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Short Review

RIFM fragrance ingredient safety assessment, 1,1-diethoxyhexane, CAS Registry Number 3658-93-3

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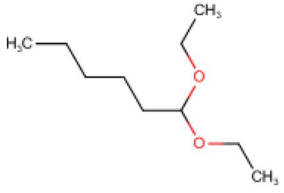
Version: 050418. This version replaces any previous versions.
Name: 1,1-Diethoxyhexane CAS Registry Number: 3658-93-3



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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 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 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.

1,1-Diethoxyhexane was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from the read-across analog octanal dimethyl acetal (CAS # 10022-28-3) show that 1,1-diethoxyhexane is not expected to be genotoxic. The skin sensitization endpoint was completed using existing data and the DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The developmental and reproductive, repeated dose, and local respiratory toxicity endpoints were completed using the TTC for a Cramer Class I material, and the exposure to 1,1-diethoxyhexane is below the TTC (0.03 mg/kg/day, 0.03 mg/kg/day, and 1.4 mg/day, respectively). The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; 1,1-diethoxyhexane is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; 1,1-diethoxyhexane 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 the TTC.
Reproductive Toxicity: No NOAEL available. Exposure is below the TTC.
Skin Sensitization: No safety concerns at current declared use levels; exposure is below the DST.
Phototoxicity/Photoallergenicity: Not phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Screening-level: 3.1 (BIOWIN 3) (EPI Suite v4.1; US EPA, 2012a)
Bioaccumulation: Screening-level: 57.29 L/kg (EPI Suite v4.1; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 22.56 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: 22.56 - mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.02256 μg/L
- **Revised PEC/PNECs (2011 IFRA VoU):** North America and Europe: Not applicable; cleared at screening-level

1. Identification

1. **Chemical Name:** 1,1-diethoxyhexane
2. **CAS Registry Number:** 3658-93-3
3. **Synonyms:** Hexanal diethyl acetal; Hexane, 1,1-diethoxy-; Hexaldehyde diethyl acetal; ﾍｷｻﾅｰﾙｼﾞｱﾙｷﾙ(C = 1,2,6)ｱｾﾀｰﾙ; 1,1-Diethoxyhexane
4. **Molecular Formula:** $C_{10}H_{22}O_2$
5. **Molecular Weight:** 174.28
6. **RIFM Number:** 6203

2. Physical data

1. **Boiling Point:** 195.26 °C (EPI Suite)
2. **Flash Point:** 103.00 °F; TCC (39.44 °C)*
3. **Log K_{ow}:** 3.17 (EPI Suite)
4. **Melting Point**: −20.44 °C (EPI Suite)
5. **Water Solubility:** 115.3 mg/L (EPI Suite)
6. **Specific Gravity:** 0.82800 to 0.83600 @ 20.00 °C*
7. **Vapor Pressure:** 0.45 mm Hg @ 20 °C (EPI Suite v4.0), 0.4 mm Hg 20 °C (FMA), 0.648 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** No significant absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark (1000 L mol^{-1} cm^{-1})
9. **Appearance/Organoleptic:** Arctander, 1969: Colorless liquid. Oily-green, rather mild, grassy odor of fair tenacity. *http://www.thegoodscentscompany.com/data/rw1026421.html, retrieved 02/09/2017.

3. Exposure

1. **Volume of Use (worldwide band):** < 1 metric tons per year (IFRA, 2011)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.018% (RIFM, 2015)
3. **Inhalation Exposure*:** 0.0000010 mg/kg/day or 0.000070 mg/day (RIFM, 2015)
4. **Total Systemic Exposure**:** 0.00046 mg/kg/day (RIFM, 2015)

*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	Toxtree v 2.6	OECD QSAR Toolbox v 3.2
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:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix below

6. Metabolism

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

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

1,1-Diethoxyhexane is reported to occur in the following foods by the VCF*:

Apple brandy (Calvados).
Apple processed (*Malus* species).
Beef.
Chinese quince (*Pseudocydonia sinensis* Schneid).
Grape brandy.
Guava and feyoa
Pear brandy.
Plum (*Prunus* species).
Strawberry (*Fragaria* species).
Vaccinium species.
Whisky.

*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 that contains 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.

