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# RIFM fragrance ingredient safety assessment, (Z)-non-6-enyl acetate, CAS Registry Number 76238-22-7

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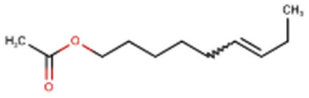

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Name: (Z)-Non-6-enyl acetate
CAS Registry Number: 76238-22-7

**Abbreviation/Definition List:**

**2-Box Model** - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
**AF** - Assessment Factor
**BCF** - Bioconcentration Factor

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**CNIH** – Confirmation of No Induction in Humans test. A Confirmation of No Induction in Humans test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
**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., 2015a, 2017) compared to a deterministic aggregate approach
**DRF** - Dose Range Finding
**DST** - Dermal Sensitization Threshold
**ECHA** - European Chemicals Agency
**ECOSAR** - Ecological Structure-Activity Relationships Predictive Model
**EU** - Europe/European Union
**GLP** - Good Laboratory Practice
**IFRA** - The International Fragrance Association
**LOEL** - Lowest Observed 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
**Perfumery** - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
**QRA** - Quantitative Risk Assessment
**QSAR** - Quantitative Structure-Activity Relationship
**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 as described in this safety assessment.**

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

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

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

**Summary: The existing information supports the use of this material as described in this safety assessment.**

(Z)-Non-6-enyl acetate was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs hex-3-enyl acetate (CAS # 1708-82-3) and *cis*-3-hexenyl butyrate (CAS # 16491-36-4) show that (Z)-non-6-enyl acetate is not expected to be genotoxic. Data on analog *cis*-3-hexenyl acetate (CAS # 3681-71-8) provide a calculated MOE >100 for the repeated dose toxicity and reproductive toxicity endpoints. Data from analog hex-3-enyl acetate (CAS # 1708-82-3) and its additional materials (isomers) *trans*-3-hexenyl acetate (CAS # 3681-82-1) and *cis*-3-hexenyl acetate (CAS # 3681-71-8) provided (Z)-non-6-enyl acetate a NESIL of 1000 μg/cm$^2$ for the skin sensitization endpoint. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra; (Z)-non-6-enyl acetate is not expected to be phototoxic/photoallergenic. The local respiratory toxicity endpoint was evaluated using the TTC for a Cramer Class I material; exposure is below the TTC (1.4 mg/day). The environmental endpoints were evaluated; (Z)-non-6-enyl 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.

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**Human Health Safety Assessment**

| | |
|---|---|
| **Genotoxicity:** Not expected to be genotoxic. | (RIFM, 2016a; RIFM, 2014) |
| **Repeated Dose Toxicity:** No Observed Adverse Effect Level (NOAEL) = 333 mg/kg/day. | (ECHA REACH Dossier: (Z)-Hex-3-enyl acetate; ECHA, 2013) |
| **Reproductive Toxicity:** NOAEL = 1000 mg/kg/day. | (ECHA REACH Dossier: (Z)-Hex-3-enyl acetate; ECHA, 2013) |
| **Skin Sensitization:** No Expected Sensitization Induction Level (NESIL) = 1000 μg/cm$^2$. | RIFM (2018) |
| **Phototoxicity/ Photoallergenicity:** Not expected to be phototoxic/ photoallergenic. | (UV/Vis Spectra; RIFM Database) |

**Local Respiratory Toxicity:** No Observed Adverse Effect Concentration (NOAEC) not available. Exposure is below the Threshold of Toxicological Concern (TTC).

