therefore, the hexyl acetate MOE for the developmental toxicity endpoint can be calculated by dividing the octyl acetate NOAEL in mg/kg/day by the total systemic exposure to hexyl acetate, 500/0.0053 or 94340.

There are no fertility data on hexyl acetate or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to hexyl acetate (5.3 µg/kg/day) is below the TTC (30 µg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 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: 08/16/17.

10.1.4. Skin sensitization

Based on the existing data and the read-across analog 2-butoxyethyl acetate (CAS# 112-07-2), hexyl acetate does not present a concern for skin sensitization.

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for hexyl acetate. Based on the read-across analog 2-butoxyethyl acetate (CAS# 112-07-2; see Section 5), hexyl acetate does not present a concern for skin sensitization. The chemical structure of these materials indicate that they would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). Read-across analog 2-butoxyethyl acetate was found to be negative in the *in vitro* KeratinoSens, U937-CD86, and human Cell Line Activation Test (h-CLAT) tests but positive in a direct peptide reactivity assay (DPRA) (Natsch et al., 2013; Otsubo, 2017). However, in a murine local lymph node assay (LLNA), read-across analog 2-butoxyethyl acetate was found to be negative up to the maximum tested concentration of 50%, which resulted in a Stimulation Index (SI) of 1.2 (Kern et al., 2010). In guinea pigs, a Buehler test did not present reactions indicative of sensitization for the read-across material 2-butoxyethyl acetate (ECHA dossier: 2-butoxyethyl acetate, accessed 7/25/17). In a human maximization test, no skin sensitization reactions were observed with 4% or 2760 µg/cm2 hexyl acetate in petrolatum (RIFM, 1973). Based on weight of evidence from structural analysis, animal and human studies, and from the read-across material 2-butoxyethyl acetate, hexyl acetate does not present a concern for skin sensitization.

Additional References: Roberts et al., 2007c.

Literature Search and Risk Assessment Completed On: 07/28/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, hexyl 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 hexyl acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, hexyl acetate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/12/17.

10.1.6. Local respiratory toxicity

There are insufficient inhalation data available on hexyl acetate; however, in a 13-week inhalation study for the analog n-butyl acetate (CAS # 123-86-4; see Section 5), a NOAEC of 2375 mg/m^3 is reported (ECHA REACH Dossier, accessed 08/03/2017; David et al., 2001).

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data from scientific literature to calculate the MOE for local respiratory toxicity. In a 13-week, whole-body inhalation study conducted in rats, a NOAEC of 2375 mg/m^3 (500 ppm) was reported (ECHA REACH Dossier, accessed 08/03/2017; David et al., 2001). Whole-body inhalation exposure of read-across material n-butyl acetate was administered at target concentrations (0 (sham), 2375, 7126, 14253 mg/m^3) to both male and female Sprague Dawley rats (15 animals/sex/concentration). Clinical observations, body weight, food consumption, ophthalmology, hematology, clinical chemistry, organ weights, gross pathology, and histopathology were all considered. Body weights and food consumption decreased among animals in the mid- and high-concentration treatment groups. Organ weight changes were also dependent upon treatment and concentration. Lung weights increased among males exposed to 14253 mg/m^3 n-butyl acetate compared to the control group. Additionally, histopathology for both the mid- and high-concentration treatment groups demonstrated degenerated olfactory epithelial tissue as well as dorsal medial meatus and ethmotubinates of the nasal passages. Severity of the histopathological findings ranged from mild to moderate for the high-concentration group but minimal to mild for the mid-concentration

group. As there were no observable adverse effects documented for the low-concentration treatment group, the NOAEC was determined to be 2375 mg/m^3.

