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Provisional Peer-Reviewed Toxicity Values for

Diphenyl Ether
(CASRN 101-84-8)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

[1]Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR DIPHENYL ETHER (CASRN 101-84-8)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by at least two National Center for Environment Assessment (NCEA) scientists and an independent external peer review by at least three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

PPRTV assessments are eligible to be updated on a 5-year cycle to incorporate new data or methodologies that might impact the toxicity values or characterization of potential for adverse human-health effects and are revised as appropriate. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. Environmental Protection Agency (EPA) Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVs

Questions regarding the content of this PPRTV assessment should be directed to the EPA Office of Research and Development's (ORD's) NCEA, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Diphenyl ether, CASRN 101-84-8, belongs to the class of compounds known as aromatic ethers. It is used mainly as a perfume, particularly in soaps, and as a heat-transfer medium for laminated electrical insulation (Lewis and Hawley, 2007). It can also be used as a chemical intermediate for polyesters and surfactants and for such reactions as halogenation, acylation, and alkylation (HSDB, 2015; Lewis and Hawley, 2007). Diphenyl ether is listed on U.S. EPA's Toxic Substances Control Act's public inventory (U.S. EPA, 2015), it is registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2017), and it was assessed under the U.S. EPA High Production Volume (HPV) program (U.S. EPA, 2016).

Commercial production of diphenyl ether occurs by heating potassium or sodium phenolate with bromo- or chlorobenzene under pressure. It is also manufactured as a byproduct during phenol production by the high-pressure hydrolysis of chlorobenzene (HSDB, 2015).

The empirical formula for diphenyl ether is $C_{12}H_{10}O$. Its chemical structure is shown in Figure 1. Table 1 summarizes the physicochemical properties of diphenyl ether. Diphenyl ether is a white or colorless crystalline solid at room temperature (HSDB, 2015). Diphenyl ether's vapor pressure indicates that it will exist almost entirely as a vapor in the atmosphere. The estimated half-life of vapor-phase diphenyl ether in air by reaction with photochemically produced hydroxyl radicals is 1.7 days. Diphenyl ether's Henry's law constant indicates that it may volatilize from moist surfaces, but volatilization from dry soil surfaces is not expected based on its vapor pressure. The moderate water solubility and soil adsorption coefficient indicate that diphenyl ether will have low mobility in soil, but that it may still leach to groundwater or undergo runoff after a rain event. Bioconcentration in aquatic organisms may also occur, based on experimental bioconcentration factor (BCF) values (HSDB, 2015).

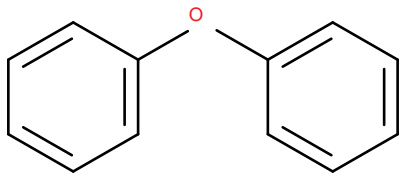

Figure 1. Diphenyl Ether Structure

Table 1. Physicochemical Properties of Diphenyl Ether (CASRN 101-84-8)

Property (unit)	Value
Physical state	Solid[a]
Boiling point (°C)	258[b]
Melting point (°C)	26.8[b]
Density (g/cm^3 at 20°C)	1.075[a]
Vapor pressure (mm Hg at 25°C)	0.0225[b]
pH (unitless)	NA
pKb (unitless)	5.79[c]
Solubility in water (mg/L at 25°C)	18[b]
Octanol-water partition coefficient (log K_{ow})	4.21[b]
Henry's law constant (atm-m^3/mol at 25°C)	2.8×10^{-4} (estimated)[b]
Soil adsorption coefficient K_{oc} (L/kg)	1,950[c]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	9.60×10^{-12} [b]
Atmospheric half-life (d)	1.087 (estimated)[b]
Relative vapor density (air = 1)	5.86[c]
Molecular weight (g/mol)	170.21[b]
Flash point (open cup in °C)	115[a]

[a]European Chemicals Agency (ECHA, 2016).
[b]U.S. EPA (2012b).
[c]Hazardous Substance Data Bank, ToxNet, NIH (HSDB, 2015).

NA = not applicable; NIH = National Institutes of Health.

A summary of available toxicity values for diphenyl ether from EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Diphenyl Ether (CASRN 101-84-8)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2017)
WHO (ADI)	Acceptable	No safety concern at current levels of intake when used as a flavoring agent	WHO (2003); WHO (2004a); WHO (2004b)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2017a); Cal/EPA (2017b)
OSHA (PEL)	1 ppm (7 mg/m^3)	8-hr TWA for vapor (general industry, construction, and shipyard employment)	OSHA (2011); OSHA (2006a); OSHA (2006b)
NIOSH (REL)	1 ppm (7 mg/m^3)	10-hr TWA for vapor	NIOSH (2015)
NIOSH (IDLH)	100 ppm	Based on being 100 times the NIOSH REL or OSHA PEL	NIOSH (2014)
ACGIH (TLV)	1 ppm	8-hr TWA; vapor; based on upper respiratory tract irritation, eye irritation, and nausea due in part to disagreeable odor	ACGIH (2016)
ACGIH (STEL)	2 ppm	15-min TWA; vapor; based on upper respiratory tract irritation, eye irritation, and nausea due in part to disagreeable odor	ACGIH (2015)
DOE (PAC)	PAC-1: 2 ppm; PAC-2: 16 ppm; PAC-3: 96 ppm	Based on TEELs	DOE (2016)
USAPHC (air-MEG)	1-hr critical: 600 mg/m^3; 1-hr marginal: 130 mg/m^3; 1-hr negligible: 13 mg/m^3; 8-hr negligible: 7 mg/m^3; 14-d negligible: 2.4 mg/m^3; 1-yr negligible: 2.4 mg/m^3	Vapor; based on upper respiratory tract irritation, eye irritation, and nausea	U.S. APHC (2013)
Cancer			
IRIS	NV	NA	U.S. EPA (2017)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2017)

Table 2. Summary of Available Toxicity Values for Diphenyl Ether (CASRN 101-84-8)

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2017a); Cal/EPA (2017b)
ACGIH	NV	NA	ACGIH (2016)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DOE = U.S. Department of Energy; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; USAPHC = U.S. Army Public Health Command; WHO = World Health Organization.
[b]Parameters: ADI = acceptable daily intake; IDLH = immediately dangerous to life or health concentrations; MEG = military exposure guideline; PAC = protective action criteria; PEL = permissible exposure level; REL = recommended exposure level; STEL = short-term exposure level; TLV = threshold limit value.

NA = not applicable; NV = not available; TEEL = temporary emergency exposure limit; TWA = time-weighted average.

