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RIFM fragrance ingredient safety assessment, β-sinensal, CAS Registry Number 60066-88-8

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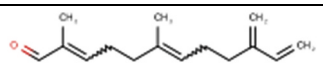


Name: β-Sinensal
CAS Registry Number: 60066-88-8

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
CNIH – Confirmation of No Induction in Humans test. A human repeat insult patch test that is performed to confirm an already determined safe use level for fragrance ingredients (Na et al., 2021)
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015a, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DRF - Dose Range Finding
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
ECOSAR - Ecological Structure-Activity Relationships Predictive Model
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observed Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
Perfumery - In this safety assessment, perfumery refers to fragrances made by a perfumer used in consumer products only. The exposures reported in the safety assessment include consumer product use but do not include occupational exposures.
QRA - Quantitative Risk Assessment
QSAR - Quantitative Structure-Activity Relationship
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use
vPvB - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

The Expert Panel for Fragrance Safety* concludes that this material is safe as described in this safety assessment.

This safety assessment is based on the RIFM Criteria Document (Api 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

(*continued on next column*)

(*continued*)

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

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

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

β-Sinensal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analogs 3,7-dimethyl-2-methylenocta-6-enal (CAS # 22418-66-2) and β-farnesene (CAS # 18794-84-8) show that β-sinensal is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material, and the exposure to β-sinensal is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The skin sensitization endpoint was completed using the Dermal Sensitization Threshold (DST) for reactive materials (64 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on ultraviolet/visible (UV/Vis) spectra from read-across material farnesal (CAS # 19317-11-4); β-sinensal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; β-sinensal was found not to be Persistent, Bioaccumulative, and Toxic (PBT) as per the International Fragrance Association (IFRA) Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., Predicted Environmental Concentration/Predicted No Effect Concentration [PEC/PNEC]), are <1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic. (RIFM, 2002; RIFM, 2017a; ECHA REACH Dossier: (E)-7, 11-dimethyl-3-methylenedodeca-1,6, 10-triene; ECHA, 2015)
Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below TTC.
Skin Sensitization: Not a concern for skin sensitization under the declared use levels; exposure is below the DST.
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic. (UV/Vis Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 2.74 (BIOWIN 3) (EPI Suite v4.11; US EPA, 2012a)
Bioaccumulation: Screening-level: 2615 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 0.19 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: 0.19 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.00019 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America (No VoU) and Europe: Not applicable; cleared at screening-level.

1. Identification

1. **Chemical Name:** β-Sinensal
2. **CAS Registry Number:** 60066-88-8

3. **Synonyms:** 2,6-Dimethyl-10-methylene-2,6,11-dodecatrienal; 2,6,11-Dodecatrienal, 2,6-dimethyl-10-methylene-; 2,6-Dimethyl-10-methylenedodeca-2,6,11-trienal; β-Sinensal
4. **Molecular Formula:** $C_{15}H_{22}O$
5. **Molecular Weight:** 218.34 g/mol
6. **RIFM Number:** 98
7. **Stereochemistry:** *Trans*-isomer specified. Two geometric centers and 4 possible isomers.

2. Physical data

1. **Boiling Point:** 295.41 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 5.68 (EPI Suite)
4. **Melting Point**: 15.46 °C (EPI Suite)
5. **Water Solubility:** 0.4912 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available
7. **Vapor Pressure:** 0.00249 mm Hg at 25 °C (EPI Suite)
8. **UV Spectra:** Not Available
9. **Appearance/Organoleptic:** Not Available

3. Volume of use (Worldwide band)

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

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

1 **95**th **Percentile Concentration in Fine Fragrance:** 0.0016% (RIFM, 2017b)
2 **Inhalation Exposure*:** 0.000015 mg/kg/day or 0.0011 mg/day (RIFM, 2017b)
3 **Total Systemic Exposure**:** 0.00032 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., 2015a; Safford et al., 2017; Comiskey et al., 2017).

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

5. Derivation of systemic absorption

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

6. Computational toxicology evaluation

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

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

2. Analogs Selected:
   a. **Genotoxicity:** 3,7-Dimethyl-2-methylenocta-6-enal (CAS # 22418-66-2) and β-farnesene (CAS # 18794-84-8)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** Farnesal (CAS # 19317-11-4)
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

7. Metabolism

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

8. Natural occurrence

β-Sinensal is reported to occur in the following foods by the VCF*: Citrus fruits.

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

9. REACH dossier

β-Sinensal has been pre-registered for 2010; no dossier available as of 02/18/22.

