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Short Review

RIFM fragrance ingredient safety assessment, diphenyl ether, CAS Registry Number 101-84-8

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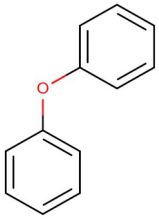
Version: 111218. This version replaces any previous versions.
Name: Diphenyl ether
CAS Registry Number: 101-84-8



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., 2015a, 2017) compared to a deterministic aggregate approach

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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.
Diphenyl ether (CAS # 101-84-8) was evaluated for genotoxicity, repeated dose toxicity, developmental and reproductive toxicity, local respiratory toxicity, phototoxicity/photoallergenicity, skin sensitization, and environmental safety. Data show that diphenyl ether is not genotoxic. Target data and data from read-across analog 3-phenoxytoluene (CAS # 3586-14-9) provide a calculated MOE >100 for the developmental and reproductive toxicity endpoints. Target data provide a calculated MOE > 100 for the repeated dose and local respiratory endpoints. The skin sensitization endpoint was completed using DST for non-reactive materials (900 μg/cm^2); exposure is below the DST. The phototoxicity/photoallergenicity endpoints were evaluated based on UV spectra; diphenyl ether is not expected to be phototoxic/photoallergenic. The environmental endpoints were evaluated; diphenyl ether was found not to be a 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.	(ECHA Dossier: Diphenyl ether; ECHA, 2011; Monsanto Co, 1989a)
Repeated Dose Toxicity: NOAEL = 230 mg/kg/day.	RIFM (1990a)
Developmental toxicity: NOAEL = 367.5 mg/kg/day.	(ECHA Dossier: Diphenyl ether; ECHA, 2011; JECDB: 3-Phenoxytoluene)
Reproductive Toxicity: NOAEL = 100 mg/kg/day.	(ECHA Dossier: Diphenyl ether; ECHA, 2011; JECDB: 3-Phenoxytoluene)
Skin Sensitization: No safety concerns at current, declared use levels; exposure is below the DST.	
Phototoxicity/Photoallergenicity: Not expected to be phototoxic/photoallergenic.	(UV Spectra, RIFM Database)
Local Respiratory Toxicity: NOEC = 34.81 mg/m^3.	(ECHA Dossier: Diphenyl ether; ECHA, 2011; Hefner et al., 1975)

Environmental Safety Assessment

Hazard Assessment:	
Persistence: Critical Measured Value: 91% OECD 301F	RIFM (2010a)
Bioaccumulation: Critical Measured Value: BCF: 594 OECD 305C	Hardy (2004)
Ecotoxicity: Critical Ecotoxicity Endpoint: 21-day *Daphnia magna* NOEC: 0.12 mg/L	RIFM (2017b)
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: 21-day *Daphnia magna* NOEC: 0.12 mg/L	RIFM (2017b)
RIFM PNEC is: 2.4 μg/L	
• Revised PEC/PNECs (2015 IFRA VoU): North America and Europe: < 1	

1. Identification

1. **Chemical Name:** Diphenyl ether
2. **CAS Registry Number:** 101-84-8
3. **Synonyms:** Benzene, 1,1′-oxybis; Diphenyl oxide; Phenyl ether; ｼﾞﾌｪﾆﾙｴｰﾃﾙ; 1,1′-Oxydibenzene; Diphenyl ether
4. **Molecular Formula:** $C_{12}H_{10}O$
5. **Molecular Weight:** 170.21
6. **RIFM Number:** 132
7. **Stereochemistry:** Isomer not specified. No stereocenter and no stereoisomers possible.

2. Physical data

1. **Boiling Point:** 257.9 °C (Dow Chemical, USA), 259 °C (FMA Database), 269.66 °C (US EPA, 2012a)
2. **Flash Point:** 115 °C (GHS), > 200 °F; CC (FMA Database), 239 °F
3. **Log K_{OW}:** 3.6 (RIFM, 2010b), 4.05 (US EPA, 2012a)
4. **Melting Point**: 35.35 °C (US EPA, 2012a)
5. **Water Solubility:** 15.58 mg/L (US EPA, 2012a)
6. **Specific Gravity:** 1.073 (FMA Database), 1.070 @ 25 °C (Dow Chemical, USA)
7. **Vapor Pressure:** 0.00973 mm Hg @ 20 °C (US EPA, 2012a), 0.01 mm Hg 20 °C (FMA Database), 0.017 mm Hg @ 25 °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:** EOA Spec. no. 43: A colorless liquid with an aromatic ether odor

3. Exposure

1. **Volume of Use (worldwide band):** > 1000 metric tons per year (IFRA, 2015)
2. **95**th **Percentile Concentration in Hydroalcoholics:** 0.041% (RIFM, 2017a)
3. **Inhalation Exposure*:** 0.00062 mg/kg/day or 0.044 mg/day (RIFM, 2017a)
4. **Total Systemic Exposure**:** 0.0012 mg/kg/day (RIFM, 2017a)

