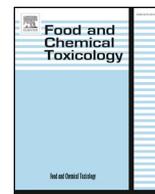




Contents lists available at ScienceDirect

# Food and Chemical Toxicology

journal homepage: [www.elsevier.com/locate/foodchemtox](http://www.elsevier.com/locate/foodchemtox)

## Short Review

### RIFM fragrance ingredient safety assessment, nonyl acetate, CAS Registry Number 143-13-5



A.M. Api<sup>a</sup>, D. Belsito<sup>b</sup>, D. Botelho<sup>a</sup>, M. Bruze<sup>c</sup>, G.A. Burton Jr.<sup>d</sup>, J. Buschmann<sup>e</sup>, M.L. Dagli<sup>f</sup>, M. Date<sup>a</sup>, W. Dekant<sup>g</sup>, C. Deodhar<sup>a</sup>, M. Francis<sup>a</sup>, A.D. Fryer<sup>h</sup>, L. Jones<sup>a</sup>, K. Joshi<sup>a</sup>, S. La Cava<sup>a</sup>, A. Lapczynski<sup>a</sup>, D.C. Liebler<sup>i</sup>, D. O'Brien<sup>a</sup>, A. Patel<sup>a</sup>, T.M. Penning<sup>j</sup>, G. Ritacco<sup>a</sup>, J. Romine<sup>a</sup>, N. Sadekar<sup>a</sup>, D. Salvito<sup>a</sup>, T.W. Schultz<sup>k</sup>, I.G. Sipes<sup>l</sup>, G. Sullivan<sup>a,\*</sup>, Y. Thakkar<sup>a</sup>, Y. Tokura<sup>m</sup>, S. Tsang<sup>a</sup>

<sup>a</sup> Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, 07677, USA

<sup>b</sup> Member RIFM Expert Panel, Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave, New York, NY, 10032, USA

<sup>c</sup> Member RIFM Expert Panel, Malmo University Hospital, Department of Occupational & Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo, SE, 20502, Sweden

<sup>d</sup> Member RIFM Expert Panel, School of Natural Resources & Environment, University of Michigan, Dana Building G110, 440 Church St., Ann Arbor, MI, 48109, USA

<sup>e</sup> Member RIFM Expert Panel, Fraunhofer Institute for Toxicology and Experimental Medicine, Nikolai-Fuchs-Strasse 1, 30625, Hannover, Germany

<sup>f</sup> Member RIFM Expert Panel, University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. dr. Orlando Marques de Paiva, 87, Sao Paulo, CEP, 05508-900, Brazil

<sup>g</sup> Member RIFM Expert Panel, University of Wuerzburg, Department of Toxicology, Versbacher Str. 9, 97078, Würzburg, Germany

<sup>h</sup> Member RIFM Expert Panel, Oregon Health Science University, 3181 SW Sam Jackson Park Rd., Portland, OR, 97239, USA

<sup>i</sup> Member RIFM Expert Panel, Vanderbilt University School of Medicine, Department of Biochemistry, Center in Molecular Toxicology, 638 Robinson Research Building, 2200 Pierce Avenue, Nashville, TN, 37232-0146, USA

<sup>j</sup> Member of RIFM Expert Panel, University of Pennsylvania, Perelman School of Medicine, Center of Excellence in Environmental Toxicology, 1316 Biomedical Research Building (BRB) II/III, 421 Curie Boulevard, Philadelphia, PA, 19104-3083, USA

<sup>k</sup> Member RIFM Expert Panel, The University of Tennessee, College of Veterinary Medicine, Department of Comparative Medicine, 2407 River Dr., Knoxville, TN, 37996-4500, USA

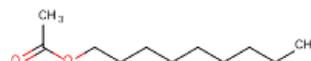
<sup>l</sup> Member RIFM Expert Panel, Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ, 85724-5050, USA

<sup>m</sup> Member RIFM Expert Panel, The Journal of Dermatological Science (JDS), Editor-in-Chief, Professor and Chairman, Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan

**Version: 032018. This version replaces any previous versions.**

**Name:** Nonyl acetate

**CAS Registry Number:** 143-13-5



#### 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

\* Corresponding author.

E-mail address: [gsullivan@rifm.org](mailto:gsullivan@rifm.org) (G. Sullivan).

