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Short review

RIFM fragrance ingredient safety assessment, 1,1-diethoxyisooctane, CAS Registry Number 69178-43-4

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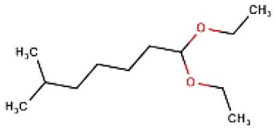
Version: 101317. This version replaces any previous versions.

Name: 1,1-Diethoxyisooctane

CAS Registry Number: 69178-43-4



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; Safford et al., 2015; Safford et al., 2017; Comiskey et al., 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

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Development Testing Guidelines
PBT- Persistent, Bioaccumulative, and Toxic
PEC/PNEC- Predicted Environmental Concentration/Predicted No Effect Concentration
QRA- Quantitative Risk Assessment
REACH- Registration, Evaluation, Authorisation, and Restriction of Chemicals
RIFM- Research Institute for Fragrance Materials
RQ- Risk Quotient
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- Ultra Violet/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 two-digit month/day/year), both in the RIFM database (consisting of publicly available and proprietary data) and through publicly available information sources (i.e., SciFinder and PubMed). Studies selected for this safety assessment were based on appropriate test criteria, such as acceptable guidelines, sample size, study duration, route of exposure, relevant animal species, most relevant testing endpoints, etc. A key study for each endpoint was selected based on the most conservative 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 guidance relevant to human health and environmental protection.

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

1,1-Diethoxyisooctane was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, as well as environmental safety. Data from read across analog 2-methylundecanal dimethyl acetal (CAS # 68141-17-3) show that 1,1-diethoxyisooctane is not expected to be genotoxic. The skin sensitization endpoint was completed using DST for non-reactive materials (900 μg/cm^2/day); exposure is below the DST. The repeated dose, developmental and reproductive, and local respiratory toxicity endpoints were completed using the TTC (Threshold of Toxicological Concern) for a Cramer Class I material; exposure to 1,1-diethoxyisooctane is below the TTC (0.03, 0.03 mg/kg/day and 1.4 mg/day). The phototoxicity/photoallergenicity endpoint was completed based on UV spectra; 1,1-diethoxyisooctane is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated, 1,1-diethoxyisooctane 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, 2016b; RIFM, 2016a)

Repeated Dose Toxicity: No NOAEL available. Exposure is below TTC.

Reproductive Toxicity: No NOAEL available. Exposure is below TTC.

Skin Sensitization: No safety concerns at current, declared use levels; Exposure is below 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: 2.7 (Biowin 3) (US EPA, 2012a)

Bioaccumulation: Screening-Level: 227 L/kg (US EPA, 2012a)

Ecotoxicity: Screening-Level: Fish LC50: 4.224 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: 4.224 mg/L (RIFM Framework; Salvito et al., 2002)

RIFM PNEC is: 0.004224 μg/L

- **Revised PEC/PNECs (2011 IFRA Volume of Use):** North America and Europe: Not applicable; Cleared at screening-level

1. Identification

1. **Chemical Name**: 1,1-diethoxyisooctane
2. **CAS Registry Number**: 69178-43-4
3. **Synonyms**: Iso-Octanal diethylacetal; Isooctane, 1,1-diethoxy-; 1,1-Diethoxyisooctane
4. **Molecular Formula**: $C_{12}H_{26}O_2$
5. **Molecular Weight**: 202.38
6. **RIFM Number**: 5954

2. Physical data

1. **Boiling Point**: 222.5 °C (US EPA, 2012a)
2. **Flash Point**: 52.78 °C*
3. **Log K_{ow}**: 4.08 (US EPA, 2012a)
4. **Melting Point**: −8.72 °C (US EPA, 2012a)
5. **Water Solubility**: 14.01 mg/L (US EPA, 2012a)
6. **Specific Gravity**: Not Available
7. **Vapor Pressure**: 0.174 mm Hg @ 25 °C (US EPA, 2012a), 0.117 mmHg @ 20 °C (US EPA, 2012a)
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**: colorless clear liquid*

*http://www.thegoodscentscompany.com/data/rw1045391.html, retrieved 02/03/2017.

