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Short Review

RIFM fragrance ingredient safety assessment, guaiyl acetate, CAS Registry Number 134-28-1

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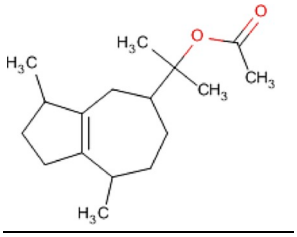
Version: 032618. This version replaces any previous versions.
Name: Guaiyl acetate
CAS Registry Number: 134-28-1



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Abbreviation/Definition List:

2-Box Model - A RIFM, Inc. proprietary *in silico* tool used to calculate fragrance air exposure concentration
AF - Assessment Factor
BCF - Bioconcentration Factor
Creme RIFM Model - The Creme RIFM Model uses probabilistic (Monte Carlo) simulations to allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey et al., 2015, 2017; Safford et al., 2015, 2017) compared to a deterministic aggregate approach
DEREK - Derek Nexus is an *in silico* tool used to identify structural alerts
DST - Dermal Sensitization Threshold
ECHA - European Chemicals Agency
EU - Europe/European Union
GLP - Good Laboratory Practice
IFRA - The International Fragrance Association
LOEL - Lowest Observable Effect Level
MOE - Margin of Exposure
MPPD - Multiple-Path Particle Dosimetry. An *in silico* model for inhaled vapors used to simulate fragrance lung deposition
NA - North America
NESIL - No Expected Sensitization Induction Level
NOAEC - No Observed Adverse Effect Concentration
NOAEL - No Observed Adverse Effect Level
NOEC - No Observed Effect Concentration
NOEL - No Observed Effect Level
OECD - Organisation for Economic Co-operation and Development
OECD TG - Organisation for Economic Co-operation and Development Testing Guidelines
PBT - Persistent, Bioaccumulative, and Toxic
PEC/PNEC - Predicted Environmental Concentration/Predicted No Effect Concentration
QRA - Quantitative Risk Assessment
REACH - Registration, Evaluation, Authorisation, and Restriction of Chemicals
RfD - Reference Dose
RIFM - Research Institute for Fragrance Materials
RQ - Risk Quotient
Statistically Significant - Statistically significant difference in reported results as compared to controls with a $p < 0.05$ using appropriate statistical test
TTC - Threshold of Toxicological Concern
UV/Vis spectra - Ultraviolet/Visible spectra
VCF - Volatile Compounds in Food
VoU - Volume of Use **vPvB** - (very) Persistent, (very) Bioaccumulative
WoE - Weight of Evidence

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

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

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

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

Summary: The use of this material under current conditions is supported by existing information.

Guaiyl acetate was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that guaiyl acetate is not genotoxic. The repeated dose toxicity endpoint was completed using terpinyl acetate (CAS # 8007-35-0) as a read-across analog, which provided an MOE > 100. Data from read-across analog α-terpineol acetate (CAS # 80-26-2) show that guaiyl acetate is not a concern for skin sensitization. The developmental, reproductive, and local respiratory toxicity endpoints were completed using the Threshold of Toxicological Concern (TTC) for a Cramer Class I material (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra. The environmental endpoints were evaluated; guaiyl acetate was found not to be PBT as per the IFRA Environmental Standards, and its risk quotients, based on its current volume of use in Europe and North America (i.e., PEC/PNEC), are < 1.

