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Short review

RIFM fragrance ingredient safety assessment, (2E,6Z)-Nona-2,6-dien-1-ol, CAS registry number 28069-72-9

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Environmental toxicology

1. Identification

1. **Chemical name:** (2E, 6Z)-Nona-2,6-dien-1-ol
2. **CAS registry number:** 28069-72-9
3. **Synonyms:** 2,6-Nonadien-1-ol, (E,Z)-, (2E, 6Z)-Nona-2,6-dien-1-ol, 2-trans-6-cis-Nonadien-1-ol, 脂肪族不飽和アルコール(C = 9 ~ 24), Nona-2,6-dien-1-ol
4. **Molecular formula:** $C_9H_{16}O$
5. **Molecular weight:** 140.26
6. **RIFM number:** 5639

2. Physical data

1. **Boiling point:** 231.61 °C [EPI Suite]
2. **Flash point:** 203.00 °F. TCC (95.00 °C)
3. **Log K_{OW}:** 2.87 [EPI Suite]
4. **Melting point:** −4.87 °C [EPI Suite]
5. **Water solubility:** 963.8 mg/L [EPI Suite]
6. **Specific gravity:** 0.86000– 0.88000 @ 25 °C[1]
7. **Vapor pressure:** 0.00623 mm Hg @ 20 °C [EPI Suite 4.0], 0.0105 mm Hg @ 25 °C [EPI Suite]
8. **UV spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L/mol cm^{-1}).
9. **Appearance/organoleptic:** Colorless to pale yellow clear oily liquid with a high odor at 1% solution that was described as

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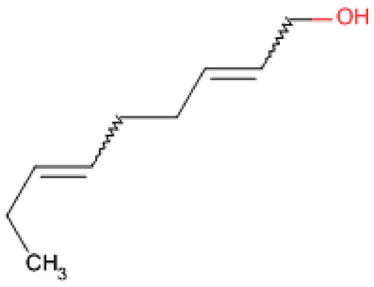
Name: (2E,6Z)-Nona-2,6-dien-1-ol
CAS registry number: 28069-72-9



Abbreviation list:
2-box model – a RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
97.5th percentile- The concentration of the fragrance ingredient is obtained from examination of several thousand commercial fine fragrance formulations. The upper 97.5th percentile concentration is calculated from these data and is then used to estimate the dermal systemic exposure in ten types of the most frequently used personal care and cosmetic products. The dermal route is the major route in assessing the safety of fragrance ingredients. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).
AF- Assessment Factor
BCF- Bioconcentration Factor
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
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
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
TTC- Threshold of Toxicological Concern
UV/Vis Spectra- Ultra Violet/Visible spectra
VCF- Volatile Compounds in Food
VoU- Volume of Use
vPvB- (very) Persistent, (very) Bioaccumulative
WOE – Weight of Evidence

RIFM's Expert Panel* concludes that this material is safe under the limits described in this safety assessment.
This safety assessment is based on RIFM's Criteria Document (Api et al., 2014) and should be referred to for clarifications.
Each endpoint discussed in this safety assessment reviews 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 two digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., 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 end-point value (e.g., PNEC, NOAEL, LOEL, and NESIL).
*RIFM's Expert Panel 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 guidance relevant to human health and environmental protection.

Summary: The use of this material under current use conditions is supported by the existing information.
This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose, developmental, and reproductive toxicities were based on the Threshold of Toxicological Concern (TTC) of 0.03 mg/kg/day for a Cramer Class I material. The estimated systemic exposure is determined to be below this value while assuming 100% absorption from skin contact and inhalation. A systemic exposure below the TTC value is acceptable.

Human Health Safety Assessment
Genotoxicity: Not genotoxic. (RIFM, 2012; RIFM, 2014)
Repeated dose toxicity: No NOAEL available. Exposure is below the TTC.
Developmental and reproductive toxicity: No NOAEL available. Exposure is below the TTC.