**Environmental Safety Assessment**

**Hazard Assessment:**

| | |
|---|---|
| **Persistence:** Screening-level: 3.2 (BIOWIN 3) | (EPI Suite v4.11; US EPA, 2012a) |
| **Bioaccumulation:** Screening-level: 231 L/kg | (EPI Suite v4.11; US EPA, 2012a) |
| **Ecotoxicity:** Screening-level: Fish LC50: 3.78 mg/L | (RIFM Framework; Salvito, 2002) |

**Conclusion:** Not Persistent, Bioaccumulative, and Toxic (PBT) or very persistent *and* very bioaccumulative (vPvB) as per IFRA Environmental Standards

**Risk Assessment:**

| | |
|---|---|
| **Screening-level:** Predicted Environmental Concentration/ Predicted No Effect Concentration [PEC/PNEC] (North America and Europe) < 1 | (RIFM Framework; Salvito, 2002) |
| **Critical Ecotoxicity Endpoint:** Fish LC50: 3.78 mg/L | (RIFM Framework; Salvito, 2002) |

**RIFM PNEC is:** 0.00378 μg/L

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

## 1. Identification

1. **Chemical Name:** (Z)-Non-6-enyl acetate
2. **CAS Registry Number:** 76238-22-7
3. **Synonyms:** 6-Nonen-1-ol, acetate, (Z)-; Nonenyl acetate, 6-*cis*; *cis*-6-Nonenyl acetate; (Z)-6-Nonenyl acetate; 6-Nonen-1-ol, acetate, (6Z)-; (Z)-Non-6-enyl acetate
4. **Molecular Formula:** $C_{11}H_{20}O_2$
5. **Molecular Weight:** 184.27 g/mol
6. **RIFM Number:** 5990
7. **Stereochemistry:** Z isomer specified. One stereocenter present and a total of 2 stereoisomers possible.

## 2. Physical data

1. **Boiling Point:** 235.33 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log $K_{OW}$:** 4.09 (EPI Suite)
4. **Melting Point:** 0.78 °C (EPI Suite)
5. **Water Solubility:** 16.97 mg/L (EPI Suite)

6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.0592 mm Hg at 25 °C (EPI Suite), 0.0382 mm Hg at 20 °C (EPI Suite v4.0)
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:** Not Available

## 3. Volume of use (worldwide band)

1. <0.1 metric ton per year (IFRA, 2015)

## 4. Exposure to fragrance ingredient (Creme RIFM aggregate exposure model v1.0)

1. **95**th **Percentile Concentration in Fine Fragrance:** 0.0034% (RIFM, 2017a)
2. **Inhalation Exposure*:** 0.0000002 mg/kg/day or 0.000018 mg/day (RIFM, 2017a)
3. **Total Systemic Exposure**:** 0.000029 mg/kg/day (RIFM, 2017a)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015, 2017).

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

## 5. Derivation of systemic absorption

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

## 6. Computational toxicology evaluation

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

| Expert Judgment | Toxtree v3.1 | OECD QSAR Toolbox v4.2 |
|---|---|---|
| I | I | I |

2. Analogs Selected:
   a. **Genotoxicity:** Hex-3-enyl acetate (CAS # 1708-82-3); *cis*-3-Hexenyl butyrate (CAS # 16491-36-4)
   b. **Repeated Dose Toxicity:** *cis*-3-Hexen-1-yl acetate (CAS # 3681-71-8)
   c. **Reproductive Toxicity:** *cis*-3-Hexen-1-yl acetate (CAS # 3681-71-8)
   d. **Skin Sensitization:** Hex-3-enyl acetate (CAS # 1708-82-3) and its additional materials (isomers) *trans*-3-hexenyl acetate (CAS # 3681-82-1) and *cis*-3-hexenyl acetate (CAS # 3681-71-8)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

## 7. Metabolism

No relevant data available for inclusion in this safety assessment. **Additional References:** None.

## 8. Natural occurrence

(Z)-Non-6-enyl acetate is reported to occur in the following foods by the VCF*:

Melon
Pepino fruit (*Solanum muricatum*)

*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.

## 9. REACH dossier

(Z)-Non-6-enyl acetate pre-registered for 2013; no dossier available as of 12/07/21.