<https://doi.org/10.1016/j.fct.2018.10.012>

Received 17 April 2018; Received in revised form 26 July 2018; Accepted 3 October 2018

Available online 05 October 2018

0278-6915/ © 2018 Elsevier Ltd. All rights reserved.

**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

**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.**

Nonyl acetate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog hexyl propionate (CAS# 2445-76-3) show that nonyl acetate is not expected to be genotoxic. Data from nonyl acetate and read-across analog 2-butoxyethyl acetate (CAS# 112-07-2) show that nonyl acetate 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; nonyl 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, 2016a; RIFM, 2016b)

**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; RIFM, 1981; RIFM, 1980b)

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

## Environmental Safety Assessment

### Hazard Assessment

**Persistence:** Critical Measured Value: 84% (OECD 301F)

(RIFM, 2014a)

**Bioaccumulation:** Screening-level: 13.5 L/kg

(EPI Suite v4.11; US EPA, 2012a)

**Ecotoxicity:** Screening-level: 96-h algae EC50: 0.541 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: 0.541 mg/L

(ECOSAR; US EPA, 2012b)

RIFM PNEC is: 0.0541 µg/L

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

## 1. Identification

1. **Chemical Name:** Nonyl acetate
2. **CAS Registry Number:** 143-13-5
3. **Synonyms:** Acetate C-9; Acetic acid, nonyl ester; Pelargonyl acetate; 1-Acetoxyonane; n-Nonyl ethanoate; 酢酸アルキル(c = 7–20) エステル; Acetate C9 nonylic; Nonyl acetate
4. **Molecular Formula:** C<sub>11</sub>H<sub>22</sub>O<sub>2</sub>
5. **Molecular Weight:** 186.3
6. **RIFM Number:** 254
7. **Stereochemistry:** Isomer not specified. No stereocenters and no stereoisomers possible.

## 2. Physical data

1. **Boiling Point:** 212 °C (FMA), 229.67 °C (US EPA, 2012a)
2. **Flash Point:** > 93 °C (GHS), > 200 °F; CC (FMA)
3. **Log K<sub>ow</sub>:** Log Pow = 4.8 (RIFM, 2014b), 0.52 (Biobyte Corp.), 0.22 (Biobyte Corp.), 4.3 (US EPA, 2012a)
4. **Melting Point:** 1.67 °C (US EPA, 2012a)
5. **Water Solubility:** 10.87 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.867 (FMA)
7. **Vapor Pressure:** 0.146 mm Hg @ 20 °C (US EPA, 2012a), 0.03 mm Hg 20C (FMA), 0.218 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption is below the benchmark (1000 L mol<sup>-1</sup> · cm<sup>-1</sup>)
9. **Appearance/Organoleptic:** Colorless, clear liquid with a waxy, clean, green, and fruity odor.\*

\*<http://www.thegoodscentscompany.com/data/rw1015611.html>, 08/23/17.

## 3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric ton per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcohols:** 0.0011% (RIFM, 2016c)
3. **Inhalation Exposure\*:** 0.000010 mg/kg/day or 0.00073 mg/day (RIFM, 2016c)
4. **Total Systemic Exposure\*\*:** 0.00019 mg/kg/day (RIFM, 2016c)

\*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 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; 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 (OECD, 2012)
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:** None
  - g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

## 6. Metabolism

No relevant data available for inclusion in this safety assessment.

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

Nonyl acetate is reported to occur in the following foods\*:

Apple fresh ( <i>Malus</i> species)	Melon
Beer	Milk and milk products
Cheese, various types	Pepino fruit ( <i>Solanum muricatum</i> )
Citrus fruits	Plum ( <i>Prunus</i> species)
Grape ( <i>Vitis</i> species)	

\*VCF Volatile Compounds in Food: database/Nijssen, L.M.; Ingen-Visscher, C.A. van; Donders, J.J.H. (eds). – Version 15.1 – Zeist (The Netherlands): TNO Triskelion, 1963–2014. A continually updated database containing information on published volatile compounds that have been found in natural (processed) food products. Includes FEMA GRAS and EU-Flavis data.

## 8. IFRA standard

None.

## 9. REACH dossier

Available dossier: 08/23/17.

## 10. Summary

### 10.1. Human health endpoint summaries

#### 10.1.1. Genotoxicity

Based on the current existing data, nonyl acetate does not present a concern for genetic toxicity.

