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Short Review

# RIFM fragrance ingredient safety assessment, hexyl butyrate, CAS Registry Number 2639-63-6

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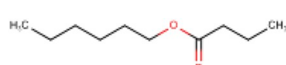
Version: 032318. This version replaces any previous versions.



Name: Hexyl butyrate CAS Registry Number: 2639-63-6

**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
**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

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**Statistically Significant** - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
**TTC** - Threshold of Toxicological Concern
**UV/Vis spectra** - Ultraviolet/Visible spectra
**VCF** - Volatile Compounds in Food
**VoU** - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
**WoE** - Weight of Evidence
**The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.**
This safety assessment is based on the RIFM Criteria Document (Api et al., 2015), which should be referred to for clarifications.

Each endpoint discussed in this safety assessment includes the relevant data that were available at the time of writing (version number in the top box is indicative of the date of approval based on a 2-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (e.g., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative endpoint value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*The Expert Panel for Fragrance Safety is an independent body that selects its own members and establishes its own operating procedures. The Expert Panel is comprised of internationally known scientists that provide RIFM with guidance relevant to human health and environmental protection.

**Summary: The existing information supports the use of this material as described in this safety assessment.**
Hexyl butyrate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog hexyl isobutyrate (CAS # 2349-07-7) show that hexyl butyrate is not expected to be genotoxic. Data from hexyl butyrate and read-across analog 2-butoxyethyl acetate (CAS# 112-07-2) show that hexyl butyrate does not have skin sensitization potential. Data from read-across analog octyl acetate (CAS # 112-14-1) provide a calculated MOE > 100 for the repeated dose and developmental toxicity endpoints. The fertility endpoint was completed using the TTC for a Cramer Class I material, and the exposure to hexyl butyrate is below the TTC (0.03 mg/kg/day). Data from read-across *n*-butyl acetate (CAS # 123-86-4) provide a calculate MOE > 100 for the local respiratory toxicity endpoint. The phototoxicity/photoallergenicity endpoints were completed based on suitable UV spectra; hexyl butyrate is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; hexyl butyrate 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 expected to be genotoxic. (RIFM, 2003; RIFM, 2014)
**Repeated Dose Toxicity:** NOAEL = 500 mg/kg/day. (Daughtrey et al., 1989b; ECHA REACH Dossier: Octyl acetate; ECHA, 2017)
**Reproductive Toxicity:** Developmental: NOAEL = 500 mg/kg/day Fertility: No NOAEL available. Exposure is below the TTC. (Daughtrey et al., 1989a)
**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: n-Butyl acetate; ECHA, 2011b; data also available in David et al., 2001)
**Environmental Safety Assessment**
**Hazard Assessment:**
**Persistence:** Critical Measured Value: 74% (OECD 301F) (RIFM, 2011)
**Bioaccumulation:** Screening-level: 151.8 L/kg (EPI Suite v4.11; US EPA, 2012a)
**Ecotoxicity:** Screening-level: 96-h algae EC50: 1.104 mg/L (ECOSAR; US EPA, 2012b)
**Conclusion:** Not PBT or vPvB as per IFRA Environmental Standards
**Risk Assessment:**
**Screening-Level**: PEC/PNEC (North America and Europe) > 1 (RIFM Framework; Salvito et al., 2002; Salvito et al., 2002)
**Critical Ecotoxicity Endpoint:** 96-h algae EC50: 1.104 mg/L (ECOSAR; US EPA, 2012b)
**RIFM PNEC is:** 0.1104 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: < 1

## 1. Identification

1. **Chemical Name:** Hexyl butyrate
2. **CAS Registry Number:** 2639-63-6
3. **Synonyms:** Butanoic acid, hexyl ester; Hexyl butanoate; ﾌﾞﾀﾝ酸ｱﾙｷﾙ (C = 1 ~ 7); Hexyl butyrate
4. **Molecular Formula:** $C_{10}H_{20}O_2$
5. **Molecular Weight:** 172.27
6. **RIFM Number:** 899
7. **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