Literature searches were conducted in January 2016 and updated in August 2017 for studies relevant to the derivation of provisional toxicity values for diphenyl ether, CASRN 101-84-8. Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (Cal/EPA), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), and Occupational Safety and Health Administration (OSHA).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer databases, respectively, for diphenyl ether and include all potentially relevant repeated-dose, short-term-, subchronic-, and chronic-duration studies, as well as reproductive and developmental toxicity studies. Principal studies are identified in bold. The phrase "statistical significance," used throughout the document, indicates a p-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Diphenyl Ether (CASRN 101-84-8)							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
Subchronic	10 M/10 F, S-D albino rat, diet, 13 wk; 0, 200, 1,000, 5,000 ppm	0, 11.7, 60.7, 301 (M); 0, 14.5, 73.9, 335 (F)	Decreases in mean body weights and food consumption, but magnitude of changes not reported; data insufficient to evaluate study authors' attribution of decreases to palatability of diet	NDr	NDr	Dow Chemical Co (2003); Johnson et al. (1992) [Abstract]	NPR
2. Inhalation (mg/m^3)							
Subchronic	**20 or 10 M/10 F, S-D Spartan rat, whole body, 7 hr/d, 5 d/wk for 20 exposures in 31 or 33 d; 0, 4.9 ± 1.5 (males only), 10.0 ± 2.0 (males only), 20 ppm (males and females)**	**HEC_{ET}: 0, 1.3, 2.66, 5.3 (M); 0, 4.3 (F)** **$HEC_{SYSTEMIC}$: 0, 7.1, 14.5, 29 (M); 0, 29 (F)**	**Eye and nasal irritation, decreased relative and absolute liver weights, increased relative brain weight, decreased WBC counts, and decreased Hb**	**NDr (HEC)**	**7.1 (HEC)**	**Dow Chemical Co (1986a); Hefner et al. (1975)**	**PR, PS**
Subchronic	4 M, New Zealand White rabbit, whole body, 7 hr/d, 5 d/wk for 20 exposures in 31 or 33 d; 0, 4.9 ± 1.5, 10.0 ± 2.0 ppm	HEC_{ET}: 0, 3.8, 7.66	Eye and nasal irritation	3.8 (HEC)	7.66 (HEC)	Dow Chemical Co (1986a); Hefner et al. (1975)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for Diphenyl Ether (CASRN 101-84-8)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Subchronic	2 M, Beagle dog, whole body, 7 hr/d, 5 d/wk for 20 exposures in 31 or 33 d; 0, 4.9 ± 1.5, 10.0 ± 2.0 ppm	$HEC_{SYSTEMIC}$: 0, 7.1, 14.5	Increased absolute kidney weight	NDr	7.1 (HEC)	Dow Chemical Co (1986a); Hefner et al. (1975)	PR

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).

[b]Dosimetry: Values are presented as ADDs (mg/kg-day) for oral noncancer effects and as HECs (mg/m^3) for inhalation noncancer effects. Because the observed effect in the inhalation studies in rats and rabbits was nasal irritation, the HECs were calculated using the equation for extrathoracic respiratory effects from a Category 1 gas (U.S. EPA, 1994): HEC_{ET} = continuous concentration in mg/m^3 × ratio of regional gas dose in laboratory animal species to that of humans for the extrathoracic region = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$. For dogs, only systemic effects were observed, and the HECs were calculated using the equation for systemic effects from a Category 3 gas (U.S. EPA, 1994): $HEC_{SYSTEMIC}$ = (ppm × MW ÷ 24.45) × (hours per day exposed ÷ 24) × (days exposed ÷ total days observed) × blood-air partition coefficient (U.S. EPA, 1994).

[c]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; CONC = concentration; ET = extrathoracic; F = female(s); Hb = hemoglobin; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); MW = molecular weight; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; RGDR = regional gas dose ratio; S-D = Sprague-Dawley; WBC = white blood cell.

Table 3B. Summary of Potentially Relevant Cancer Data for Diphenyl Ether (CASRN 101-84-8)							
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration, Reported Doses**	**Dosimetry**	**Critical Effects**	**NOAEL**	**LOAEL**	**Reference**	**Notes**
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							

LOAEL = lowest-observed-adverse-effect level; ND = no data; NOAEL = no-observed-adverse-effect level.

HUMAN STUDIES

Oral Exposures

No studies examining possible associations between health effects in humans and oral exposure to diphenyl ether were identified.

Inhalation Exposures

Data on the inhalation effects of diphenyl ether in humans are limited to qualitative descriptions of short-term exposures of volunteers to diphenyl ether vapor. Short exposures of ≤1 minute to 5 ppm (34.76 mg/m^3) perfume-grade diphenyl ether vapor were reportedly "well tolerated" (Dow Chemical Co, 1986a; Hefner et al., 1975). At 10 ppm (69.53 mg/m^3), subjects experienced distaste and upper respiratory irritation (Dow Chemical Co, 1973). No further data on the possible associations between health effects in humans, and inhalation exposure to diphenyl ether were identified.

ANIMAL STUDIES

Oral Exposures

Overview of Animal Oral Exposure Studies

Potentially relevant data for noncancer effects from oral exposure to diphenyl ether are limited to short-term-duration studies using a single rabbit or dog (Dow Chemical Co, 1986b, 1936a, b, 1935) and a 13-week feeding study in rats (Dow Chemical Co, 2003; Johnson et al., 1992).

Short-Term-Duration Studies

Dow Chemical Co (1935); Dow Chemical Co (1936b); Dow Chemical Co (1936a); Dow Chemical Co (1986b)

A rabbit received diphenyl ether at a dose of 100 mg/kg via stomach tube 5 days/week over a period of 29 days for a total of 19 doses. The test article was suspended in 5−10% gum acacia solution and feedings were prepared daily. The animal was monitored for clinical observations during the dosing period. At necropsy, the animal was examined for gross pathology. The animal survived the dosing period and no clinical signs of toxicity were observed. The only reported change was gross pathology in one lobe of the liver.

A dog (8.93 kg body weight) was fed 2.11 g/kg body weight of diphenyl ether for 1 week. The animal survived the dosing period and no clinical signs of toxicity were observed. No further study details were provided.

Subchronic-Duration Studies

Dow Chemical Co (2003); Johnson et al. (1992) [abstract]

Groups of Sprague-Dawley (S-D) albino rats (10/sex/group) were fed commercial-grade diphenyl ether in the diet at target concentrations of 0, 200, 1,000, or 5,000 ppm for 13 weeks. Additional groups of S-D rats (10/sex/group) were retained for a 4-week recovery period following the 13-week dosing period. The test article (study author stated purity >98%) was prepared neat in a premix and subsequent diets were prepared weekly. Periodic analysis of feed confirmed homogeneity and test article concentration levels. Measured doses were reported as 0, 11.7, 60.7, and 301 mg/kg-day for males and 0, 14.5, 73.9, and 335 mg/kg-day for females. Clinical observations were made daily. Feed consumption and body-weight gain were recorded weekly. Blood samples were collected prior to necropsy for standard hematology and serum chemistry. Urine samples were also collected prior to necropsy for urinalysis (appearance,

volume, specific gravity, occult blood, protein, pH, ketones, urobilinogen, glucose, bilirubin, and sediments). At necropsy, all animals were grossly examined. Organ weights for the brain, gonads, heart, kidneys, liver, and spleen were recorded. A complete histopathological examination was performed on all animals from the control and high-dose groups. Selected organs and tissues (lungs, liver, kidneys, and gross lesions) from the low- and mid-dose groups were also submitted for histopathology. This study was only available as an abstract (Johnson et al., 1992) and as a submission included within the Organisation for Economic Co-operation and Development's (OECD's) International Uniform Chemical Information Database (IUCLID) data set submitted for diphenyl ether by the Dow Chemical Company. The IUCLID submission is limited to a qualitative presentation of analytical results that does not include quantitative data for each endpoint evaluated. However, this study was flagged as a valid study that was conducted under Good Laboratory Practices (GLPs) consistent with OECD Test Guideline 408. Statistical analyses included multivariate repeated-measure analysis of variance (ANOVA) for body weights and gains, food consumption, ratio data, and both multivariate and univariate two-factor fixed effect ANOVA on log-transformed data for other endpoints. Additionally, Dunnett's test for multiple comparisons was used for comparisons of combined data of sexes.