## 10. Conclusion

The maximum acceptable concentrations[a] in finished products for (Z)-non-6-enyl acetate are detailed below.

| IFRA Category[b] | Description of Product Type | Maximum Acceptable Concentrations[a] in Finished Products (%)[c] |
|---|---|---|
| 1 | Products applied to the lips (lipstick) | 0.077 |
| 2 | Products applied to the axillae | 0.023 |
| 3 | Products applied to the face/body using fingertips | 0.46 |
| 4 | Products related to fine fragrances | 0.43 |
| 5A | Body lotion products applied to the face and body using the hands (palms), primarily leave-on | 0.11 |
| 5B | Face moisturizer products applied to the face and body using the hands (palms), primarily leave-on | 0.11 |
| 5C | Hand cream products applied to the face and body using the hands (palms), primarily leave-on | 0.11 |
| 5D | Baby cream, oil, talc | 0.037 |
| 6 | Products with oral and lip exposure | 0.25 |
| 7 | Products applied to the hair with some hand contact | 0.88 |
| 8 | Products with significant ano-genital exposure (tampon) | 0.037 |
| 9 | Products with body and hand exposure, primarily rinse-off (bar soap) | 0.84 |
| 10A | Household care products with mostly hand contact (hand dishwashing detergent) | 3.0 |
| 10B | Aerosol air freshener | 3.0 |
| 11 | Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate (feminine hygiene pad) | 0.037 |
| 12 | Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin | No restriction |

Note: [a]Maximum acceptable concentrations for each product category are based on the lowest maximum acceptable concentrations (based on systemic toxicity, skin sensitization, or any other endpoint evaluated in this safety assessment). For (Z)-non-6-enyl acetate, the basis was the subchronic reference dose of 3.33 mg/kg/day, a predicted skin absorption value of 40%, and a skin sensitization NESIL of 1000 μg/$cm^2$.
[b]For a description of the categories, refer to the IFRA RIFM Information Booklet (https://www.rifm.org/downloads/RIFM-IFRA%20Guidance-for-the-use-of-IFRA-Standards.pdf; December 2019).
[c]Calculations by Creme RIFM Aggregate Exposure Model v3.1.3.

## 11. Summary

### 11.1. Human health endpoint summaries

#### 11.1.1. Genotoxicity

Based on the current existing data, (Z)-non-6-enyl acetate does not present a concern for genotoxicity.

*11.1.1.1. Risk assessment.* (Z)-Non-6-enyl acetate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (Birrell et al., 2014).

There are no studies assessing the mutagenic activity of (Z)-non-6-enyl acetate. However, read-across can be made to hex-3-enyl acetate (CAS # 1708-82-3; see Section VI).

The mutagenic activity of hex-3-enyl acetate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation and preincubation methods. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with hex-3-enyl acetate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2016a). Under the conditions of the study, hex-3-enyl acetate was not mutagenic in the Ames test, and this can be extended to (Z)-non-6-enyl acetate.

There are no studies assessing the clastogenic activity of (Z)-non-6-enyl acetate. However, read-across can be made to *cis*-3-hexenyl butyrate (CAS # 16491-36-4; see Section VI). The clastogenic activity of *cis*-3-hexenyl butyrate 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 *cis*-3-hexenyl butyrate in DMSO at concentrations up to 1703 μg/mL in the presence and absence of S9 for 4 and 24 h *cis*-3-Hexenyl butyrate 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, *cis*-3-hexenyl butyrate was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to (Z)-non-6-enyl acetate.

Based on the data available, (Z)-non-6-enyl acetate does not present a concern for genotoxic potential.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 08/21/20.

#### 11.1.2. Repeated dose toxicity

The margin of exposure (MOE) for (Z)-non-6-enyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

*11.1.2.1. Risk assessment.* There are insufficient repeated dose toxicity data on (Z)-non-6-enyl acetate for the repeated dose toxicity endpoint. Read-across material *cis*-3-hexenyl acetate (CAS # 3681-71-8; see Section VI) has an OECD 422/GLP oral gavage combined repeated dose toxicity study with reproduction/developmental screening test conducted in Wistar rats. Groups of 11 rats/sex/dose were administered the test material *cis*-3-hexenyl acetate daily via gavage at doses of 0, 100, 300, or 1000 mg/kg/day in a polyethylene glycol vehicle. The males were dosed for a minimum of 4 weeks, while the females were dosed for approximately 7 weeks. There were no dose-responsive, treatment-related adverse effects observed on body weight, hematological and clinical chemistry parameters, and organ weights. Macroscopic and microscopic findings were not attributed to treatment and were within the historical control range among animals of this strain and age. Thus, the NOAEL was considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013).