## 2. Physical data

1. **Boiling Point:** 208 °C (FMA), 210.7 °C (US EPA, 2012a)
2. **Flash Point:** 70 °C (GHS), 158 °F; CC (FMA)
3. **Log $K_{OW}$:** 3.81 (US EPA, 2012a)
4. **Melting Point**: -9.5 °C (US EPA, 2012a)
5. **Water Solubility:** 33.39 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.870 (FMA)
7. **Vapor Pressure:** 0.162 mm Hg @ 20 °C (US EPA, 2012a), 0.1 mm Hg 20 °C (FMA), 0.241 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 mobile liquid with a green, fruity, and vegetative odor with a waxy nuance.*

*http://www.thegoodscentscompany.com/data/rw1023951.html#tosafrf, 08/17/17.

## 3. Exposure

1. **Volume of Use (worldwide band):** 10–100 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0092% (RIFM, 2017)
3. **Inhalation Exposure*:** 0.00025 mg/kg/day or 0.019 mg/day (RIFM, 2017)
4. **Total Systemic Exposure**:** 0.00089 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM aggregate exposure model (Comiskey et al., 2015; Safford, 2015, 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, 2015, 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:** Hexyl isobutyrate (CAS # 2349-07-7)

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

| Acerola (*Malpighia*) | Hog plum (*Spondias mombins l.*) |
|---|---|
| Apple brandy (*Calvados*) | *Mangifera* species |
| Apple fresh (*Malus* species) | Mountain papaya (*C. candamarcensis, C. pubescens*) |
| Apple processed (*Malus* species) | Nectarine |
| Apricot (*Prunus armeniaca l.*) | Olive (*Olea europaea*) |
| Babaco fruit (*Carica pentagona heilborn*) | Passion fruit (*Passiflora* species) |
| Banana (*Musa sapientum l.*) | Pear (*Pyrus communis l.*) |
| Beer | Plum (*Prunus* species) |
| Capsicum species | Pomegranate juice (*Punica granatum l.*) |
| Cheese, various types | Quince, marmelo (*Cydonia oblonga mill.*) |
| Cherimoya (*Annona cherimolia mill.*) | Spineless monkey orange (*Strychnos madagasc.*) |
| Chinese quince (*Pseudocydonia sinensis schneid*) | Starfruit (*Averrhoa carambola l.*) |
| Cider (apple wine) | Strawberry (*Fragaria* species) |
| Citrus fruits | Tea |
| Grape (*Vitis* species) | Thyme (*Thymus* species) |
| Grape brandy | Vaccinium species |
| Guava and feyoa | |

*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 03/15/2018.

## 10. Summary

### 10.1. Human health endpoint summaries

#### 10.1.1. Genotoxicity

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

*10.1.1.1. Risk assessment.* Hexyl butyrate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of hexyl butyrate; however, read-across can be made to hexyl isobutyrate (CAS # 2349-07-7; see Section V). The mutagenic activity of hexyl isobutyrate 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/preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with hexyl isobutyrate 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, 2003). Under the conditions of the study, hexyl isobutyrate was not mutagenic in the Ames test and this can be extended to hexyl butyrate.

There are no studies assessing the clastogenic activity of hexyl butyrate; however, read-across can be made to hexyl isobutyrate (CAS # 2349-07-7; see Section V). The clastogenic activity of hexyl isobutyrate 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 isobutyrate in ethanol at concentrations up to 1720 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Hexyl isobutyrate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2014). Under the conditions of the study, hexyl isobutyrate was considered to be non-clastogenic in the *in vitro* micronucleus test and this can be extended to hexyl butyrate.

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

**Additional References:** None.

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

#### 10.1.2. Repeated dose toxicity

The margin of exposure for hexyl butyrate 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 butyrate. 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-2u-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., 1989a; also available in ECHA, 2017). Therefore, the hexyl butyrate 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 butyrate, 500/0.00089 or 561798.

