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Short review

RIFM fragrance ingredient safety assessment, acetaldehyde dihexyl acetal, CAS Registry Number 5405-58-3

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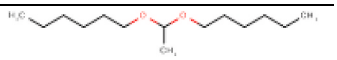


Name: Acetaldehyde dihexyl acetal CAS Registry Number: 5405-58-3

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

(*continued on next column*)

(*continued*)

Acetaldehyde dihexyl acetal was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from read-across analog octanal dimethyl acetal (CAS # 10022-28-3) show that acetaldehyde dihexyl acetal is not expected to be genotoxic. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to acetaldehyde dihexyl acetal is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). Data from read-across hydroxycitronellal diethyl acetal (CAS # 7779-94-4) show that there are no safety concerns for acetaldehyde dihexyl acetal for skin sensitization under the current declared levels of use. The phototoxicity/photoallergenicity endpoints were evaluated based on UV/Vis spectra from read-across material nonane, 1,1-diethoxy- (CAS # 54815-13-3); acetaldehyde dihexyl acetal is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; acetaldehyde dihexyl acetal 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 expected to be genotoxic. (RIFM, 2014a; RIFM, 2014b)
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 at the current, declared use levels. RIFM (1988)
Phototoxicity/ Photoallergenicity: Not expected to be phototoxic/ photoallergenic. (UV Spectra; RIFM Database)
Local Respiratory Toxicity: No NOAEL available. Exposure is below TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence:
Screening-level: 3.27 (BIOWIN 3) (EPI Suite v4.11;US EPA, 2012a)
Bioaccumulation:
Screening-level: 47.85 L/kg (EPI Suite v4.11;US EPA, 2012a)
Ecotoxicity:
Screening-level: Fish LC50: 0.59 mg/L (RIFM Framework; Salvito, 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, 2002)
Critical Ecotoxicity Endpoint: Fish LC50: 0.59 mg/L (RIFM Framework; Salvito, 2002)
RIFM PNEC is: 0.00059 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:** Acetaldehyde dihexyl acetal
2. **CAS Registry Number:** 5405-58-3
3. **Synonyms:** 1,1-Bis(hexyloxy)ethane; Hexane, 1,1'-[ethylidenebis (oxy)bis]-; 1,1'-[Ethane-1,1-diylbis (oxy)]dihexane; Acetaldehyde dihexyl acetal
4. **Molecular Formula:** $C_{14}H_{30}O_2$
5. **Molecular Weight:** 230.39
6. **RIFM Number:** 55
7. **Stereochemistry:** Isomer not specified. No stereocenter present and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 268.53 °C (EPI Suite)
2. **Flash Point:** Not Available
3. **Log K_{OW}:** 5.13 (EPI Suite)
4. **Melting Point**: 23.49 °C (EPI Suite)
5. **Water Solubility:** 1.25 mg/L (EPI Suite)
6. **Specific Gravity:** Not Available

7. **Vapor Pressure:** 0.017 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:** 0.0045% (RIFM, 2017)
2. **Inhalation Exposure*:** 0.0000017 mg/kg/day or 0.00011 mg/day (RIFM, 2017)
3. **Total Systemic Exposure**:** 0.00023 mg/kg/day (RIFM, 2017)

*95th percentile calculated exposure derived from concentration survey data in the Creme RIFM Aggregate Exposure Model (Comiskey, 2015, 2017; Safford, 2015, 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, 2015, 2017; Safford, 2015, 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 v3.2
I	I	I

2. Analogs Selected:
   a. **Genotoxicity:** Octanal dimethyl acetal (CAS # 10022-28-3)
   b. **Repeated Dose Toxicity:** None
   c. **Reproductive Toxicity:** None
   d. **Skin Sensitization:** Hydroxycitronellal diethyl acetal (CAS # 7779-94-4)
   e. **Phototoxicity/Photoallergenicity:** Nonane, 1,1-diethoxy- (CAS # 54815-13-3)
   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

Acetaldehyde dihexyl acetal is reported to occur in the following foods by the VCF*:

Apple processed (*Malus* species)
Cider (apple wine)
Strawberry (*Fragaria* species)

*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

Pre-registered for 2010; no dossier available as of 06/10/20.