A default safety factor of 3 was used when deriving a NOAEL from an OECD 422 study (ECHA, 2012). The safety factor has been approved by the Expert Panel for Fragrance Safety*.

Thus, the derived NOAEL for the repeated dose toxicity data is 1000/3 or 333 mg/kg/day.

Therefore, the (Z)-non-6-enyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the *cis*-3-hexenyl acetate NOAEL in mg/kg/day by the total systemic exposure to (Z)-non-6-enyl acetate, 333/0.000029, or 11482759.

In addition, the total systemic exposure to (Z)-non-6-enyl acetate (0.029 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a subchronic reference dose (RfD) of 3.33 mg/kg/day.

*11.1.2.1.1. Derivation of subchronic RfD.* The RIFM Criteria Document (Api, 2015) calls for a default MOE of 100 (10 × 10), based on uncertainty factors applied for interspecies (10 × ) and intraspecies (10 × ) differences. The subchronic RfD for (Z)-non-6-enyl acetate was calculated by dividing the lowest NOAEL (from the Repeated Dose and Reproductive Toxicity sections) of 333 mg/kg/day by the uncertainty factor, 100 = 3.33 mg/kg/day.

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

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 08/13/20.

#### 11.1.3. Reproductive toxicity

The MOE for (Z)-non-6-enyl acetate is adequate for the reproductive toxicity endpoint at the current level of use.

*11.1.3.1. Risk assessment.* There are insufficient reproductive toxicity data on (Z)-non-6-enyl acetate for the reproductive toxicity endpoint. Read-across material *cis*-3-hexenyl acetate (CAS # 3681-71-8; see Section VI) has an OECD 422/GLP oral gavage combined repeated dose toxicity study with reproduction/developmental screening test conducted in Wistar rats. Groups of 11 rats/sex/dose were administered daily via gavage with test material, *cis*-3-hexenyl acetate at doses of 0, 100, 300, or 1000 mg/kg/day in a polyethylene glycol vehicle. The males were dosed for a minimum of 4 weeks, while the females were dosed for approximately 7 weeks. In addition to systemic toxicity parameters, the fertility and developmental toxicity parameters were also assessed. There were no effects observed in the male and female reproductive function and performance (estrous cycling and sperm measures). The mean precoital time, fertility index, gestation index, conception rate, and implantation rate were not affected by the treatment with the test material. There was no toxicologically significant difference in the mean numbers of corpora lutea per dam and no impact on the post-implantation loss was observed. There were no treatment-related alterations on the development of the pups (body weights, macroscopic or histopathological findings, birth and viability index, and sex ratio) observed at the first litter check or on day 4 post-partum. Thus, the NOAELs for maternal toxicity, developmental toxicity, and fertility were considered to be 1000 mg/kg/day, the highest dose tested (ECHA, 2013). **Therefore, the (Z)-non-6-enyl acetate MOE for the reproductive toxicity endpoint can be calculated by dividing the *cis*-3-hexenyl acetate NOAEL in mg/kg/day by the total systemic exposure to (Z)-non-6-enyl acetate, 1000/0.000029, or 34482759.**

In addition, the total systemic exposure to (Z)-non-6-enyl acetate (0.029 μg/kg/day) is below the TTC (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012) for the reproductive toxicity endpoint of a Cramer

Class I material at the current level of use.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 08/16/20.

*11.1.4. Skin sensitization*

Based on read-across material hex-3-enyl acetate (CAS # 1708-82-3) and its additional materials (isomers) *trans*-3-hexenyl acetate (CAS # 3681-82-1) and *cis*-3-hexenyl acetate (CAS # 3681-71-8), (Z)-non-6-enyl acetate is considered a skin sensitizer with a defined NESIL of 1000 μg/cm$^2$.