10. Conclusion

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

11. Summary

11.1. Human health endpoint summaries

11.1.1. Genotoxicity

Based on the current existing data, β-sinensal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic or clastogenic activity of β-sinensal; however, read-across can be made to 3,7-dimethyl-2-methylenocta-6-enal and β-farnesene (CAS # 22418-66-2 and 18794-84-8; see Section VI).

The mutagenic activity of 3,7-dimethyl-2-methylenocta-6-enal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with 3,7-dimethyl-2-methylenocta-6-enal 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 concentration in the presence or absence of S9 (RIFM, 2002). Under the conditions of the study, 3,7-dimethyl-2-methylenocta-6-enal was not mutagenic in the Ames test, and this can be extended to β-sinensal.

The mutagenic activity of β-farnesene has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the preincubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA97a, and *Escherichia coli* strain WP2uvrA were treated with β-farnesene in DMSO at concentrations up to 5 μL/plate (4065 μg/plate). No increases in the mean number of revertant colonies were observed at any tested concentration in the presence or absence of S9 (ECHA, 2015). Under the conditions of the study, β-farnesene was not mutagenic in the

Ames test, and this can be extended to β-sinensal.

The clastogenic activity of 3,7-dimethyl-2-methylenocta-6-enal 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 3,7-dimethyl-2-methylenocta-6-enal in DMSO at concentrations up to 1660 μg/mL in the dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 50 μg/mL in the presence and absence of metabolic activation. 3,7-Dimethyl-2-methylenocta-6-enal did not induce binucleated cells with micronuclei when tested up to the cytotoxic concentration in either the presence or absence of an S9 activation system (RIFM, 2017a). Under the conditions of the study, 3,7-dimethyl-2-methylenocta-6-enal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to β-sinensal.

The clastogenicity of β-farnesene was assessed in an *in vitro* chromosome aberration study conducted in compliance with GLP regulations and in accordance with OECD TG 473. Human peripheral blood lymphocytes were treated with β-farnesene in DMSO at concentrations up to 100 μg/mL in the presence and absence of metabolic activation. No statistically significant increases in the frequency of cells with structural chromosomal aberrations or polyploid cells were observed with any concentration of the test material, either with or without S9 metabolic activation (ECHA, 2015). Under the conditions of the study, β-farnesene was considered to be non-clastogenic in the *in vitro* chromosome aberration assay, and this can be extended to β-sinensal.

Based on the data available, 3,7-dimethyl-2-methylenocta-6-enal and β-farnesene do not present a concern for genotoxic potential, and this can be extended to β-sinensal.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/15/21.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on β-sinensal or any read-across materials. The total systemic exposure to β-sinensal is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.2.1. Risk assessment. There are no repeated dose toxicity data on β-sinensal 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 β-sinensal (30 μg/kg/day; Kroes et al., 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/16/21.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on β-sinensal or any read-across materials. The total systemic exposure to β-sinensal is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

11.1.3.1. Risk assessment. There are no reproductive toxicity data on β-sinensal or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.32 μg/kg/day) is below the TTC for β-sinensal (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/16/21.

11.1.4. Skin sensitization

Based on the application of DST, β-sinensal does not present a safety concern for skin sensitization under the current, declared levels of use.

Table 1
Maximum acceptable concentrations for β-sinensal 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	0.0049%	7.9×10^{-6}%
2	Products applied to the axillae	0.0015%	4.5×10^{-4}%
3	Products applied to the face using fingertips	0.029%	2.2×10^{-4}%
4	Fine fragrance products	0.027%	0.0020%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.0070%	5.6×10^{-4}%
6	Products with oral and lip exposure	0.016%	0.011%
7	Products applied to the hair with some hand contact	0.056%	5.0×10^{-5}%
8	Products with significant ano-genital exposure	0.0029%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.054%	0.0018%
10	Household care products with mostly hand contact	0.19%	0.0011%
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	0.002%

Note: [a]For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b]No reported use.
cFragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

11.1.4.1. Risk assessment. No skin sensitization studies are available for β-sinensal. The chemical structure of this material indicates that it would be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree v3.1.0; OECD Toolbox v4.2). Acting conservatively due to the lack of data, the reported exposure was benchmarked utilizing the reactive DST of 64 μg/cm^2 (Safford, 2008; Safford et al., 2011; Roberts et al., 2015; Safford et al., 2015b). 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 β-sinensal that present no appreciable risk for skin sensitization based on the reactive DST. These levels represent maximum acceptable concentrations based on the DST approach. However, additional studies may show it could be used at higher levels.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/08/21.