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

4. Derivation of systemic absorption

1. **Dermal:** Considered 23%

RIFM, 1990b; Ford and Api, 1993; RIFM, 2003; EC, 2012; ECHA, 2011: Absorption, distribution, and elimination of diphenyl ether was evaluated in male Sprague Dawley CD rats at approximately 9 weeks of age. Four male rats per group received 1 topical application with a mixture of radiolabeled (specific activity of 67.1 μCi/mg) and non-radiolabeled diphenyl ether formulated in diethyl phthalate at dose concentrations of 0.5%, 5%, and 50% (approximately equivalent to 10, 100, and 1000 mg/kg). Doses were applied to a gauze square with a dose volume of 2 mL/kg; these patches were placed on the shaved skin of the animal backs and held in place by semi-occlusive dressing and tape. Animals were placed in Jencons all-glass metabolism cages specially designed for separate collection of urine, feces, and expired air. Urine was collected at 4 different time points: 0–6, 6–24, 24–48, and 48–72 h after treatment. Feces and expired air were collected at 0–24, 24–48, and 48–72 h after treatment. After 6 h of exposure to the radiolabeled diphenyl ether, the dose area of the animals was swabbed with cotton wool and soaked in diethyl phthalate. Skin dressings, swabs, and gloves worn by operators were retained for further analysis. Seventy-two hours post dosing, animals were euthanized by carbon dioxide, and blood samples were removed from the vena cava and placed into a heparinized tube. Total radioactivity was measured in all samples of urine, feces, expired air, cage wash, skin swabs, skin dressings, whole blood, plasma, liver, kidneys, gastrointestinal tract, treated skin, untreated skin, and remaining carcasses by a liquid scintillation counter. All biological samples were processed in duplicate whenever possible. After 6 h of exposure, 73%, 70%, and 71% of the dose was removed from the dosed skin sites during skin washing of dose groups 10, 100, and 1000 mg/kg, respectively. Recovery of total radioactivity over 72 h was 18.65%, 17.52%, and 15.84% in urine; 1.72%, 1.18%, and 3.79% in feces; 4.91%, 4.38%, and 4.70% in cage wash; 0.5%, 2.8%, and 0.19% in cage air; 0.82%, 0.75%, and 1.37% in treated skin; 0.17%, 0.27%, and 0.13% in untreated skin; 0.28%, 0.39%, and 0.41% in tissues; and 0.19%, 0.22%, and 0.23% in carcasses for dose groups 10, 100, and 1000 mg/kg, respectively. About 0.2% of the dose was retained in the body, with low levels observed in the liver, kidneys, and gastrointestinal tract at 72 h. Approximately 1% of the radioactivity was reported to be associated with the dosed skin even after 72 h post dosing. 30–60% of this 1% was reportedly bound to the skin. A small amount (0.13–0.27%) of radioactivity detected in non-dosed skin was attributed to the rats spreading labeled material during grooming after the semi-occluded binding was removed. Moreover, a small amount (approximately 0.19–2.80%) of radiolabeled diphenyl ether was found in the cage and air, suggesting a chance of either volatility from the skin and/or expiration into the air by the animals. This study has indicated a steady dermal penetration of 19–23% of the administered dose over a 72-h period. This range was calculated from the amount of radioactivity found in urine, feces, tissues, skin washings, carcasses, and treated skin. The highest level of radioactivity was found in the gastrointestinal tract.

Dow, 1935: In an *in vivo* study, a saturated water solution of diphenyl ether was applied to the shaved skin of the guinea pig. Reportedly, the test substance was not absorbed to any extent.

EastmanKodak Co, 1989: In an *in vivo* study, undiluted diphenyl ether was applied to the skin of 2 guinea pigs at concentrations of 1–10 mL/kg. No evidence of skin absorption was reported up to 10 mL/kg.

Hotchkiss (1998); EC, 2012: In an *in vitro* dermal absorption study, the percutaneous absorption of diphenyl ether was studied in the human skin absorption model (SAM) under both occlusive and non-occlusive conditions. The *in vitro* SAM system was constructed with freshly obtained circles of human skin placed into flow-through diffusion cells. The surface temperature was maintained at 32 °C. Skin was either occluded with a Teflon cap or left open to the atmosphere. The radiolabeled test substance was applied to the skin surface. A buffer or tissue culture medium flowed across the underside of the skin to aid the maintenance of skin viability; this receptor fluid was collected at hourly intervals for up to 72 h and assayed for penetrated parent compound and metabolites by liquid scintillation spectrometry and/or HPLC. At the end of the experiment, the skin surface was washed to remove any unabsorbed material, and the skin was digested to assess residual radioactive material (parent compound and/or metabolites). The 72-h dermal absorption of the test substance was reported to be 0.2% of the applied dose in the human SAM under both occlusive and non-occlusive conditions.

Hotchkiss (1998); EC, 2012: In an *in vitro* dermal absorption study, the percutaneous absorption of diphenyl ether was studied in the rat

SAM under both occlusive and non-occlusive conditions. The *in vitro* SAM system was constructed with freshly obtained circles of rat skin placed into flow-through diffusion cells. Surface temperature was maintained at 32 °C. Skin was either occluded with a Teflon cap or left open to the atmosphere. The radiolabeled test substance was applied to the skin surface. A buffer or tissue culture medium flowed across the underside of the skin to aid the maintenance of skin viability; this receptor fluid was collected at hourly intervals for up to 72 h and assayed for penetrated parent compound and metabolites by liquid scintillation spectrometry and/or HPLC. At the end of the experiment, the skin surface was washed to remove any unabsorbed material, and the skin was digested to assess residual radioactive material (parent compound and/or metabolites). The 72-h dermal absorption of the test substance was reported to be 0.3% of the applied dose in the rat SAM under both occlusive and non-occlusive conditions.