Human Health Safety Assessment

Genotoxicity: Not genotoxic. (RIFM, 2004; RIFM, 2017)
Repeated Dose Toxicity: NOAEL = 400 mg/kg/day. (Hagan et al., 1967)
Developmental and Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: No safety concerns for skin sensitization under the current, declared levels of use. (RIFM, 2012)
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: NOAEC is not available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 80% (OECD 310) RIFM (2009)
Bioaccumulation: Screening-level: 615 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: 48-h *Daphnia magna* LC50: 0.028 mg/L (ECOSAR; US EPA, 2012b)
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: 48-h *Daphnia magna* LC50: 0.028 mg/L (ECOSAR; US EPA, 2012b)
RIFM PNEC is: 0.0028 μg/L
- **Revised PEC/PNECs (2015 IFRA VoU):** North America and Europe < 1

1. Identification

1. **Chemical Name:** Guaiyl acetate
2. **CAS Registry Number:** 134-28-1
3. **Synonyms:** 5-Azulenemethanol, 1,2,3,4,5,6,7,8-octahydro-.α.,.α.,3,8-tetramethyl-, acetate, (3S,5R,8S)-; Guaiac acetate; Guaiol acetate; 1-Methyl-1-((3S,8S)-1,2,3,4,5,6,7,8-octahydro-3,8-dimethylazulen-5-yl) ethyl acetate; アルキル（C = 1 ~ 3）カルボン酸グアイオールエステル; 1-(3,8-Dimethyl-1,2,3,4,5,6,7,8-octahydroazulen-5-yl)-1-methylethyl acetate; Guaiyl acetate
4. **Molecular Formula:** $C_{17}H_{28}O_2$
5. **Molecular Weight:** 264.09
6. **RIFM Number:** 5164
7. **Stereochemistry:** Isomer not specified. Three stereocenters and 8 total stereoisomers possible.

2. Physical data

1. **Boiling Point:** 316.16 °C (US EPA, 2012a)
2. **Flash Point:** > 93 °C (GHS)
3. **Log K_{OW}:** 6.25 (US EPA, 2012a)
4. **Melting Point**: 83.62 °C (US EPA, 2012a)
5. **Water Solubility:** 0.0908 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 0.97500 to 0.98700 @ 25.00 °C*
7. **Vapor Pressure:** 0.000117 mm Hg @ 20 °C (US EPA, 2012a), 0.000226 mm Hg @ 25 °C (US EPA, 2012a)
8. **UV Spectra:** No absorbance between 290 and 400 nm; molar absorption is below the benchmark (1000 L mol cm^{-1})
9. **Appearance/Organoleptic:** A yellow viscous liquid with a tea, rose, woody, spicy, green, and fatty odor

*The Good Scents Company, accessed 09/15/17.

3. Exposure

1. **Volume of Use (worldwide band):** 1–10 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.090% (RIFM, 2016)

3. **Inhalation Exposure*:** 0.00040 mg/kg/day or 0.029 mg/day (RIFM, 2016)
4. **Total Systemic Exposure**:** 0.0020 mg/kg/day (RIFM, 2016)

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

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

4. Derivation of systemic absorption

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

5. Computational toxicology evaluation

1. **Cramer Classification:** Class I, Low (Expert Judgment)

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

*See appendix below for explanation.

2. Analogs Selected:
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** Terpinyl acetate (CAS # 8007-35-0)
   c. **Developmental and Reproductive Toxicity:** None
   d. **Skin Sensitization:** α-Terpineol acetate (CAS # 80-26-2)
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

No relevant data available for inclusion in this safety assessment.

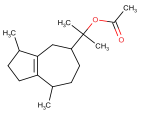
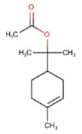
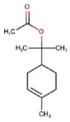
7. Natural occurrence (discrete chemical) or composition(NCS)

Guaiyl acetate is not reported to occur in foods by the VCF* and is not found in natural complex substances (NCS).

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

8. IFRA standard

None.