11.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis absorption spectra for the structurally

related material, farnesal (CAS # 19317-11-4), β-sinensal would not be expected to present a concern for phototoxicity or photoallergenicity.

11.1.5.1. Risk assessment. There are no phototoxicity studies available for β-sinensal in experimental models. UV/Vis absorption spectra were not available for the target material β-sinensal. UV/Vis absorption spectra on the structurally related material, farnesal, indicate no absorption between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance for the structurally related analog, β-sinensal does not present a concern for phototoxicity or photoallergenicity.

11.1.5.2. UV spectra analysis. UV/Vis absorption spectra were not available for the target material β-sinensal. UV/Vis absorbance spectra for the structurally related material, farnesal (CAS # 19317-11-4), indicate no 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: 10/13/21.

11.1.6. Local Respiratory Toxicity

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

11.1.6.1. Risk assessment. There are no inhalation data available on β-sinensal. Based on the Creme RIFM Model, the inhalation exposure is 0.0011 mg/day. This exposure is 1272.7 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: 10/15/21.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of β-sinensal 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, β-sinensal 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) identified β-sinensal as not possibly persistent but 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 $\geq$2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

11.2.2. Risk assessment

Based on the current Volume of Use (2015), β-sinensal presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies

11.2.2.1.1. Biodegradation. No data available.

11.2.2.1.2. Ecotoxicity. No data available.

11.2.2.1.3. Other available data. β-Sinensal has been pre-registered for REACH with no additional data available at this time.

11.2.3. Risk assessment refinement

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

Endpoints used to calculate PNEC are highlighted.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	5.68	5.68
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	No Volume of Use
Risk Characterization: PEC/PNEC	**<1**	**NA**

Based on available data, the RQ for this material is > 1. Additional assessment is necessary.

The RIFM PNEC is 0.00019 μg/L. The revised PEC/PNECs for EU and NA (No VoU) are not applicable. The material was cleared at the screening-level; therefore, it does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 09/20/21.

12. Literature Search*

- **RIFM Database:** Target, Fragrance Structure-Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** https://echa.europa.eu/
- **NTP:** https://ntp.niehs.nih.gov/
- **OECD Toolbox:** https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	0.19			1000000	0.00019	

- **SciFinder:** https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed
- **National Library of Medicine's Toxicology Information Services:** https://toxnet.nlm.nih.gov/
- **IARC:** https://monographs.iarc.fr
- **OECD SIDS:** https://hpvchemicals.oecd.org/ui/Default.aspx
- **EPA ACToR:** https://actor.epa.gov/actor/home.xhtml
- **US EPA HPVIS:** https://ofmpub.epa.gov/oppthpv/public_search.publicdetails?submission_id=24959241&ShowComments=Yes&sqlstr=null&recordcount=0&User_title=DetailQuery%20Results&EndPointRpt=Y#submission
- **Japanese NITE:** https://www.nite.go.jp/en/chem/chrip/chrip_search/systemTop
- **Japan Existing Chemical Data Base (JECDB):** http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google:** https://www.google.com
- **ChemIDplus:** https://chem.nlm.nih.gov/chemidplus/

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 02/18/22.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2022.113223.

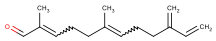
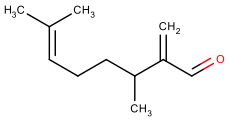
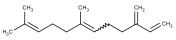
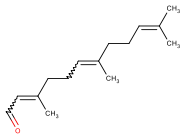
Appendix

Read-across Justification

Methods

The read-across analogs were identified using RIFM fragrance chemicals inventory clustering and read-across search criteria (RIFM, 2020). These criteria are in compliance with the strategy for structuring and reporting a read-across prediction of toxicity as described in Schultz et al. (2015) and are consistent with the guidance provided by OECD within Integrated Approaches for Testing and Assessment (OECD, 2015) and the European Chemical Agency read-across assessment framework (ECHA, 2017).

- First, materials were clustered based on their structural similarity. Second, data availability and data quality on the selected cluster were examined. Third, appropriate read-across analogs from the cluster were confirmed by expert judgment.
- Tanimoto structure similarity scores were calculated using FCFC4 fingerprints (Rogers and Hahn, 2010).
- The physical–chemical properties of the target material and the read-across analogs were calculated using EPI Suite (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 v4.2 (OECD, 2018).
- ER binding and repeat dose categorization were generated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010), and skin sensitization was predicted using Toxtree v2.6.13.
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2018).
- The major metabolites for the target material and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2018).
- To keep continuity and compatibility with *in silico* alerts, OECD QSAR Toolbox v4.2 was selected as the alert system.