Dow Chemical Co (2003) only reported results qualitatively; no data were provided in the available study report. No clinical signs of toxicity or mortality were observed. The study authors reported a significant decrease in mean weekly body weight and food consumption in high-dose animals during the entire dosing period, and in mid-dose females during most of the study (specific time points not reported). The magnitude of the observed changes was not reported. Food consumption, body-weight gains, and food conversion ratios were reported by the study authors to be significantly increased during ≥1 week of the recovery period. On this basis, the study authors attributed the decreases in body weight and food consumption, observed during the dosing period, to unpalatability of the test diet. Specific significant changes observed based on hematology, clinical chemistry, or urinalysis were not described in detail within the IUCLID submission. However, the study authors noted that the few statistically significant differences in these parameters were not dose related, were within range of historical laboratory values, or occurred only in the recovery animals. No significant changes in absolute organ weights were reported. Dow Chemical Co (2003) indicated that some statistically significant differences were observed in relative organ weights in high-dose rats and mid-dose females, but did not provide additional information. The study authors attributed changes in relative organ weights to the significant decreases in body weights seen at termination and not direct target organ toxicity. No significant pathological changes were reported.

No-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values cannot be assigned for this study based on the available description in the IUCLID submission. Decreases in food consumption and body weight were reported in high-dose males, and mid- and high-dose females, but no data on the magnitude of the observed changes were provided. The study authors suggested palatability of the diet to be the cause of the observed changes, rather than a toxic effect, but this conclusion cannot be independently evaluated without the associated data.

Chronic-Duration Studies

No studies examining the chronic or carcinogenic effects in animals from oral exposure to diphenyl ether were identified.

Reproductive/Developmental Studies

No studies examining the reproductive or developmental effects in animals from oral exposure to diphenyl ether were identified.

Inhalation Exposures

Overview of Animal Inhalation Exposure Studies

Potentially relevant data for noncancer effects from inhalation exposure to diphenyl ether come from a single study that used rats, rabbits, and dogs (Dow Chemical Co, 1986a; Hefner et al., 1975).

Subchronic-Duration Studies

Dow Chemical Co (1986a); Hefner et al. (1975)

Groups of male Spartan S-D rats (n = 20), male New Zealand White rabbits (n = 4), and male Beagle dogs (n = 2) were exposed to diphenyl ether vapor (perfume-grade, purity 99.85% containing 0.01−0.04% diphenyl) at target concentrations of 0, 5, or 10 ppm for 7 hours/day, 5 days/week for a total of 20 exposures over 31−33 days. The animals were exposed whole-body using exposure chambers. Measured chamber concentrations were 4.9 ± 1.5 and 10.0 ± 2.0 ppm (34 and 69.5 mg/m^3, respectively[2]). Additional groups of 10 male and 10 female Spartan S-D rats were exposed to diphenyl ether vapor at target concentrations of 0 or 20 ppm (140 mg/m^3) for 7 hours/day, 5 days/week for a total of 20 exposures in 27 days. Only the nominal concentration was determined for the 20 ppm (140 mg/m^3) exposure chamber. The converted mg/m^3 value for this high-exposure group was based on nominal concentration, but was not verified by analytical sampling of the chamber air. It should be noted that the exposure methodology for the two experiments in rats was considerably different. For the first experiment, the exposure chamber for the animals was 1,000 liters, and nitrogen gas was used as the carrier for diphenyl ether. For the additional exposure group with the higher concentration, the exposure chamber was 160 liters and filtered room air was used as the carrier. Food and water were provided ad libitum to all animals between exposures. Clinical observations were made on all animals during exposures and periodically between exposures. Body weights were recorded at regular intervals. Blood samples were collected from all rats exposed to diphenyl ether at 140 mg/m^3 after 1, 4, and 19 days of exposure. Blood samples were also collected at the end of the exposure period from 10 rats per dose group, and all of the rabbits and dogs. Hematologic and biochemical evaluations on blood samples included red, white, and differential cell counts, hemoglobin (Hb) concentrations, packed cell volume, blood urea nitrogen (BUN), serum alanine aminotransferase (ALT), and alkaline phosphatase (ALP). At necropsy, all animals were grossly examined. Organ weights for the brain, heart, liver, kidney, and testes were obtained for all animals exposed to 0, 34, or 69.5 mg/m^3 diphenyl ether vapor and from 10 rats (5/sex) exposed to 0 or 140 mg/m^3 diphenyl ether vapor. The spleen and thymus from 10 rats (5/sex) exposed to 0 or 140 mg/m^3 diphenyl ether vapor, and the adrenal glands from all of the dogs included in the study were also weighed. All major organs and tissues as well as any other grossly visible pathologic lesions were examined histologically. Statistical analyses employed ANOVA and Dunnett's test.

Rats exposed to ≥69.5 mg/m^3 diphenyl ether experienced eye and nasal irritation (incidence, severity, or statistical significance is not reported). Body- and organ-weight changes

[2]Concentrations converted to mg/m^3 by ppm × (MW ÷ 24.45). For example, 4.9 ppm × 170 g/mol ÷ 24.45 L/mol = 34 mg/m^3.

are shown in Table B-1. Mean terminal body weight among male rats exposed to 140 mg/m^3 was statistically significantly lower than concurrent controls (−7%), but was not biologically significant (<10%) and was similar to the other treated groups, which did not differ from their control group. Similarly, relative brain weight among male rats exposed to 140 mg/m^3 was statistically significantly elevated over concurrent controls (9%), but was identical to the value for the controls for the low- and mid-exposure groups. Conversely, mean absolute and relative liver weights among male rats exposed to 34 and 69.5 mg/m^3 were statistically and biologically significantly decreased compared to their concurrent control (−12% or more based on absolute weights; −8% or more based on relative weights), but liver weights among rats exposed to the high-exposure level of 140 mg/m^3 were comparable to their concurrent control. Body weight and organ weights were not different compared to controls in female rats exposed to 140 mg/m^3 diphenyl ether vapor (see Table B-1). Hb levels were significantly decreased in male rats at 69.5 mg/m^3 (see Table B-2). White blood cell (WBC) counts were also decreased in male rats at ≥34 mg/m^3 (see Table B-2). No significant changes in biochemical parameters or pathology were observed among exposed rats (data not shown). For rats, a LOAEL of 34 mg/m^3 is identified based on reduced absolute and relative liver weights, and decreased WBC counts; all in male rats. Because 34 mg/m^3 is the lowest concentration, a NOAEL cannot be identified. Exposure concentrations of 0, 34, and 69.5 mg/m^3 are converted to human equivalent concentrations (HECs) of 0, 7.1, and 14.5 mg/m^3, using the procedures described in U.S. EPA (1994) for systemic effects for a Category 3 gas in rats.[3]