In addition, the total systemic exposure to hexyl butyrate (0.89 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

**Additional References:** None.

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

*10.1.3. Reproductive toxicity*

The margin of exposure for hexyl butyrate is adequate for the developmental toxicity endpoint at the current level of use. There are insufficient fertility data on hexyl butyrate or on any read-across materials. The total systemic exposure to hexyl butyrate 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 butyrate. 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 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., 1989a). 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 butyrate 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 butyrate, 500/0.00089 or 561798.

There are no fertility data on hexyl butyrate or any read-across materials that can be used to support the fertility endpoint. The total systemic exposure to hexyl butyrate (0.89 μg/kg/day) is below the TTC (30 μg/kg/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 2-butoxyethyl acetate (CAS# 112-07-2), hexyl butyrate does not present a concern for skin sensitization.

*10.1.4.1. Risk assessment.* Limited skin sensitization studies are available for hexyl butyrate. Based on the read-across analog 2-butoxyethyl acetate (CAS # 112-07-2; see Section V), hexyl butyrate 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, 2011a). In a human maximization test, no skin sensitization reactions were observed with 12% or 8280 μg/cm$^2$ hexyl butyrate in petrolatum (RIFM, 1976). Based on weight of evidence from structural analysis, animal and human studies, and from the read-across analog 2-butoxyethyl acetate, hexyl butyrate does not present a concern for skin sensitization.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 07/27/17.

*10.1.5. Phototoxicity/photoallergenicity*

Based on the available UV/Vis spectra, hexyl butyrate 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 butyrate 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 butyrate 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 butyrate; 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 Last 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, 2011b; 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 $mg/m^3$) ($1m^3$/1000L) = 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 butyrate was reported to be 0.019 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015; and Safford, 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 0.029 mg/kg lung weight/day resulting in a MOE of 3132552 (i.e., [90844 mg/kg lung weight/day]/[0.029 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 0.019 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:**

Smyth et al., 1954; Smyth and Smyth, 1928; Haglund et al., 1980; Nelson et al., 1943; McOmie and Anderson, 1949; NIOSH, 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; Kodak, 1996; Union Carbide Co, 1993; Saillenfait et al., 2007.

**Literature Search and Risk Assessment Completed On:** 08/03/17.

### *10.2. Environmental endpoint summary*

#### *10.2.1. Screening-level assessment*

A screening-level risk assessment of hexyl butyrate 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 ECHA, 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 butyrate 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 butyrate 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 (2015), hexyl butyrate presents a risk to the aquatic compartment in the screening-level assessment.

*10.2.2.1. Biodegradation*. RIFM, 2011: The ready biodegradability of the test material was evaluated using the Manometric Respirometry Test according to the OECD 301F method. Under the conditions of the study, biodegradation of 74% was observed after 28 days.

*10.2.2.2. Ecotoxicity*. No data available.

*10.2.2.3. Other available data*. Hexyl butyrate was pre-registered for REACH with no additional data at this time.

#### *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)** | 6.312 | X | X | 1,000,000 | 0.006312 | X |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 2.017 | 3.455 | 1.104 | 10,000 | 0.1104 | Esters |
| ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11*** | 3.346 | 2.246 | 3.339 | | | Neutral Organic |

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

| Exposure | Europe | North America |
|---|---|---|
| Log $K_{ow}$ used | 3.8 | 3.8 |
| Biodegradation Factor Used | 1 | 1 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | 1–10 | 1–10 |
| **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 0.1104 µg/L. The revised PEC/PNECs for EU and NA are < 1 and therefore does not present a risk to the aquatic environment at the current reported volumes of use.**

Literature Search and Risk Assessment Completed On: 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.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110608.