	Target Material	Read-across Material	Read-across Material	Read-across Material
Principal Name	β-Sinensal	3,7-Dimethyl-2-methylenocta-6-enal	β-Farnesene	Farnesal
CAS No.	60066-88-8	22418-66-2	18794-84-8	19317-11-4
Structure				
Similarity (Tanimoto Score)		0.29	0.68	0.42
Endpoint		• Genotoxicity	• Genotoxicity	• Phototoxicity/ photoallergenicity
Molecular Formula	$C_{15}H_{22}O$	$C_{11}H_{18}O$	$C_{15}H_{24}$	$C_{15}H_{24}O$
Molecular Weight (g/mol)	218.34	166.26	204.36	220.36
Melting Point (°C, EPI Suite)	15.46	−26.86	−17.46	16.65
Boiling Point (°C, EPI Suite)	295.41	217.71	254.57	302.17
Vapor Pressure (Pa @ 25°C, EPI Suite)	0.33	19.60	4.65	0.23
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	0.49	27.56	0.01	0.43
Log K_{OW}	5.68	3.94	7.17	5.74
J_{max} (μg/cm^2/h, SAM)	0.08	3.89	0.00	0.07
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	83.90	42.86	226968.00	163.13
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	AN2|AN2 ≫ Nucleophilic addition to α, β-unsaturated carbonyl compounds|AN2 ≫ Nucleophilic addition to α, β-unsaturated carbonyl compounds ≫ α, β-Unsaturated Aldehydes|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ α, β-Unsaturated Aldehydes	AN2|AN2 ≫ Nucleophilic addition to α, β-unsaturated carbonyl compounds|AN2 ≫ Nucleophilic addition to α, β-unsaturated carbonyl compounds ≫ α, β-Unsaturated Aldehydes|AN2 ≫ Schiff base formation|AN2 ≫ Schiff base formation ≫ α, β-Unsaturated Aldehydes	No alert found	
DNA Binding (OECD QSAR Toolbox v4.2)	Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition ≫ α, β- unsaturated aldehydes	Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition|Michael addition ≫ Polarized Alkenes-Michael addition ≫ α, β- unsaturated aldehydes	No alert found	
Carcinogenicity (ISS)	α,β-unsaturated carbonyls (Genotox)| Structural alert for genotoxic carcinogenicity	α,β-unsaturated carbonyls (Genotox)| Structural alert for genotoxic carcinogenicity	No alert found	
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found	No alert found	
In Vitro Mutagenicity (Ames, ISS)	α,β-unsaturated carbonyls	α,β-unsaturated carbonyls	No alert found	
In Vivo Mutagenicity (Micronucleus, ISS)	α,β-unsaturated carbonyls	α,β-unsaturated carbonyls	No alert found	
Oncologic Classification	Aldehyde-type Compounds	Aldehyde-type Compounds	Not classified	
Metabolism				
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v4.2)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3	See Supplemental Data 4

Summary

There are insufficient toxicity data on β-sinensal (CAS # 60066-88-8). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, physical–chemical properties, and expert judgment, 3,7-dimethyl-2-methylenocta-6-enal (CAS # 22418-66-2), β-farnesene (CAS # 18794-84-8), and farnesal (CAS # 19317-11-4) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- 3,7-Dimethyl-2-methylenocta-6-enal (CAS # 22418-66-2) was used as a read-across analog for the target material, β-sinensal (CAS # 60066-88-8), for the genotoxicity endpoint.
  - o The target material and the read-across analog belong to a class of α,β-unsaturated aldehydes.
  - o The key difference between the target material and the read-across analog is that the target material has a vinylene bond at the α,β positions, whereas the read-across analog has a vinyl bond at the α,β positions. Moreover, the target material has a substituted vinylene and 2 isolated vinyl

