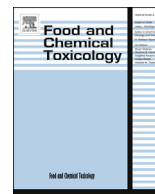




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Short review

RIFM fragrance ingredient safety assessment, (Z)-2-penten-1-ol, CAS Registry Number 1576-95-0



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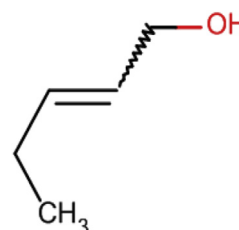
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Name: (Z)-2-Penten-1-ol

CAS Registry Number: 1576-95-0



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 toxicity was determined to have the most conservative systemic exposure derived NO(A)EL of 65.4 mg/kg/day based on an oral (drinking water) 90-day subchronic toxicity study conducted in rats on a read across analog, that resulted in a MOE of 121111 considering 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

Human Health Safety Assessment

Genotoxicity: Not genotoxic.

Repeated Dose Toxicity: NOAEL = 65.4 mg/kg/day

Developmental and Reproductive Toxicity: NOAEL = 200 mg/kg/day

Skin Sensitization: Not a sensitization concern. Exposure is below the DST.

Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic

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

Environmental safety assessment

Hazard assessment:

Persistence: Screening level: 3.47 (BIOWIN 3)

Bioaccumulation: Screening level: 2.5 L/Kg

Ecotoxicity: Screening level: 678.91 mg/L

Conclusion: Not PBT or vPvB as per IFRA environmental standards

Risk assessment:

Screening-level: PEC/PNEC (North America and Europe) < 1

Critical ecotoxicity endpoint: 678.91 mg/L

RIFM PNEC is: 0.679 µg/L

- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: NA: Cleared at screening level

(RIFM, 2012; RIFM, 2014b)

(RIFM, 2002b)

(RIFM, 2002a)

(UV Spectra, RIFM DB)

(EPISUITE ver 4.1)

(EPISUITE ver 4.1)

(Salvito et al., 2002)

(Salvito et al., 2002)

(Salvito et al., 2002)

1. Identification

- 1 **Chemical name:** (Z)-2-Penten-1-ol
- 2 **CAS registry number:** 1576-95-0
- 3 **Synonyms:** (Z)-2-Penten-1-ol, cis-Pent-2-en-1-ol, 2-Penten-1-ol, (Z)-, Pent-2-en-1-ol, cis-2-Pentenol
- 4 **Molecular formula:** C₅H₁₀O
- 5 **Molecular weight:** 86.34
- 6 **RIFM number:** 5252

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 liquid with a medium, green, plastic, ethereal, fruity odor at 10.00% solution or less*

* (<http://www.thegoodscentcompany.com/data/rw1002171.html>, retrieved 08/09/14).

3. Exposure

1.	Volume of use (worldwide band): <1 metric tons per year	[IFRA, 2011]
2.	Average maximum concentration in hydroalcohols: 0.002%	[IFRA, 2007]
3.	97.5th percentile: 0.02%	[IFRA, 2007]
4.	Dermal exposure*: 0.0005 mg/kg/day	[IFRA, 2007]
5.	Oral exposure: Not available	
6.	Inhalation exposures**: 0.000040 mg/kg/day	[IFRA, 2007]
7.	Total systemic exposure (dermal + inhalation): 0.00054 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, 2002; Ford, 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 hydroalcohols for a 60 kg individual.

2. Physical data

- 1 **Boiling point:** 143.87 °C [EPI Suite]
- 2 **Flash point:** 119.00 °F. TCC (48.33 °C)*
- 3 **Log K_{ow}:** 1.12 [EPI Suite]
- 4 **Melting point:** -50.48 °C [EPI Suite]
- 5 **Water solubility:** 45720 mg/L [EPI Suite]
- 6 **Specific gravity:** 0.85300 @ 25 °C*
- 7 **Vapor pressure:** 1.81 mm Hg @ 20 °C [EPI Suite], 2.63 mm Hg @ 25 °C [EPI Suite]

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 = 0.00054 mg/kg/day

5. Computational toxicology evaluation

1 Cramer classification: Class I, Low

Expert Judgment	Toxtree (v 2.6.0)	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:** 3-Methyl-2-buten-1-ol (CAS # 556-82-1)
 - c **Developmental and reproductive toxicity:** 3-Methyl-2-buten-1-ol (CAS # 556-82-1)
 - d **Skin sensitization:** None
 - e **Phototoxicity/photoallergenicity:** None
 - f **Local respiratory toxicity:** None
 - g **Environmental toxicity:** None
- 3 **Read across justifications:** 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)