	Target Material	Read-across Material	Read-across Material
Principal Name	Guaiyl acetate	Terpinyl acetate (Isomer mixture)	α-Terpineol acetate
CAS No.	134-28-1	8007-35-0	80-26-2
Structure			
Similarity (Tanimoto Score)		0.79	0.79
Read-across Endpoint		• Repeated dose	• Skin sensitization
Molecular Formula	$C_{17}H_{28}O_2$	$C_{12}H_{20}O_2$	$C_{12}H_{20}O_2$
Molecular Weight	264.41	196.29	196.9
Melting Point (°C, EPI Suite)	83.62	21.47	21.47
Boiling Point (°C, EPI Suite)	316.16	238.66	238.66
Vapor Pressure (Pa @ 25 °C, EPI Suite)	0.032	6.63	6.63
Log Kow (KOWWIN v1.68 in EPI Suite)	6.25	3.96	3.96
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	0.0908	18.97	18.97
J_{max} (mg/cm^2/h, SAM)	14.362	235.584	235.58
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	2.21E-003	1.03E-003	1.03E-003
	Repeated Dose Toxicity		
Repeated Dose (HESS)	• Not categorized	• Not categorized	
	Skin Sensitization		
Protein Binding (OASIS v1.1)	• No alert found		• No alert found
Protein Binding (OECD)	• No alert found		• No alert found
Protein Binding Potency	• Not possible to classify		• Not possible to classify
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	• No alert found		• No alert found
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	• No alert found		• No alert found
	Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2	See Supplemental Data 3

9. REACH dossier

Pre-registered for 2010; no dossier available as of 03/19/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on current existing data, guaiyl acetate does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic potential of guaiyl acetate was evaluated in a bacterial reverse mutation assay. This study was conducted in compliance with GLP regulations and in accordance with OECD TG 471, using both standard plate incorporation method and preincubation conditions. *Salmonella typhimurium* strains TA98, TA1535, TA100, TA1537, and TA102 were treated with guaiyl

acetate in DMSO (dimethyl sulfoxide) at concentrations up to 5000 μg/plate with or without S9 metabolic activation. No increases in the mean number of revertant colonies were observed at any tested dose in the presence or absence of S9 (RIFM, 2004). Under the conditions of the study, guaiyl acetate is negative for mutagenicity.

The clastogenic activity of guaiyl acetate 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 guaiyl acetate in dimethyl formamide (DMF) at concentrations up to 2000 μg/mL in the presence and absence of metabolic activation (S9) for 3 and 24 h. Guaiyl acetate did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (RIFM, 2017). Under the conditions of the study, guaiyl acetate was considered to be non-clastogenic in the *in vitro* micronucleus test.

Based on the data available, guaiyl acetate does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/21/17.

10.1.2. Repeated dose toxicity

The margin of exposure for guaiyl acetate is adequate for the repeated dose toxicity endpoint at the current level of use.

10.1.2.1. Risk assessment. There are insufficient repeated dose toxicity data on guaiyl acetate to support the repeated dose toxicity endpoint. Read-across material, terpinyl acetate (CAS # 8007-35-0; see Section V) has sufficient repeated dose toxicity data. A dietary 20-week chronic toxicity study was conducted in Osborne-Mendel rats. Groups of 10 rats/sex/dose were administered diets containing 0, 1000, 2500, or 10000 ppm terpinyl acetate (isomer mixture, equivalent to 0, 50, 250, or 500 mg/kg/day) for 20 weeks. No effects on growth, no alterations on hematology, and no macroscopic or microscopic changes were observed up to the highest dose of 10000 ppm. The animals exposed to 10000 ppm in the diet consumed between 400 and 500 mg/kg/day terpinyl acetate. Thus, the NOAEL for repeated dose toxicity was considered to be 10000 ppm or 400 mg/kg/day (Hagan et al., 1967; data also available in Bar and Griepentrog, 1967 and ECHA Dossier: p-menth-1-en-8-yl acetate).

Therefore, the guaiyl acetate MOE for the repeated dose toxicity endpoint can be calculated by dividing the terpinyl acetate NOAEL in mg/kg/day by the total systemic exposure to guaiyl acetate, 400/0.002 or 200000.

In addition, the total systemic exposure to guaiyl acetate (2.0 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007) for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/21/17.