(*continued*)

Skin sensitization: Not a sensitization concern. Exposure is below 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: Screening level: 3.35	(EPISUITE ver 4.1)
Bioaccumulation: Screening level: 36.2 L/Kg	(EPISUITE ver 4.1)
Ecotoxicity: Screening level: 33.12 mg/L	(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	(Salvito et al., 2002)
Critical ecotoxicity endpoint: 33.12 mg/L	(Salvito et al., 2002)
RIFM PNEC is 0.033 μg/L	
• **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe NA; cleared at screening level	

green, cucumber, oily, violet, leafy, with a mild fatty and oxidized nutty nuance. (http://www.thegoodscentscompany.com/data/rw1031571.html, retrieved 09/17/13).

3. Exposure

1. Volume of use (worldwide band): <1 metric tons per year	[IFRA, 2011]
2. Average maximum concentration in hydroalcoholics: 0.05%	[IFRA, 2007]
3.97.5th percentile: 0.01%	[IFRA, 2007]
4. Dermal exposure*: 0.0003 mg/kg/day	[IFRA, 2007]
5. Oral exposure: Not available	
6. Inhalation exposures:** 0.000022 mg/kg/day	[IFRA, 2007]
7. Total systemic exposure (dermal + inhalation): 0.00032 mg/kg/day	

*Calculated using the reported 97.5th percentile concentration based on the levels of the same fragrance ingredient in ten of the most frequently used personal care and cosmetic products (i.e., anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap). (Cadby et al., 2002; Ford et al., 2000).

**Combined (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins) result calculated using RIFM's 2-Box/MPPD *in silico* models, based on the IFRA survey results for the 97.5th percentile use in hydroalcoholics for a 60 kg individual.

4. Derivation of systemic absorption

1. **Dermal:** Assumed 100%
2. **Oral:** Data not available – not considered.
3. **Inhalation:** Assumed 100%
4. **Total:** Since data not available, assume Dermal + Inhalation exposure is 100% absorbed = 0.00032 mg/kg/day

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. **Analogues selected:**
   a **Genotoxicity:** 2, 6-Nonadien-1-ol (CAS # 7786-44-9); trans-2-hexenol (CAS # 928-95-0)
   b **Repeated dose toxicity:** None
   c **Developmental and 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

Not considered for this risk assessment and therefore not reviewed except where it may pertain in specific endpoint sections as discussed below.

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

(2E, 6Z)-Nona-2,6-dien-1-ol is reported to occur in the following foods*:

Cucumber (*Cucumis sativus L.*)	Prickly pear (*Opuntia ficus indica*)
Fish	Melon
Malt	

*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, contains information on published volatile compounds which 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 04/20/15.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, (2E, 6Z)-nona-2,6-dien-1-ol does not present a concern for genetic toxicity.

10.1.2. Risk assessment

(2E, 6Z)-Nona-2,6-dien-1-ol was tested using the BlueScreen assay and found to be negative for both cytotoxicity and genotoxicity indicating a lack for genotoxic concern (RIFM, 2013b). There are no studies assessing the mutagenic potential of (Z)-2-penten-ol.

Read across can be made to the analogue, 2, 6-nonadien-1-ol (CAS # 7786-44-9; see Section V) which was assessed in an Ames study conducted in compliance with GLP regulations and in accordance with OECD 471 using both the standard plate incorporation and preincubation methods (RIFM, 2012). Under the conditions of the study, 2, 6-nonadien-1-ol is not mutagenic and this can be extended to (2E, 6Z)-nona-2,6-dien-1-ol.

There are no studies assessing the clastogenic activity of the (2E, 6Z)-nona-2,6-dien-1-ol. The read across material, *trans*-2-hexenol was assessed for clastogenic activity in an *in vitro* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD 487 Human peripheral blood lymphocytes were treated with *trans*-2-hexenol in DMSO (dimethyl sulfoxide) under the following conditions: in the 4 h treatment without S9 mix at concentrations 10, 50, 100, 250, 500, 750 and 1000 μg/ml; in the 24 h treatment recovery without S9 mix at concentrations 10, 50, 100, 250, 275, 300 μg/ml; and in the 4 h treatment with S9 at concentrations 10, 50, 100, 250, 500, 750 and 1000 μg/ml. The percentage of cells with micronuclei in the test material-treated group was not significantly increased relative to vehicle control at any dose level (RIFM, 2014). Under the conditions of the study, *trans*-2-hexenol was considered to be negative for the induction of micronuclei in the *in vitro* micronucleus assay and this can be extended to (2E, 6Z)-nona-2,6-dien-1-ol.