Rabbits exposed to 69.5 mg/m^3 diphenyl ether vapor experienced mild eye and nasal irritation (incidence and severity data not reported). Because no numerical information was provided, statistical significance cannot be determined. No significant exposure-related changes in body weights, organ weights, or hematology were observed among exposed rabbits (body-, liver-, kidney-, and brain-weight data are shown in Table B-1; all other data not shown). Serum chemistry revealed significant decreases in BUN values among rabbits exposed to ≥34 mg/m^3 compared to controls (see Table B-2). The study authors indicated that the BUN levels among exposed rabbits were within the normal range of variation observed for control rabbits at their laboratory (15−27 mg/100 mL). Both control and exposed rabbits demonstrated lesions in the respiratory tract (incidence data not reported). The study authors noted that these lesions were associated with an inflammatory response to some type of respiratory infection. Additionally, the abdominal viscera of some rabbits contained granulomatous foci as a result of infestation with tapeworm larvae. No treatment-related pathological changes among exposed rabbits were reported. For rabbits, a LOAEL of 69.5 mg/m^3 is identified for eye and nasal irritation, with a corresponding NOAEL of 34 mg/m^3. Exposure concentrations of 0, 34, and 69.5 mg/m^3 are converted to HECs of 0, 3.8, and 7.66 mg/m^3, respectively, using the procedures described in U.S. EPA (1994) for extrathoracic respiratory effects of a Category 1 gas in rabbits.[4]

Dogs exposed to diphenyl ether vapor exhibited no clinical signs of toxicity or irritation. Changes observed in the terminal body weights and serum chemistry (BUN) of dogs exposed to diphenyl ether did not demonstrate a clear concentration-response; body weight (see Table B-1) and BUN (see Table B-2) decreased in dogs exposed to 34 mg/m^3 but not 69.5 mg/m^3. Biologically significant absolute kidney-weight increases were observed in male dogs with a

[3]$HEC_{SYSTEMIC}$ = Concentration × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood-gas partition coefficient.
[4]HEC_{ET} = Concentration × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × $RGDR_{ET}$.

19.6% increase at 34 mg/m^3 and 35.3% at 69.5 mg/m^3 (see Table B-1). Both control and exposed dogs demonstrated lesions in their lungs (incidence data not reported). The study authors noted that these lesions were characteristic of a focal minimal inflammatory reaction and were accompanied by the presence of nematode parasites. No treatment-related pathological changes among exposed dogs were reported. Based on increased absolute kidney weight in male dogs, a LOAEL of 34 mg/m^3 is identified. Because 34 mg/m^3 is the lowest concentration tested, a NOAEL cannot be identified. Exposure concentrations of 0, 34, and 69.5 mg/m^3 are converted to HECs of 0, 7.1, and 14.5 mg/m^3, using the procedures described in U.S. EPA (1994) for systemic effects for a Category 3 gas in dogs.[5]

Chronic-Duration Studies

No studies examining the chronic or carcinogenic effects in animals from inhalation exposure to diphenyl ether were identified.

Reproductive/Developmental Studies

No studies examining the reproductive or developmental effects in animals from inhalation exposure to diphenyl ether were identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Table 4A provides an overview of genotoxicity studies of diphenyl ether, and Table 4B provides an overview of acute studies of diphenyl ether.

[5]$HEC_{SYSTEMIC}$ = Concentration × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood-gas partition coefficient.

Table 4A. Summary of Diphenyl Ether (CASRN 101-84-8) Genotoxicity						
Endpoint	**Test System**	**Doses/Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**Reference**
Genotoxicity studies in prokaryotic organisms						
Mutation	*Salmonella typhimurium* TA98, TA100, TA1535, and TA1537	0, 3.3, 10, 33.3, 100, 333.3 µg/plate	−	−	Preincubation assay; cytotoxicity was observed at 333.3 µg/plate (−S9).	Haworth et al. (1983)
Mutation	*S. typhimurium* TA98, TA100, TA1535, and TA1537	3 µmol/plate	−	−	Spot test.	Florin et al. (1980)
Mutation	*S. typhimurium* TA97, TA98, TA100, TA1535, and TA1537? (five tester strains not specified)	Not specified	−	−	Nonmutagenic up to cytotoxic dose.	Bronzetti et al. (1981) [abstract]
Mutation	*S. typhimurium* TA98, TA100, TA1535, and TA1537	0, 1, 3, 10, 30, 100 µg/plate without S9 activation; 0, 3, 10, 30, 100, 300 µg/plate with S9 activation	−	−	Plate incorporation assay; cytotoxicity was observed at 300 and 100 µg/plate, with and without S9 activation, respectively. Test substance: Therminol® VP-1 (diphenyl ether 73.5%, biphenyl 26.5%).	Monsanto (1990a)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538, and/or TA1978	0, 5 (1:9), 10 (conc.) µL/plate (±S9); 10 µL/plate (+S9)	−	−	NA	Westinghouse Electric Corporation (1977)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538, TA2636, and TA1532	0, 0.1−500 µg/plate	−	−	Plate incorporation or preincubation assay; cytotoxicity was observed at 50−100 µg/plate, depending on strain (not specified). Similar results were obtained in an experiment with Dowtherm A® (diphenyl ether ~74%, biphenyl ~26%) using the same protocol.	Pagano et al. (1983)

Table 4A. Summary of Diphenyl Ether (CASRN 101-84-8) Genotoxicity

Endpoint	Test System	Doses/Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	Reference
Genotoxicity studies in nonmammalian eukaryotic organisms						
Gene conversion	*Saccharomyces cerevisiae* diploid D7 strain	Up to 10^{-3} M (−S9)	−	−	A nonsignificant increase in *trp*+ conversion and *ilv*+ reversion was reported. Moderate cytotoxicity was observed with direct exposure and enhanced when diphenyl ether was dissolved in DMSO (concentration was not specified).	Pagano et al. (1983)
Genotoxicity studies in mammalian cells in vitro						
CAs	CHO cells	0, 10, 50, 100, 150 µg/mL (−S9); 0, 5, 30, 50 µg/mL (+S9)	−	−	Cytotoxicity was observed at 150 µg/mL (−S9).	Monsanto (1989b)
UDS	Primary rat hepatocytes	Preliminary assay: 0, 0.1, 0.5, 1, 5, 10, 50, 100, 250, 500, 1,000 µg/mL; Repeat assay: 0, 1, 5, 10, 50, 100, 250, 1,000 µg/mL	−	−	Cytotoxicity was observed ≥100 µg/mL; precipitate was noted at ≥250 µg/mL. Test substance: Therminol® VP-1 (diphenyl ether 73.5%, biphenyl 26.5%).	Monsanto (1987a)
UDS	Primary rat hepatocytes	Preliminary assay: 0, 0.05, 0.1, 0.5, 1.0, 5.0, 10, 50, 100, 250, 500 µg/mL; Repeat assay: 1, 5, 10, 50, 100, 250 µg/mL	−	−	Cytotoxicity was observed at ≥200 µg/mL.	SRI International (1987)
Genotoxicity studies in nonmammalian cells in vivo						
Mitotic effects; Induction of larval malformations	*Paracentrotus lividus* embryos; 100 embryos were scored	0, 3×10^{-5}, 6×10^{-5}, 9×10^{-5} M	+	+	Lethality was observed at 9×10^{-5} M; observations included an increase in percentage of embryos at interphase, and percentage of mitotic abnormalities and a decrease in mitoses/embryo.	Pagano et al. (1983)