9. REACH dossier

Pre-registered for 2010; no dossier available as of 05/04/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1,1-diethoxyhexane does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. 1,1-Diethoxyhexane was assessed in the BlueScreen assay and found negative for genotoxicity, with and without metabolic activation, indicating a lack of concern regarding genotoxicity (RIFM, 2014c). There are no studies assessing the mutagenic activity of 1,1-diethoxyhexane. However, read-across can be made to octanal dimethyl acetal (CAS # 10022-28-3; see Section V). 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, and 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 dose 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 1,1-diethoxyhexane.

There are no studies assessing the clastogenic activity of 1,1-diethoxyhexane. However, read-across can be made to octanal dimethyl acetal (CAS # 10022-28-3; see Section V). 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 for 2 and 24 h with octanal dimethyl acetal in DMSO at concentrations up to 1744 μg/mL in the presence and absence of metabolic activation (S9). Octanal dimethyl acetal did not induce binucleated cells with micronuclei when tested up to cytotoxic levels in either non-activated or S9-activated test systems (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 1,1-diethoxyhexane.

Based on the data available, octanal dimethyl acetal does not present a concern for genotoxic potential, and this can be extended to 1,1-diethoxyheptane.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/26/17.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 1,1-diethoxyhexane or any read-across materials. The total systemic exposure to 1,1-diethoxyhexane is below the TTC for the repeated dose toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.2.1. Risk assessment. There are no repeated dose toxicity data on 1,1-diethoxyhexane or any read-across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 1,1-diethoxyhexane (0.46 μg/kg/day) is below the TTC (30 μg/kg/day) 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: 05/24/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 1,1-diethoxyhexane or any read-across materials. The total systemic exposure to 1,1-diethoxyhexane is below the TTC for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

10.1.3.1. Risk assessment. There are no reproductive toxicity data on 1,1-diethoxyhexane or any read-across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 1,1-diethoxyhexane (0.46 µg/kg/day) is below the TTC (30 µg/kg/day) for the reproductive toxicity endpoint of a Cramer Class I material at the current level of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 05/24/17.

10.1.4. Skin sensitization

Based on the existing data and application of DST, 1,1-diethoxyhexane does not present a safety concern for skin sensitization at current, declared levels of use.

10.1.4.1. Risk assessment. The chemical structure of this material indicates that it would not be expected to react with skin proteins directly (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No predictive skin sensitization studies are available for 1,1-diethoxyhexane. However, in a human repeated insult patch test, no skin sensitization reactions were observed with 0.25% 1,1-diethoxyhexane (RIFM, 1965). Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive DST of 900 µg/cm^2. The current exposure from the 95th percentile concentration is below the DST for non-reactive materials when evaluated in all QRA categories. Table 1 provides the acceptable concentration for 1,1-diethoxyhexane, which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/26/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 1,1-diethoxyhexane 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 1,1-diethoxyhexane in experimental models. UV/Vis absorption spectra 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 et al., 2009). Based on lack of absorbance, 1,1-diethoxyhexane does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) were obtained. The spectra 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} cm^{-1} (Henry et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 01/11/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level for 1,1-diethoxyhexane 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 1,1-diethoxyhexane. Based on the Creme RIFM Model, the inhalation exposure is 0.000070 mg/day. This exposure is 20000 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: 01/27/17.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1,1-diethoxyhexane 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

Table 1
Acceptable concentrations for 1,1-diethoxyhexane based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products	95th Percentile Concentration
1	Products applied to the lips	00%[b]	0%[b]
2	Products applied to the axillae	0.021%	0.00%[c]
3	Products applied to the face using fingertips	0.41%	0.00%[c]
4	Fine fragrance products	0.39%	0.02%[c]
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.00%[c]
6	Products with oral and lip exposure	0%[b]	0%[b]
7	Products applied to the hair with some hand contact	0.79%	0.00%[c]
8	Products with significant ano-genital exposure	0.04%	No Data
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.00%[c]
10	Household care products with mostly hand contact	2.70%	0.00%[c]
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.00%[c]

Notes:[a]For a description of the categories, refer to the IFRA/RIFM Information Booklet (www.rifm.org/doc).
[b]This material is not an approved flavor ingredient.
[c]Negligible exposure (< 0.01%).

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, 1,1-diethoxyhexane 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 v4.1 did not identify 1,1-diethoxyhexane as either being possibly persistent nor 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 v4.1). 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 (IFRA, 2011), 1,1-diethoxyhexane does not present a risk to the aquatic compartment in the screening-level assessment.

10.2.2.1. Biodegradation. No data available.

10.2.2.2. Ecotoxicity. No data available.

10.2.2.3. Other available data. 1,1-Dethoxyhexane has been pre-registered for REACH with no additional data at this time.