3. Exposure

1. **Volume of Use (Worldwide Band)**: < 0.1 metric tons per year (IFRA, 2011)
2. **95th Percentile Concentration in Bar Soaps**: 0.021% (RIFM, 2015)
   (No reported use in Hydroalcoholics)
3. **Inhalation Exposure***: < 0.0001 mg/kg/day or < 0.0001 mg/day (RIFM, 2015)

4. **Total Systemic Exposure****: 0.00059 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, 2017; Comiskey et al., 2017).

**95th percentile calculated exposure; assumes 100% absorption unless modified by dermal absorption data as reported in Section 4. 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, 2017; 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**: 2-methylundecanal dimethyl acetal (CAS # 68141-17-3)
   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

No relevant data available for inclusion in this safety assessment.

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

1,1-diethoxyisooctane is not reported to occur in food by the VCF*:

*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 which 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 11/30/2010; no dossier available as of 09/29/2017.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

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

10.1.1.1. Risk assessment. The material, 1,1-diethoxyisooctane, was assessed in the BlueScreen assay and found negative for both cytotoxicity and genotoxicity, with and without metabolic activation (RIFM, 2013). There are no studies assessing the mutagenic activity of 1,1-diethoxyisooctane; however, read across can be made to 2-methylundecanal dimethyl acetal (CAS # 68141-17-3; see Section 5). The mutagenic activity of 2-methylundecanal 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 2-methylundecanal dimethyl acetal in DMSO (dimethyl sulfoxide) 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, 2016b). Under the conditions of the study, 2-methylundecanal dimethyl acetal was not mutagenic in the Ames test, and this can be extended to 1,1-diethoxyisooctane.

There are no studies assessing the clastogenic activity of 1,1-diethoxyisooctane; however, read across can be made to 2-methylundecanal dimethyl acetal (CAS # 68141-17-3; see Section 5). The clastogenic activity of 2-methylundecanal 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 3 and 24 h with 2-methylundecanal dimethyl acetal in DMSO at concentrations up to 2000 μg/mL in the presence and absence of S9 metabolic activation. The material, 2-methylundecanal dimethyl acetal, did not induce binucleated cells with micronuclei when tested up to the maximum dose in either non-activated or S9-activated test systems (RIFM, 2016a). Under the conditions of the study, 2-methylundecanal dimethyl acetal was considered to be non-clastogenic in the *in vitro* micronucleus test, and this can be extended to 1,1-diethoxyisooctane.

Based on the data available on the read across material 2-methylundecanal dimethyl acetal (CAS # 68141-17-3), 1,1-diethoxyisooctane does not present a concern for genotoxic potential.

Additional References: RIFM, 2013.

Literature Search and Risk Assessment Completed on: 01/18/2017.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 1,1-diethoxyisooctane or any read across materials. The total systemic exposure to 1,1-diethoxyisooctane 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-diethoxyisooctane or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 1,1-diethoxyisooctane (0.59 μg/kg bw/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: 01/12/2017.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 1,1-

diethoxyisooctane or any read across materials. The total systemic exposure to 1,1-diethoxyisooctane 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-diethoxyisooctane or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 1,1-diethoxyisooctane (0.59 μg/kg bw/day) is below the TTC (30 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012) 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: 01/12/2017.

10.1.4. Skin sensitization

Based on application of DST, 1,1-diethoxyisooctane does not present a safety concern for skin sensitization under the 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 (Roberts et al., 2007; Toxtree 2.6.13; OECD toolbox v3.4). No skin sensitization studies are available for 1,1-diethoxyisooctane. Acting conservatively, due to insufficient data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (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 1,1-diethoxyisooctane l which presents no appreciable risk for skin sensitization based on the non-reactive DST.

Additional References: None.