Conclusion: An *In vivo* dermal absorption study of diphenyl ether (formulated in diethyl phthalate) in rats under occluded conditions showed a dermal penetration of 19–23% of the administered dose over a 72-h period. The total dermal absorption of diphenyl ether in an *in vitro* study using a rat skin model under occlusive and non-occlusive conditions was 0.3% of the applied dose. The total dermal absorption of diphenyl ether in an *in vitro* study using a human skin model under occlusive and non-occlusive conditions was 0.2% of the applied dose. Conservatively, the rat *in vivo* dermal absorption of 23% can be considered for this risk assessment.

2. **Oral:** Considered 100%

Law and Chakrabarti, 1983a; WHO, 2004: (^{14}C) diphenyl ether (2.2 μCi/2.2 mg) was administered once orally to male Crl:CD Sprague Dawley rats (number not reported) at the dose level of 10 mg/kg via stomach tube. The test substance was dissolved in an aqueous mixture of 0.1 w/v Tween 80 in water:ethanol (6:4 v/v) prior to administration. Post dosing, rats were individually housed in metabolic cages. Urine and fecal samples were collected at different time points for 6 days. Radioactivity was determined by a liquid scintillation counter. The test substance was reportedly readily absorbed after the intragastrical administration. The absorption rate constant was reported to be 0.024/hour. Maximum blood concentration of the test substance was reportedly reached within 15 h and decreased linearly with time. Greater than 90% of the administered dose was reportedly excreted in urine and feces within 3 days. Conservatively, oral absorption can be considered as 100%.

3. **Inhalation:** Assumed 100%

5. Computational toxicology evaluation

1. **Cramer Classification:** Class III, High

Expert Judgment	Toxtree v 2.6	OECD QSAR Toolbox v 3.2 (OECD, 2012)
III	III	III

2. **Analogs Selected:**
   a. **Genotoxicity:** None
   b. **Repeated Dose Toxicity:** None
   c. **Developmental and Reproductive Toxicity:** 3-Phenoxytoluene (CAS # 3586-14-9)
   d. **Skin Sensitization:** None
   e. **Phototoxicity/Photoallergenicity:** None
   f. **Local Respiratory Toxicity:** None
   g. **Environmental Toxicity:** None
3. Read-across Justification: See Appendix

6. Metabolism

In vivo studies in animals have shown that diphenyl ether undergoes absorption following oral administration (80–90% of dose, Law and Chakrabarti, 1983a) and dermal application (19–23% of applied dose, RIFM, 1990b). Following oral administration to rats, diphenyl ether equivalents are distributed to most tissues, with highest concentrations found in liver, lungs, kidney, and spleen (Law and Chakrabarti, 1983a). Small amounts of diphenyl ether equivalents were considered to be irreversibly bound (based on unextractable ^{14}C-diphenyl ether equivalents) to liver, lungs, and kidneys at 2–4 h after intraperitoneal administration (Law et al., 1983b). The amount of this binding decreased in all tissues by 8 h. Orally administered diphenyl ether undergoes extensive metabolism following absorption. These metabolites are then excreted primarily in the urine and minimally in the feces (Law and Chakrabarti, 1983a). Based on studies in rats, rabbits, and guinea pigs, the metabolites are identified as 2-hydroxy, 4-hydroxy, 4,4′-dihydroxy, 4-methoxymonohydroxy, and/or methoxy-dihydroxy derivatives of diphenyl ether or glucuronide/sulfate conjugates of some of these hydroxy-derivatives (Bray et al., 1953). The results also confirm that ether cleavage is not a major route of biotransformation (Law and Chakrabarti, 1983a). It is expected that the metabolism of diphenyl ether following dermal application would be similar to that following oral administration.

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

Fragrance Ingredient is a component of the following naturals:

Diphenyl ether is reported to occur in the following foods by the VCF*:

Beef.
Buckwheat.
Capers (*Capparis spinoza*)
Grape (*Vitis* species)
Lemon Balm (*Melissa officinalis* L.)
Potato Chips (American)
Tea.
Vanilla (*Vanilla spp.*)

*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

accessed 11/03/14.

10. Summary

10.1. Human health endpoint summaries

10.1.1. Genotoxicity

Based on the current existing data and use levels, diphenyl ether does not present a concern for genetic toxicity.

10.1.1.1. Risk assessment. The mutagenic activity of diphenyl ether has been evaluated in a bacterial reverse mutation assay conducted equivalent with OECD TG 471 using the standard plate incorporation method. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were treated with diphenyl ether in dimethyl sulfoxide (DMSO)

at concentrations up to 500 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, 2011). Under the conditions of the study, diphenyl ether was not mutagenic in the Ames test. The mutagenicity of diphenyl ether was also evaluated in an *in vitro* mammalian cell gene mutation test conducted in compliance with GLP regulations and equivalent with OECD TG 476. Chinese hamster ovary cells deficient in HPRT were treated with diphenyl ether in acetone at concentrations of 10, 50, 100, 167, and 333 μg/mL in the presence and absence of metabolic activation. No increase was observed in the mean mutation frequencies of the cells (ECHA, 2011). Under the conditions of the study, diphenyl ether was considered not mutagenic in mammalian cells.

The clastogenic activity of diphenyl ether was evaluated in a GLP-compliant *in vitro* chromosome assay conducted by the National Toxicology Program (NTP) in accordance with OECD TG 473. Chinese hamster ovary cells were treated with diphenyl ether in acetone at concentrations of 5, 50, 100, 250, 500, 750, 1000, 2500, and 5000 μg/mL in the presence and absence of metabolic activation. No significant increase in the number of aberrations per cell was observed at any dose level, with and without S9 mix (Monsanto Co, 1989a). Under the conditions of the study, diphenyl ether was considered not clastogenic in mammalian cells.