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

- (2375 mg/m^3) (1m^3/1000 L) = 2.375 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (2.375 mg/L) (61.2 L/day) = 145.35 mg/day
- (145.35 mg/day)/(0.0016 kg lung weight of rat*) = 90844 mg/kg lung weight/day

The 95th percentile calculated exposure to hexyl acetate was reported to be 0.080 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; and Safford et al., 2015). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.12 mg/kg lung weight/day resulting in a MOE of 757033 (i.e., [90844 mg/kg lung weight/day]/[0.12 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to inter-species and intra-species variation, the material exposure by inhalation at 0.080 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

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

Additional References: Carpenter et al., 1974; Smyth et al., 1969; Smyth et al., 1954; Smyth et al., 1928; Haglund, 1980; Nelson, 1943; McOmie, 1949; NIOSH, 1982; Burleigh-Flayer, 1991; Querci, 1970a; Ambrosio, 1962a; Ambrosio, 1962b; Frantik, 1994; Querci, 1970b; Osina, 1959; Sayers, 1936; Iregren, 1993; Ashley, 1997; Bowen, 1997; Norris, 1997; Silver, 1992; Prah, 1998; David, 1998; Kodak, 1996; UnionCarbide, 1993; Saillenfait, 2007.

Literature Search and Risk Assessment Completed On: 08/03/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of hexyl 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, hexyl acetate was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify hexyl 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 ≥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 current Volume of Use (2015), hexyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation

RIFM, 1996b: The Ready Biodegradability of the test material was determined by the manometric respirometry test according to the OECD 301 F method. Under the conditions of the study, biodegradation of 56% was observed after 28 days.

RIFM, 1999a: The Inherent Biodegradability of the test material was determined by the respirometric method following the OECD TG 302C. Under the conditions of this study, biodegradation of 85% was observed after 28 days.

RIFM, 2000a: In a 28-day biodegradation study using the closed bottle according to the OECD 301D method, hexyl acetate at 2.9 mg/L was considered readily biodegradable with 66% biodegradation observed.

10.2.2.2. Ecotoxicity

No data available.

10.2.2.3. Other available data

Hexyl acetate has been registered under REACH and the following data is available:

A 96-h fish (*Pimephales promelas*) acute toxicity study was conducted according to the OECD 203 method under flow-through conditions. The LC50 was reported to be 4.4 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 9.1 mg/L based on time weighted mean concentrations.

An algae growth inhibition test was conducted according to the OECD 201 method. The 72-h EC50 based on biomass was reported to be 9.7 mg/L.

10.2.3. 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.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	14.38			1,000,000	0.01438	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	6.327	12.03	4.492	10,000	0.4492	Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	21.35	13.08	13.37			Neutral Organic SAR (Baseline toxicity)

Tier 3: Measured Data (including REACH data)

	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	4.4			1,000		
Daphnia		9.1				
Algae		9.7				

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.3	3.3
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	100–1000
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 4.4 μg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore does not present a risk to the aquatic environmental at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 8/1/17.

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 http://dx.doi.org/10.1016/j.fct.2018.06.043.

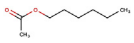
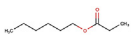
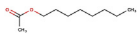
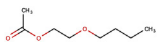
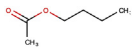
Appendix

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 was 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	Hexyl acetate	Hexyl propionate	Octyl acetate	2-Butoxyethyl acetate	n-Butyl acetate
CAS No.	142-92-7	2445-76-3	112-14-1	112-07-2	123-86-4
Structure					
Similarity (Tanimoto Score)		0.935	0.89	0.758	0.824
Read-across Endpoint		• Genotoxicity	• Repeated Dose toxicity • Developmental toxicity	• Skin sensitization	• Respiratory
Molecular Formula	$C_8H_{16}O_2$	$C_9H_{18}O_2$	$C_{10}H_{20}O_2$	$C_8H_{16}O_3$	$C_6H_{12}O_2$
Molecular Weight	144.22	158.24	172.27	160.21	116.16
Melting Point (°C, EPI Suite)	−32.64	−20.94	−9.50	−15.23	−56.-83
Boiling Point (°C, EPI Suite)	170.05	190.83	210.70	191.62	125.79
Vapor Pressure (Pa @ 25°C, EPI Suite)	194	79	29.1	71.5	1.59E+003
Log K_{ow} (KOWWIN v1.68 in EPI Suite)	2.83	3.32	3.81	1.57	1.78
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	511	101.9	33.39	3103	8400
J_{max} (mg/cm^2/h, SAM)	27.519	78.149	33.5	26.22	301.124
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	7.33E+001	9.73E+001	1.29E+002	6.46E-001	4.16E+001
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• Schiff base formation • Nucleophilic attack • Acylation	• No alert found			
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found			
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)			
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found			
***In Vitro* Mutagenicity (Ames, ISS)**					