Literature Search and Risk Assessment Completed on: 1/26/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 1,1-diethoxyisooctane 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-diethoxyisooctane in experimental models. UV/Vis absorption spectra indicate no significant absorption between 290 and 700 nm. Corresponding molar absorption coefficient is well below the benchmark of concern for phototoxicity and photoallergenicity, 1000 L mol^{-1} cm^{-1} (Henry et al., 2009). Based on lack of absorbance, 1,1-diethoxyisooctane does not present a concern for phototoxicity or photoallergenicity.

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 material, 1,1-diethoxyisooctane, exposure level 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-diethoxyisooctane. Based on the Creme RIFM model, the inhalation exposure is < 0.00010 mg/day. This exposure is at least 14000 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: 01/27/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

A screening-level risk assessment of 1,1-diethoxyisooctane was performed following the RIFM Environmental Framework (Salvito et al., 2002) which provides for 3 levels of screening for aquatic risk. In Tier 1, only the material's volume of use in a region, its log K_{ow} and molecular weight are needed to estimate a conservative risk quotient (RQ; Predicted Environmental Concentration/Predicted No Effect Concentration or PEC/PNEC). In Tier 1, a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito et al. (2002). At Tier 2, the model ECOSAR (US EPA, 2012b; providing chemical class specific ecotoxicity estimates) is used, and a lower uncertainty factor is applied. Finally, if needed, at Tier 3, measured biodegradation and ecotoxicity data are used to refine the RQ (again, with lower uncertainty factors applied to calculate the PNEC). Provided in the table below are the data necessary to calculate both the PEC and the PNEC determined within this safety assessment. For the PEC, while the actual regional tonnage, which is considered proprietary information, is not provided, the range from the most recent IFRA Volume of Use Survey is reported. The PEC is calculated based on the actual tonnage and not the extremes noted for the range. Following the RIFM Environmental Framework, 1,1-diethoxyisooctane was identified as a

Table 1
Acceptable concentrations limits for 1,1-diethoxyisooctane 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	0.069%	0.000%
2	Products applied to the axillae	0.021%	0.000%
3	Products applied to the face using finger tips	0.41%	0.000%
4	Fine fragrance products	0.39%	0.000%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.000%
6	Products with oral and lip exposure	0.23%	0.000%
7	Products applied to the hair with some hand contact	0.79%	0.000%
8	Products with significant ano-genital exposure	0.04%	0.000%
9	Products with body and hand exposure, primarily rinse off	0.75%	0.021%[b]
10	Household care products with mostly hand contact	2.70%	0.000%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	0.000%
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	0.000%

[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet. (www.rifm.org/doc/QRAInfoJuly2011.pdf).
[b] Negligible exposure (< 0.01%).

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 1,1-diethoxyisooctane as either being possibly persistent nor bioaccumulative based on its structure and physical-chemical properties. This screening-level hazard assessment is a weight of evidence review of a material's physical-chemical properties, available data on environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies) and fish bioaccumulation, and review of model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPI Suite v4.11).

10.2.2. Risk assessment

Based on current Volume of Use (2011), 1,1-diethoxyisooctane 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.

Other available data:

1,1-diethoxyisooctane has been pre-registered under 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.

	LC50 (Fish)	EC50 (*Daphnia*)	EC50 (Algae)	AF	PNEC	Chemical Class
RIFM Framework Screening-Level **(Tier 1)**	4.224 mg/L			1,000,000	0.004224 μg/L	

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

Exposure	Europe (EU)	North America (NA)
Log K_{ow} Used	4.04	4.04
Biodegradation Factor Used	0	0
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	< 1	Not reported
Risk Characterization: PEC/PNEC	**< 1**	**N/A**

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

The RIFM PNEC is 0.004224 μg/L. The revised PEC/PNECs for EU and NA (not reported): not applicable; Cleared at screening-level therefore, does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed on: 01/11/2017.

