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Short review

RIFM fragrance ingredient safety assessment, hexyl formate, CAS Registry Number 629-33-4

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Version: 032218. This version replaces any previous versions.
Name: Hexyl formate
CAS Registry Number: 629-33-4

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 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 formate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the read-across analog amyl formate (CAS# 638-49-3) show that hexyl formate is not expected to be genotoxic. Data from hexyl formate and read-across analog 2-butoxyethyl acetate (CAS# 112-07-2) show that hexyl formate 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 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 formate 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, 2017b; RIFM, 2017a)
Repeated Dose Toxicity: NOAEL = 500 mg/kg/day. (Daughtrey et al., 1989a)
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, 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: Screening-level: 3.35 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level:14 L/kg (EPI Suite v4.11; US EPA, 2012a)

Ecotoxicity: Screening-level: Fish LC50: 100.2 mg/L	(RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards	
Risk Assessment:	
Screening-level: PEC/PNEC (North America and Europe) < 1	(RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 100.2 mg/L	(RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.1002 μg/L	
•**Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening level	

1. Identification

1. **Chemical Name:** Hexyl formate
2. **CAS Registry Number:** 629-33-4
3. **Synonyms:** Formic acid, hexyl ester; n-Hexyl formate; ｷﾞ酸ｱﾙｷﾙ (C = 6 ~ 12); Hexyl formate
4. **Molecular Formula:** $C_7H_{14}O_2$
5. **Molecular Weight:** 130.19
6. **RIFM Number:** 1144
7. **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 155 °C (FMA Database), 150.42 °C (US EPA, 2012a)
2. **Flash Point:** 99 °F; CC (FMA Database)
3. **Log K_{OW}:** 2.28 (US EPA, 2012a)
4. **Melting Point:** −35.82 °C (US EPA, 2012a)
5. **Water Solubility:** 1034 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.879–0.885 (RIFM), 0.89 (FMA Database)
7. **Vapor Pressure:** 2.22 mm Hg @ 20 °C (US EPA, 2012a), 1.8 mm Hg 20 °C (FMA Database), 3.1 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 $mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless clear liquid (est) with an apple, plum, banana, and sweet odor.*

*http://www.thegoodscentscompany.com/data/rw1023931.html, accessed on 08/16/17.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric ton per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** no reported use in hydroalcoholics (RIFM, 2017c)
3. **Inhalation Exposure*:** 0.0000007 mg/kg/day or 0.000061 mg/day (RIFM, 2017c)
4. **Total Systemic Exposure**:** 0.00013 mg/kg/day (RIFM, 2017c)

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

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

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:** Amyl formate (CAS # 638-49-3)
   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
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)

Hexyl formate is reported to occur in the following foods by the VCF*:

Black choke berry juice (*Aronia melanocarpa* Ell.)	
Grape (*Vitis* species)	Plum (*Prunus* species)
Licorice (*Glycyrrhiza* species)	Strawberry (*Fragaria* species)
Maize (*Zea mays* L.)	Tea
Peach (*Prunus persica* L.)	Wax gourd, winter melon (*Benincasa hispada cogn*)

*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

Pre-registered for 11/30/2010; no dossier available as of 03/14/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. Hexyl formate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2014a). There are no studies assessing the mutagenic activity of hexyl formate; however, read-across can be made to amyl formate (CAS # 638-49-3; see Section V). The mutagenic activity of amyl formate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with amyl formate 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, 2017b). Under the conditions of the study, amyl formate was not mutagenic in the Ames test, and this can be extended to hexyl formate.

There are no studies assessing the clastogenic activity of hexyl formate; however, read-across can be made to amyl formate (CAS # 638-49-3; see Section V). The clastogenic activity of amyl formate 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 amyl formate in DMSO at concentrations up to 1162 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h. Amyl formate did not induce binucleated cells with micronuclei when tested up to cytotoxic conditions in the non-activated 24-h treatment. A statistically significant increase in the frequency of micronucleated binucleated (MNBN) cells was observed in the 3-h treatments at 988 μg/mL without S9 and 840 μg/mL with S9. The MNBN frequencies were within the historical vehicle control range for these test conditions, were not dose dependent, and were therefore considered biologically non-relevant. (RIFM, 2017a). Under the conditions of the study, amyl formate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to hexyl formate.

Based on the data available, amyl formate does not present a concern for genotoxic potential, and this can be extended to hexyl formate.

Additional References: RIFM, 2014b.

Literature Search and Risk Assessment Completed On: 07/28/2017.

10.1.2. Repeated dose toxicity

The margin of exposure for hexyl formate 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 formate. Read-across material octyl acetate (CAS # 112-14-1; see Section V) 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 and Caudill, 1992; and Lehman-McKeeman et al., 1990). 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 formate 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 formate, 500/0.00013 or 3846154.

In addition, the total systemic exposure to hexyl formate (0.13 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: 08/14/17.

10.1.3. Reproductive toxicity

The margin of exposure for hexyl formate is adequate for the developmental toxicity endpoint at the current level of use. There are insufficient fertility data on hexyl formate or on any read-across materials. The total systemic exposure to hexyl formate 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 formate. Read-across material octyl acetate (CAS # 112-14-1; see Section V) 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 formate 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 formate, 500/0.00013 or 3846154.

There are no fertility data on hexyl formate or on any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to hexyl formate (0.13 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: 08/17/17.

