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Short Review

RIFM Fragrance Ingredient Safety Assessment,(E,Z)-2,6-nonadien-1-ol acetate, CAS Registry Number 68555-65-7

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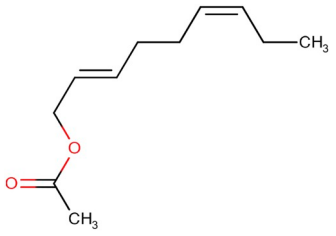
Version: 031918. This version replaces any previous versions.
Name: (E,Z)-2,6-Nonadien-1-ol acetate
CAS Registry Number: 68555-65-7
Additional CAS Numbers*:
67674-47-9 (2E,6E)-Nona-2,6-dienyl acetate
*This material is included in this safety assessment because the materials are isomers.



Abbreviation/Definition List:
2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015b, 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

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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.

(E,Z)-2,6-Nonadien-1-ol acetate was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization, and environmental safety. Data from read-across analog geranyl formate (CAS # 105-86-2) show that (E,Z)-2,6-nonadien-1-ol acetate is not expected to be genotoxic. Based on the application of the reactive DST, E,Z)-2,6-nonadien-1-ol acetate does not present a concern for skin sensitization. The repeated dose, reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on suitable UV spectra. The environmental endpoints were evaluated, (E,Z)-2,6-nonadien-1-ol acetate was found not to be a 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, 2015; RIFM, 2017a)
Repeated Dose Toxicity: No NOAEL available. Exposure is below the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 75% (OECD 301F) RIFM (2012b)
Bioaccumulation: Screening-level: 166 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 5.61 mg/L (RIFM Framework; Salvito et al., 2002)
Conclusion: Not PBT or vPvB as per IFRA Environmental Standards

Risk Assessment:
Screening-level: PEC/PNEC (North America and Europe) < 1 (RIFM Framework; Salvito et al., 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 5.61 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00561 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe: Not applicable; cleared at the screening level

1. Identification

Chemical Name: (E,Z)-2,6-Nonadien-1-ol acetate	Chemical Name: (2E,6E)-Nona-2,6-dienyl acetate
CAS Registry Number: 68555-65-7	**CAS Registry Number:** 67674-47-9
Synonyms: trans-2-cis-6-Nonadien-1-yl acetate; Nona-2,6-dien-1-yl acetate; Nonadienyl acetate; (E,Z)-2,6-Nonadien-1-ol acetate	**Synonyms:** (2E,6E)-Nona-2,6-dienyl acetate; 2,6-Nonadien-1-ol, acetate, (E,E)-; Nona-2,6-dien-1-yl acetate
Molecular Formula: $C_{11}H_{18}O_2$	**Molecular Formula:** $C_{11}H_{18}O_2$
Molecular Weight: 182.25	**Molecular Weight:** 182.25
RIFM Number: 5238	**RIFM Number:** N/A
Stereochemistry: Isomer unspecified. Two stereocenters and 4 total stereoisomers possible.	**Stereochemistry:** Trans and cis Isomer. Two stereocenters and 4 total stereoisomers possible.

2. Physical data**

1. **Boiling Point:** 240.9 °C (US EPA, 2012a)
2. **Flash Point:** 200.00 °F. TCC (93.33 °C)*
3. **Log K_{OW}:** log Pow = 3.6 and 3.7 (RIFM, 2013a), 3.87 (US EPA, 2012a)
4. **Melting Point**: −0.13 °C (US EPA, 2012a)
5. **Water Solubility:** 26.5 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.90500 to 0.90700 @ 25.00 °C*
7. **Vapor Pressure:** 0.0441 mm Hg @ 25 °C (US EPA, 2012a), 0.0283 mm Hg @ 20 °C (US EPA, 2012a)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} · cm^{-1})
9. **Appearance/Organoleptic:** Colorless clear liquid with a green, leafy, fatty, and nutty odor*

*http://www.thegoodscentscompany.com/data/rw1047861.html, retrieved 08/14/17.