Based on the available data, (2E, 6Z)-nona-2,6-dien-1-ol does not present a concern for genotoxic potential.

Additional references: RIFM, 2013c; RIFM, 2013a.

Literature search and risk assessment completed on: 09/06/13.

10.1.3. Repeated dose toxicity

There are insufficient repeated dose toxicity data on (2E, 6Z)-nona-2,6-dien-1-ol or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC).

10.1.4. Risk assessment

There are no repeated dose toxicity data on (2E, 6Z)-nona-2,6-dien-1-ol or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.32 μg/kg/day) is below the TTC for (2E, 6Z)-nona-2,6-dien-1-ol (30 μg/kg bw/day).

Additional references: ECHA REACH Dossier: cis-Hex-3-en-1-ol (http://apps.echa.europa.eu/registered/data/dossiers/DISS-dceb962c-f1ce-2476-e044-00144f67d031/DISS-dceb962c-f1ce-2476-e044-00144f67d031_DISS-dceb962c-f1ce-2476-e044-00144f67d031.html); Gaunt et al., 1969; McGinty et al., 2010a; Belsito et al., 2010; Hagan et al., 1967; Bar and Griepentrog, 1967; RIFM, 2010a; RIFM, 2010b; Gilpin et al., 2010; Lapczynski et al., 2008a; Belsito et al., 2008; RIFM, 2001; RIFM, 1954; Vieira et al., 2011; Fielden et al., 2007; Hood et al., 1978; Abramovici and Feder, 1980; Abramovici, 1972, Abramovici and Rachmuth-Roizman, 1983; Forschmidt et al., 1979; Howes et al., 2002; Buchbauer et al., 1993; Chadha and Madyastha, 1984; King and Dickinson, 2000, 2003; Westfall et al., 1997; Piccinini, 1962; Longenecker et al., 1939; Sporn and Abramovici, 1976; Leclerc et al., 2002; Chadha and Madyastha, 1982; Boutin et al., 1985; Schmitt et al., 2009, 2010; Gregoire et al., 2009; Doan et al., 2010; Meyer and Meyer, 1959; Godwin and Michniak, 1997, Godwin and Michniak, 1999; Ota et al., 2003; ECHA REACH Dossier: Nerol; Lapczynski et al., 2008b; Horn et al., 2005; Horn et al., 2004; Lapczynski et al., 2008c; Rao et al., 2002; Hanley et al., 1999, 1997; Desiderio et al., 2004; Fliesler and Keller, 1995; Westfall et al., 1997; Crick et al., 1995; Johnson and Shah, 1985; Elliott and Lachance, 1980; DeBarber et al., 2004; Staines et al., 2004; Bobin et al., 1997; RIFM, 2002a; RIFM, 2002b; McGinty et al., 2010b; RIFM, 2003a; RIFM, 2003b; RIFM, 2003c; RIFM, 2003d; Strubelt et al., 1999; McGinty et al., 2010c; Leroy, 1984; Steinberg et al., 1966; Mackie et al., 2009; Atshaves et al., 2004; Arnhold et al., 2002; Fort et al., 1999; Fell et al., 1962; Bernhard et al., 1967; Hidiroglou and Jenkins, 1972; Baxter et al., 1967; Mize et al., 1969; Morin and Srikantaiah, 1982; Gloerich et al., 2005; Steinberg et al., 1965; Krywawych et al., 1985; Dawson et al., 1990.

Literature search and risk assessment completed on: 04/10/15.

10.1.5. Developmental and reproductive toxicity

There are insufficient developmental or reproductive toxicity data on (2E, 6Z)-nona-2,6-dien-1-ol or any read across materials. The exposure is below the Threshold of Toxicological Concern (TTC).

10.1.6. Risk assessment

There are no developmental or reproductive toxicity data on (2E, 6Z)-nona-2,6-dien-1-ol or any read across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure (0.32 μg/kg/day) is below the TTC for (2E, 6Z)-nona-2,6-dien-1-ol (30 μg/kg bw/day).