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, acetaldehyde dihexyl acetal does not present a concern for genotoxicity.

11.1.1.1. Risk assessment. There are no studies assessing the mutagenic or clastogenic activity of acetaldehyde dihexyl acetal; however, read-across can be made to octanal dimethyl acetal (CAS # 10022-28-3; see Section VI).

The mutagenic activity of octanal dimethyl acetal has been evaluated in a bacterial reverse mutation assay conducted in compliance with GLP regulations and in accordance with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2uvrA were treated with octanal dimethyl acetal 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, 2014a). Under the conditions of the study, octanal dimethyl acetal was not mutagenic in the Ames test, and this can be extended to acetaldehyde dihexyl acetal.

The clastogenic activity of octanal dimethyl acetal 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 octanal dimethyl acetal in DMSO at concentrations up to 1744 μg/mL in a dose range finding (DRF) study; micronuclei analysis was conducted at concentrations up to 225 μg/mL in the presence and absence of metabolic activation. Octanal dimethyl acetal did not induce binucleated cells with micronuclei when tested up to the cytotoxic level concentration in either the presence or absence of an S9 activation system (RIFM, 2014b). Under the conditions of the study, octanal dimethyl acetal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to acetaldehyde dihexyl acetal.

Based on the data available, octanal dimethyl acetal does not present a concern for genotoxic potential, and this can be extended to acetaldehyde dihexyl acetal.

Additional References: None.

Literature Search and Risk Assessment Completed On: 07/02/20.

11.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on acetaldehyde dihexyl acetal or any read-across materials. The total systemic exposure

to acetaldehyde dihexyl acetal 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 acetaldehyde dihexyl acetal or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure (0.23 μg/kg/day) is below the TTC for acetaldehyde dihexyl acetal (30 μg/kg/day; Kroes, 2007).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/15/20.

11.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on acetaldehyde dihexyl acetal or any read-across materials. The total systemic exposure to acetaldehyde dihexyl acetal 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 acetaldehyde dihexyl acetal or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure (0.23 μg/kg/day) is below the TTC for acetaldehyde dihexyl acetal (30 μg/kg/day; Kroes, 2007; Laufersweiler, 2012).

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/26/20.

11.1.4. Skin sensitization

Based on read-across analog hydroxycitronellal diethyl acetal (CAS # 7779-94-4), acetaldehyde dihexyl acetal presents no concern for skin sensitization under the current, declared levels of use.

11.1.4.1. Risk assessment. No data skin sensitization studies are available for acetaldehyde dihexyl acetal. Based on read-across material hydroxycitronellal diethyl acetal (CAS # 7779-94-4; see Section VI), acetaldehyde dihexyl acetal is not considered a skin sensitizer. The chemical structures of these materials indicate that they would not be expected to react with skin proteins directly (Roberts, 2007; Toxtree v3.1.0; OECD Toolbox v4.2). In a guinea pig Buehler test, the read-across material did not present reactions indicative of sensitization (RIFM, 1988).

Based on the weight of evidence (WoE) from structural analysis and read-across material hydroxycitronellal diethyl acetal, acetaldehyde dihexyl acetal does not present a concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/25/20.

11.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorbance spectra for the structurally related read-across material nonane, 1,1-diethoxy- (CAS # 54815-13-3; see Section VI), acetaldehyde dihexyl acetal 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 acetaldehyde dihexyl acetal in experimental models. UV/Vis absorption spectra are not available for the target material acetaldehyde dihexyl acetal. UV/Vis absorbance spectra on the structurally related read-across material nonane, 1,1-diethoxy- (CAS # 54815-13-3) indicate no significant absorption between 290 and 700 nm. The corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity (Henry, 2009). Based on the lack of absorbance for the structurally related read-across analog, acetaldehyde dihexyl acetal 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 acetaldehyde dihexyl acetal. UV/Vis absorbance spectra on the structurally related read-across material nonane, 1,1-diethoxy- (CAS # 54815-13-3) indicate no significant absorbance in the range of 290–700 nm. The molar absorption coefficient is below the benchmark of concern for phototoxic effects, 1000 L $mol^{-1} \cdot cm^{-1}$ (Henry, 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/02/20.