(Z)-2-Penten-1-ol is reported to occur in the following foods*:

Cauliflower and broccoli	Mate (<i>Ilex paraguayensis</i>)
Cherimoya (<i>Annona cherimolia</i> Mill.)	Melon
Citrus fruits	Mentha oils
Clam	Nectarine
Cucumber (<i>Cucumis sativus</i> L.)	Olive (<i>Olea europaea</i>)
Dill (<i>Anethum</i> species)	Papaya (<i>Carica papaya</i> L.)
Endive (<i>Cichorium endivia</i> L.)	Passion fruit (<i>passiflora</i> species)
Fish	Peas (<i>Pisum sativum</i> L.)
Ginger (<i>Zingiber</i> species)	Plum (<i>Prunus</i> species)
Guava and feyoa	Potato (<i>Solanum tuberosum</i> L.)
Honey	Rambutan (<i>Nephelium lappaceum</i> L.)
Katsuobushi (dried bonito)	Rooibos tea (<i>Aspalathus linearis</i>)
Kiwifruit (<i>Actinidia chinensis</i> , syn. <i>A. deliciosa</i>)	<i>Syzygium</i> species
Lamb's lettuce (<i>Valerianella locusta</i>)	Tea
Loquat (<i>Eriobotrya japonica</i> Lindl.)	Thyme (<i>Thymus</i> species)
Lovage (<i>Levisticum officinale</i> Koch)	Tomato (<i>Lycopersicon esculentum</i> Mill.)
Malt	Walnut (<i>Juglans</i> species)
<i>Mangifera</i> species	Wine

*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-Fla.

8. IFRA standard

None.

9. REACH dossier

Pre-registered for 2010; No dossier available as of 04/21/15.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, (Z)-2-pentenol does not present a concern for genetic toxicity.

10.1.2. Risk assessment

(Z)-2-Penten-ol was tested using the BlueScreen assay and found negative for both cytotoxicity and genotoxicity indicating a lack for genotoxic concern (RIFM, 2014a). There are no studies assessing the mutagenic potential of (Z)-2-penten-ol. Read across can be made to 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 (Z)-2-penten-ol.

There are no studies assessing the clastogenic activity of the (Z)-2-penten-ol. The read across material, trans-2-hexenol (CAS # 928-95-0; see Section V) 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, 2014b). 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 (Z)-2-penten-ol.

Based on the available data, (Z)-2-penten-ol does not present a concern for genotoxic potential.

10.1.3. Additional references

RIFM, 2013b; RIFM, 2013a.

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

10.2. Repeated dose toxicity

The margin of exposure for (Z)-2-penten-1-ol is adequate for the repeated dose toxicity endpoint at the current level of use.

10.2.1. Risk assessment

There are no repeated dose toxicity data on (Z)-2-penten-1-ol. Read across material 3-methyl-2-buten-1-ol (CAS # 556-82-1; see Section V) has an enhanced OECD 408 oral (drinking water) 90-day subchronic toxicity study conducted in rats which determined the NOAEL to be 1000 ppm, or 65.4 and 82.1 mg/kg/day for males and females, respectively, based on decreased body weight, food and water consumption, and urine volume (RIFM, 2002a). **Therefore, the MOE is equal to the 3-methyl-2-buten-1-ol NOAEL in mg/kg/day divided by the total systemic exposure, 65.4/0.00054 or 121111.**