Additional references: ECHA REACH Dossier: cis-Hex-3-en-1-ol (http://apps.echa.europa.eu/registered/data/dossiers/DISS-dceb962c-f1ce-2476-e044-00144f67d031/DISS-dceb962c-f1ce-2476-e044-00144f67d031_DISS-dceb962c-f1ce-2476-e044-00144f67d031.html); Gaunt et al., 1969; McGinty et al., 2010a; Belsito et al., 2010; Hagan et al., 1967; Bar and Griepentrog, 1967; RIFM, 2010a; RIFM, 2010b; Gilpin et al., 2010; Lapczynski et al., 2008a; Belsito et al., 2008; RIFM, 2001; RIFM, 1954; Vieira et al., 2011; Fielden et al., 2007; Hood et al., 1978; Abramovici and Feder, 1980; Abramovici, 1972, Abramovici and Rachmuth-Roizman, 1983; Forschmidt et al., 1979; Howes et al., 2002; Buchbauer et al., 1993; Chadha and Madyastha, 1984; King and Dickinson, 2000, 2003; Westfall et al., 1997; Piccinini, 1962; Longenecker et al., 1939; Sporn and Abramovici, 1976; Leclerc et al., 2002; Chadha and Madyastha, 1982; Boutin et al., 1985; Schmitt et al., 2009, 2010; Gregoire et al., 2009; Doan et al., 2010; Meyer and Meyer, 1959; Godwin and Michniak, 1997, Godwin and Michniak, 1999; Ota et al., 2003; ECHA REACH Dossier: Nerol; Lapczynski et al., 2008b; Horn et al., 2005; Horn et al., 2004; Lapczynski et al., 2008c; Rao et al., 2002; Hanley et al., 1999, 1997; Desiderio et al., 2004; Fliesler and Keller, 1995; Westfall et al., 1997; Crick et al., 1995; Johnson and Shah, 1985; Elliott and Lachance, 1980; DeBarber et al., 2004; Staines et al., 2004; Bobin et al., 1997; RIFM, 2002a; RIFM, 2002b; McGinty et al., 2010b; RIFM, 2003a; RIFM, 2003b; RIFM, 2003c; RIFM, 2003d; Strubelt et al., 1999; McGinty et al., 2010c; Leroy, 1984; Steinberg et al., 1966; Mackie et al., 2009; Atshaves et al., 2004; Arnhold et al., 2002; Fort et al., 1999; Fell et al., 1962; Bernhard et al., 1967; Hidiroglou and Jenkins, 1972; Baxter et al., 1967; Mize et al., 1969; Morin and Srikantaiah, 1982; Gloerich et al., 2005; Steinberg et al., 1965; Krywawych et al., 1985; Dawson et al., 1990.

Literature search and risk assessment completed on: 04/10/15.

10.1.7. Skin sensitization

Based on the application of the DST, (2E, 6Z)-nona-2,6-dien-1-ol does not present a concern for skin sensitization.

10.1.8. Risk assessment

The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.5.0; OECD toolbox v3.1). The application of the non-reactive DST demonstrates that the exposure to this material does not present a concern for skin sensitization. The reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST). The current dermal exposure from hydroalcoholic products, 0.05%, is below the DST for non-reactive materials when

evaluated in QRA categories 3 and 4 (DST levels of 0.14% and 0.41%, respectively). Based on the application of the DST, (2E, 6Z)-nona-2,6-dien-1-ol does not present a concern for skin sensitization.

Additional references: None.

Literature search and risk assessment completed on: 09/06/13.

10.1.9. Phototoxicity/photoallergenicity

Based on a the available UV/Vis spectra, (2E, 6Z)-nona-2,6-dien-1-ol does not present a concern for phototoxicity or photoallergenicity.

10.1.10. Risk assessment

There are no phototoxicity studies available for (2E, 6Z)-nona-2,6-dien-1-ol. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark (1000 L mol^{-1} cm^{-1}) of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of absorbance, (2E, 6Z)-nona-2,6-dien-1-ol does not present a concern for phototoxicity or photoallergenicity.