10.1.3. Developmental and reproductive toxicity

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

10.1.3.1. Risk assessment. There are no developmental or reproductive toxicity data on guaiyl acetate or any read-across materials that can be used to support the developmental or reproductive toxicity endpoints. The total systemic exposure to guaiyl acetate (2.0 μg/kg/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) for the developmental and reproductive toxicity endpoints of a Cramer Class I material at the current level of use.

Key Studies: None.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/21/17.

10.1.4. Skin sensitization

Based on read-across material α-terpineol acetate (CAS # 80-26-2), guaiyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structures of guaiyl acetate and read-across material α-terpineol acetate (CAS # 80-26-2; see Section V) indicate that they would not be expected to react with skin proteins (Roberts et al., 2007; Toxtree 2.6.6; OECD toolbox v3.3). No predictive skin sensitization studies are available for guaiyl acetate. In a murine local lymph node assay (LLNA), read-across material α-terpineol acetate was found to be negative up to the maximum tested concentration of 100% which resulted in a Stimulation Index (SI) of 2.4 (RIFM, 2012). Based on the weight of evidence from structural analysis and read-across to α-terpineol acetate, guaiyl acetate does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 09/11/17.

10.1.5. Phototoxicity/photoallergenicity

Based on available UV/Vis spectra, guaiyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.1. Risk assessment. There are no phototoxicity studies available for guaiyl acetate in experimental models. The available UV/Vis spectra for guaiyl acetate indicate no absorbance between 290 and 400 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on the lack of absorbance, guaiyl acetate would not be expected to present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. The available spectra indicate no significant absorbance in the range of 290–400 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: 08/02/17.

10.1.6. Local Respiratory Toxicity

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

10.1.6.1. Risk assessment. There are no inhalation data available on guaiyl acetate. Based on the Creme RIFM Model, the inhalation exposure is 0.029 mg/day. This exposure is 48.3 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew et al., 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 08/03/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of guaiyl acetate was performed

following the RIFM Environmental Framework (Salvito et al., 2002), which provides 3 tiered levels of screening for aquatic risk. In Tier 1, only the material's regional VoU, its log K_{OW}, and its molecular weight are needed to estimate a conservative risk quotient (RQ), expressed as the ratio Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC). A general QSAR with a high uncertainty factor applied is used to predict fish toxicity, as discussed in Salvito et al. (2002). In Tier 2, the RQ is refined by applying a lower uncertainty factor to the PNEC using the ECOSAR model (US EPA, 2012b), which provides chemical class–specific ecotoxicity estimates. Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors. The data for calculating the PEC and PNEC for this safety assessment are provided in the table below. For the PEC, the range from the most recent IFRA Volume of Use Survey is reviewed. The PEC is then calculated using the actual regional tonnage, not the extremes of the range. Following the RIFM Environmental Framework, guaiyl acetate was 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 EPI Suite v4.11 (US EPA, 2012a) identified guaiyl acetate as possibly persistent and bioaccumulative based on its structure and physical–chemical properties. This screening-level hazard assessment considers the potential for a material to be persistent *and* bioaccumulative *and* toxic, or very persistent *and* very bioaccumulative as defined in the Criteria Document (Api et al., 2015). As noted in the Criteria Document, the screening criteria applied are the same as those used in the EU for REACH (ECHA, 2012). For persistence, if the EPI Suite model BIOWIN 3 predicts a value < 2.2 and either BIOWIN 2 or BIOWIN 6 predicts a value < 0.5, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPI Suite model BCFBAF predicts a fish BCF ≥2000 L/kg. Ecotoxicity is determined in the above screening-level risk assessment. If, based on these model outputs (Step 1), additional assessment is required, a WoE-based review is then performed (Step 2). This review considers available data on the material's physical–chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher-tier model outputs (e.g., US EPA's BIOWIN and BCFBAF found in EPI Suite v4.11). Data on persistence and bioaccumulation are reported below and summarized in the Environmental Safety Assessment section prior to Section 1.