Based on the available data, diphenyl ether does not present a concern for genotoxic potential.

Additional References: Pagano et al., 1983; Florin et al., 1980; Haworth et al., 1983; Bronzetti et al., 1981; Pagano et al., 1988; Clark et al., 1979; Boecker et al., 1977; Monsanto Co, 1987; Monsanto Co, 1989b; Westinghouse, 1984

Literature Search and Risk Assessment Completed On: 11/27/2017.

10.1.2. Repeated dose toxicity

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

10.1.2.1. Risk assessment. There are sufficient repeated dose toxicity data on diphenyl ether via the dermal, inhalation, and oral routes.

10.1.2.1.1. Dermal. In a GLP-compliant (details on guideline followed not indicated) dermal toxicity study, 12 Sprague Dawley rats/sex/dose were treated dermally daily (6 h/day, semi-occlusive) for 13 weeks with diphenyl ether to the clipped skin at dose levels of 0 (vehicle: diethyl phthalate), 100, 300, and 1000 mg/kg/day (dose volume: 2 mL/kg). Additionally, another group of 12 animals/sex was used as distilled water control. No recovery groups were included. No treatment-related mortality or clinical signs were reported. Desquamation and erythema at the application site were reported in all animals, including vehicle control groups. Statistically significant reduction in bodyweight gain in high-dose males (13%) was observed, but this change was within the normal variability. No change in body weight was reported in females. Slight intergroup differences in total food consumption were reported but remained within normal variability, whereas no differences were reported for water consumption. A statistically significant increase in mean corpuscular volume (MCV) in the high-dose males was observed, but due to absence of any other changes in the red blood cell parameters, this change was not considered to be an adverse effect. High-dose group animals showed statistically significant increases in albumin and phosphate levels, while reduced cholesterol levels were reported among high-dose females. Statistically significant increases in albumin levels were also observed in mid-dose females. No changes were observed in urinalysis parameters among any groups. Statistically significant increases in liver weights were reported in both the sexes of mid- and high-dose group animals. Also, statistically significant increases in kidneys and brain weights were observed among males of the high-dose group. No treatment-related changes were reported in both microscopic and macroscopic evaluations. Necrotizing papillitis in the kidney was reported in one high-dose male but was not accompanied by pelvic dilation. Mild/minimal epidermal thickening with or without slight hyperkeratosis was seen in all animals except 1 female in the control group. In summary, the findings at the high dose were reduction in bodyweight gain in males, changes in skin application sites, and organ weight changes (increase in liver, kidney, and brain weights). The findings at the mid dose consisted of changes in skin sites and increased liver weights. The findings at the low dose were limited to slight application reactions on the skin. None of organ weight changes in any dose group was accompanied by any microscopic changes. Therefore, the highest dose of 1000 mg/kg/day was considered as the systemic NOAEL, considering the lack of any biologically and toxicologically significant systemic effects (RIFM, 1990a; RIFM, 2003; ECHA, 2011; EC, 2012). Further, to account for bioavailability following dermal application, data from the *in vivo* dermal absorption study (RIFM, 1990b; RIFM, 2003) was used to revise the NOAEL of 1000 mg/kg/day to reflect the systemic dose. At a dermal penetration of 23% of the applied dose, the revised repeated dose toxicity NOAEL from the dermal study is 230 mg/kg/day.

10.1.2.1.2. Inhalation. Sub-acute inhalation repeated dose toxicity studies were performed on Sprague Dawley rats (Spartan sub-strain). In the first experiment, groups of male rats (20 animals/dose) were exposed via whole-body exposure to vapors of diphenyl oxide at concentrations of 0 (control: ambient air), 4.9, and 10 ppm (equivalent to 0, 35, and 71 mg/m^3, respectively) under dynamic airflow conditions in 1-m^3 glass-walled chambers for 7 h/day, 5 days/week, for a total of 20 exposures over 31–33 days. In another experiment, 10 rats/sex/dose were exposed to diphenyl oxide vapor at concentrations of 0 and 20 ppm (equivalent to 0 and 142 mg/m^3, respectively), 7 h/day, 5 days/week, for a total of 20 exposures over 27 days. A statistically significant decrease in body weights of male rats was observed in the 20 ppm group. There were statistically significant decreases in mean white blood cell counts in the 4.9 and 10 ppm groups, and there were decreases in levels of hemoglobin in the 10 ppm group. The authors did not consider the alterations in body weight at 10 or 20 ppm and hematology at 10 ppm among males to be of toxicological significance, since such effects were not reported consistently among the animals of either sex among treatment groups. The NOAEC for systemic toxicity was considered to be 20 ppm (equivalent to 142 mg/m^3), the highest dose tested. In another sub-acute inhalation repeated dose toxicity study, male New Zealand white rabbits (4/group) were exposed via whole-body exposure to vapors of diphenyl oxide at concentrations of 0 (control: ambient air), 4.9, and 10 ppm (0, 35, and 71 mg/m^3, respectively) under dynamic airflow conditions in 1-m^3 glass-walled chambers 7 h/day, 5 days/week, for a total of 20 exposures over 31–33 days. There were no treatment-related alterations reported among treated animals; therefore, the NOAEC for systemic toxicity was considered to be 10 ppm (equivalent to 71 mg/m^3) due to no toxic effects observed up to the highest dose tested. In another sub-acute inhalation repeated dose toxicity study, male beagle dogs (2/group) were exposed via whole-body exposure to vapors of diphenyl oxide at concentrations of 0 (control: ambient air), 4.9, and 10 ppm (0, 35, and 71 mg/m^3, respectively) under dynamic airflow conditions in 1-m^3 glass-walled chambers 7 h/day, 5 days/week, for a total of 20 exposures over 31–33 days. No treatment-related effects were observed among treated animals. Therefore, the NOAEC for systemic toxicity was considered to be 10 ppm (71 mg/m^3), based on no adverse effects observed in all treated dogs.