Additional references: None.

Literature Search and Risk Assessment Completed on: 09/06/13.

10.1.11. Local respiratory toxicity

The (2E, 6Z)-nona-2,6-dien-1-ol exposure level is below the inhalation TTC Cramer Class I limit for local effects.

10.1.12. Risk assessment

There are no inhalation data available on (2E, 6Z)-nona-2,6-dien-1-ol. Based on the IFRA survey results for hydroalcoholics, the 97.5th percentile was reported to be 0.01%. Assuming the same amount is used in all product types (fine fragrances, hair sprays, antiperspirants/deodorants, candles, aerosol air fresheners, and reed diffusers/heated oil plug-ins), the inhalation combined exposure would be 0.0013 mg/day (calculated by the RIFM 2 Box Model using the 97.5th percentile). This exposure level is below the Cramer Class I TTC level of 1.4 mg/day. Therefore, if the material is used at 0.01% in a combination of personal aerosol spray products, it is deemed to be safe under the most conservative consumer exposure scenario.

Additional references: None.

Literature search and risk assessment completed on: 09/06/13.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening level risk assessment of (2E, 6Z)-nona-2,6-dien-1-ol was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Following the RIFM Environmental Framework, (2E, 6Z)-nona-2,6-dien-1-ol was not 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 EPISUITE ver 4.1 did not identify (2E, 6Z)-nona-2,6-dien-1-ol as either being possibly persistent nor bio-accumulative based on its structure and physical–chemical properties. This screening level hazard assessment is a weight of evidence review of a material's physical–chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE ver.4.1). Specific key data on biodegradation and fate and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section I.

10.2.2. Risk assessment

Based on current VoU from 2011, (2E, 6Z)-nona-2,6-dien-1-ol does not present a risk to the aquatic compartment.

10.2.3. Key studies

None.

10.2.4. Biodegradation

None.

10.2.5. Ecotoxicity

None.

10.2.6. Other available data

This material has been pre-registered under REACH. No additional data are available at this time.

10.2.7. 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. ECOSAR ecotoxicity estimates are provided for completeness, but were not necessary for risk assessment.

	LC50 (Fish)	EC50 (Daphnia)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	33.12 mg/L			1,000,000	0.033 μg/L	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	19.20 mg/L	11.81 mg/L	12.55 mg/L			Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	2.02 mg/L	0.30 mg/L	6.53 mg/L			Neutral Organic

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} used	2.87	2.87
Biodegradation factor used	0	0
Dilution factor	3	3
Regional volume of use tonnage band	<1	<1
Risk characterization: PEC/PNEC	**<1**	**<1**

The RIFM PNEC is 0.033 μg/L. The revised PEC/PNECs for EU and NA: Not Applicable; Cleared at Screening Level 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: 09/06/13.

11. Literature search*

- RIFM database: Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- ECHA: http://echa.europa.eu/
- NTP: http://tools.niehs.nih.gov/ntp_tox/index.cfm
- 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://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- EPA Actor: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- US EPA HPVIS: http://www.epa.gov/hpv/hpvis/index.html
- US EPA Robust Summary: http://cfpub.epa.gov/hpv-s/
- Japanese NITE: http://www.safe.nite.go.jp/english/db.html
- Japan Existing Chemical Data Base: http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- Google: https://www.google.com/webhp?tab=ww&ei=KMSoUpiQK-arsQS324GwBg&ved=0CBQQ1S4

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment.

This is not an exhaustive list.

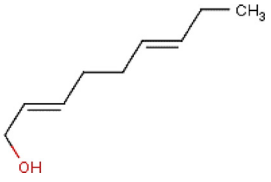
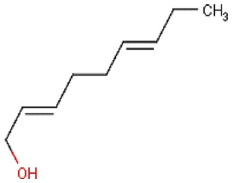
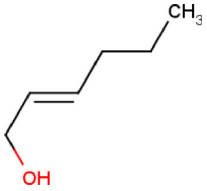
Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2015.06.023.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2015.06.023.