Table 4A. Summary of Diphenyl Ether (CASRN 101-84-8) Genotoxicity						
Endpoint	**Test System**	**Doses/Concentrations Tested**	**Results without Activation[a]**	**Results with Activation[a]**	**Comments**	**Reference**
Sperm inactivation assay	*Sphaerechinus granularis* sperm; 2-, 5-, 10-, 30-, or 60-min exposure; 1% DMSO (control)	0, 10^{-5} M	+	+	Fertilization rates were −9.5, −31, −84, −89, and −50% (2, 5, 10, 30, and 60 min, respectively) compared to vehicle control.	Pagano et al. (1983)
Induction of developmental abnormalities	*S. granularis* sperm, zygotes	0, 10^{-5} M	+	+	After exposure, observations made on eggs following fertilization included early cytolysis and abnormal cleavage (5 hr); cytolysis and pathologic survivors (24 hr); cytolysis (48 hr). Observations made on sperm included undifferentiated or filled blastulae (24 hr); and loss of motility and cytolysis (48 hr).	Pagano et al. (1983)
Genotoxicity studies in mammalian cells in vivo						
Bone marrow micronucleus assay	CD-1 mice (15/sex/dose); single injection (i.p.); corn oil vehicle; sacrifice 24, 48, and 72 hr after exposure	0, 100, 500, 1,000 mg/kg body weight	−	−	No significant increase in micronucleated PCEs was observed in any group; however, a significant decrease in the PCE:total erythrocyte ratio was noted in mice at 1,000 mg/kg (48-hr sacrifice). Mortalities included one male and three females in the high-dose group. Test substance: Therminol® VP-1 (diphenyl ether 73.5%, biphenyl 26.5%).	Monsanto (1990b)

[a]+ = positive; − = negative.

CA = chromosomal aberration; CHO = Chinese hamster ovary; DMSO = dimethylsulfoxide; DNA = deoxyribonucleic acid; i.p. = intraperitoneal; PCE = polychromatic erythrocyte; UDS = unscheduled DNA synthesis.

Table 4B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute studies				
Acute oral study	Three rats (strain not specified) exposed orally to diphenyl ether at doses ranging from 50−1,600 mg/kg.	Animals appeared moderate to quite weak; rough coats, slight ataxia.	Approximate LD_{50} for diphenyl ether is 400−1,600 mg/kg.	Eastman Kodak (1979)
Acute oral study	S-D albino rats (5/group) given a single oral dose of diphenyl ether of 2,000, 2,510, or 3,160 mg/kg. Rats were observed for 14 d.	Mortality: 0/5 at low dose; 3/5 at mid dose; 5/5 at high dose. Animals died within 1−2 d. Rats exhibited reduced appetite and activity (1−3 d in survivors), increased weakness.	Oral LD_{50} for diphenyl ether was 2,450 mg/kg (95% confidence limits of 2,200−2,720 mg/kg).	Monsanto (1977)
Acute inhalation study	S-D rats (6/sex) exposed to Therminol® VP-1 aerosol at concentrations ranging from 1,000−5,300 mg/m^3 for 4 hr. Rats were observed for 14 d and sacrificed for necropsy. Test substance: Therminol® VP-1 (diphenyl ether 73.5%, biphenyl 26.5%).	11/12 rats exposed to 5,300 mg/m^3 died. Clinical signs during exposure included salivation, hypoactivity, and active animals. Following exposure, the rats exhibited labored breathing, red encrustation around the nose and eyes, salivation, and hypoactivity. The animals also showed decreases in body weights. No macroscopic abnormalities were observed.	Inhalation LC_{50} for Therminol® VP-1 was 4,450 mg/m^3 for males, and 2,660 mg/m^3 for combined males and females. Insufficient data to calculate an LC_{50} for females.	Monsanto (1986)

LC_{50} = median lethal concentration; LD_{50} = median lethal dose; S-D = Sprague-Dawley.

Genotoxicity

Diphenyl ether was negative in tests for mutagenicity in bacteria (Monsanto, 1990a; Haworth et al., 1983; Pagano et al., 1983; Bronzetti et al., 1981; Florin et al., 1980; Westinghouse Electric Corporation, 1977) and gene conversion, and mitotic recombination in yeast (Pagano et al., 1983). Assays for chromosomal aberrations (CAs) in Chinese hamster ovary (CHO) cells and unscheduled deoxyribonucleic acid (DNA) synthesis in primary rat hepatocytes were also negative (Monsanto, 1989b, 1987a; SRI International, 1987). In vivo, diphenyl ether was negative for the induction of micronuclei (MN) in bone marrow cells collected from CD-1 mice receiving a single intraperitoneal (i.p.) injection of diphenyl ether (Monsanto, 1990a), but did induce developmental and mitotic abnormalities in sea urchin embryos and gametes (Pagano et al., 1983). The study authors suggested a possible health concern to humans, and urged mutagenicity and carcinogenicity testing in mammals, but admittedly, the possible hazard is only "suggested."

Metabolism/Toxicokinetic Studies

No studies on the toxicokinetics of diphenyl ether in humans were available. Toxicokinetic studies in animals show that diphenyl ether is readily absorbed and distributed to various rat tissues, with highest levels found in the liver and kidneys, and is rapidly excreted in urine and feces.

Api and Ford (2003) applied ^{14}C-diphenyl ether to the clipped skin of S-D rats using a semi-occlusive dressing for 6 hours. Diphenyl ether was diluted in diethyl phthalate to administer a total application volume of 2 mL/kg and concentrations of 0.5, 5, and 50% (approximately 10, 100, and 1,000 mg/kg). At 72 hours post application, approximately 0.2% of the administered doses were retained in the body, with low levels measured in the liver, kidney, and gastrointestinal (GI) tract (0.01−0.05, 0.01−0.05, and 0.24−0.35%, respectively). Diphenyl ether was also found in the cage and air (0.19−2.8%). The study authors suggested that this indicated that the ^{14}C-label volatilized from the skin and/or was expired from the animals. Diphenyl ether was primarily eliminated in the urine (15.84−18.65%), with smaller amounts also found in the feces (1.18−3.79%).

Following a single i.p. injection of 5 mg/kg ^{14}C-diphenyl ether to 12 male S-D rats, Law and Chakrabarti (1983) measured radioactivity irreversibly bound to tissue proteins in the livers and kidneys of treated rats 2 hours postinjection, and in the lungs after 4 hours. Additional similar investigations by Law et al. (1983) found radioactivity in all organs and tissues within 1 hour (peaked between 1 and 4 hours; remained at 8 hours postadministration). The highest levels of diphenyl ether were detected in the liver, lung, kidney, and spleen.

Following intragastric administration of 10 mg/kg ^{14}C-diphenyl ether to male S-D rats, Law et al. (1983) observed maximum concentration of unchanged diphenyl ether in the blood within 15 hours. The study authors described the blood concentration time curve as a one-compartment open pharmacokinetic model. More than 90% of the administered dose was excreted within 3 days; roughly 80% of the administered dose was detected in the urine, and about 10% in the feces. Mass spectral data of the urinary extract showed that the treated rats metabolized diphenyl ether to its 2-hydroxy-, 4-hydroxy-, 4,4'-dihydroxy-, 4-methoxy-monohydroxy-, and 4-methoxy-dihydroxy- derivatives. Similarly, Poon et al. (1986) measured these same metabolites in the urine of guinea pigs following i.p. administration with diphenyl ether.