10.2.2. Additional references

McGinty, 2010a; Belsito, 2010; Hagan, 1967; Bar, 1967; RIFM, 2010a; RIFM, 2010b; Gilpin, 2010; Lapczynski, 2008a; Belsito, 2008; RIFM, 2001; RIFM, 1954; Vieira, 2011; Fielden, 2007; Hood, 1978; Abramovici, 1980; Abramovici, 1972; Abramovici and Rachmuth-Roizman, 1983; Forschmidt, 1979; Howes, 2002; Buchbauer, 1993; Chadha, 1984; King, 2000, 2003; Westfall, 1997; Piccinini, 1962; Longenecker, 1939; Sporn, 1976; Leclerc, 2002; Chadha, 1982; Boutin, 1985; Schmitt, 2009, 2010; Gregiore, 2009; Doan, 2010; Meyer, 1959; Godwin, 1997; Godwin and Michniak, 1999; Ota, 2003; ECHA REACH Dossier: Nerol; Lapczynski, 2008b; Horn, 2005; Horn, 2004; Lapczynski, 2008c; Rao, 2002; Hanley, 1999, 1997; Desiderio, 2004; Fliesler, 1995; Westfall, 1997; Crick, 1995; Johnson, 1985; Elliott, 1980; DeBarber, 2004; Staines, 2004; Bobin, 1997; McGinty, 2010b; RIFM, 2003a; RIFM, 2003b; RIFM, 2003c; RIFM, 2003d; Strubelt, 1999; McGinty, 2010c; Leroy, 1984; Steinberg, 1966; Mackie, 2009; Atshaves, 2004; Arnhold, 2002; Fort, 1999; Fell, 1962; Bernhard, 1967; Hidiroglou, 1972; Baxter, 1967; Mize, 1969; Morin, 1982; Gaoerich, 2005; Steinberg, 1965; Krywawych, 1985; Gaunt, 1969; 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.html>); Dawson et al., 1990;

10.2.3. Literature search and risk assessment completed on 04/13/15.

10.3. Developmental and reproductive toxicity

The margin of exposure for (Z)-2-penten-1-ol is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.3.1. Risk assessment

There are no developmental toxicity data on (Z)-2-penten-1-ol. Read across material 3-methyl-2-buten-1-ol (CAS # 556-82-1; see Section V) has an OECD 414 gavage developmental toxicity study conducted in rats which determined the NOAEL for developmental

toxicity to be 600 mg/kg/day, the highest dosage tested (RIFM, 2002b). **Therefore, the MOE is equal to the 3-methyl-2-buten-1-ol NOAEL in mg/kg/day divided by the total systemic exposure, 600/0.00054 or 1,111,111.**

There are no reproductive toxicity data on (Z)-2-penten-1-ol. Read across material 3-methyl-2-buten-1-ol (CAS # 556-82-1) has an OECD 414 gavage developmental toxicity study conducted in rats which determined the NOAEL for maternal toxicity to be 200 mg/kg/day, based on clinical signs and decreased body weight and food consumption (RIFM, 2002b). In the enhanced OECD 408 oral (drinking water) 90-day subchronic toxicity study conducted in rats with 3-methyl-2-buten-1-ol there were no effects on sperm parameters up to the high dosage of 5000 ppm, or 243.8 mg/kg/day for males (RIFM, 2002b). Together, these data indicate so specific concern for reproductive toxicity. The most conservative NOAEL was selected for this safety assessment. **Therefore, the MOE for developmental and reproductive toxicity is equal to the 3-methyl-2-buten-1-ol NOAEL in mg/kg/day divided by the total systemic exposure, 200/0.00054 or 370370.**

10.3.2. Additional references

McGinty, 2010a; Belsito, 2010; Hagan, 1967; Bar, 1967; RIFM, 2010a; RIFM, 2010b; Gilpin, 2010; Lapczynski, 2008a; Belsito, 2008; RIFM, 2001; RIFM, 1954; Vieira, 2011; Fielden, 2007; Hood, 1978; Abramovici, 1980; Abramovici, 1972; Abramovici and Rachmuth-Roizman, 1983; Forschmidt, 1979; Howes, 2002; Buchbauer, 1993; Chadha, 1984; King, 2000, 2003; Westfall, 1997; Piccinini, 1962; Longenecker, 1939; Sporn, 1976; Leclerc, 2002; Chadha, 1982; Boutin, 1985; Schmitt, 2009, 2010; Gregiore, 2009; Doan, 2010; Meyer, 1959; Godwin, 1997; Godwin and Michniak, 1999; Ota, 2003; ECHA REACH Dossier: Nerol; Lapczynski, 2008b; Horn, 2005; Horn, 2004; Lapczynski, 2008c; Rao, 2002; Hanley, 1999, 1997; Desiderio, 2004; Fliesler, 1995; Westfall, 1997; Crick, 1995; Johnson, 1985; Elliott, 1980; DeBarber, 2004; Staines, 2004; Bobin, 1997; McGinty, 2010b; RIFM, 2003a; RIFM, 2003b; RIFM, 2003c; RIFM, 2003d; Strubelt, 1999; McGinty, 2010c; Leroy, 1984; Steinberg, 1966; Mackie, 2009; Atshaves, 2004; Arnhold, 2002; Fort, 1999; Fell, 1962; Bernhard, 1967; Hidiroglou, 1972; Baxter, 1967; Mize, 1969; Morin, 1982; Gaoerich, 2005; Steinberg, 1965; Krywawych, 1985; Gaunt, 1969; 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.html>); Dawson et al., 1990;

10.3.3. Literature search and risk assessment completed on 04/13/15.

10.4. Skin sensitization

Based on the available data and application of the Dermal Sensitization Threshold (DST), (Z)-2-penten-1-ol does not present a concern for skin sensitization.