substituents, whereas the read-across analog has a substituted vinylene. These structural differences make the read-across more reactive towards the Michael addition than the target material.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - Both the target material and the read-across analog have several alerts for Michael addition and Schiff base formation typical for α,β-unsaturated aldehydes. An initial Michael addition mechanism has been suggested to be primarily responsible for the ability of α,β-unsaturated aldehydes to alkylate DNA. A subsequent Schiff base reaction at the carbonyl can result in cross-linked DNA adducts. Additionally, compounds with an α,β-unsaturated carbonyl are bis-electrophiles, reactive molecules that may interact with electron-rich biological macromolecules. Because of conjugation with the carbonyl group, the β-carbon is positively polarized and becomes the preferred site of nucleophilic attack, as in a classic Michael type addition. Despite being a common structural feature, α,β-unsaturated carbonyl compounds can undergo different interactions with DNA, which lead to different genotoxic and mutagenic responses. The following genotoxic mechanisms are conceivable: formation of cyclic adducts, frameshift interaction, strand breaks, and crosslinking. In addition to direct interactions, other metabolic activations are conceivable, such as metabolic epoxidation and the formation of radicals. The predominant interaction of α,β-unsaturated carbonyl compounds with DNA components is the formation of cyclic 1,N_2-deoxyguanosine adducts. This reaction occurs through an initial Michael addition to the exocyclic nitrogen of deoxyguanosine (dG), followed by ring closure and formation of the 8-hydroxypropano adduct. Further reactions are also possible, including the formation of cross-links with proteins and nucleic acids. The data for the read-across analog confirm that the material does not pose a concern for genotoxicity. Therefore, the predictions are superseded by the data.
  - The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.
- β-Farnesene (CAS # 18794-84-8) was used as a weight-of-evidence (WoE) analog for the target material, β-sinensal (CAS # 60066-88-8), for the genotoxicity endpoint.
  - The target material belongs to a class of α,β-unsaturated aldehydes, whereas the WoE analog belongs to a class of sesquiterpenes.
  - The key difference between the target material and the WoE analog is that the target material is an aldehyde whereas the WoE analog is whereas the WoE analog is a sesquiterpene and contains a similar pattern of unsaturation as the target. The target substance has α,β unsaturation which makes it reactive towards Michael addition. However, the main structural features present in the WoE cover all the secondary structural features present in the target substance.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto scores. Differences between the structures that affect the Tanimoto scores are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material has several alerts for Michael addition and Schiff base formation typical for α,β-unsaturated aldehydes. An initial Michael addition mechanism has been suggested to be primarily responsible for the ability of α,β-unsaturated aldehydes to alkylate DNA. A subsequent Schiff base reaction at the carbonyl can result in cross-linked DNA adducts. Additionally, compounds with an α,β-unsaturated carbonyl are bis-electrophiles, reactive molecules that may interact with electron-rich biological macromolecules. Because of conjugation with the carbonyl group, the β-carbon is positively polarized and becomes the preferred site of nucleophilic attack, as in a classic Michael type addition. Despite being a common structural feature, α,β-unsaturated carbonyl compounds can undergo different interactions with DNA, which lead to different genotoxic and mutagenic responses. The following genotoxic mechanisms are conceivable: formation of cyclic adducts, frameshift interaction, strand breaks, and crosslinking. In addition to direct interactions, other metabolic activations are conceivable, such as metabolic epoxidation and the formation of radicals. The predominant interaction of α,β-unsaturated carbonyl compounds with DNA components is the formation of cyclic 1,N_2-deoxyguanosine adducts. This reaction occurs through an initial Michael addition to the exocyclic nitrogen of deoxyguanosine (dG), followed by ring closure and formation of the 8-hydroxypropano adduct. Further reactions are also possible, including the formation of cross-links with proteins and nucleic acids. The data for the read-across analog confirm that the material does not pose a concern for genotoxicity. Therefore, the predictions are superseded by the data.
  - The target material and the WoE analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - The structural alerts for the endpoints evaluated are consistent between the metabolites of the WoE analog and the target material.
- Farnesal (CAS # 19317-11-4) was used as a read-across analog for the target material, β-sinensal (CAS # 60066-88-8), for the phototoxicity/photoallergenicity endpoint.
  - The target material and the read-across analog belong to a class of α,β-unsaturated aldehydes.
  - The key difference between the target material and the read-across analog is that the target material has a methyl substituent at the α position whereas the read-across has a methyl substituent at the β position. Moreover, the target material has a substituted vinylene and 2 isolated vinyl substituents, whereas the read-across analog has 2 isolated substituted vinylene bonds. These structural differences are toxicologically insignificant for this endpoint.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - According to the OECD QSAR Toolbox v4.2, structural alerts for toxicological endpoints are consistent between the target material and the read-across analog.
  - The target material and the read-across analog do not have a chromophore that is expected to absorb in the UV/Vis range of the electromagnetic spectrum that is of interest to human health toxicity. The data on the read-across analog confirm that the substance does not absorb in the UV/Vis

range. Therefore, the structural difference between the target material and the read-across analog is toxicologically insignificant for the photo-toxicity endpoint, and the target material can be predicted to not absorb in the UV/Vis range.

- o The target material 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.

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