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Short Review

RIFM fragrance ingredient safety assessment, 1,2-dimethoxybenzene, CAS Registry Number 91-16-7

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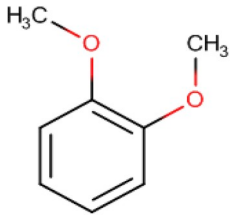


Abbreviation/Definition List:

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 guidance relevant to human health and environmental protection.

Summary: The existing information supports the use of this material as described in this safety assessment.
1,2-Dimethoxybenzene was evaluated for genotoxicity, repeated dose toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data from 1,2-dimethoxybenzene and read-across analog 1,4-dimethoxybenzene (CAS # 150-78-7) show that 1,2-dimethoxybenzene is not expected to be genotoxic. Data show that there are no safety concerns for 1,2-dimethoxybenzene for skin sensitization under the current declared levels of use. The repeated dose, reproductive, and local respiratory toxicity endpoints were evaluated using the TTC for a Cramer Class I material, and the exposure to 1,2-dimethoxybenzene 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; 1,2-dimethoxybenzene is not expected to be phototoxic/photoallergenic. For the environmental endpoints, 1,2-dimethoxybenzene is not a PBT as per the IFRA Environmental Standards, and its risk quotients (i.e., PEC/PNEC) for the aquatic environment, based on its current volume of use in Europe and North America, are < 1.

Human Health Safety Assessment

Genotoxicity: Not expected to be genotoxic.
(ECHA REACH Dossier: Veratrole; ECHA, 2013; ECHA REACH Dossier: 1,4-Dimethoxybenzene; ECHA, 2011)
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. (ECHA REACH Dossier: Veratrole; ECHA, 2013)
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic. (UV Spectra, RIFM DB)
Local Respiratory Toxicity: No NOAEC available. Exposure is below the TTC.

Environmental Safety Assessment

Hazard Assessment:
Persistence: Critical Measured Value: 97% (OECD 301C) (ECHA REACH Dossier: Veratrole; ECHA, 2013)
Bioaccumulation: Screening-level: 5.28 L/kg (EPI Suite v4.11; US EPA, 2012a)
Ecotoxicity: Screening-level: Fish LC50: 415.1 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: 415.1 mg/L (RIFM Framework; Salvito et al., 2002)
RIFM PNEC is: 0.4151 μg/L
- Revised PEC/PNECs (2015 IFRA VoU): North America and Europe

1. Identification

1. **Chemical Name:** 1,2-Dimethoxybenzene
2. **CAS Registry Number:** 91-16-7
3. **Synonyms:** Benzene, 1,2-dimethoxy-; Catechol dimethyl ether; Veratrol; Veratrol-E; 1,2-Dimethoxybenzene
4. **Molecular Formula:** $C_8H_{10}O_2$
5. **Molecular Weight:** 138.17
6. **RIFM Number:** 6268
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible

2. Physical data

1. **Boiling Point:** 192.33 °C (EPI Suite)
2. **Flash Point:** 95 °C (GHS)
3. **Log K_{OW}:** 1.64 (EPI Suite)
4. **Melting Point:** 5.6 °C (EPI Suite)
5. **Water Solubility:** 3666 mg/L (EPI Suite)
6. **Specific Gravity:** 1.08200 to 1.08600 @ 25.00 °C*
7. **Vapor Pressure:** 0.179 mm Hg @ 20 °C (EPI Suite), 0.267 mm Hg @ 25 °C (EPI Suite)
8. **UV Spectra:** Minor absorbance between 290 and 700 nm; molar absorption coefficient is below the benchmark ($1000\ L\ mol^{-1} \cdot cm^{-1}$)
9. **Appearance/Organoleptic:** A colorless clear liquid with a sweet, creamy, vanilla, phenolic, and musty odor.*

* http://www.thegoodscentscompany.com/data/rw1040471.html, 12/06/17.

3. Exposure to fragrance ingredient

1. **Volume of Use (Worldwide Band):** < 0.1 metric tons per year (IFRA, 2015)
2. **95th Percentile Concentration in Hydroalcoholics:** 0.0060% (RIFM, 2014)
3. **Inhalation Exposure*:** 0.000022 mg/kg/day or 0.0015 mg/day (RIFM, 2014)
4. **Total Systemic Exposure**:** 0.00025 mg/kg/day (RIFM, 2014)

*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:** 1,4-dimethoxybenzene (CAS # 150-78-7)
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)

1,2-Dimethoxybenzene is reported to occur in nature in the following foods by the VCF*:

Allium species.
Katsuobushi (dried bonito).
Asparagus (*Asparagus officinalis* L.)
Litchi (*Litchi chinensis* Sonn.)
Beans.
Olive (*Olea europaea*).
Buckwheat.
Peas (*Pisum sativum* L.)
Cauliflower and broccoli.
Pulasan (*Nephelium ramboutan-ake* [Labill.] Leenh.)
Cheese, various types.
Rambutan (*Nephelium lappaceum* L.)
Chinese quince (*Pseudocydonia sinensis* Schneid).
Rhubarb.
Endive (*Cichorium endivia* L.)
Rice (*Oryza sativa* L.)
Fish.
Starfruit (*Averrhoa carambola* L.)
Grape (*Vitis* species).
Tea.
Grape brandy.
Vanilla.
Guava and feyoa

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

8. IFRA standard

None.