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 acetaldehyde dihexyl acetal 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 acetaldehyde dihexyl acetal. Based on the Creme RIFM Model, the inhalation exposure is 0.00011 mg/day. This exposure is 12727 times lower than the Cramer Class I TTC value of 1.4 mg/day (based on human lung weight of 650 g; Carthew, 2009); therefore, the exposure at the current level of use is deemed safe.

Additional References: None.

Literature Search and Risk Assessment Completed On: 06/15/20.

11.2. Environmental endpoint summary

11.2.1. Screening-level assessment

A screening-level risk assessment of acetaldehyde dihexyl acetal was performed following the RIFM Environmental Framework (Salvito, 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, acetaldehyde dihexyl acetal was identified as a fragrance material with no potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC <1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify acetaldehyde dihexyl acetal as possibly

persistent or 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, 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), acetaldehyde dihexyl acetal presents no risk to the aquatic compartment in the screening-level assessment.

11.2.2.1. Key studies. Biodegradation

No data available.

Ecotoxicity

No data available.

Other available data

Acetaldehyde dihexyl acetal has been pre-registered for REACH with no additional information 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 underlined.

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

Exposure	Europe (EU)	North America (NA)
Log K_{OW} Used	5.13	5.13
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	<1	No VoU
Risk Characterization: PEC/PNEC	**<1**	**NA**

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

The RIFM PNEC is 0.00059 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: 06/16/20.

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
- **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 Results&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 09/30/20.

	LC50 (Fish) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level **(Tier 1)**	<u>0.59</u>			1000000	0.00059	

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.2021.112171.

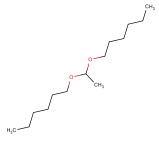
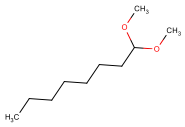
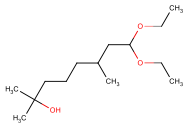
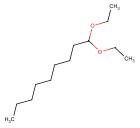
Appendix

Read-across Justification

Methods

The read-across analogs were identified using the RIFM fragrance materials chemical inventory clustering and read-across search criteria (RIFM, 2020). These criteria follow 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 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, oncologic classification, ER binding, and repeat dose categorization predictions were generated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- Developmental toxicity was predicted using CAESAR v2.1.7 (Cassano et al., 2010).
- Protein binding was predicted using OECD QSAR Toolbox v4.2 (OECD, 2020), and skin sensitization was predicted using Toxtree.
- The major metabolites for the target and read-across analogs were determined and evaluated using OECD QSAR Toolbox v4.2 (OECD, 2020).
- 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	Acetaldehyde dihexyl acetal	Octanal dimethyl acetal	Hydroxycitronellal diethyl acetal	Nonane, 1,1-diethoxy-
CAS No.	5405-58-3	10022-28-3	7779-94-4	54815-13-3
Structure				
Similarity (Tanimoto Score)		0.52	0.53	0.70
Endpoint		• Genotoxicity	• Skin sensitization	• Phototoxicity
Molecular Formula	$C_{14}H_{30}O_2$	$C_{10}H_{22}O_2$	$C_{14}H_{30}O_3$	$C_{13}H_{28}O_2$
Molecular Weight	230.392	174.284	246.391	216.365
Melting Point (°C, EPI Suite)	23.49	−20.44	53.89	12.90
Boiling Point (°C, EPI Suite)	268.53	195.26	290.04	251.57
Vapor Pressure (Pa @ 25°C, EPI Suite)	2.27E+00	8.64E+01	1.84E-02	5.43E+00
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	1.25E+00	1.15E+02	8.48E+01	3.90E+00
Log K_{OW}	5.13	3.17	3.48	4.64
J_{max} (μg/cm^2/h, SAM)	0.17	7.57	1.77	0.48
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.16E+02	3.73E+01	4.23E-03	8.71E+01
Genotoxicity				
DNA Binding (OASIS v1.4, QSAR Toolbox v4.2)	No alert found	No alert found		
DNA Binding (OECD QSAR Toolbox v4.2)	No alert found	No alert found		
Carcinogenicity (ISS)	No alert found	No alert found		
DNA Binding (Ames, MN, CA, OASIS v1.1)	No alert found	No alert found		
***In Vitro* Mutagenicity (Ames, ISS)**	No alert found	No alert found		
***In Vivo* Mutagenicity (Micronucleus, ISS)**	No alert found	No alert found		
Oncologic Classification	Not classified	Not classified		
Repeated Dose Toxicity				