10.2.2. Risk assessment

Based on the current Volume of Use (2015), guaiyl acetate presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key Studies

10.2.3.1. Biodegradation. RIFM, 2009**:** The CO_2 headspace test was conducted to evaluate the biodegradability of the test material under aerobic conditions following the OECD 310 method. Under the conditions of the study, the biodegradation percentage reached 80% at day 28.

10.2.3.2. Ecotoxicity. No data available.

10.2.3.3. Other available data. Guaiyl acetate has been pre-registered for REACH with no additional data at this time.

10.2.4. Risk assessment refinement

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

Endpoints used to calculate PNEC are underlined.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (µg/L)	Chemical Class
RIFM Framework Screening Level **(Tier 1)**	0.0715			1,000,000	7.15E-05	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.117	0.154	0.033			Esters
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	0.033	0.028	0.105	10,000	0.0028	Neutral Organic SAR

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

Exposure	Europe	North America
Log K_{ow} used	6.25	6.25
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	1–10	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.0028 µg/L. The revised PEC/PNECs for EU and NA are < 1 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: 08/09/17.

11. Literature Search*

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

Search keywords: CAS number and/or material names.

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2018.11.002.

Appendix

Read-across Justification

Methods

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

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

Summary

There are insufficient toxicity data on guaiyl acetate (CAS # 134-28-1). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, terpinyl acetate (isomer mixture; CAS # 8007-35-0) and α-terpineol acetate (CAS # 80-26-2) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Terpinyl acetate (isomer mixture; CAS # 8007-35-0) was used as a read-across analog for the target material guaiyl acetate (CAS # 134-28-1) for the repeated dose toxicity endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to a class of esters.
  - ○ The target material and the read-across analog share a common acetate fragment on the acid portion of the ester.
  - ○ The key difference between the target material and the read-across analog is that the target has a bicyclic ring on the alcohol portion while the read-across analog has a monocyclic ring on the alcohol portion of the ester. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated cyclic aliphatic ester fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for the toxicological endpoint are consistent between the target material and the read-across analog.
  - ○ Data are consistent with *in silico* alerts.
  - ○ The target material and the read-across analog are expected to be metabolized similarly, as shown by the metabolism simulator.
  - ○ The structural alerts for the endpoint evaluated are consistent between the metabolites of the read-across analog and the target material.
- α-Terpineol acetate (CAS # 80-26-2) was used as a read-across analog for the target material guaiyl acetate (CAS # 134-28-1) for the skin sensitization endpoint.
  - ○ The target material and the read-across analog are structurally similar and belong to a class of esters.
  - ○ The target material and the read-across analog share a common acetate fragment on the acid portion of the ester.
  - ○ The key difference between the target material and the read-across analog is that the target has a bicyclic ring on the alcohol portion while the read-across analog has a monocyclic ring on the alcohol portion of the ester. This structural difference is toxicologically insignificant.
  - ○ Similarity between the target material and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the unsaturated aliphatic cyclic ester fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - ○ The physical–chemical properties of the target material and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - ○ According to the OECD QSAR Toolbox v3.4, structural alerts for the toxicological endpoint are consistent between the target material and the read-across analog.
  - ○ 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 endpoint evaluated are consistent between the metabolites of the read-across analog and the target material.

Explanation of Cramer Classification

Due to potential discrepancies between the current *in silico* tools (Bhatia et al., 2015), the Cramer Class of the target material was determined using expert judgment, based on the Cramer decision tree (Cramer et al., 1978).

Q1. Normal constituent of the body? No.

Q2. Contains functional groups associated with enhanced toxicity? No.

Q3. Contains elements other than C, H, O, N, divalent S? No.

Q5. Simply branched aliphatic hydrocarbon or a common carbohydrate? No.

Q6. Benzene derivative with certain substituents? No.

Q7. Heterocyclic? No.

Q16. Common terpene? Yes, Low (Class I).

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