11. Literature search*

- **RIFM database**: target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS
- **ECHA**: http://echa.europa.eu/
- **NTP**: http://tools.niehs.nih.gov/ntp_tox/index.cfm
- **OECD Toolbox**
- **SciFinder**: https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
- **PUBMED**: http://www.ncbi.nlm.nih.gov/pubmed
- **TOXNET**: http://toxnet.nlm.nih.gov/
- **IARC**: (http://monographs.iarc.fr)
- **OECD SIDS**: http://www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html
- **EPA Actor**: http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=0EF5C212B7906229F477472A9A4D05B7
- **US EPA HPVIS**: http://www.epa.gov/hpv/hpvis/index.html
- **US EPA Robust Summary**: http://cfpub.epa.gov/hpv-s/
- **Japanese NITE**: http://www.safe.nite.go.jp/english/db.html
- **Japan Existing Chemical Data Base**: http://dra4.nihs.go.jp/mhlw_data/jsp/SearchPageENG.jsp
- **Google**: https://www.google.com/webhp?tab=ww&ei=KMSoUpiQKarsQS324GwBg&ved=0CBQQ1S4

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

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2018.01.032.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2018.01.032.

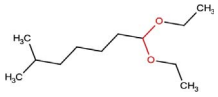
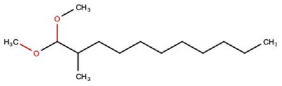
Appendix

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 structural 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).

	Target material	Read across material
Principal Name	1,1-diethoxyisooctane	2-methylundecanal dimethyl acetal
CAS No.	69178-43-4	68141-17-3
Structure		
Similarity (Tanimoto score)		0.71
Read across endpoint		• Genotoxicity
Molecular Formula	$C_{12}H_{28}O_2$	$C_{14}H_{30}O_2$
Molecular Weight	202.38	230.39
Melting Point (°C, EPISUITE)	−8.72	13.03
Boiling Point (°C, EPISUITE)	222.5	258.42
Vapor Pressure (Pa @ 25°C, EPISUITE)	23.3	3.82
Log Kow (KOWWIN v1.68 in EPISUITE)	4.08	5.06
Water Solubility (mg/L, @ 25°C, WSKOW v1.42 in EPISUITE)	14.01	1.445
J_{max} (mg/cm^2/h, SAM)	12.755	3.337
Henry's Law (Pa·m^3/mol, Bond Method, EPISUITE)	6.48E-004	1.14E-003
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)	• Carcinogen (moderate 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-diethoxyisooctane (CAS # 69178-43-4). Hence, *in silico* evaluation was conducted by determining a read across analog for this material. Based on structural similarity, reactivity, metabolism data, physical-chemical properties and expert judgment, the analog 2-methylundecanal dimethyl acetal (CAS # 68141-17-3) was identified as a read across material with data for the respective toxicological endpoints.

Conclusion/Rationale

- 2-methylundecanal dimethyl acetal (CAS # 68141-17-3) could be used as a read across analog for the target material 1,1-diethoxyisooctane (CAS # 69178-43-4) for the genotoxicity endpoint.
  - o The target substance and the read across analog are structurally similar and belong to the same structural class of aliphatic acetals.
  - o The target substance and the read across analog share branched aliphatic acetal structures.
  - o The key difference between the target substance and the read across analog is the length and branching of the aliphatic acetal. For the target

substance, there is branching (isopropyl group) at the end of the chain while the read across analog has a methyl group alpha to the acetal carbon. The differences in structure between the target substance and the read across analog do 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 in the table above. The Tanimoto score is mainly driven by the acetal with the long aliphatic chain on the aldehyde group. The differences in the structure 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 J_{max} value for the read across analog is lower than the target substance, so the read across analog is predicted to have skin absorbance in the range of 10%–40% compared to the range for the target substance which is 40%–80%. This difference in skin absorption does not create a significant difference in the toxicity profile of the substances. 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 According to the ISS model, the read across analog is predicted to be a carcinogen with moderate reliability, while the target is predicted to be a non-carcinogen with low probability. The negative genotoxicity data supersedes this prediction.
- o Other structural alerts for the genotoxicity endpoints are consistent between the target substance and the read across analog as shown in the table above.
- o The target substance and the read across analog 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 and the target substance.

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