9. REACH Dossier

Available, accessed 07/27/18.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data, 1,2-dimethoxybenzene does not present a concern for genotoxicity.

10.1.1.1. Risk assessment. The mutagenic activity of 1,2-dimethoxybenzene 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/pre-incubation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were treated with 1,2-dimethoxybenzene 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 (ECHA, 2013). Under the conditions of the study, 1,2-dimethoxybenzene was not mutagenic in the Ames test.

There are no studies assessing the clastogenicity of 1,2-dimethoxybenzene. The clastogenic activity of the read-across material 1,4-dimethoxybenzene (CAS # 150-78-7) was evaluated in an *in vivo* micronucleus test conducted in compliance with GLP regulations and in accordance with OECD TG 474. 1,4-dimethoxybenzene was administered in starch mucilage via oral gavage administration, to groups of male and female NMRI mice; doses of 0 or 2000 mg/kg body weight were administered. Mice from each dose level were euthanized at 12, 24, or 48 h, the bone marrow was extracted and examined for polychromatic erythrocytes. The test material did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow (ECHA, 2011). Under the conditions of the study, 1,4-dimethoxybenzene was considered to be not clastogenic in the *in vivo* micronucleus test.

Based on the data available, 1,2-dimethoxybenzene does not present a concern for genotoxic potential.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/29/17.

10.1.2. Repeated dose toxicity

There are insufficient repeated dose toxicity data on 1,2-dimethoxybenzene or any read-across materials. The total systemic exposure to 1,2-dimethoxybenzene 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 1,2-dimethoxybenzene or any read across materials that can be used to support the repeated dose toxicity endpoint. The total systemic exposure to 1,2-dimethoxybenzene (0.25 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: 11/28/17.

10.1.3. Reproductive toxicity

There are insufficient reproductive toxicity data on 1,2-dimethoxybenzene or any read-across materials. The total systemic exposure to 1,2-dimethoxybenzene 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 1,2-dimethoxybenzene or any read across materials that can be used to support the reproductive toxicity endpoint. The total systemic exposure to 1,2-dimethoxybenzene (0.25 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: 11/28/17.

10.1.4. Skin sensitization

Based on the existing data, 1,2-dimethoxybenzene does not present a safety concern for skin sensitization under the current, declared levels of use.

10.1.4.1. Risk assessment. Based on the existing data, 1,2-dimethoxybenzene does not present a safety concern for skin sensitization under the current, declared levels of use. The chemical structure of this material indicates that it would not be expected to react with skin proteins (Toxtree 2.6.13; OECD toolbox v3.4). In a murine local lymph node assay, 1,2-dimethoxybenzene was found to be negative up to maximum tested concentration of 100% which resulted in a Stimulation Index (SI) of 1.70 (ECHA, 2013).

Based on weight of evidence from structural analysis and animal studies, 1,2-dimethoxybenzene does not present a safety concern for skin sensitization under the current, declared levels of use.

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/31/17.

10.1.5. Phototoxicity/photoallergenicity

Based on the available UV/Vis spectra, 1,2-dimethoxybenzene 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 1,2-dimethoxybenzene in experimental models. UV/Vis absorption spectra indicate minor absorbance between 290 and 700 nm. The corresponding molar absorption coefficient is below the benchmark of concern for phototoxicity and photoallergenicity (Henry et al., 2009). Based on lack of significant absorbance in the critical range, 1,2-dimethoxybenzene does not present a concern for phototoxicity or photoallergenicity.

10.1.5.2. UV spectra analysis. UV/Vis absorption spectra (OECD TG 101) for 1,2-dimethoxybenzene were obtained. The spectra indicate minor 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 et al., 2009).

Additional References: None.

Literature Search and Risk Assessment Completed On: 10/12/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure could not be calculated due to lack of appropriate data. The exposure level 1,2-dimethoxybenzene 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 1,2-dimethoxybenzene. Based on the Creme RIFM Model, the inhalation exposure is 0.0015 mg/day. This exposure is 933 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: 12/01/2017.