**All physical data for both materials included in this assessment are identical.

3. Exposure

1. **Volume of Use (worldwide band):** 0.1–1 metric ton per year (IFRA, 2015)
2. 95th Percentile Concentration in Hydroalcoholics: 0.0020% (RIFM, 2017b)
3. **Inhalation Exposure*:** 0.0000035 mg/kg/day or 0.00024 mg/day (RIFM, 2017b)
4. **Total Systemic Exposure**:** 0.000049 mg/kg/day (RIFM, 2017b)

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

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section IV. It is derived from concentration survey data in the Creme RIFM aggregate exposure model and includes exposure via dermal, oral and inhalation

routes whenever the fragrance ingredient is used in products that include these routes of exposure (Comiskey et al., 2015; Safford et al., 2015b; Safford et al., 2017; and Comiskey et al., 2017).

***When a safety assessment includes multiple materials, the highest exposure out of all included materials will be recorded here for the 95th Percentile Concentration in hydroalcoholics, inhalation exposure and total exposure.

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. Cramer Classification: Class I, Low

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Geranyl formate (CAS # 105-86-2); 2,6-nonadien-1-ol (CAS # 7786-44-9); *trans*-2-hexenol (CAS # 928-95-0)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   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)

(E,Z)-2,6-Nonadien-1-ol acetate is not reported to occur in food by the VCF.*:

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

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 03/19/2018.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, (E,Z)-2,6-nonadien-1-ol acetate does not present a concern for genotoxicity.

10.1.1. Risk assessment. (E,Z)-2,6-Nonadien-1-ol acetate was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013b). BlueScreen is a screening assay that assesses genotoxic stress through human-derived gene expression. Additional assays on a more reactive read-across material were considered to fully assess the potential mutagenic or clastogenic effects of the target material.

There are no studies assessing the mutagenic activity of (E,Z)-2,6-nonadien-1-ol acetate; however, read-across can be made to geranyl formate (CAS # 105-86-2; see Section V). The mutagenic activity of geranyl formate has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with geranyl formate in dimethyl sulfoxide (DMSO) at concentrations up to 5000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2015). Under the conditions of the study, geranyl formate was not mutagenic in the Ames test, and this can be extended to (E,Z)-2,6-nonadien-1-ol acetate. The target material is predicted to be metabolized (see Appendix) to geraniol (CAS # 106-24-1) and acetic acid (CAS # 64-19-7). Alcohols trans-2-hexenol (CAS # 928-95-0) and 2,6-nonadien-1-ol (CAS # 7786-44-9) are structurally similar to geraniol. Hence, these 2 alcohols can be used as an additional weight of evidence. The mutagenic activity of 2,6-nonadien-1-ol (CAS # 7786-44-9) was tested in accordance with OECD TG 471 using the standard plate incorporation/pre-incubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 2,6-nonadien-1-ol in DMSO at concentrations up to 1000 μg/plate. No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (RIFM, 2012a). Under the conditions of the study, 2,6-nonadien-1-ol was not mutagenic in the Ames test. Acetic acid is also negative in mutagenicity studies (ECHA REACH Dossier).

There are no studies assessing the clastogenic activity of (E,Z)-2,6-nonadien-1-ol acetate; however, read-across can be made to geranyl formate (CAS # 105-86-2; see Section V). The clastogenic activity of geranyl formate was evaluated in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with geranyl formate in solvent DMSO at concentrations up to 1820 μg/mL in the presence and absence of metabolic activation (S9) for 4 and 24 h. Geranyl formate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2017a). Under the conditions of the study, geranyl formate was considered to be non-clastogenic in the *in vitro* micronucleus test and this can be extended to (E,Z)-2,6-nonadien-1-ol acetate. Since this ester will break up in to an α,ß-unsaturated alcohol and acetic acid, an additional weight of evidence read-across can be made by to the alcohol and acid part of the ester (see Section V). The clastogenic potential of *trans*-2-hexenol (CAS # 928-95-0) was evaluated in an *in vitro* micronucleus test in compliance with GLP regulations and in accordance with OECD TG 487. Human peripheral blood lymphocytes were treated with *trans*-2-hexenol in DMSO at concentrations up to 1000 μg/mL in the presence and absence of metabolic activation (S9) at the 4 h and 24 h time points. *Trans*-2-hexenol 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, *trans*-2-hexenol was considered to be non-clastogenic in the *in vitro* micronucleus test. Acetic acid is also negative in *in vitro* as well as *in vivo* studies (ECHA REACH Dossier).