10.1.2.1.3. Oral. In a GLP OECD 408-compliant repeated dose toxicity study, 20 rats/sex/dose were fed with diets containing diphenyl ether at concentrations of 0, 200, 1000, and 5000 ppm for 13 weeks (actual doses ingested: males—0, 11.7, 60.7, and 301.1 mg/kg/day, respectively, and females—0, 14.5, 73.9, and 334.8 mg/kg/day, respectively). After 13 weeks treatment, 10 animals/sex/dose from

control and all treatment groups were kept for 4 weeks as a recovery period. No mortality was observed in any group. No treatment-related clinical signs were reported in any group. Redness around the eyes and/or nose and alopecia was observed in animals across all groups; these were considered incidental and unrelated to the treatment. Significant decreases in mean weekly body weight and food consumption were observed in both sexes at 5000 ppm and only in females at 1000 ppm during the treatment period. These changes might have been due to decreased palatability of the test diet, since similar findings were not reported among recovery group animals. No statistically significant changes were observed in hematology parameters either in the main or recovery dose groups. Statistically significant decreases in glucose and albumin levels were reported in males and females of the mid-dose group, respectively. These changes were not dose-dependent; hence, they were not considered treatment-related. Significant increases in phosphorus levels were reported in high-dose males, and these values were within the range of in-house historical control data; hence, they were not considered treatment-related. Statistically significant decreases in total protein and globulin levels in mid-dose males and potassium in low- and high-dose females at the end of recovery period were reported. However, these changes were not related to treatment as these effects were observed only in recovery groups and not in the main dose groups. No treatment-related effects were reported in urinalysis. Chorioretinal degeneration was reported in 1 low- and 2 high-dose animals after ophthalmic examinations. However, these changes were typical post-inflammatory lesions and not indicative of treatment-related alterations. Statistically significant reductions in absolute weights of the heart were reported in high-dose (male and female) and mid-dose (female) groups. Adrenals weights were also significantly reduced in high-dose females. Since no microscopic lesions were reported in heart and adrenals, these changes were not considered to be toxicologically significant. No changes were observed in absolute organ weights, whereas relative weights of brain, liver, spleen, kidneys, and gonads were statistically significantly increased in high-dose males and females at both terminal and recovery periods. Since the absolute weights of these organs were not increased, it was reported that these effects were attributable to the decreased palatability of the test diet rather than considered toxic effects. Enlarged mandibular lymph nodes, lung foci, and urinary bladder calculi in males were observed in both treatment and control groups; these changes were not considered related to test substance administration. No test substance-related microscopic lesions were reported. Based on an absence of treatment-related adverse effects, the NOAEL for systemic toxicity was considered to be 301 mg/kg/day and 335 mg/kg/day (highest dose tested) for males and females, respectively (Johnson et al., 1992; ECHA, 2011; EC, 2012).

The 13-week dermal toxicity study in rats was considered the most relevant study for the selection of a systemic toxicity NOAEL for the risk assessment of diphenyl ether. Further, to account for bioavailability following dermal application, data from the *in vivo* dermal absorption study (RIFM, 1990b; RIFM, 2003) was used to revise the NOAEL of 1000 mg/kg/day to reflect the systemic dose. At a dermal penetration of 23% of the applied dose, the revised repeated dose toxicity NOAEL from the dermal study is 230 mg/kg/day.

Therefore, the diphenyl ether margin of exposure for the repeated dose toxicity endpoint can be calculated by dividing the diphenyl ether NOAEL in mg/kg/day by the total systemic exposure to diphenyl ether, 230/0.0012 or 191667.

In addition, the total systemic exposure to diphenyl ether (1.2 μg/kg bw/day) is below the TTC (1.5 μg/kg bw/day; Kroes et al., 2007; Laufersweiler et al., 2012 of a Cramer Class III material) for the repeated dose toxicity endpoint at the current level of use.

Additional References: Pecchiai and Saffiotti, 1957.

Literature Search and Risk Assessment Completed On: 12/06/2017.

10.1.3. Developmental and reproductive toxicity

The margin of exposure for diphenyl ether is adequate for the developmental and reproductive toxicity endpoints at the current level of use.