**10.1.1.1. Risk assessment.** Nonyl acetate was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of nonyl acetate; however, read-across can be made to hexyl propionate (CAS # 2445-76-3; see Section V). The mutagenic activity of hexyl propionate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 (OECD, 2015) using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with hexyl propionate 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, 2016a). Under the conditions of the study, hexyl propionate was not mutagenic in the Ames test.

There are no studies assessing the clastogenic activity of nonyl 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, 2016b). Under the conditions of the study, hexyl propionate was considered to be non-clastogenic in the *in vitro* micronucleus test.

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

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 07/31/2017.

#### 10.1.2. Repeated dose toxicity

The margin of exposure for nonyl 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 nonyl 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 as 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 as 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 kidney alterations among high-dose males were consistent with documented changes of  $\alpha$ -2 $\mu$ -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 increased kidney weight among high-dose females (Daughtrey et al., 1989a; also available in ECHA Dossier: Octyl acetate). Therefore, the nonyl 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 nonyl acetate, 500/0.00019 or 2631579.

In addition, the total systemic exposure to nonyl acetate (0.19 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 nonyl acetate is adequate for the developmental toxicity endpoint at the current level of use. There are insufficient fertility data on nonyl acetate or on any read-across materials. The total systemic exposure to nonyl 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 nonyl 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 (GD) 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 died 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 that were not statistically significantly different as 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 hence 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 report 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 nonyl 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 nonyl acetate, 500/0.00019 or 2631579.

There are no fertility data on nonyl acetate or on any read-across materials that can be used to support the fertility toxicity endpoint. The total systemic exposure to nonyl acetate (0.19 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 material 2-butoxyethyl acetate (CAS# 112-07-2), nonyl acetate does not present a concern for skin sensitization.

**10.1.4.1. Risk assessment.** Limited skin sensitization studies are available for nonyl acetate. Based on the read-across material 2-butoxyethyl acetate (CAS# 112-07-2; see Section 5), nonyl acetate does not present a concern for skin sensitization. The chemical structures 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 material 2-butoxyethyl acetate was found to be negative in the *in vitro* KeratinoSens, U937-CD86, and h-CLAT tests, but positive in the Direct Peptide Reactivity Assay (DPRA) (Natsch et al., 2013; Otsubo et al., 2017). In guinea pigs, an open epicutaneous test and Freund's complete adjuvant test with nonyl acetate did not present reactions indicative of sensitization (Klecak, 1985; RIFM, 1980b; RIFM, 1980c). However, in a murine local lymph node assay, read-across material 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 2% or 1380 µg/cm<sup>2</sup> nonyl acetate in petrolatum (RIFM, 1972). Based on weight of evidence from structural analysis, animal and human studies, and from the read-across material 2-butoxyethyl acetate, nonyl acetate does not present a concern for skin sensitization.

**Additional References:** Roberts et al., 2007.

**Literature Search and Risk Assessment Completed On:** 08/01/17.

#### 10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra along with existing data, nonyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

**10.1.5.1. Risk assessment.** 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). In phototoxicity and photoallergenicity studies conducted in guinea pigs, 10% nonenyl acetate in rectified alcohol did not result in phototoxic or photoallergenic reactions (RIFM, 1980a; RIFM, 1981). Based on lack of absorbance and *in vivo* study data, nonyl 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<sup>-1</sup> · cm<sup>-1</sup> (Henry et al., 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 07/24/17.

#### 10.1.6. Local respiratory toxicity

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

**10.1.6.1. Risk assessment.** There are no inhalation data available on nonyl acetate. Based on the Creme RIFM model, the inhalation exposure is 0.00073 mg/day. This exposure is 1918 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 01/09/18.

### 10.2. Environmental endpoint summary

#### 10.2.1. Screening-level assessment

A screening-level risk assessment of nonyl 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<sub>OW</sub>, 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, nonyl 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 nonyl acetate as possibly being either 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

### 10.2.3. Risk assessment refinement

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

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 ( <i>Daphnia</i> ) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening Level (Tier 1)	<u>0.9233</u>			1,000,000	0.0009233	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	1.127	1.831	<u>0.541</u>	10,000	0.0541	Esters
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	1.311	0.920	1.651			Neutral Organic

value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF  $\geq 2000$  L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical-chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). 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), nonyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

**10.2.2.1. Biodegradation.** RIFM, 2014a: The ready biodegradability of the test material was evaluated in a Manometric Respirometry test according to the OECD 301F method. Under the conditions of the study, biodegradation of 84% was observed after 28 days.