Based on the data available, geranyl formate does not present a concern for genotoxic potential and this can be extended to (E,Z)-2,6-nonadien-1-ol acetate.

Table 1
Maximum acceptable concentrations for (E,Z)-2,6-nonadien-1-ol acetate that present no appreciable risk for skin sensitization based on reactive DST.

IFRA Category[a]	Description of Product Type	Maximum Acceptable Concentrations in Finished Products Based on Reactive DST	Reported 95th Percentile Use Concentrations in Finished Products
1	Products applied to the lips	0.005%	0.00%
2	Products applied to the axillae	0.001%	0.00%[b]
3	Products applied to the face using fingertips	0.03%	0.00%[b]
4	Fine fragrance products	0.03%	0.00%[b]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.01%	0.00%[b]
6	Products with oral and lip exposure	0.02%	0.00%
7	Products applied to the hair with some hand contact	0.06%	0.00%[b]
8	Products with significant ano-genital exposure	0.003%	No data[c]
9	Products with body and hand exposure, primarily rinse-off	0.05%	0.00%[b]
10	Household care products with mostly hand contact	0.19%	0.00%[b]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	0.11%	No data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.015%

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/20/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on (E,Z)-2,6-nonadien-1-ol acetate or any read-across materials. The total systemic exposure to (E,Z)-2,6-nonadien-1-ol acetate is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on (E,Z)-2,6-nonadien-1-ol acetate or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to (E,Z)-2,6-nonadien-1-ol acetate (0.049 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: 07/17/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on (E,Z)-2,6-nonadien-1-ol acetate or any read-across materials. The total systemic exposure to (E,Z)-2,6-nonadien-1-ol 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 reproductive toxicity data on (E,Z)-2,6-nonadien-1-ol acetate or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to (E,Z)-2,6-nonadien-1-ol acetate (0.049 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 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: 07/17/17.

10.1.4. Skin sensitization

Based on the application of the Dermal Sensitization Threshold (DST), (E,Z)-2,6-nonadien-1-ol acetate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for (E,Z)-2,6-nonadien-1-ol acetate or read-across materials. Acting conservatively, due to the insufficient data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Roberts et al., 2015b; Safford, 2008; Safford et al., 2011; Safford et al., 2015a). The current exposure from the 95th percentile concentration is below the DST for reactive materials when evaluated in all QRA categories. Table 1 provides the maximum acceptable concentrations for (E,Z)-2,6-nonadien-1-ol acetate that present no appreciable risk for skin sensitization based on the reactive DST. These concentrations are not limits; they represent maximum acceptable concentrations based on the DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/27/2017.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, (E,Z)-2,6-nonadien-1-ol acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for (E,Z)-2,6-nonadien-1-ol acetate in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, (E,Z)-2,6-nonadien-1-ol acetate does not present a concern for phototoxicity or photoallergenicity.

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

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/06/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of

appropriate data. The exposure level for (E,Z)-2,6-nonadien-1-ol 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 (E,Z)-2,6-nonadien-1-ol acetate. Based on the Creme RIFM model, the inhalation exposure is 0.00024 mg/day. This exposure is 5833 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: 08/02/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of (E,Z)-2,6-nonadien-1-ol acetate was performed following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, (E,Z)-2,6-nonadien-1-ol 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 (E,Z)-2,6-nonadien-1-ol acetate as possibly persistent nor bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on current Volume of Use (2015), (E,Z)-2,6-nonadien-1-ol acetate does not present a risk to the aquatic compartment in the screening level assessment.