10.1.3.1. Risk assessment. There are sufficient developmental toxicity data on diphenyl ether.

In a GLP and OECD 414-compliant prenatal developmental toxicity study, Therminol VP-1—a mixture of 73.5% diphenyl ether (CAS # 101-84-8) and 26.5% biphenyl (CAS # 92-52-4)—in corn oil was gavaged to 24 mated Sprague Dawley (Crl:CD) female rats/group at dose levels of 0 (vehicle: corn oil), 50, 200, and 500 mg/kg/day during days 6–15 of gestation. All surviving females were euthanized on day 20 of gestation. At 500 mg/kg/day, treatment-related mortality was reported in 2 rats (mortality rate = 8.3%) on day 11 of gestation. Staining of the fur in the ano-genital (A-G) area was reported to be a common finding in both dead animals. No treatment-related mortality was reported in other groups. At 200 and 500 mg/kg/day, treatment-related excessive salivation (3/24 and 9/24), A-G stains (4/24 and 8/24), and alopecia (8/24 and 14/24) were reported. A-G stains were also reported in 1 female rat in the control group. At 500 mg/kg/day, mean body weights were slightly lower than controls throughout the gestation period. The difference was statistically significant on day 15. Mean bodyweight gain using the corrected day 20 body weights were reportedly lower than the controls in all treated groups (−13.2%, −21.1%, and −36.4% at 50, 200, and 500 mg/kg/day, respectively). The decrease was reported to be statistically significant at 200 and 500 mg/kg/day. At 200 and 500 mg/kg/day, a statistically significant treatment-related decrease in the mean food consumption compared to controls was reported for GDs 6–10 and 10–15. Mean gravid uterine weights and pregnancy rates were comparable between the control and treated groups. No treatment-related effects were reported on number of corpora lutea, uterine implantations, viable fetuses, and resorptions per pregnant female, mean pre-implantation loss index, mean resorption/implant ratio, and uterine implants. Mean fetal weights and fetal sex distribution were comparable among the groups. Examination of the fetuses revealed no malformations or variations at any dose level. At 50 mg/kg/day, 2 fetuses with non-treatment-related external malformations were reported. In the absence of dose response, these changes were not considered treatment-related. No treatment-related incidences of fetuses with visceral and skeletal malformations were reported. No treatment-related effects on the ossification variations were reported. The incidence of rudimentary rib structures adjacent to the first-lumbar vertebra transverse process at the 200 mg/kg/day was not considered treatment-related based on historical control data and the absence of a dose response relationship. The NOAEL for maternal toxicity was 50 mg/kg/day based on the adverse effects observed at ≥200 mg/kg/day (reduced food intake, retarded bodyweight gain, alopecia, A-G stains, and salivation) and mortality at 500 mg/kg/day. The NOAEL for developmental toxicity was 500 mg/kg/day based on the absence of embryotoxicity or teratogenicity up to the highest tested dose level.

The test material contained diphenyl ether (73.5%) and biphenyl (26.5%). Therefore, the developmental NOAEL derived for diphenyl ether was 367.50 mg/kg/day (=500 mg/kg/day *73.5%/100%) (ECHA, 2011; EC, 2012, https://www.google.co.in/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0ahUKEwic8NLO6ZzXAhUIrY8KHbpZAv4QFgglMAA&url=http%3A%2F%2Fec.europa.eu%2Fsocial%2FBlobServlet%3FdocId%3D10148%26langId%3Den&usg=AOvVaw1pJ4ANuV9z580Vyr1pvF-v). A NOAEL of 367.50 mg/kg/day was considered for risk assessment of the developmental toxicity endpoint.

Therefore, the diphenyl ether MOE for the developmental toxicity endpoint can be calculated by dividing the diphenyl ether NOAEL by the total systemic exposure for diphenyl ether, 367.50/0.0012 or 306250.

Table 1
Acceptable concentrations for diphenyl ether that present no appreciable risk for skin sensitization based on non-reactive DST.

IFRA Category[a]	Description of Product Type	Acceptable Concentrations in Finished Products Based on Non-reactive DST	Reported 95th Percentile Concentration in Finished Products
1	Products applied to the lips	0.07%	0.01%
2	Products applied to the axillae	0.02%	0.02%
3	Products applied to the face using fingertips	0.41%	0.00%[b]
4	Fine fragrance products	0.39%	0.04%
5	Products applied to the face and body using the hands (palms), primarily leave-on	0.10%	0.02%
6	Products with oral and lip exposure	0.23%	0.00%[b]
7	Products applied to the hair with some hand contact	0.79%	0.01%
8	Products with significant ano-genital exposure	0.04%	No Data[c]
9	Products with body and hand exposure, primarily rinse-off	0.75%	0.07%
10	Household care products with mostly hand contact	2.70%	0.13%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	1.50%	No Data[c]
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted	2.72%

Note.
[a] For a description of the categories, refer to the IFRA/RIFM Information Booklet.
[b] Negligible exposure (< 0.01%).
[c] Fragrance exposure from these products is very low. These products are not currently in the Creme RIFM Aggregate Exposure Model.

There are no reproductive toxicity data on diphenyl ether. Read-across material 3-phenoxytoluene (CAS # 3586-14-9; see Section 5) has an oral reproduction/developmental toxicity screening test conducted in rats. Groups of 12 Crj:CD (SD) IGS rats/sex/dose were dosed orally with 3-phenoxytoluene at 0, 25, 100, or 400 mg/kg/day. Male rats were dosed for a total of 47 days. Females were dosed for 2 weeks premating, through gestation, and through 4 days of lactation. There were no effects of treatment on fertility parameters among treated animals except for an increase in relative epididymal weights. The NOAEL for reproductive toxicity was considered to be 100 mg/kg/day, based on increased relative epididymis weights (JECDB: 3-Phenoxytoluene).

Therefore, the MOE for reproductive toxicity is equal to the 3-phenoxytoluene NOAEL in mg/kg/day divided by the total systemic exposure, 100/0.0012 or 83333.

Additional References: None.

Literature Search and Risk Assessment Completed On: 12/06/2017.