10.2.3. 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 Framework: Salvito et al., 2002).

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	3.17	3.17
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	< 1
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 0.02256 μg/L. The revised PEC/PNECs for EU and NA: Not applicable; cleared at screening-level and therefore does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 01/12/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA:** http://echa.europa.eu/
- **NTP:** http://tools.niehs.nih.gov
- **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.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

	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>22.56</u>			1,000,000	0.02256	

influence the work reported in this paper. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. RIFM staff are employees of the Research Institute for Fragrance Materials, Inc. (RIFM). The Expert Panel receives a small honorarium for time spent reviewing the subject work.

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.2019.110612.

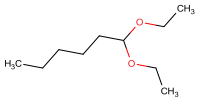
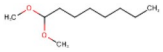
Appendix

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.

- 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 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).

	Target material	Read-across material
Principal Name	1,1-Diethoxyhexane	Octanal dimethyl acetal
CAS No.	3658-93-3	10022-28-3
Structure		
Similarity (Tanimoto score)		0.86
Read-across endpoint		• Genotoxicity
Molecular Formula	$C_{10}H_{22}O_2$	$C_{10}H_{22}O_2$
Molecular Weight	174.29	174.28
Melting Point (°C, EPI Suite)	−20.44	−20.44
Boiling Point (°C, EPI Suite)	195.26	195.26
Vapor Pressure (Pa @ 25°C, EPI Suite)	86.4	86.4
Log Kow (KOWWIN v1.68 in EPI Suite)	3.17	3.17
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPI Suite)	115.3	115.3
J_{max} (μg/cm^2/h, SAM)	43.761	45.652
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	3.68E-004	3.68E-004
Genotoxicity		
DNA binding (OASIS v 1.4 QSAR Toolbox 3.4)	• No alert found	• No alert found
DNA binding by OECD QSAR Toolbox (3.4)	• No alert found	• No alert found
Carcinogenicity (genotoxicity and non-genotoxicity) alerts (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)
DNA alerts for Ames, MN, CA by OASIS v 1.1	• No alert found	• No alert found
***In vitro* Mutagenicity (Ames test) alerts by ISS**	• No alert found	• No alert found
***In vivo* mutagenicity (Micronucleus) alerts by ISS**	• No alert found	• No alert found
Oncologic Classification	• Not classified	• Not classified
Metabolism		
OECD QSAR Toolbox (3.4) Rat liver S9 metabolism simulator	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on the target material 1,1-diethoxyhexane (CAS # 3658-93-3). Hence, *in silico* evaluation was conducted to determine a read-across analog for this material. Based on structural similarity, reactivity, metabolism data, physical–chemical properties, and expert judgment, analog octanal dimethyl acetal (CAS # 10022-28-3) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- The following material could be used as a read-across analog for the target material 1,1-diethoxyhexane (CAS # 3658-93-3) for the genotoxicity endpoint: octanal dimethyl acetal (CAS # 10022-28-3).
  - o The target substance and the read-across analog are structurally similar and belong to the structural class of aliphatic acetals.
  - o The target substance and the read-across analog have an acetal functional group with saturated aliphatic chains on the alcohol.
  - o The key difference between the target substance and the read-across analog is that the target substance has longer saturated aliphatic chains attached to the alcohol portion of the molecule compared to the read-across analog. The differences in structure between the target substance and the read-across analog does not raise additional structural alerts, so the structural differences are not relevant from a toxicological endpoint perspective.
  - o Similarity between the target substance and the read-across analog is indicated by the Tanimoto score provided in the above table. The Tanimoto score is mainly driven by the acetal functional group with dimethyl groups. The differences in the structures which are responsible for a Tanimoto score < 1 are not relevant from a toxicological endpoint perspective.
  - o The target substance and the read-across analog have similar physical–chemical properties. The read-across substance and the target material fall into the same category of 40%–80% skin absorption. Any other differences in the physical–chemical properties of the target substance and the read-across analog are estimated to be toxicologically insignificant for the genotoxicity endpoint.
  - o Structural alerts for genotoxicity endpoints are consistent between the target substance and the read-across analog as seen in the table above.
  - o The target substance and the read-across analog octanal dimethyl acetal are expected to be metabolized similarly as shown by the metabolism simulator.
  - o The structural alerts for the genotoxicity endpoint are consistent between the metabolites of the read-across analog octanal dimethyl acetal and the target substance.

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