Other Routes

Api and Ford (2003) applied diphenyl ether (purity >99%) to the skin of S-D rats (12/sex/dose) using a semi-occlusive dressing at 0, 100, 300, or 1,000 mg/kg-day, 6 hours/day for 13 weeks. Animals were monitored during the study for clinical signs, skin irritation, and changes in body weights and/or food consumption. Prior to necropsy, blood samples and urine were collected and submitted for analysis. At necropsy, selected organs were examined and weighed. Major tissues were collected from the control and high-dose animals, and submitted for histopathology; kidneys from all dose groups were submitted for histopathology. Slight skin reactions at the site of application were observed among treated rats with incidence exhibiting a dose-response. High-dose males exhibited a slight reduction in body weight. Absolute and relative liver weights were significantly higher in male rats at 300 mg/kg-day compared to controls, but only relative liver weights were significantly higher than controls at 1,000 mg/kg-day. Relative brain and kidney weights were also higher among high-dose male rats compared to controls. In female rats, relative liver weights were increased over controls at ≥300 mg/kg-day, and absolute liver weight was increased at 1,000 mg/kg-day. No histopathological lesions were seen in any organ examined.

Mixture Studies and Developmental Studies as a Mixture

Biodynamics (1989); Monsanto (1989a); Biodynamics (1987); Monsanto (1987b)

Biodynamics, Inc. conducted oral developmental toxicity studies in rats using eutectic mixture of biphenyl and diphenyl ether known as Therminol® VP-1 Heat Transfer Fluid (73.5% diphenyl ether; 26.5% biphenyl). In these studies, groups of mated S-D CD rats received daily doses of Therminol® VP-1 via gavage in corn oil on Gestation Days (GDs) 6−15. Animals had free access to food and water. Survival and clinical signs were monitored twice daily. Body weights were measured on GDs 0, 6, 10, 12, 15, and 20. Food consumption was recorded on GDs 0−6, 6−10, 10−15, and 15−20. Dams were sacrificed on GD 20 and subjected to a complete gross necropsy. The intact uterus (ovaries attached) was removed from all animals, weighed, and examined for numbers of live and dead fetuses, resorptions, and implantation sites. Ovaries were examined for the presence and number of corpora lutea. All fetuses were removed, weighed, sexed, and subjected to gross examination for external malformations. Data were not evaluated statistically by the study authors. Monsanto (1987b) reported the findings of the initial range-finding study among rats (5/group) dosed with Therminol® VP-1 at 0, 100, 200, 400, 800, or 1,500 mg/kg-day, and Biodynamics (1989)/Biodynamics (1987) reported the findings of the definitive developmental study among rats (24/group) dosed with Therminol® VP-1 at 0, 50, 200, or 500 mg/kg-day.

Maternal toxicity in rats, based on decreases in maternal body weights and weight gains, as well as food consumption, were observed in these developmental studies at doses of Therminol® VP-1 ≥100 mg/kg-day (Biodynamics, 1989, 1987; Monsanto, 1987b). Additionally, dams exhibited increased incidence of excessive salivation, staining of the skin/fur in the ano-genital area, and alopecia at ≥200 mg/kg-day. No embryotoxic or fetotoxic effects were seen below 800 mg/kg-day. Embryotoxicity, characterized by significantly increased frequencies of uterine resorptions and significantly decreased numbers of viable fetuses per litter, was observed at 800 mg/kg-day in conjunction with maternal toxicity. Fetotoxic effects, characterized by a higher female:male sex ratio and significantly lower fetal weights, were noted in the single litter recovered from the surviving dam receiving Therminol® VP-1 at 1,500 mg/kg-day.

The same researchers also conducted a subchronic-duration inhalation study in S-D rats using the Therminol® VP-1 Heat Transfer Fluid (Monsanto, 1989a). In this study, groups of rats (25/sex) were exposed whole-body to Therminol® VP-1 aerosol at target concentrations of 0, 10, 50, or 125 mg/m^3 for 6 hours/day, 5 days/week for 7 or 14 weeks. Rats were monitored for clinical signs and body-weight changes. Ten rats per group were sacrificed at 7 weeks, and sampled for hematology and serum biochemical analysis only. The remaining animals (15/group) were sacrificed at 14 weeks and subjected to gross examination. Adrenals, brain, heart, kidneys, liver, spleen, and testes were weighed and a complete histopathological examination was conducted. Measured concentrations in the exposure chambers were 0, 10, 51, or 130 mg/m^3. Animals in all exposure groups exhibited clinical signs, including focal loss of hair and red/pink discharge around the nose. Additionally, mid- and high-exposure animals exhibited salivation, red discharge around the eye, and lacrimation. Significant reductions in body weights were observed in the high-exposure animals from Weeks 2–6. Changes in hematology parameters did not demonstrate a clear exposure-response. Relative liver weights in males, and relative liver, brain, and spleen weights in females were significantly lower than controls among high-exposure rats. No microscopic changes were observed.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer references values, respectively.

Table 5. Summary of Noncancer Reference Values for Diphenyl Ether (CASRN 101-84-8)

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HEC)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	NDr						
Chronic p-RfD (mg/kg-d)	NDr						
Screening Subchronic p-RfC (mg/m^3)	Rat/M	Eye and nasal irritation	4×10^{-3}	NOAEL (HEC)	1.3	300	Dow Chemical Co (1986a); Hefner et al. (1975)
Screening Chronic p-RfC (mg/m^3)	Rat/M	Eye and nasal irritation	4×10^{-4}	NOAEL (HEC)	1.3	3,000	Dow Chemical Co (1986a); Hefner et al. (1975)

HEC = human equivalent concentration; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 6. Summary of Cancer Reference Values for Diphenyl Ether (CASRN 101-84-8)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

Information on the oral toxicity of diphenyl ether is available from a 13-week feeding study in rats (Dow Chemical Co, 2003; Johnson et al., 1992), and short-term-duration studies in rabbits and dogs using a single test subject per experiment. The available information is not sufficient for use in deriving subchronic or chronic provisional reference doses (p-RfDs). A description of the study is available only as an abstract (Johnson et al., 1992) and a summary submission within the IUCLID data set (Dow Chemical Co, 2003). The available study description does not include any data. Decreases in food consumption and body weight were reported in high-dose males, and mid- and high-dose females, but no data on the magnitude of the observed changes were provided. The study authors suggested palatability of the diet as the cause of the observed changes, rather than a toxic effect, but this conclusion cannot be independently evaluated without the associated data. NOAEL and LOAEL values could not be assigned for this study based on the available description in the IUCLID submission. As a result

of the uncertainties in the available data for diphenyl ether, subchronic and chronic p-RfDs are not derived.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The database of potentially relevant studies for deriving subchronic and chronic inhalation reference values for diphenyl ether is limited to a single study that used rats, rabbits, and dogs (Dow Chemical Co, 1986a; Hefner et al., 1975). This study was peer-reviewed with adequate numbers of exposure groups and investigated numerous endpoints. However, the critical effect (i.e., eye and nasal irritation in rats; see Appendix A for a detailed discussion for the selection of the critical effect) is based solely on qualitative statements made by the study authors (Dow Chemical Co, 1986a; Hefner et al., 1975). Due to the uncertainty in this critical effect given the complete lack of quantitative data, it is not sufficiently reliable to use in deriving subchronic or chronic provisional reference concentrations (p-RfCs) for diphenyl ether. However, the available inhalation study (Dow Chemical Co, 1986a; Hefner et al., 1975) is suitable for the derivation of "screening-level" values for subchronic and chronic inhalation exposure to diphenyl ether (see Appendix A).