*11.1.4.1. Risk assessment.* Insufficient skin sensitization studies are available for (Z)-non-6-enyl acetate. Based on the existing data and the read-across material hex-3-enyl acetate and additional materials (isomers) *trans*-3-hexenyl acetate and *cis*-3-hexenyl acetate (CAS # 1708-82-3, CAS # 3681-71-8, CAS # 3681-82-1, respectively; see Section VI), (Z)-non-6-enyl acetate is a skin sensitizer. The chemical structure of these materials indicates that they would not be expected to react with skin proteins (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). The read-across material hex-3-enyl acetate was found to be positive in an *in vitro* direct peptide reactivity assay (DPRA) and human cell line activation test (h-CLAT) (RIFM, 2017b; RIFM, 2016b). In a murine local lymph node assay (LLNA), read-across material hex-3-enyl acetate was found to be negative up to 100% (RIFM, 2016c). In a guinea pig maximization test, read-across material *cis*-3-hexen-1-yl acetate led to skin sensitization reactions (RIFM, 1996; RIFM, 1997). In a human maximization test, no skin sensitization reactions were observed with additional read-across material *cis*-3-hexen-1-yl acetate (RIFM, 1974). In 2 separate Confirmation of No Induction in Humans test (CNIH) with less than 52 and 55 subjects, respectively, no reactions indicative of sensitization were observed with the target material, 0.05% (28 μg/cm$^2$) (Z)-non-6-enyl acetate in 3:1 specially denatured alcohol (SDA) 39C: diethyl phthalate (DEP) (RIFM, 1993a; RIFM, 1993b). In a CNIH with 1102 μg/cm$^2$ of additional read-across material *cis*-3-hexen-1-yl acetate in 1:3 ethanol:diethyl phthalate (EtOH:DEP), a reaction indicative of sensitization was observed in 1 of the 104 volunteers (RIFM, 2012). However, in CNIHs with 969 μg/cm$^2$ and 1003 μg/cm$^2$ of additional read-across material *cis*-3-hexen-1-yl acetate in ethanol and 1:3 EtOH: DEP, respectively, no reactions indicative of sensitization were observed in any of the 38 or 110 volunteers, respectively (RIFM, 1965; RIFM, 2018).

Based on weight of evidence (WoE) from structural analysis, human studies, and data on the read-across material hex-3-enyl acetate, (Z)-non-6-enyl acetate is a sensitizer with a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL) of 1000 μg/cm$^2$ (see Table 1).

**Table 1**
Data summary for hex-3-enyl acetate as read-across material for (Z)-non-6-enyl acetate.

| LLNA Weighted Mean EC3 Value μg/cm$^2$ [No. Studies] | Potency Classification Based on Animal Data[a] | Human Data | | | |
|---|---|---|---|---|---|
| | | NOEL-CNIH (Induction) μg/cm$^2$ | NOEL-HMT (Induction) μg/cm$^2$ | LOEL[b] (Induction) μg/cm$^2$ | WoE NESIL[c] μg/cm$^2$ |
| NA [1] | Weak | 1003 | 6900 | 1102 | 1000 |

NOEL = No observed effect level; CNIH = Confirmation of No Induction in Humans test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[a] Based on animal data (guinea pig maximization test) using classification defined in ECETOC, Technical Report No. 87, 2003.

[b] Data derived from CNIH or HMT.

[c] WoE NESIL limited to 2 significant figures.

Section X provides the maximum acceptable concentrations in finished products, which take into account skin sensitization and application of the Quantitative Risk Assessment (QRA2) described by Api et al. (RIFM, 2020b) and a subchronic RfD of 3.33 mg/kg/day.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 08/27/20.

*11.1.5. Phototoxicity/photoallergenicity*

Based on the available UV/Vis spectra, (Z)-non-6-enyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

*11.1.5.1. Risk assessment.* There are no phototoxicity studies available for (Z)-non-6-enyl acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance, (Z)-non-6-enyl acetate does not present a concern for phototoxicity or photoallergenicity.