10.2. Environmental endpoint summary

10.2.1. Screening-level assessment

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

10.2.2. Risk assessment

Based on the current Volume of Use (2015), 1,2-dimethoxybenzene 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. 1,2-Dimethoxybenzene has been registered under REACH, and the following data is available:

A ready biodegradability of the test material was evaluated according to the MITI test following the OECD 301C method. After 14 days, biodegradation of 97% was observed.

A *Daphnia magna* immobilization test was conducted according to the OECD 202 method under static conditions. The 48-h EC50 was reported to be greater than 100 mg/L.

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) (mg/L)	EC50 (*Daphnia*) (mg/L)	EC50 (Algae) (mg/L)	AF	PNEC (μg/L)	Chemical Class
RIFM Framework Screening-level (**Tier 1**)	415.1			1,000,000	0.4151	

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

Exposure	Europe	North America
Log K_{ow} used	1.64	1.64
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 the available data, the RQ for this material is < 1. No further assessment is necessary.

The RIFM PNEC is 0.4151 μg/L. The revised PEC/PNECs for EU and NA: not applicable. The material was cleared at the 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: 11/29/17.

11. Literature Search*

- **RIFM Database:** Target, Fragrance Structure Activity Group materials, other references, JECFA, CIR, SIDS

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

Search keywords: CAS number and/or material names.

*Information sources outside of RIFM's database are noted as appropriate in the safety assessment. This is not an exhaustive list. The links listed above were active as of 07/27/2018.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Declaration of interests

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. 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110618.

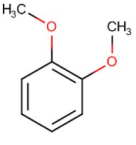
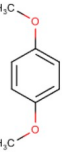
Appendix

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 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 (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	1,2-Dimethoxybenzene	1,4-Dimethoxybenzene
CAS No.	91-16-7	150-78-7
Structure		
Similarity (Tanimoto Score)		0.84
Read Across Endpoint		• Genotoxicity
Molecular Formula	$C_8H_{10}O_2$	$C_8H_{10}O_2$
Molecular Weight	138.17	138.17
Melting Point (°C, EPI Suite)	−5.60	−5.60
Boiling Point (°C, EPI Suite)	192.33	192.33
Vapor Pressure (Pa @ 25 °C, EPI Suite)	35.6	11.4
Log Kow (KOWWIN v1.68 in EPI Suite)	1.60	2.04
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	3666	1543
J_{max} (μg/cm^2/h, SAM)	93.774	154.265
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.89E-005	1.89E-005
Genotoxicity		

DNA Binding (OASIS v1.4, QSAR Toolbox v3.4)	• No alert found	• No alert found
DNA Binding (OECD QSAR Toolbox v3.4)	• Michael addition	• Michael addition
Carcinogenicity (ISS)	• Non-carcinogen (low reliability)	• Non-carcinogen (low reliability)
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)	• H-acceptor-path 3H acceptor	• No alert found
Oncologic Classification	• Not classified	• Not classified
Metabolism		
Rat Liver S9 Metabolism Simulator and Structural Alerts for Metabolites (OECD QSAR Toolbox v3.4)	See Supplemental Data 1	See Supplemental Data 2

Summary

There are insufficient toxicity data on 1,2-dimethoxybenzene (CAS # 91-16-7). Hence, *in silico* evaluation was conducted to determine read-across analogs for this material. Based on structural similarity, reactivity, metabolism, physical–chemical properties, and expert judgment, 1,4-dimethoxybenzene (CAS # 150-78-7) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- 1,4-Dimethoxybenzene (CAS # 150-78-7) was used as a read-across analog for the target material 1,2-dimethoxybenzene (CAS # 91-16-7) for the genotoxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aryl alkyl ethers.
  - o The target substance and the read-across analog share a common aromatic ether fragment.
  - o The key structural difference between the target substance and the read-across analog is that the read-across analog has a 1,4 dimethoxy fragment, while the target material has 1,2 dimethoxy fragment. This structural difference is toxicologically insignificant.
  - o Structural similarity between the target substance and the read-across analog is indicated by the Tanimoto score. The Tanimoto score is mainly driven by the common aromatic ether fragment. Differences between the structures that affect the Tanimoto score are toxicologically insignificant.
  - o The physical–chemical properties of the target substance and the read-across analog are sufficiently similar to enable comparison of their toxicological properties.
  - o According to the OECD QSAR Toolbox v3.4, structural alerts for toxicological endpoints are consistent between the target substance and the read-across analog.
  - o The read-across analog and target material are predicted to cause a Michael addition alert by the OECD model. In addition, the target material is also predicted to have an *in vivo* mutagenicity alert. The data described for the read-across analog in the genotoxicity section shows the read-across analog substance does not pose a concern under current exposure level. All the other alerts for genotoxicity are negative for both of the substances. Therefore, the alert for the read-across analog and the target material will be superseded by the data.
  - 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 endpoints evaluated are consistent between the metabolites of the read-across analog and the target material.

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