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 7 identifies the cancer WOE descriptor for diphenyl ether.

Table 7. Cancer WOE Descriptor for Diphenyl Ether

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	There are no human data to support this.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no suitable animal studies to support this.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There are no suitable animal studies to support this.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**This descriptor is selected due to the lack of any information on the carcinogenicity of diphenyl ether.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	There are no suitable animal studies to support this.

NA = not applicable; NS = not selected; WOE = weight of evidence.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of diphenyl ether precludes derivation of quantitative estimates for either oral (provisional oral slope factor [p-OSF]) or inhalation (provisional inhalation unit risk [p-IUR]) exposure.

APPENDIX A. SCREENING PROVISIONAL VALUES

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional toxicity values for diphenyl ether. However, information is available for this chemical, which although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the main documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

DERIVATION OF A SUBCHRONIC PROVISIONAL REFERENCE CONCENTRATION

The database of potentially relevant studies for deriving subchronic and chronic inhalation reference values for diphenyl ether is limited to a single study that used rats, rabbits, and dogs (Dow Chemical Co, 1986a; Hefner et al., 1975). The study is a whole-body inhalation toxicity study that exposed rats (20 males), rabbits (4 males), and dogs (2 males) to diphenyl ether 7 hours/day, 5 days/week for 31–33 days with chamber concentrations of 0, 34, and 69.5 mg/m^3. An additional group of 10 male and 10 female rats were exposed to 140 mg/m^3 under modified experimental conditions (e.g., smaller volume in exposure chamber, different carrier gas for diphenyl ether exposure, etc.) (Dow Chemical Co, 1986a; Hefner et al., 1975). This study was peer reviewed with adequate numbers of exposure groups and investigated numerous endpoints.

Both male rats and rabbits, but not dogs, exhibited eye and nasal irritation following exposure to chamber concentrations of 69.5 and 140 mg/m^3 diphenyl ether. After the no-observed-adverse-effect levels (NOAELs) of 34 mg/m^3 for both rats and rabbits were converted to human equivalent concentrations (HECs), rats were more sensitive than rabbits to eye and nasal irritation (male rat HEC_{ET} = 1.3 mg/m^3, rabbit HEC_{ET} = 3.8 mg/m^3).[6] Other possible effects in rats include statistically significantly decreased absolute and relative liver weights in male rats at ≥7.1 mg/m^3 ($HEC_{SYSTEMIC}$). These liver-weight changes are of uncertain toxicological significance in consideration of the inconsistent dose-response relationship, the absence of histological changes, and because no clinical chemistry abnormalities (i.e., serum glutamic pyruvic transaminase [SGPT]) were observed to support that the liver is indeed a target organ for diphenyl ether-induced toxicity. In addition, no benchmark response (BMR) level has been established for the decrease in liver weight in adult animals. Hematological effects were observed in male rats including significantly decreased hemoglobin (Hb) at 14.5 mg/m^3 ($HEC_{SYSTEMIC}$) and significantly decreased white blood cell (WBC) counts at ≥7.1 mg/m^3 ($HEC_{SYSTEMIC}$). The biological relevance of decreased WBC counts in male rats is unclear

[6]Human equivalent concentration extrathoracic (HEC_{ET}) = Concentration × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × $RGDR_{ET}$.

because the study authors did not perform immune function tests to verify that a toxic functional change was associated with this effect (Dow Chemical Co, 1986a; Hefner et al., 1975).

Other possible effects observed in the study was a biologically significant kidney-weight increase in male dogs with a 19.6% increase at 7.1 mg/m^3 ($HEC_{SYSTEMIC}$) and 35.3% at 14.5 mg/m^3 ($HEC_{SYSTEMIC}$) (see Table B-1) (Dow Chemical Co, 1986a; Hefner et al., 1975). Although not statistically significant, the weight change in the dog kidney is exposure related and of large magnitude. However, the dog study (Dow Chemical Co, 1986a; Hefner et al., 1975) uses a small number of animals (two male Beagles/exposure group). Related to pathology, specifically for the kidney, the study authors report that all major organs and tissues were examined grossly and histologically, and concluded that no discernible, attributable lesions were revealed. There is no clinical evidence examined or reported by the study authors for renal effects. Blood urea nitrogen (BUN) was reduced, rather than increased, as would be expected for possible kidney effects in rabbits and dogs (statistically significant at the low and high exposure in rabbits, and the low exposure, but not at the high exposure, in dogs; see Table B-2). Therefore, there is a lack of evidence to support that the kidney is indeed a target organ for diphenyl ether-induced toxicity.

Based on the available inhalation data for diphenyl ether, there is sufficient support for the selection of eye and nasal irritation in male rats as the critical effect. For example, red discharge around the eye and lacrimation at the mid and high concentration (51 and 130 mg/m^3, respectively) were observed in the subchronic-duration rat inhalation study of aerosolized Therminol® VP-1 mixture containing 73.5% diphenyl ether and 26.5% biphenyl (Monsanto, 1989a). Animals in all exposure groups of aerosolized Therminol® VP-1 mixture also exhibited red/pink discharge around the nose. Furthermore, eye and nasal irritation was also observed in both sexes of rats, and male rabbits exposed to diphenyl ether (Dow Chemical Co, 1986a; Hefner et al., 1975). This endpoint also represents an effect relevant to human health following diphenyl ether inhalation exposure because human subjects experienced upper respiratory irritation at 69.53 mg/m^3 following prolonged exposures (duration not provided) (Dow Chemical Co, 1973). Therefore, nasal and eye irritation in male rats is selected as the critical point of departure (POD) based on a weight-of-evidence (WOE) approach.

No numerical data was provided for the eye and nasal irritation reported in Dow Chemical Co (1986a); Hefner et al. (1975); only qualitative statements were provided in the text summary of the paper. The lack of numerical data precludes applying benchmark dose (BMD) methodology and, therefore, requires reliance on the rat NOAEL value. The following dosimetric adjustments are made for male rats with a NOAEL for respiratory effects in the extrathoracic (ET) region:

Exposure concentration adjustment for continuous exposure:

$$\begin{aligned} CONC_{ADJ} &= CONC_{CHAMBER} \times (MW \div 24.45) \times (\text{hours exposed} \div 24) \times \\ &\quad (\text{days exposed} \div 7 \text{ days per week}) \\ &= 4.9 \text{ ppm} \times (170 \div 24.45) \times (7 \text{ hours} \div 24 \text{ hours}) \times (5 \text{ days} \div 7 \text{ days}) \\ &= 7.1 \text{ mg/m}^3 \end{aligned}$$

HEC conversion for respiratory effects:

$$CONC_{RESP}\ (HEC) = CONC_{ADJ} \times RGDR_{ET}$$

where

$RGDR_{ET}$ = $(V_E/SA_{ET})_{[rat]} \div (V_E/SA_{ET})_{[human]}$

where

$V_{E[rat]}$ = Rat minute volume determined according to the following[7]:

$\ln(V_E)$ = $b_0 + b_1 \times \ln(BW)$

$SA_{ET[rat]}$ = Rat default surface area of the ET region (15 cm^2) [see Table 4-4 in U.S. EPA (1994)].