10.1.4. Skin sensitization

Based on the available data and the application of DST, diphenyl ether 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 (Toxtree 2.6.13; OECD toolbox v3.4). In guinea pigs, a maximization test and an open epicutaneous test did not present reactions indicative of sensitization (RIFM, 1982; Klecak, 1985). In a human maximization test, no skin sensitization reactions were observed (RIFM, 1970).

Acting conservatively, due to the limited data, the reported exposure was benchmarked utilizing the non-reactive Dermal Sensitization Threshold (DST) of 900 μg/cm^2 (Safford, 2008; Safford et al., 2011; Safford et al., 2015b; Roberts et al., 2015). 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 concentrations for diphenyl ether that present no appreciable risk for skin sensitization based on the non-reactive DST. These concentrations are not limits; they represent acceptable concentrations based on the DST approach.

Additional References: None.

Literature Search and Risk Assessment Completed On: 11/21/17.

10.1.5. Phototoxicity/photoallergenicity

Based on UV/Vis absorption spectra, diphenyl ether 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 diphenyl ether 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, diphenyl ether 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: 11/30/17.

10.1.6. Local Respiratory Toxicity

The margin of exposure for diphenyl ether is adequate for the respiratory endpoint at the current level of use.

10.1.6.1. Risk assessment. The inhalation exposure estimated for combined exposure was considered along with toxicological data observed in the scientific literature to calculate the MOE from inhalation exposure when used in perfumery. In a 4-week repeat dose inhalation study conducted with whole-body exposure, the NOEC was determined to be 34.81 mg/m^3 (ECHA, 2011; Hefner et al., 1975). Twenty male Sprague Dawley rats per group were exposed to either 34.81 or 69.62 mg/m^3 (nominal concentrations) diphenyl ether vapor (control group: ambient air) 7 h/day, 5 days/week, for a total of 20 exposures. In a follow-up to these exposures, an additional group of both male and female Sprague Dawley rats of Spartan strain (10/sex/group) were exposed to 139.23 mg/m^3 (nominal concentration) diphenyl ether vapor (control group: ambient air) for 4 weeks (7 h/day, 5 days/week, 20 total exposures). The different groups were monitored regularly for signs of both irritation and toxicity. Body weights, hematology (including differential cell counts, hemoglobin, and hematocrit), BUN, SGPT and ALP activity, organ weights, gross pathology, and histopathology were all considered. Physical irritation

of the eyes and nostrils was observed in the rats (69.62 mg/m^3 and 139.23 mg/m^3). In the case of the rats exposed to 34.81 or 69.62 mg/m^3 diphenyl ether vapor, there was a significant decrease in white blood cell count and hemoglobin concertation. These hematological changes were not present in the 139.23 mg/m^3 exposure group (male or female). Overall, no acute adverse effects were observed in animals exposed to 34.81 mg/m^3 diphenyl ether vapor. Therefore, due to irritancy effects reported for rats at higher concentrations, the NOEC was determined to be 34.81 mg/m^3.

This NOEC expressed in mg/kg lung weight/day is:

- (34.81 mg/m^3) (1m^3/1000L) = 0.03481 mg/L
- Minute ventilation (MV) of 0.17 L/min for a Sprague Dawley rat × duration of exposure of 360 min per day (min/day) (according to GLP study guidelines) = 61.2 L/day
- (0.03481 mg/L) (61.2 L/day) = 2.13 mg/day
- (2.13 mg/day)/(0.0016 kg lung weight of rat*) = 1331.25 mg/kg lung weight/day

The 95th percentile calculated exposure was reported to be 0.044 mg/day—this value was derived from the concentration survey data in the Creme RIFM exposure model (Comiskey et al., 2015 and Safford et al., 2015a). To compare this estimated exposure with the NOAEC expressed in mg/kg lung weight/day, this value is divided by 0.65 kg human lung weight (Carthew et al., 2009) to give 0.068 mg/kg lung weight/day resulting in an MOE of 19577 ([1331.25 mg/kg lung weight/day]/[0.068 mg/kg lung weight/day]).

The MOE is greater than 100. Without adjustment for specific uncertainty factors related to interspecies and intraspecies variation, the material exposure by inhalation at 0.044 mg/day is deemed to be safe under the most conservative consumer exposure scenario.

*Phalen, R.F. Inhalation Studies. Foundations and Techniques, 2 nd Ed 2009. Published by Informa Healthcare USA, Inc., New York, NY. Chapter 9, Animal Models, in section: “Comparative Physiology and Anatomy,” subsection, “Comparative Airway Anatomy.”

Additional References: Dorgelo et al., 1985; UGCM, 1997; Monsanto Co, 1992; EastmanKodak Co, 1989.

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 diphenyl ether 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, diphenyl ether was identified as a fragrance material with the potential to present a possible risk to the aquatic environment (i.e., its screening-level PEC/PNEC > 1).

A screening-level hazard assessment using EPI Suite v4.11 (US EPA, 2012a) did not identify diphenyl ether as possibly being either 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 v4.11). 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), diphenyl ether presents a risk to the aquatic compartment in the screening-level assessment.

10.2.3. Key studies

10.2.3.1. Biodegradation. RIFM, 1993a: A sealed vessel test based on OECD 301B guidelines was conducted to determine the ready and ultimate biodegradability of the test material. Diphenyl ether (10 mg/L) was added to vessels containing mineral salts medium inoculated with secondary effluent and incubated for 28 days. The biodegradation rate at 10 and 28 days was 13.5% and 2.9%, respectively.