## Appendix

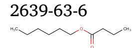
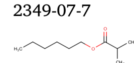
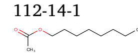
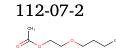
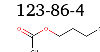
*Read-across Justification*

*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 ECHA, 2012).
- $J_{max}$ 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 butyrate | Hexyl isobutyrate | Octyl acetate | 2-Butoxyethyl acetate | n-Butyl acetate |
| CAS No. | 2639-63-6 | 2349-07-7 | 112-14-1 | 112-07-2 | 123-86-4 |
| Structure |  |  |  |  |  |
| Similarity (Tanimoto Score) | | 0.90 | 0.91 | 0.69 | 0.65 |
| Read Across Endpoint | | • Genotoxicity | • Repeated dose toxicity<br>• Developmental toxicity | • Skin sensitization | • Respiratory toxicity |
| Molecular Formula | $C_{10}H_{20}O_2$ | $C_{10}H_{20}O_2$ | $C_{10}H_{20}O_2$ | $C_8H_{16}O_3$ | $C_6H_{12}O_2$ |
| Molecular Weight | 172.27 | 172.27 | 172.27 | 160.21 | 116.16 |
| Melting Point (°C, EPI Suite) | −9.50 | −20.47 | −9.50 | −15.23 | −56.-83 |
| Boiling Point (°C, EPI Suite) | 210.70 | 198.83 | 210.70 | 191.62 | 125.79 |
| Vapor Pressure (Pa @ 25°C, EPI Suite) | 32.2 | 51 | 29.1 | 71.5 | 1.59E+003 |
| Log Kow (KOWWIN v1.68 in EPI Suite) | 3.81 | 3.74 | 3.81 | 1.57 | 1.78 |
| Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite) | 33.39 | 38.59 | 33.39 | 3103 | 8400 |
| $J_{max}$ (μg/cm$^2$/h, SAM) | 42.234 | 61.193 | 33.500 | 26.220 | 301.12 |
| Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite) | 1.29E+002 | 1.29E+002 | 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 | • 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) | • Non-toxicant (low relaibilty) | | • 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 butyrate (CAS # 2639-63-6). 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 isobutyrate (CAS # 2349-07-7), octyl acetate (CAS # 112-14-1), 2-butoxyethyl acetate (CAS # 112-07-2), and n-butyl acetate were identified as read-across materials with sufficient data for toxicological evaluation.

*Conclusions*

- Hexyl isobutyrate (CAS # 2349-07-7) was used as a read-across analog for the target material hexyl butyrate (CAS # 2639-63-6) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a straight chain primary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a straight chain acid fragment and the read-across analog has a branched acid fragment. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by a straight chain primary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Octyl acetate (CAS # 112-14-1) was used as a read-across analog for the target material hexyl butyrate (CAS # 2639-63-6) for the repeated dose toxicity and developmental toxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a straight chain primary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a C6 alcohol fragment attached to a butyrate moiety, and the read-across analog has a C8 alcohol fragment attached to an acetyl moiety. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by a straight chain primary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- 2-Butoxyethyl acetate (CAS # 112-07-2) was used as a read-across analog for the target material hexyl butyrate (CAS # 2639-63-6) for the skin sensitization endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters.
  - o The target substance and the read-across analog share a straight chain primary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a C6 alcohol fragment, and the read-across analog has a C7 alcohol fragment. The read-across analog has an additional inert ether linkage in the alcohol fragment. This structural difference is toxicologically insignificant.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by a straight chain primary alcohol fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The target substance and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- *n*-Butyl acetate (CAS # 123-86-4) was used as a read-across analog for the target material hexyl butyrate (CAS # 2639-63-6) for the respiratory endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aliphatic esters
  - o The target substance and the read-across analog share a straight chain primary alcohol fragment.
  - o The key difference between the target substance and the read-across analog is that the target substance has a C6 alcohol fragment attached to the butyrate moiety, whereas the read-across analog has a C4 alcohol fragment attached to the acetyl moiety. This structural difference is toxicologically insignificant.
  - o 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 fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.

- o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
- o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
- o 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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