10.1.4. Skin sensitization

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

10.1.4.1. Risk assessment. Limited skin sensitization studies are available for hexyl formate. Based on read-across material 2-butoxyethyl acetate (CAS # 112-07-2; see Section V), hexyl formate 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 et al., 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; 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/cm^2 hexyl formate in petrolatum (RIFM, 1981). Based on weight of evidence from structural analysis, animal and human studies, and from the read-across 2-butoxyethyl acetate, hexyl formate does not present a concern for skin sensitization.

Additional References: None.

Literature Search and Risk Assessment Completed On: 7/26/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, hexyl formate 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 formate 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; Henry et al., 2009). Based on lack of absorbance, hexyl formate 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 no inhalation data available on hexyl formate; however, in a 13-week inhalation study for the analog *n*-butyl acetate (CAS # 123-86-4; see Section V), a NOAEC of 2375 mg/m^3 was 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 formate was reported to be 0.000061 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 0.000094 mg/kg lung weight/day resulting in a MOE of 966425532 (i.e., [90844 mg/kg lung weight/day]/[0.000094 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 0.000061 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2nd 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."

10.1.6.2. Additional References. Smyth et al., 1954; Smyth and Smyth, 1928; Haglund et al., 1980; Nelson et al., 1943; McOmie and Anderson,

1949; National Institute for Occupational Safety and Health, 1982; Burleigh-Flayer et al., 1991; Querci and Mascia, 1970a; Ambrosio and D'Arrigo, 1962a; Ambrosio et al., 1962b; Frantik et al., 1994; Querci et al., 1970b; Osina, 1959; Sayers et al., 1936; Iregren et al., 1993; Ashley and Prah, 1997; Bowen and Balster, 1997; Norris et al., 1997; Silver, 1992; Prah et al., 1998; David et al., 1998; Union Carbide, 1993; Saillenfait et al., 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 formate 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 formate 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 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 the current Volume of Use (IFRA, 2015), hexyl formate does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. Hexyl formate has been pre-registered for REACH with no information at this time.

10.3. 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)**	100.2			1,000,000	0.1002	

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

Exposure	Europe	North America
Log K_{ow} used	2.28	2.28
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 0.1002 μg/L. The revised PEC/PNECs for EU and NA are: Not applicable; cleared at the screening level; therefore, the material does not present a risk to the aquatic environment 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 S. Supplementary data

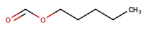
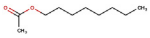
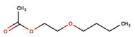
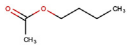
Supplementary data related to this article can be found at https://doi.org/10.1016/j.fct.2018.08.038.

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).

Principal Name	Target Material	Read-across Material	Read-across Material	Read-across Material	Read-across Material
	Hexyl formate	Amyl formate	Octyl acetate	2-Butoxyethyl acetate	*n*-Butyl acetate
CAS No.	629-33-4	638-49-3	112-14-1	112-07-2	123-86-4
Structure					
Similarity (Tanimoto Score)		0.92	0.78	0.68	0.72
Read-across Endpoint		• Genotoxicity	• Repeated Dose toxicity • Developmental toxicity	• Skin sensitization	• Respiratory
Molecular Formula	$C_7H_{14}O_2$	$C_6H_{12}O_2$	$C_{10}H_{20}O_2$	$C_8H_{16}O_3$	$C_6H_{12}O_2$
Molecular Weight	130.19	116.16	172.27	160.21	116.16
Melting Point (°C, EPI Suite)	−35.82	−48.03	−9.50	−15.23	−56.-83
Boiling Point (°C, EPI Suite)	150.42	127.92	210.70	191.62	125.79
Vapor Pressure (Pa @ 25°C, EPI Suite)	414	1.31E+003	29.1	71.5	1.59E+003
Log Kow (KOWWIN v1.68 in EPI Suite)	2.28	1.79	3.81	1.57	1.78
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1034	3066	33.39	3103	8400
J_{max} (mg/cm^2/h, SAM)	79.996	164.704	33.5	26.22	301.124
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.00E+002	7.55E+001	1.29E+002	6.46E-001	4.16E+001

Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• 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	• Aldehyde type compound	• Aldehyde type compound			
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 (low reliability)		• Non-toxicant (low reliability)		
Skin Sensitization					
Protein Binding (OASIS v1.1)	• No alert found			• No alert found	
Protein Binding (OECD)	• No alert found			• No alert found	
Protein Binding Potency	• Not possible to classify			• 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 formate (CAS # 629-33-4). 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, amyl formate (CAS # 638-49-3), 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.

12. Conclusions

- Amyl formate (CAS # 638-49-3) was used as a read-across analog for the target material hexyl formate (CAS # 629-33-4) 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 with formyl moiety.
  - ○ 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 C5 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 with a formyl moiety. 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 classified as aldehyde type compounds. The data described in the genotoxicity section show that the read-across analog does not pose a concern for genotoxicity. Therefore, the alert will be superseded by the availability of the data.
  - 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 formate (CAS # 629-33-4) for the repeated dose 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 with a formyl moiety, whereas the read-across analog has a C8 alcohol portion with an acetyl 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 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 developmental toxicity section confirms 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 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 formate (CAS # 629-33-4) 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 attached to the formyl moiety, whereas the read-across analog has a C5 alcohol portion attached to the acetyl moiety. 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 formate (CAS # 629-33-4) 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 attached to the formyl moiety, whereas the read-across analog has a C4 alcohol portion attached to the acetyl 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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