10.2.2.1. Biodegradation. RIFM, 2012b**:** The ready biodegradability of the test material was evaluated using a Manometric Respirometry Test according to the OECD 301F method. Under the conditions of this study, the test material underwent 75% biodegradation after 28 days.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. (E,Z)-2,6-Nonadien-1-ol acetate has been pre-registered for REACH with no additional data at this time.

10.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	<u>5.61</u>			1,000,000	0.00561	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	3.8	3.8
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	Not reported	N/A
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.00561 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the

aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 7/24/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox**
- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET:** http://toxnet.nlm.nih.gov/
- **IARC:** http://monographs.iarc.fr
- **OECD SIDS:** http://webnet.oecd.org/hpv/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.023.

Conflicts of interest

The authors declare that they have no conflicts of interest.

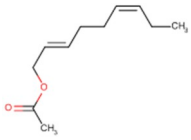
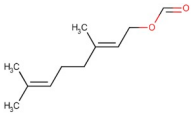
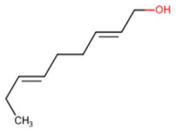
Appendix

Read-across Justification

Methods

The read-across analogs were identified following the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015). The strategy is also consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2016).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster was examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target substance and the read-across analogs were calculated using EPI Suite v4.11 (US EPA, 2012a).
- J_{max} values were calculated using RIFM's Skin Absorption Model (SAM). The parameters were calculated using the consensus model (Shen et al., 2014).
- DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v3.4 (OECD, 2012).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree 2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v3.4 (OECD, 2012).
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v3.4 (OECD, 2012).

	Target Material	Read-across Material	Weight of Evidence (WoE)	Weight of Evidence (WoE)	Weight of Evidence (WoE)
Principal Name	(E,Z)-2,6-Nonadien-1-ol acetate	Geranyl formate	trans-2-Hexenol	2,6-Nonadien-1-ol	Acetic acid
CAS No.	**68555–65–7** and 67674-47-9	105-86-2	928-95-0	7786-44-9	64-19-7
Structure					
Similarity (Tanimoto Score)		0.76	NA	NA	NA
Read-across Endpoint		• Genotoxicity	• Genotoxicity	• Genotoxicity	• Genotoxicity
Molecular Formula	$C_{11}H_{18}O_2$	$C_{11}H_{18}O_2$	$C_6H_{12}O$	$C_9H_{16}O$	$C_2H_4O_2$
Molecular Weight	182.26	182.26	100.16	140.23	60.05
Melting Point (°C, EPI Suite)	−0.13	−8.31	−38.47	−4.87	16
Boiling Point (°C, EPI Suite)	240.90	232.67	165.73	231.61	118
Vapor Pressure (Pa @ 25°C, EPI Suite)	5.89	9.07	121	1.4	12.9
Log Kow (KOWWIN v1.68 in EPI Suite)	3.87	3.93	1.61	2.87	0.09
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	26.5	23.73	16000	963.8	475900

J_{max} (mg/cm^2/h, SAM)	14.372	26.320	508.142	76.124	6283.04
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.31E-003	3.31E-003	1.57E + 000	3.23E-005	5.477E-007
Genotoxicity					
DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• AN2, Schiff base formation • SN1, Nucllephilic attack • SN2, Acylation	• No alert found	• No alert found	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v3.4)	• No alert found	• No alert found	• No alert found	• No alert found	• No alert found
Carcinogenicity (ISS)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)	• Non-carcinogen (moderate reliability)	• Non-carcinogen (moderate reliability)
DNA Binding (Ames, MN, CA, OASIS v1.1)	• No alert found	• No alert found	• No alert found	• No alert found	• No alert found
***In Vitro* Mutagenicity (Ames, ISS)**	• No alert found	• No alert found	• No alert found	• No alert found	• No alert found
***In Vivo* Mutagenicity (Micronucleus, ISS)**	• No alert found	• No alert found	• No alert found	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Aldehyde type compound	• Not classified	• Not classified	• Not classsified
Metabolism					
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4	No metabolism possible

Summary

There are insufficient toxicity data on (E,Z)-2,6-nonadien-1-ol acetate (CAS # 68555-65-7). 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, geranyl formate (CAS # 105-86-2) was identified as a read-across analog with sufficient data for toxicological evaluation.