*11.1.5.2. UV spectra analysis.* UV/Vis absorption spectra (OECD TG 101) for (Z)-non-6-enyl acetate were obtained. The spectra indicate minor absorbance in the range of 290–700 nm. The molar absorption coefficients (119 L mol$^{-1}$ • cm$^{-1}$ under basic conditions and 0 L mol$^{-1}$ • cm$^{-1}$ under neutral and acidic conditions) are below the benchmark of concern for phototoxic effects, 1000 L mol$^{-1}$ • cm$^{-1}$ (Henry, 2009).

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 08/05/20.

*11.1.6. Local Respiratory Toxicity*

The MOE could not be calculated due to a lack of appropriate data. The exposure level for (Z)-non-6-enyl acetate is below the Cramer Class I TTC value for inhalation exposure local effects.

*11.1.6.1. Risk assessment.* There are no inhalation data available on (Z)-non-6-enyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.000018 mg/day. This exposure is 77778 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

**Additional References:** None.

**Literature Search and Risk Assessment Completed On:** 07/29/20.

*11.2. Environmental endpoint summary*

*11.2.1. Screening-level assessment*

A screening-level risk assessment of (Z)-non-6-enyl acetate was performed following the RIFM Environmental Framework (Salvito, 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log $K_{OW}$, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio 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 tables below (Table 2 and Table 3). 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

**Table 2**
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)** | <u>3.78</u> | | | 1000000 | 0.00378 | |

**Table 3**
Exposure information and PEC calculation (following RIFM Environmental Framework: Salvito, 2002).

| Exposure | Europe (EU) | North America (NA) |
|---|---|---|
| Log $K_{ow}$ Used | 4.09 | 4.09 |
| Biodegradation Factor Used | 0 | 0 |
| Dilution Factor | 3 | 3 |
| Regional Volume of Use Tonnage Band | <1 | <1 |
| **Risk Characterization: PEC/PNEC** | **<1** | **<1** |

tonnage, not the extremes of the range. Following the RIFM Environmental Framework, (Z)-non-6-enyl acetate was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify (Z)-non-6-enyl acetate as possibly persistent or bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api, 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

*11.2.2. Risk assessment*

Based on the current Volume of Use (2015), (Z)-non-6-enyl acetate does not present a risk to the aquatic compartment in the screening-level assessment.

*11.2.2.1. Key studies*

*11.2.2.1.1. Biodegradation.* No data available.

*11.2.2.1.2. Ecotoxicity.* No data available.

*11.2.2.1.3. Other available data.* (Z)-Non-6-enyl acetate has been pre-registered for REACH with no additional data at this time.

*11.2.3. Risk assessment refinement*

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

The RIFM PNEC is 0.00378 μg/L. The revised PEC/PNECs for EU and NA are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported VoU.

**Literature Search and Risk Assessment Completed On:** 08/20/20.

## 12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/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:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **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. The links listed above were active as of 12/07/21.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Declaration of competing interest

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.2022.113090.

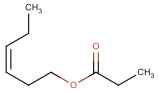
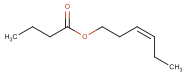
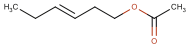
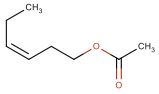
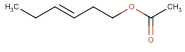
## Appendix

*Read-across Justification*

*Methods*

The read-across analogs were identified using RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020a). These criteria follow the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are 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, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018), and skin sensitization was predicted using Toxtree (Patlewicz et al., 2008).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