RIFM, 1993b: A sealed vessel test based on OECD 301B guidelines was conducted to determine the ready and ultimate biodegradability of the test material. Diphenyl ether (10 mg/L) was added to vessels containing mineral salts medium inoculated with secondary effluent and incubated for 28 days. The biodegradation rate at 28 days was −0.9%.

RIFM, 2010a: The ready biodegradability of the test material was evaluated using a Manometric Respirometry Test according to the OECD 301F method. 30 mg/L of sludge and 20 mg/L of diphenyl oxide were incubated for 33 days. Diphenyl oxide underwent 91% biodegradation in 28 days and was non-toxic to the inoculum.

Hardy (2004): A bioaccumulation study according to the OECD 305 method was conducted using *Cyprinus carpio* (Japanese carp). The carp were tested at 2 concentrations of the test material for 6–8 weeks (until equilibrium in fish tissue). Concentrations of the test material in water and fish were determined periodically. The bioconcentration factor for diphenyl oxide was 594.

10.2.3.2. Ecotoxicity. NITE, 2011: An algae inhibition test was conducted using *Pseudokircheneriella subcapitata*. The 72-h EC50 and NOEC based on growth inhibition were reported to be 0.58 mg/L and 0.32 mg/L, respectively.

NITE, 2011: A 96-h acute toxicity study was conducted in fish (*Oryzias latipes*). The 96-h LC50 of the test material was reported to be 1.8 mg/L.

NITE, 2011: A 48-h acute toxicity test was conducted in *Daphnia magna*. The 48-h EC50 for diphenyl ether in *Daphnia magna* was 2.0 mg/L.

RIFM, 2017b: A *Daphnia magna* flow-through Life Cycle Toxicity test was conducted according to OECD 211 guidance. The 21-day NOEC based on mean measured test concentrations was reported to be 0.12 mg/L (total length and dry weight).

10.2.4. Other available data

Diphenyl ether has been registered under REACH and additional

data is available.

A 48-hr *Daphnia magna* acute toxicity study was conducted, and an EC50 of 1.7 mg/L was reported.

10.2.5. 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)**	9.311			1,000,000	0.009311	
ECOSAR Acute Endpoints **(Tier 2)** ***Ver 1.11***	5.112	3.365	4.617	10,000	0.3365	Neutral organics
Tier 3: Measured Data (including REACH data)						
	LC50	EC50	NOEC	AF	PNEC	Comments
Fish	1.8					
Daphnia		1.7	0.12	50	2.4	
Algae		0.58	0.32			

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

Exposure	Europe	North America
Log K_{ow} used	3.6	3.6
Biodegradation Factor Used	1	1
Dilution Factor	3	3
Regional Volume of Use Tonnage Band	100–1000	10–100
Risk Characterization: PEC/PNEC	**< 1**	**< 1**

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

The RIFM PNEC is 2.4 μg/L. The revised PEC/PNECs for EU and NA are < 1; therefore, the material does not present a risk to the aquatic environment at the current reported volumes of use.

Literature Search and Risk Assessment Completed On: 12/1/17.

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 10/09/2018.

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.2019.110632.

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 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	Diphenyl ether	Benzene, 1-methyl-3-phenoxy-
CAS No.	101-84-8	3586-14-9
Structure		
Similarity (Tanimoto Score)		0.75
Read-across Endpoint		• Developmental and reproductive
Molecular Formula	$C_{12}H_{10}O$	$C_{13}H_{12}O$
Molecular Weight	170.21	184.24
Melting Point (°C, EPI Suite)	35.35	51.91
Boiling Point (°C, EPI Suite)	269.66	285.65
Vapor Pressure (Pa @ 25 °C, EPI Suite)	2.266	0.6426
Log Kow (KOWWIN v1.68 in EPI Suite)	4.21	4.60
Water Solubility (mg/L, @ 25 °C, WSKOW v1.42 in EPI Suite)	15.58	6.232
J_{max} (μg/cm^2/h, SAM)	2.399	0.98
Henry's Law (Pa·m^3/mol, Bond Method, EPI Suite)	1.18E-004	4.37E-004
Reproductive and Developmental Toxicity		
ER Binding (OECD QSAR Toolbox v3.4)	• Non-binder, without OH or NH2 group	• Non-binder, without OH or NH2 group
Developmental Toxicity (CAESAR v2.1.6)	• Toxicant (low reliability)	• Toxicant (low reliability)
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 diphenyl ether (CAS # 101-84-8). 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, benzene, 1-methyl-3-phenoxy- (CAS # 3586-14-9) was identified as a read-across material with sufficient data for toxicological evaluation.

Conclusions

- Benzene, 1-methyl-3-phenoxy- (CAS # 3586-14-9) was used as a read-across analog for the target material diphenyl ether (CAS # 101-84-8) for the developmental and reproductive toxicity endpoint.
  - o The target substance and the read-across analog are structurally similar and belong to the class of aromatic ethers.
  - o The target substance and the read-across analog share a common diphenyl ether structure.
  - o The key structural difference between the target substance and the read-across analog is the read-across analog has a methyl substitution on one of the aromatic rings, whereas the target does not. 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 reflects the similarity of these diphenyl ether structures. 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 target and read-across analog are shown to be toxicants by the CAESAR v2.1.6 model. The data described for the read-across analog in the developmental and reproductive toxicity section show that the read-across analog does not pose a concern under the current exposure level. The ER binding alert, which is another fertility toxicity indicator, is negative for both substances. Therefore, the alert will be superseded by the data for the read-across analog.
- 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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