10.4.1. Risk assessment

The chemical structure of this material indicates that it would not be expected to react with skin proteins (Roberts, 2007; OECD toolbox v3.1). In a human repeated insult patch test no reactions to (Z)-2-penten-1-ol were observed (RIFM, 1971). The reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST). The current dermal exposure from hydroalcoholic products, 0.002%, 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 available data and application of the Dermal Sensitization Threshold (DST), (Z)-2-

penten-1-ol does not present a concern for skin sensitization.

10.4.2. Additional references

None.

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

10.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, (Z)-2-penten-1-ol would not be expected to present a concern for phototoxicity or photoallergenicity.

10.5.1. Risk assessment

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

10.5.2. Additional references

None.

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

10.6. Local respiratory toxicity

The margin of exposure for (Z)-2-penten-1-ol could not be calculated due to lack of appropriate data. The (Z)-2-penten-1-ol exposure level is below the inhalation TTC Cramer Class I limit for local effects.

10.6.1. Risk assessment

There are no relevant inhalation data available on (Z)-2-penten-1-ol. Based on the IFRA survey results for hydroalcohols, the 97.5th percentile was reported to be 0.02%. If 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 0.002 mg/day (calculated by the RIFM 2 Box Model using the 97.5th percentile). This exposure level would be below the Cramer Class I TTC level of 1.4 mg/day. Therefore, if the material is used at 0.02% in a combination of personal aerosol spray products, it is deemed to be safe under the most conservative consumer exposure scenario.

10.6.2. Additional references

Helmig et al., 1999.

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

10.7. Environmental endpoint summary

10.7.1. Screening-level assessment

A screening level risk assessment of (Z)-2-penten-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, (Z)-2-penten-1-ol was identified as a fragrance material without 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 (Z)-2-penten-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 bio-accumulation, 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.

10.7.2. Risk assessment

Based on current VoU (2011), (Z)-2-Penten-1-ol does not present a risk to the aquatic compartment in the screening level assessment.

10.7.3. Key studies

10.7.3.1. Biodegradation. None.

10.7.3.2. Ecotoxicity. None.

10.7.4. Other available data

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

10.7.5. Risk assessment refinement

Ecotoxicological data and PNEC derivation (all endpoints reported in mg/L; PNECs in $\mu\text{g/L}$).

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)	<u>678.9 mg/L</u>			1,000,000	0.679 $\mu\text{g/L}$	
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	439.3 mg/L	229.9 mg/L	122.2 mg/L			Vinyl/Allyl Alcohols
ECOSAR Acute Endpoints (Tier 2) Ver 1.11	2.26 mg/L	0.29 mg/L	41.95 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	1.12	1.12
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 0.679 $\mu\text{g/L}$. The revised PEC/PNECs for EU and NA Cleared at Screening Level, and therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

10.7.6. 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/oecd/sids/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.

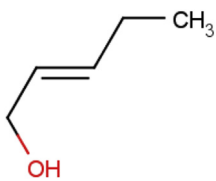
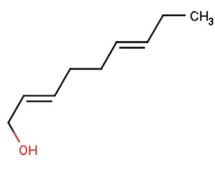
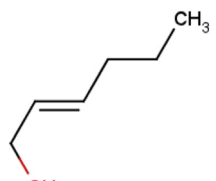
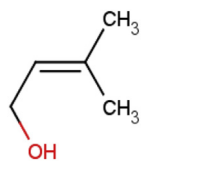
Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2015.06.022>.

Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2015.06.022>.