Appendix

	Target material	Read across material	
Principal name	(2E,6Z)-Nona-2,6-dien-1-ol	2,6-Nonadien-1-ol	trans-2-Hexenol
CAS No.	28069-72-9	7786-44-9	928-95-0
Structure			
3D structure	http://www.thegoodscentscompany.com/opl/28069-72-9.html	http://www.thegoodscentscompany.com/opl/7786-44-9.html	http://www.thegoodscentscompany.com/opl/928-95-0.html
Read-across endpoint		• Genotoxicity • Phototox	• Genotoxicity
Molecular formula	C9H16O	C9H16O	C6H12O
Molecular weight	140.23	140.23	100.16
Melting point (°C, EPISUITE)	−4.87	−4.87	−38.47
Boiling point (°C, EPISUITE)	231.61	231.61	165.73
Vapor pressure (Pa @ 25 °C, EPISUITE)	1.4	1.4	121.5
Log Kow (KOWWIN v1.68 in EPISUITE)	2.87	2.87	1.61
Water solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	963.8	963.8	1.6e + 004
J_{max} **(mg/cm^2**/h, SAM)	76.12367058	76.12367058	508.1415934
Henry's Law (Pa·m^3/mol, Bond method, EPISUITE)	3.227201	3.227201	1.568511
Similarity (Tanimoto score)[1]		100%	84%
Genotoxicity			
DNA binding (OASIS v1.1)	• No alert found	• No alert found	• No alert found
DNA binding (OECD)	• No alert found	• No alert found	• No alert found
Carcinogenicity (genotox and non-genotox) alerts (ISS)	• No alert found	• No alert found	• No alert found
DNA alerts for Ames, MN, CA (OASIS v1.1)	• No alert found	• No alert found	• No alert found
In vitro mutagenicity (Ames test) alerts (ISS)	• No alert found	• No alert found	• No alert found
In vivo mutagenicity (Micronucleus) alerts (ISS)	• No alert found	• No alert found	• No alert found
Oncologic classification (OECD)	• Not classified	• Not classified	• Not classified
Metabolism			
Rat liver S9 metabolism simulator (OECD)	Supplementary data 1	Supplementary data 2	Supplementary data 3

[1]Values calculated using JChem with FCFP4 1024 bits fingerprint (Rogers and Hahn, 2010).

Summary

There are insufficient toxicity data on (2E, 6Z)-Nona-2,6-dien-1-ol (RIFM # 5639, CAS # 28069-72-9). Hence, *in silico* evaluation was conducted to determine suitable read-across material. Based on structural similarity, reactivity, metabolism data, physicochemical properties and expert judgment, the above shown read-across materials were identified as proper read across for their respective toxicity endpoints.

Methods

- The identified read-across analogs were confirmed by using expert judgment
- The physicochemical properties of target and analogs were calculated using EPI Suite™ v4.11 developed by US EPA (USEPA, 2012)
- The Jmax were calculated using RIFM skin absorption model (SAM), the parameters were calculated using consensus model (Shen et al., 2014)
- DNA binding, mutagenicity, genotoxicity alerts and oncologic classification were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox (v3.1) (OECD, 2012)

Conclusion/rationale

- 2, 6-Nonadien-1-ol (CAS # 7786-44-9) is a stereoisomer of the target. Stereoisomers have the same atomic connectivity but differ in spatial arrangement of atoms or functional groups and usually behave in a similar chemical and toxicological manner.
- trans-2-Hexenol (analog) was used as a read-across analog for (2E, 6Z)-Nona-2,6-dien-1-ol (target) based on:
  - The target and analog belong to the generic class of alcohols, specifically, unsaturated alcohols.
  - The target and analog have common structural fragments of pentene and primary alcohol.
  - The key differences are that the target has long chain and two double bonds, while the analog has a short chain with one double bond. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the toxicity profiles are expected to be similar.
  - The target and analog show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
  - The target and analog show similar alerts for Repeated Dose (HESS) Categorization and ER Binding. ER Binding is molecular initiating event analogous to protein binding. ER binding is not necessarily predictive of endocrine disruption given the complex pre- and post-receptor events that determine activity.
  - The target and analog are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.

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