**10.2.2.2. Ecotoxicity.** RIFM, 2015a: A *Daphnia magna* immobilization test was conducted according to the OECD TG 202 method under semi-static conditions with filled and sealed test vessels. The 48-h time-weighted mean measured concentration was 1.2 mg/L.

RIFM, 2015b: An algae growth inhibition study was conducted according to the OECD 201 TG method. Based on geometric mean measured test concentrations, the 72-h EyC50, the 72-h EbC50, and the 72-h ErC50 values were calculated to be 1.2, 1.0, and 1.8 mg/L, respectively.

**10.2.2.3. Other available data.** Nonyl acetate has been pre-registered for REACH with no additional data at this time.

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

Exposure	Europe	North America
Log $K_{ow}$ used	4.8	4.8
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	1–10
<b>Risk Characterization: PEC/PNEC</b>	<b>&lt; 1</b>	<b>&lt; 1</b>

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

The RIFM PNEC is 0.0541 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/opthpv/public\\_search\\_publicdetails?submission\\_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User\\_title=DetailQuery%20Results&EndPointRpt=Y#submission](https://ofmpub.epa.gov/opthpv/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](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 to this article can be found online at <https://doi.org/10.1016/j.fct.2018.10.012>.

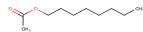
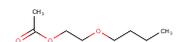
#### Appendix

##### 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 structure 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
<b>Principal Name</b>	Nonyl acetate	Hexyl propionate	Octyl acetate	2-Butoxyethyl acetate
<b>CAS No.</b>	143-13-5	2445-76-3	112-14-1	112-07-2
<b>Structure</b>				
<b>Similarity (Tanimoto Score)</b>		0.84	0.98	0.58
<b>Read-across Endpoint</b>		• Genotoxicity	• Repeated Dose toxicity • Developmental toxicity	• Skin sensitization
<b>Molecular Formula</b>	C <sub>11</sub> H <sub>22</sub> O <sub>2</sub>	C <sub>9</sub> H <sub>18</sub> O <sub>2</sub>	C <sub>10</sub> H <sub>20</sub> O <sub>2</sub>	C <sub>8</sub> H <sub>16</sub> O <sub>3</sub>
<b>Molecular Weight</b>	186.30	158.24	172.27	160.21
<b>Melting Point (°C, EPI Suite)</b>	1.67	−20.94	−9.50	−15.23
<b>Boiling Point (°C, EPI Suite)</b>	229.67	190.83	210.70	191.62
<b>Vapor Pressure (Pa @ 25°C, EPI Suite)</b>	29.1	79	29.1	71.5
<b>Log Kow (KOWWIN v1.68 in EPI Suite)</b>	4.30	3.32	3.81	1.57
<b>Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)</b>	10.87	101.9	33.39	3103
<b><math>J_{\max}</math> (mg/cm<sup>2</sup>/h, SAM)</b>	16.54	78.149	33.5	26.22
<b>Henry's Law (Pam3/mol, Bond Method, EPI Suite)</b>	1.71E+002	9.73E+001	1.29E+002	6.46E-001
<b>Genotoxicity</b>				

DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	<ul style="list-style-type: none"> <li>• Schiff base formation</li> <li>• Nucleophilic attack</li> <li>• Acylation</li> <li>• No alert found</li> </ul>	<ul style="list-style-type: none"> <li>• No alert found</li> </ul>		
DNA Binding (OECD QSAR Toolbox v3.4) Carcinogenicity (ISS)	<ul style="list-style-type: none"> <li>• Non-carcinogen (low reliability)</li> </ul>	<ul style="list-style-type: none"> <li>• No alert found</li> <li>• Non-carcinogen (low reliability)</li> </ul>		
DNA Binding (Ames, MN, CA, OASIS v1.1)	<ul style="list-style-type: none"> <li>• No alert found</li> </ul>	<ul style="list-style-type: none"> <li>• No alert found</li> </ul>		
<i>In Vitro</i> Mutagenicity (Ames, ISS)	<ul style="list-style-type: none"> <li>• No alert found</li> </ul>	<ul style="list-style-type: none"> <li>• No alert found</li> </ul>		
<i>In Vivo</i> Mutagenicity (Micronucleus, ISS)	<ul style="list-style-type: none"> <li>• No alert found</li> </ul>	<ul style="list-style-type: none"> <li>• No alert found</li> </ul>		
Oncologic Classification	<ul style="list-style-type: none"> <li>• Not classified</li> </ul>	<ul style="list-style-type: none"> <li>• Not classified</li> </ul>		
<i>Repeated Dose Toxicity</i> Repeated Dose (HESS) <i>Developmental Toxicity</i> ER Binding (OECD QSAR Toolbox v3.4) Developmental Toxicity (CAESAR v2.1.6)	<ul style="list-style-type: none"> <li>• Not categorized</li> <li>• Non binder, non cyclic structure</li> <li>• Non-toxicant (low reliability)</li> </ul>	<ul style="list-style-type: none"> <li>• Not categorized</li> <li>• Non binder, non cyclic structure</li> <li>• Non-toxicant (low reliability)</li> </ul>		
<i>Skin Sensitization</i> Protein Binding (OASIS v1.1) Protein Binding (OECD) Protein Binding Potency	<ul style="list-style-type: none"> <li>• No alert found</li> <li>• No alert found</li> <li>• Not possible to classify</li> </ul>		<ul style="list-style-type: none"> <li>• No alert found</li> <li>• No alert found</li> <li>• Not possible to classify</li> </ul>	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1) Skin Sensitization Reactivity Domains (Toxtree v2.6.13) <i>Respiratory Toxicity</i> Respiratory Sensitization (OECD QSAR Toolbox v3.4) <i>Metabolites</i> Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	<ul style="list-style-type: none"> <li>• No alert found</li> <li>• No alert found</li> <li>• No alert found</li> <li>• No alert found</li> </ul>		<ul style="list-style-type: none"> <li>• No alert found</li> <li>• No alert found</li> <li>• No alert found</li> <li>• No alert found</li> </ul>	<ul style="list-style-type: none"> <li>• No alert found</li> </ul>
	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

### Summary

There are insufficient toxicity data on nonyl acetate (CAS # 143-13-5). 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 # 123-68-4) 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 nonyl acetate (CAS # 143-13-5) 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 C9 alcohol fragment attached to the acetyl moiety, whereas the read-across analog has a C6 alcohol fragment attached to the propionate 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 compound is given an alert of Schiff base formation by the DNA binding model within OASIS. Other genotoxicity alerts for the target compound are negative. The read-across analog does not have such an alert. The data described for the read-across analog in the genotoxicity section confirms that the read-across material does not pose a concern for genetic toxicity. 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.
- 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 nonyl acetate (CAS # 143-13-5) for the repeated dose toxicity and developmental toxicity endpoints.
    - 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 C9 alcohol fragment, whereas the read-across analog has a C8 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 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.
    - 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 nonyl acetate (CAS # 143-13-5) 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 C9 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 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.
    - o The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