	• No alert found	• No alert found			
***In Vivo* Mutagenicity (Micronucleus, ISS)**	•No alert found	•No alert found			
Oncologic Classification	•Not classified	•Not classified			
Repeated Dose Toxicity					
Repeated Dose (HESS)	• Not categorized		• Not categorized		
Reproductive and Developmental Toxicity					
ER Binding (OECD QSAR Toolbox v3.4)	• Non binder, non cyclic structure		• Non binder, non cyclic structure		
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (good 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			• 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	
Local Respiratory Toxicity					
Respiratory Sensitization (OECD QSAR Toolbox v3.4)	• 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	See Supplemental Data 4	See Supplemental Data 5

Summary

There are insufficient toxicity data on hexyl acetate (CAS # 142-92-7). 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, hexyl propionate (CAS # 2445-76-3), octyl acetate (CAS # 112-14-1), 2-butoxyethyl acetate (CAS # 112-07-2), and n-butyl acetate (CAS # 123-86-4) were identified as read-across materials with sufficient data for toxicological evaluation.

Conclusions

- Hexyl propionate (CAS # 2445-76-3) was used as a read-across analog for the target material hexyl acetate (CAS # 142-92-7) for the genotoxicity endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - The target substance and the read-across analog share a straight chain primary alcohol portion.
  - The key difference between the target substance and the read-across analog is that the target substance has an acetyl moiety, whereas the read-across analog has an ethyl moiety. This structural difference is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the straight chain primary alcohol portion. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance 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 toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target is given an alert of Schiff base formation by the DNA binding model within OASIS. Other genotoxicity alerts for the target substance are negative. The read-across analog does not have such an alert. The data described for the read-across analog in the genotoxicity section confirm that the read-across material does not pose a concern for genotoxicity. Therefore, based on structural similarity between the read-across analog and the target substance and the data described for the read-across analog, this alert for the target substance will be superseded by the availability of data for the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Octyl acetate (CAS # 112-14-1) was used as a read-across analog for the target material hexyl acetate (CAS # 142-92-7) for the repeated dose toxicity and developmental toxicity endpoints.

- The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
- The target substance and the read-across analog share a straight chain primary alcohol portion.
- The key difference between the target substance and the read-across analog is that the target substance has a C6 alcohol portion and the read-across analog has a C8 alcohol portion. This structural difference is toxicologically insignificant.
- Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the straight chain primary alcohol portion. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
- The physical–chemical properties of the target substance 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 toxicological endpoints are consistent between the target substance and the read-across analog.
- The target substance is predicted to be a toxicant by the CAESAR model for developmental toxicity. The read-across analog is predicted to be a non-toxicant. The data described for the read-across analog in the reproductive and developmental toxicity section confirm that the read-across has an adequate margin of exposure at the current level of use. Therefore, based on structural similarity between the read-across analog and the target substance and the data described for the read-across analog, this alert for the target substance will be superseded by the availability of data for the read-across analog.
- The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
- The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

- 2-Butoxyethyl acetate (CAS # 112-07-2) was used as a read-across analog for the target material hexyl acetate (CAS # 142-92-7) for the skin sensitization endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - The target substance and the read-across analog share a straight chain primary alcohol portion.
  - The key difference between the target substance and the read-across analog is that the target substance has a C6 alcohol portion and the read-across analog has a C7 alcohol portion. The read-across analog has an additional inert ether linkage in the alcohol portion. This structural difference is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the straight chain primary alcohol portion. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance 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 toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- n-Butyl acetate (CAS # 123-86-4) was used as a read-across analog for the target material hexyl acetate (CAS # 142-92-7) for the respiratory endpoint.
  - The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - The target substance and the read-across analog share a straight chain primary alcohol portion.
  - The key difference between the target substance and the read-across analog is that the target substance has a C6 alcohol portion, whereas the read-across analog has a C4 alcohol portion attached to the acetate moiety. This structural difference is toxicologically insignificant.
  - Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the straight chain primary alcohol portion. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target substance 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 toxicological endpoints are consistent between the target substance and the read-across analog.
  - The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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