(*continued on next page*)

(*continued*)

	Target Material	Read-across Material	Read-across Material	Read-across Material
Repeated Dose (HESS)	Not categorized			Not categorized
Reproductive Toxicity				
ER Binding (OECD QSAR Toolbox v4.2)	Non-binder, non-cyclic structure			
Developmental Toxicity (CAESAR v2.1.6)	Non-toxicant (moderate reliability)			
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 according to these rules (GSH)		Not possible to classify according to these rules (GSH)	
Protein Binding Alerts for Skin Sensitization (OASIS v1.1)	No alert found		No alert found	
Skin Sensitization Reactivity Domains (Toxtree v2.6.13)	No skin sensitization reactivity domains alerts identified.		No skin sensitization reactivity domains alerts identified.	
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 acetaldehyde dihexyl acetal (CAS # 5405-58-3). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, octanal dimethyl acetal (CAS # 10022-28-3), hydroxycitronellal diethyl acetal (CAS # 7779-94-4), and nonane, 1,1-diethoxy- (CAS # 54815-13-3) were identified as read-across analogs with sufficient data for toxicological evaluation.

Conclusions

- Octanal dimethyl acetal (CAS # 10022-28-3) was used as a read-across analog for the target material acetaldehyde dihexyl acetal (CAS # 5405-58-3) for the genotoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of aliphatic ethers.
  - The target material and the read-across analog share an ether functionality.
  - The key difference between the target material and the read-across analog is that the target material has a hexyl group on the alcohol portion whereas the read-across analog has a methyl group on the alcohol portion. Moreover, the aldehyde in the target material is acetaldehyde whereas the aldehyde in the read-across analog is octanal. The alerts as well as data on the read-across analog suggest that the acetal functional groups with these aliphatic substructures are inert towards the genotoxicity endpoint. Therefore, these structural differences are toxicologically insignificant for the genotoxicity endpoint.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Structural differences 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 a 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.
  - There are no alerts for the read-across analog and the target material for genotoxicity. Therefore, *in silico* alerts are consistent with 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.
- Hydroxycitronellal diethyl acetal (CAS # 7779-94-4) was used as a read-across analog for the target material acetaldehyde dihexyl acetal (CAS # 5405-58-3) for the skin sensitization endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of aliphatic ethers.
  - The target material and the read-across analog share an ether functionality.
  - The key difference between the target material and the read-across analog is that the target material has a hexyl group on the alcohol portion whereas the read-across analog has an ethyl group on the alcohol portion. Moreover, the aldehyde in the target material is acetaldehyde whereas the aldehyde in the read-across analog is hydroxy citronellal. The alerts as well as data on the read-across analog suggest that the acetal functional groups on the target material and the read-across analog are inert towards the skin sensitization endpoint. Therefore, these structural differences are toxicologically insignificant for the skin sensitization endpoint.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Structural differences 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 a 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.
  - There are no alerts for the read-across analog and the target material for skin sensitization. Therefore, *in silico* alerts are consistent with 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.

- Nonane, 1,1-diethoxy- (CAS # 54815-13-3) was used as a read-across analog for the target material acetaldehyde dihexyl acetal (CAS # 5405-58-3) for the phototoxicity endpoint.
  - The target material and the read-across analog are structurally similar and belong to a class of aliphatic ethers.
  - The target material and the read-across analog share an ether functionality.
  - The key difference between the target material and the read-across analog is that the target material has a hexyl group on the alcohol portion whereas the read-across analog has an ethyl group on the alcohol portion. Moreover, the aldehyde in the target material is acetaldehyde whereas the aldehyde in the read-across analog is nonanal. Both 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. The data on the read-across analog confirm that the substance does not absorb in the UV/Vis range. Therefore, the structural differences between the target material and the read-across analog are toxicologically insignificant for the phototoxicity endpoint. The target material is predicted not to absorb in the UV/Vis range.
  - The similarity between the target material and the read-across analog is indicated by the Tanimoto score. Structural differences 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 a comparison of their toxicological properties.

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