## References

- Api, A.M., Belsito, D., Bruze, M., Cadby, P., Calow, P., Dagli, M.L., Dekant, W., Ellis, G., Fryer, A.D., Fukayama, M., Griem, P., Hickey, C., Kromidas, L., Lalko, J.F., Liebler, D.C., Miyachi, Y., Politano, V.T., Renskers, K., Ritacco, G., Salvito, D., Schultz, T.W., Sipes, I.G., Smith, B., Vitale, D., Wilcox, D.K., 2015. Criteria for the research institute for fragrance materials, inc. (RIFM) safety evaluation process for fragrance ingredients. *Food Chem. Toxicol.* 82, S1–S19.
- Carthew, P., Clapp, C., Gutsell, S., 2009. Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. *Food Chem. Toxicol.* 47 (6), 1287–1295.
- Cassano, A., Manganaro, A., Martin, T., Young, D., Piclin, N., Pintore, M., Bigoni, D., Benfenati, E., 2010. CAESAR models for developmental toxicity. *Chem. Cent. J.* 4 (Suppl 1), S4.
- Comiskey, D., Api, A.M., Barratt, C., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Safford, B., Smith, B., Tozer, S., 2015. Novel database for exposure to fragrance ingredients in cosmetics and personal care products. *Regul. Toxicol. Pharmacol.* 72 (3), 660–672.
- Comiskey, D., Api, A.M., Barrett, C., Ellis, G., McNamara, C., O'Mahony, C., Robison, S.H., Rose, J., Safford, B., Smith, B., Tozer, S., 2017. Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. *Regul. Toxicol. Pharmacol.* 88, 144–156.
- Daughtrey, W.C., Euteromoser, M., Thompson, S.W., Biles, R.W., 1989a. A subchronic toxicity study of octyl acetate in rats. *Fund. Appl. Toxicol.* 12, 313–320.
- Daughtrey, W.C., Wier, P.J., Traul, K.A., Biles, R.W., Egan, G.F., 1989b. Evaluation of the teratogenic potential of octyl acetate in rats. *Fund. Appl. Toxicol.* 13 (2), 303–309.
- ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT Assessment, November 2012 v1.1. <http://echa.europa.eu/>.
- ECHA, 2016. Read-across Assessment Framework (RAAF). Retrieved from [www.echa.europa.eu/documents/10162/13628/raaf\\_en.pdf](http://www.echa.europa.eu/documents/10162/13628/raaf_en.pdf).
- Hall, A.P., Elcombe, C.R., Foster, J.R., Harada, T., Kaufmann, W., et al., 2012. Liver hypertrophy: a review of adaptive (adverse and non-adverse) changes—conclusions from the 3rd International ESTP expert workshop. *Toxicol. Pathol.* 40 (7), 971–974.
- Henry, B., Foti, C., Alsante, K., 2009. Can light absorption and photostability data be used to assess the photosafety risks in patients for a new drug molecule? *J. Photochem. Photobiol. B Biol.* 96 (1), 57–62.
- IFRA (International Fragrance Association), 2015. Volume of Use Survey, February 2015.
- Kern, P.S., Gerberick, G.F., Ryan, C.A., Kimber, I., Aptula, A., Basketter, D.A., 2010. Local lymph node data for the evaluation of skin sensitization alternatives: a second compilation. *Dermatitis* 21 (1), 8–32.
- Klecak, G., 1985. The freund's complete adjuvant test and the open epicutaneous test. In: *Current Problems in Dermatology*, vol. 14. pp. 152–171.
- Kroes, R., Renwick, A.G., Feron, V., Galli, C.L., Gibney, M., Greim, H., Guy, R.H., Lhuguenot, J.C., van de Sandt, J.J.M., 2007. Application of the threshold of toxicological concern (TTC) to the safety evaluation of cosmetic ingredients. *Food Chem. Toxicol.* 45 (12), 2533–2562.
- Laufersweiler, M.C., Gadagbui, B., Baskerville-Abraham, I.M., Maier, A., Willis, A., et al., 2012. Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern. *Regul. Toxicol. Pharmacol.* 62 (1), 160–182.
- Lehman-McKeeman, L.D., Rivera-Torres, M.I., Caudill, D., 1990. Lysosomal degradation of alpha2u-globulin and alpha2u-globulin-xenobiotic conjugates. *Toxicol. Appl. Pharmacol.* 103 (3), 539–548.
- Lehman-McKeeman, L.D., Caudill, D., 1992. a-2u-globulin is the only member of the lipocalin protein superfamily that binds to hyaline droplet inducing agents. *Toxicol. Appl. Pharmacol.* 116 (2), 170–176.
- Natsch, A., Ryan, C.A., Foertsch, L., Emter, R., Jaworska, J., Gerberick, F., Kern, P., 2013. A dataset on 145 chemicals tested in alternative assays for skin sensitization undergoing prevalidation. *J. Appl. Toxicol.* 33 (11), 1337–1352.
- OECD, 2012. The OECD QSAR Toolbox, V 3.4. Retrieved from <http://www.qsartoolbox.org/>.
- OECD, 2015. Guidance Document on the Reporting of Integrated Approaches to Testing and Assessment (IATA). ENV/JM/HA(2015)7. Retrieved from <http://www.oecd.org/>.
- Otsubo, Y., Nishijo, T., Miyazawa, M., Saito, K., Mizumachi, H., Sakaguchi, H., 2017. Binary test battery with KeratinoSens™ and h-CLAT as part of a bottom-up approach for skin sensitization hazard prediction. *Regul. Toxicol. Pharmacol.* 88, 118–124.
- RIFM (Research Institute for Fragrance Materials, Inc.), 1972. The Contact-sensitization Potential of Fragrance Materials by Maximization Testing in Humans. Report to RIFM. RIFM report number 1804. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 1980a. Skin Irritation and Capacity of Allergic Sensitization Determined by the Open Epicutaneous Test (OET) on guinea Pigs with Nonyl Acetate. Unpublished Report from Givaudan. RIFM report number 49474. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 1980b. Determination of Phototoxicity of Nonyl Acetate in guinea Pigs. Unpublished Report from Givaudan. RIFM report number 49477. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 1980c. Capacity for Allergic Sensitization Determined by the Intradermal Test with Freund's Complete Adjuvant (FCAT) on guinea Pigs with Nonyl Acetate. Unpublished Report from Givaudan. RIFM report number 49478. RIFM, Woodcliff Lake, NJ, USA.