Appendix

	Target material	Read across material		
Principal name	(Z)-2-Penten-1-ol	2,6-Nonadien-1-ol	trans-2-Hexenol	3-Methyl-2-Buten-1-ol
CAS No.	1576-95-0	7786-44-9	928-95-0	556-82-1
Structure				
3D Structure	http://www.thegoodscentscompany.com/opl/1576-95-0.html	http://www.thegoodscentscompany.com/opl/7786-44-9.html	http://www.thegoodscentscompany.com/opl/928-95-0.html	http://www.thegoodscentscompany.com/opl/556-82-1.html
Read-across endpoint		• Genotoxicity	• Genotoxicity	• Repeated Dose • Devel/Repro
Molecular formula	C5H10O	C9H16O	C6H12O	C5H10O
Molecular weight	86.13	140.23	100.16	86.13
Melting point (°C, EPISUITE)	-50.48	-4.87	-38.47	-59.25
Boiling point (°C, EPISUITE)	143.87	231.61	165.73	137.75
Vapor pressure (Pa @ 25 °C, EPISUITE)	350.6	1.4	121.5	314.6
Log Kow (KOWWIN v1.68 in EPISUITE)	1.12	2.87	1.61	1.17
Water solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPISUITE)	4.572e+004	963.8	1.6e+004	4.094e+004
J_{max} (mg/cm ² /h, SAM)	881.0299266	76.12367058	508.1415934	1096.249958
Henry's law (Pa·m ³ /mol, Bond Method, EPISUITE)	1.18145	3.227201	1.568511	1.394232
Similarity (Tanimoto score) ¹		91%	76%	50%
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	
	• No alert found	• No alert found	• No alert found	

(continued)

	Target material	Read across material		
Carcinogenicity (genotox and non-genotox) alerts (ISS)				
DNA alerts for Ames, MN, CA (OASIS v1.1)	• No alert found	• 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	• No alert found
In vivo mutagenicity (Micronucleus) alerts (ISS)	• No alert found	• No alert found	• No alert found	• No alert found
Oncologic classification (OECD)	• Not classified	• Not classified	• Not classified	• Not classified
Repeated Dose Toxicity				
Repeated dose (HESS)	Not categorized			Not categorized
Developmental and reproductive toxicity				
ER binding (OECD)	Non binder, non cyclic structure			Non binder, non cyclic structure
Developmental toxicity model (CAESAR v2.1.6)	NON-Toxicant (low reliability)			NON-toxicant (low reliability)
Metabolism				
Rat liver S9 metabolism simulator (OECD)	Supplementary data 1	Supplementary data 2	Supplementary data 3	Supplementary data 4

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

Summary:

There are insufficient toxicity data on (Z)-2-Penten-1-ol (RIFM # 5252, CAS # 1576-95-0). 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)
- ER binding and repeat dose categorization were estimated using OECD QSAR Toolbox (v3.1) (OECD, 2012)
- Developmental toxicity was estimated using CAESAR (v.2.1.6) (Cassano et al., 2010)
- Protein binding 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

- trans-2-Hexenol and 2,6-Nonadien-1-ol (analogs) were used as read-across analog for (Z)-2-Penten-1-ol (target) based on:
 - The target and analogs belong to the generic class of alcohols, specifically, alcohol/straight chain/primary alcohols.
 - The target and analogs have common structural fragments of primary alcohol and alkene group.

- The key differences are that the target has a short chain length, while the analogs have longer chain than the target. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the genotoxicity profiles are expected to be similar.
- The target and analogs show similar alerts for DNA binding, mutagenicity, genotoxicity and oncologic classification.
- The target and analogs are expected to be metabolized similarly. As per the OECD Toolbox, they are predicted to have similar metabolites.
- 3-Methyl-2-buten-1-ol (analog) was used as a read-across for (Z)-2-penten-1-ol (target) based on:
 - The target and analog belong to the generic class of alcohol, specifically, alcohol unsaturated.
 - The target and analog have common structural fragments of primary alcohol and α , β unsaturated alcohol group.
 - The key differences are that the target has a short chain length, while the analog has a longer chain. The differences between structures do not essentially change the physicochemical properties nor raise any additional structural alerts and therefore, the reproductive and developmental toxicity profiles are expected to be similar.
 - 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.
- 3-Methyl-2-buten-1-ol (analog) was used as a read-across analog for (Z)-2-Penten-1-ol (target) based on:
 - The target and analog belong to the generic class of alcohol, specifically, alcohol/unsaturated.
 - The target and analog are α , β unsaturated alcohol.
 - The key difference is that the target has a straight chain while the analog has a methyl branch. 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 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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