| | Target Material | Read-across Material | Read-across Material | Read-across Material | Read-across Material |
|---|---|---|---|---|---|
| **Principal Name** | *cis*-3-Hexenyl propionate | *cis*-3-Hexenyl butyrate | Hex-3-enyl acetate | *cis*-3-Hexen-1-yl acetate, | *trans*-3-hexenyl acetate, Hex-3-enyl acetate |
| **CAS No.** | 33467-74-2 | 16491-36-4 | 1708-82-3 | 3681-71-8 | 3681-82-1, 1708-82-3 |
| **Structure** |  |  |  |  |  |
| **Similarity (Tanimoto Score)** | | 0.88 | 0.93 | 0.93 | |
| **Endpoint** | | • Genotoxicity | • Genotoxicity<br>• Skin sensitization | • Skin sensitization<br>• Repeated dose toxicity<br>• Reproductive toxicity | • Skin sensitization |
| **Molecular Formula** | $C_{11}H_{20}O_2$ | $C_{10}H_{18}O_2$ | $C_8H_{14}O_2$ | $C_8H_{14}O_2$ | $C_8H_{14}O_2$ |
| **Molecular Weight (g/mol)** | 184.279 | 170.252 | 142.198 | 142.198 | 142.198 |
| **Melting Point (°C, EPI Suite)** | 0.78 | −10.31 | −33.28 | −33.28 | −33.28 |
| **Boiling Point (°C, EPI Suite)** | 235.33 | 216.64 | 176.55 | 176.55 | 176.55 |
| **Vapor Pressure (Pa @ 25°C, EPI Suite)** | 7.89E+00 | 2.08E+01 | 1.52E+02 | 1.52E+02 | 1.52E+02 |
| **Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)** | 1.70E+01 | 5.21E+01 | 4.81E+02 | 4.81E+02 | 4.81E+02 |
| **Log KOW** | 4.09 | 3.6 | 2.61 | 2.61 | 2.61 |

(*continued on next page*)

(*continued*)

| | Target Material | Read-across Material | Read-across Material | Read-across Material | Read-across Material |
|---|---|---|---|---|---|
| **$J_{max}$ (μg/cm$^2$/h, SAM)** | 2.15 | 5.60 | 30.25 | 30.25 | 30.25 |
| **Henry's Law (Pa·m$^3$/mol, Bond Method, EPI Suite)** | 1.51E+02 | 1.13E+02 | 6.44E+01 | 6.44E+01 | 6.44E+01 |
| ***Genotoxicity*** | | | | | |
| **DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)** | No alert found | No alert found | AN2\|AN2 ≫ Shiff base formation after aldehyde release\|AN2 ≫ Shiff base formation after aldehyde release ≫ Specific Acetate Esters\|SN1\|SN1 ≫ Nucleophilic attack after carbenium ion formation\|SN1 ≫ Nucleophilic attack after carbenium ion formation ≫ Specific Acetate Esters\|SN2\|SN2 ≫ Acylation\|SN2 ≫ Acylation ≫ Specific Acetate Esters\|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom\|SN2 ≫ Nucleophilic substitution at sp3 Carbon atom ≫ Specific Acetate Esters | | |
| **DNA Binding (OECD QSAR Toolbox v4.2)** | No alert found | No alert found | No alert found | | |
| **Carcinogenicity (ISS)** | No alert found | No alert found | No alert found | | |
| **DNA Binding (Ames, Micronucleus, CA, OASIS v1.1)** | No alert found | No alert found | No alert found | | |
| ***In Vitro* Mutagenicity (Ames, ISS)** | No alert found | No alert found | No alert found | | |
| ***In Vivo* Mutagenicity (Micronucleus, ISS)** | No alert found | No alert found | No alert found | | |
| **Oncologic Classification** | Not classified | Not classified | Not classified | | |
| ***Repeated Dose Toxicity*** | | | | | |
| **Repeated Dose (HESS)** | Not categorized | | Not categorized | Not categorized | |
| ***Reproductive Toxicity*** | | | | | |
| **ER Binding (OECD QSAR Toolbox v4.2)** | Non-binder, non-cyclic structure | | Non-binder, non-cyclic structure | Non-binder, non-cyclic structure | |
| **Developmental Toxicity (CAESAR v2.1.6)** | Toxicant (good reliability) | | Toxicant (good reliability) | Toxicant (good reliability) | |
| ***Skin Sensitization*** | | | | | |
| **Protein Binding (OASIS v1.1)** | No alert found | | No alert found | No alert found | No alert found |
| **Protein Binding (OECD)** | No alert found | | No alert found | No alert found | No alert found |
| **Protein Binding Potency** | Not possible to classify according to these rules (GSH) | | Not possible to classify according to these rules (GSH) | Not possible to classify according to these rules (GSH) | Not possible to classify according to these rules (GSH) |
| **Protein Binding Alerts for Skin Sensitization (OASIS v1.1)** | No alert found | | No alert found | No alert found | No alert found |
| **Skin Sensitization Reactivity Domains (Toxtree v3.1)** | No skin sensitization reactivity domains alerts identified. | | No skin sensitization reactivity domains alerts identified. | No skin sensitization reactivity domains alerts identified. | No skin sensitization reactivity domains alerts identified. |
| ***Metabolism*** | | | | | |
| **Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)** | 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 (Z)-non-6-enyl acetate (CAS # 76238-22-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, *cis*-3-hexenyl butyrate (CAS # 16491-36-4), hex-3-enyl acetate (CAS # 1708-82-3), *trans*-3-hexenyl acetate (CAS # 3681-82-1), and *cis*-3-hexen-1-yl acetate (CAS # 3681-71-8) were identified as read-across materials with sufficient data for toxicological evaluation.