- RIFM (Research Institute for Fragrance Materials, Inc.), 1981. A guinea Pig Assay of Photosensitizing Potential with Nonyl Acetate. Unpublished Report from Givaudan. RIFM report number 49475. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2013. Report on the Testing of Nonyl Acetate in the BlueScreen HC Assay (-/+ S9 Metabolic Activation). RIFM report number 65253. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2014a. Ready Biodegradability of Nonyl Acetate (Acetate C9 Nonylic). Unpublished Report from Givaudan. RIFM report number 67205. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2014b. Partition Coefficient N-octanol/water of Nonyl Acetate (Acetate C9 Nonylic). Unpublished Report from Givaudan. RIFM report number 67206. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2015a. Nonyl Acetate: Acute Toxicity to *Daphnia Magna*. Unpublished Report from Givaudan. RIFM report number 70767. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2015b. Nonyl Acetate: Inhibition of Growth to the Alga *Pseudokirchneriella Subcapitata*. Unpublished Report from Givaudan. RIFM report number 70768. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2016a. Hexyl Propionate: Bacterial Reverse Mutation Assay: Plate Incorporation Method with a Confirmatory Assay. RIFM report number 69870. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2016b. Hexyl Propionate: in Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). RIFM report number 70466. RIFM, Woodcliff Lake, NJ, USA.
- RIFM (Research Institute for Fragrance Materials, Inc.), 2016c. Exposure Survey 09, January 2016.
- Roberts, D.W., Patlewicz, G., Dimitrov, S.D., Low, L.K., Aptula, A.O., 2007. Times-SS-A Mechanistic evaluation of an external validation study using reaction chemistry principles. *Chem. Res. Toxicol.* 20 (9), 1321–1330.
- Rogers, D., Hahn, M., 2010. Extended-connectivity fingerprints. *J. Chem. Inf. Model.* 50 (5), 742–754.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Daly, E.J., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Smith, B., Thomas, R., Tozer, S., 2015. Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. *Regul. Toxicol. Pharmacol.* 72, 673–682.
- Safford, B., Api, A.M., Barratt, C., Comiskey, D., Ellis, G., McNamara, C., O'Mahony, C., Robison, S., Rose, J., Smith, B., Tozer, S., 2017. Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. *Regul. Toxicol. Pharmacol.* 86, 148–156.
- Salvito, D.T., Senna, R.J., Federle, T.W., 2002. A Framework for prioritizing fragrance materials for aquatic risk assessment. *Environ. Toxicol. Chem.* 21 (6), 1301–1308.
- Schultz, T.W., Amcoff, P., Berggren, E., Gautier, F., Klaric, M., Knight, D.J., Mahony, C., Schwarz, M., White, A., Cronin, M.T.D., 2015. A strategy for structuring and reporting a read-across prediction of toxicity. *Regul. Toxicol. Pharmacol.* 72 (3), 586–601.
- Shen, J., Kromidas, L., Schultz, T., Bhatia, S., 2014. An *in silico* skin absorption model for fragrance materials. *Food Chem. Toxicol.* 74 (12), 164–176.
- US EPA, 2012a. Estimation Programs Interface Suite for Microsoft Windows, v4.0–v4.11. United States Environmental Protection Agency, Washington, DC, USA.
- US EPA, 2012b. The ECOSAR (ECOLOGICAL Structure Activity Relationship) Class Program for Microsoft Windows, v1.11. United States Environmental Protection Agency, Washington, DC, USA.