Conclusions

- Geranyl formate (CAS # 105-86-2) was used as a read-across analog for the target material (E,Z)-2,6-nonadien-1-ol acetate (CAS # 68555-65-7) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to class of esters.
  - o The target substance and the read-across analog share a common unsaturated aliphatic fragment on the alcohol portion of the ester.
  - o The key difference between the target substance and the read-across analog is that the target has a free beta carbon connected to the alcohol portion while the read-across has a methylated beta carbon connected to the alcohol portion. 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 unsaturated aliphatic ester 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 is predicted to have DNA binding alerts by OASIS for genotoxicity. The alert says that necessary conditions for eliciting direct or indirect DNA damage, described in this general mechanistic profile, are met. However, the specific structural boundaries providing sufficiency for DNA damage is not identified. This alert is likely due to aldehyde formation in second phase metabolism. All the other alerts for DNA binding are negative. The data described in the genotoxicity section above shows that the read-across analog does not pose a concern for genotoxicity. Therefore, the predictions are superseded by data.
  - o The read-across analog is classified as an aldehyde type compound. This alert is triggered due to the formic acid portion of the ester. The reversible metabolism of formic acid to formaldehyde is not predicted by the rat S9 metabolism simulator. Hence, this alert can be ignored. This shows that the read-across might have higher reactivity compared to the target substance. The target material has an acetic acid portion; therefore, it does not have such an alert.
  - 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.

Metabolism

Metabolism of the target material (E,Z)-2,6-nonadien-1-ol acetate (CAS # 68555-65-7) was predicted using the Rat Liver S9 Metabolism Simulator (OECD QSAR Toolbox v3.4). The target material is predicted to be metabolized to geraniol (CAS # 106-24-1) and acetic acid (CAS # 64-19-7) in the first step with 0.95 probability. Alcohols *trans*-2-hexenol (CAS # 928-95-0) and 2,6-nonadien-1-ol (CAS # 7786-44-9) are structurally similar to geraniol. Hence, these 2 alcohols can be used as the WoE for the target substance. Genetic toxicity studies on acetic acid confirm that the substance poses no concern for genetic toxicity. Acetic acid is one of the simplest carboxylic acids. According to the human metabolome database, it is one of the naturally occurring acids in various cellular locations and different biofluids. Also, excretion via glucuronidation is fairly well known for this acid. Hence, the proposed alcohols can be used as WoE for the target substance.

- *trans*-2-Hexenol (CAS # 928-95-0) and 2,6-nonadien-1-ol (CAS # 7786-44-9) were used as a WoE for the target material (E,Z)-2,6-nonadien-1-ol acetate (CAS # 68555-65-7) for the genotoxicity endpoint.

- o Analogous alcohols to the alcohol produced in the ester hydrolysis of the target material are used as WoE for the target ester for the genotoxicity endpoint.
- o Structural differences between the target substance and the read-across analog are mitigated by the fact that the target could be metabolically hydrolyzed to the alcohol structurally similar to WoE materials. Therefore, the toxicity profile of the target is expected to be similar to that of its metabolites.
- o Both the target alcohol geraniol and the WoE alcohols have unsaturation between positions 2 and 3. The target alcohol geraniol has a methyl substitution on position 3, while the WoE alcohols do not have a substitution on position 3. Due to this methyl substitution in geraniol, it is predicted to be slightly less reactive and slightly less toxic in nature compared to the WoE alcohols. Higher reactivity of WoE alcohols makes them appropriate WoE materials.
- o The target substance and the WoE materials have similar physical–chemical properties. Any differences in the physical–chemical properties of the target substance and the WoE materials are toxicologically insignificant.
- o According to the QSAR OECD Toolbox v3.4, structural alerts for the endpoints evaluated are consistent between the target substance and the WoE materials.
- o The structural alerts for the endpoints evaluated are consistent between the metabolites of the WoE materials and the target substance.

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