*Conclusions*

- *cis*-3-Hexenyl butyrate (CAS # 16491-36-4) was used as a read-across analog for the target material (Z)-non-6-enyl acetate (CAS # 76238-22-7) for the genotoxicity endpoint.
  - o The target material and the read-across analog are structurally similar and belong to a class of esters.
  - o The target material and the read-across analog share a common aliphatic unsaturated fragment on the alcohol portion of the ester.
  - o The key difference between the target material and the read-across analog is that the target has an acetate fragment on the acid portion and nonenyl fragment on the alcohol portion, while the read-across analog has a butyrate fragment on the acid portion and hexenyl fragment on the

alcohol portion of the ester. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated aliphatic ester fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Data are consistent with *in silico* alerts.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- Hex-3-enyl acetate (CAS # 1708-82-3) was used as a read-across analog for the target material (Z)-non-6-enyl acetate (CAS # 76238-22-7) for the genotoxicity and skin sensitiztion endpoints.
  - The target material and the read-across analog are structurally similar and belong to a class of esters.
  - The target material and the read-across analog share a common aliphatic unsaturated fragment on the alcohol portion of the ester.
  - The key difference between the target material and the read-across analog is that the target material has a nonenyl fragment on the alcohol portion, while the read-across analog has a hexenyl fragment in the alcohol portion of the ester. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated aliphatic ester fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The read-across analog is predicted to have positive DNA binding alerts by the OASIS model for genotoxicity. All the other alerts for genotoxicity were predicted to be negative. According to these predictions, the read-across analog is expected to be more reactive compared to the target material. As described in the genotoxicity section above, based on current existing data, the read-across analog does not present a concern for genotoxicity. Therefore, data superseded predictions in this case.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- *cis*-3-Hexen-1-yl acetate (CAS # 3681-71-8) was used as a read-across analog for the target material (Z)-non-6-enyl acetate (CAS # 76238-22-7) for the repeated dose toxicity, reproductive toxicity, and skin sensitization endpoints. *trans*-3-Hexenyl acetate (CAS # 3681-82-1) was used as a read-across analog for the target material (Z)-non-6-enyl acetate (CAS # 76238-22-7) for the skin sensitization endpoint.
  - The target material and the read-across analogs are structurally similar and belong to a class of esters.
  - The target material and the read-across analogs share a common aliphatic unsaturated fragment on the alcohol portion of the ester.
  - The key difference between the target material and the read-across analogs is that the target material has a nonenyl fragment on the alcohol portion, while the read-across analogs have a hexenyl fragment in the alcohol portion of the ester. This structural difference is toxicologically insignificant.
  - Similarity between the target material and the read-across analogs is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated aliphatic ester fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analogs are sufficiently similar to enable a comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analogs.
  - The read-across analogs are predicted to be toxicants by the CAESAR model for developmental toxicity. All the other alerts are negative. According to these predictions, the read-across analogs are expected to be more reactive compared to the target material. The data described in the developmental toxicity section above show that the read-across analogs have an adequate MOE at the current level of use. Therefore, the predictions are superseded by the data.
  - Data are consistent with *in silico* alerts.
  - The target material and the read-across analogs 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 analogs and the target material.

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