$V_{E[human]}$ = Human minute volume of 13.8 L (U.S. EPA, 1994).

$SA_{ET[human]}$ = Human default surface area of the ET region (200 cm^2) (U.S. EPA, 1994).

$RGDR_{ET}$ = (0.190 L/min ÷ 15 cm^2) ÷ (13.8 L/min ÷ 200 cm^2)
= 0.184

$CONC_{RESP}\ (HEC)$ = $CONC_{ADJ} \times RGDR_{ET}$
= 7.1 mg/m^3 × 0.184
= 1.3 mg/m^3

Approach for Deriving the Screening Subchronic p-RfC

The NOAEL (HEC) of 1.3 mg/m^3 for eye and nasal irritation in rats from the subchronic inhalation study (Dow Chemical Co, 1986a; Hefner et al., 1975) is selected as the POD for deriving a screening subchronic provisional reference concentration (p-RfC) for diphenyl ether. The p-RfC for diphenyl ether, based on the NOAEL (HEC) of 1.3 mg/m^3 for inducing eye and nasal irritation in rats, is derived as follows:

Screening Subchronic p-RfC = $CONC_{RESP}\ (HEC) \div UF_C$
= 1.3 ÷ 300
= **4×10^{-3} mg/m^3**

Table A-1 summarizes the uncertainty factors for the screening subchronic p-RfC for diphenyl ether.

[7]Rat minute volume determined according to the following: $\ln(V_E) = b_0 + b_1 \times \ln(BW)$ where: b_0 and b_1 ($b_0 = -0.578$, $b_1 = 0.821$), which are provided for the rat in Tables 4–6 (U.S. EPA, 1994) and default BW are provided (male = 0.267 kg for S-D rats) (U.S. EPA, 1988). $\ln(V_E)_{[male]} = -0.578 + 0.821 \times \ln(0.267) = -1.66$. $V_{E[male]} = 0.190$ L/min.

Table A-1. Uncertainty Factors for the Screening Subchronic p-RfC for Diphenyl Ether

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for residual uncertainty, including toxicodynamic differences, between rats and humans following diphenyl ether inhalation. The toxicokinetic uncertainty has been accounted for by calculating an HEC by applying an RGDR in extrapolating from animals to humans according to the procedures in the RfC methodology (U.S. EPA, 1994).
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. Repeated-exposure inhalation toxicity data for diphenyl ether alone are limited to the 31−33-d inhalation study in rats, rabbits, and dogs (Dow Chemical Co, 1986a; Hefner et al., 1975). In a mixture study, 73.5% diphenyl ether and 26.5% biphenyl (Therminol® VP-1 Heat Transfer Fluid) was tested for subchronic inhalation toxicity (as an aerosol) and oral developmental toxicity in rats. The mixture was found to produce embryo- and fetotoxic effects at maternally toxic oral doses (Biodynamics, 1989; Monsanto, 1989a; Biodynamics, 1987; Monsanto, 1987b). It is unknown to what extent the finding can be attributed to diphenyl ether or how results might be affected by route of exposure, but it suggests the possibility that diphenyl ether may affect development. Tests for the developmental or reproductive toxicity of diphenyl ether itself, however, were not located by any route of exposure.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of diphenyl ether in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because a 31 to 33-d (subchronic-duration) study is selected as the principal study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; RfC = reference concentration; RGDR = regional gas dose ratio; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

DERIVATION OF A SCREENING CHRONIC PROVISIONAL REFERENCE CONCENTRATION

There are no chronic-duration studies of humans or animals exposed via inhalation to diphenyl ether. A screening chronic p-RfC is derived using the same $CONC_{RESP}$ (HEC) for nasal and eye irritation in male rats that was selected as the POD for derivation of the screening subchronic p-RfC with an additional uncertainty factor of 10 (total of 3,000) to adjust for chronic exposure as shown in Table A-2.

$$\begin{aligned} \textbf{Screening Chronic p-RfC} &= CONC_{RESP}\ (HEC) \div UF_C \\ &= 1.3 \div 3{,}000 \\ &= \mathbf{4 \times 10^{-4}\ mg/m^3} \end{aligned}$$

Table A-2 summarizes the uncertainty factors for the screening chronic p-RfC for diphenyl ether.

Table A-2. Uncertainty Factors for the Screening Chronic p-RfC for Diphenyl Ether

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for residual uncertainty, including toxicodynamic differences, between rats and humans following diphenyl ether inhalation. The toxicokinetic uncertainty has been accounted for by calculation of an HEC through application of a RGDR in extrapolating from animals to humans according to the procedures in the RfC methodology (U.S. EPA, 1994).
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database. Repeated-exposure inhalation toxicity data for diphenyl ether alone are limited to the 31−33-d inhalation study in rats, rabbits, and dogs (Dow Chemical Co, 1986a; Hefner et al., 1975). In a mixture study, 73.5% diphenyl ether and 26.5% biphenyl (Therminol® VP-1 Heat Transfer Fluid) was tested for subchronic inhalation toxicity (as an aerosol) and oral developmental toxicity in rats. The mixture was found to produce embryo- and fetotoxic effects at maternally toxic oral doses (Biodynamics, 1989; Monsanto, 1989a; Biodynamics, 1987; Monsanto, 1987b). It is unknown to what extent the finding can be attributed to diphenyl ether or how results might be affected by route of exposure, but it suggests the possibility that diphenyl ether may affect development. Tests for the developmental or reproductive toxicity of diphenyl ether itself, however, were not located by any route of exposure.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of diphenyl ether in humans.
UF_L	1	A UF_L of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	10	A UF_S of 10 is applied because a 31−33-d (subchronic-duration) study is selected as the principal study.
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; RfC = reference concentration; RGDR = regional gas dose ratio; UC = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

APPENDIX B. DATA TABLES

Table B-1. Mean Body and Organ Weights of Animals Exposed via Inhalation to Diphenyl Ether Vapor for 7 Hours/Day, 5 Days/Week for a Total of 20 Exposures[a]

Parameter[b]	Exposure Group, mg/m^3 ($HEC_{SYSTEMIC}$)[c]				
	0 (0)	**34 (7.1)**	**69.5 (14.5)**	**0 (0)**	**140 (29)**
Rats (male)					
Mean body weight (g)	400 ± 27.9	378.2 ± 24.6 (–5.5%)	385.4 ± 18.5 (–3.7%)	409.0 ± 9.8	380.0 ± 18.3* (–7.1%)
Absolute liver weight (g)	12.1 ± 1.4	10.4 ± 1.1* (–14%)	10.7 ± 1.1* (–12%)	11.4 ± 0.8	11.1 ± 1.0 (–2.6%)
Relative liver weight (g/100 g)	3.04 ± 0.35	2.74 ± 0.20* (−10%)	2.80 ± 0.21* (−7.9%)	2.79 ± 0.18	2.92 ± 0.15 (+4.7%)
Absolute kidney weight (g)	2.9 ± 0.3	2.8 ± 0.3 (–3.5%)	2.7 ± 0.2 (–6.9%)	3.1 ± 0.1	2.8 ± 0.2 (–10%)
Relative kidney weight (g/100 g)	0.73 ± 0.08	0.73 ± 0.05 (0%)	0.71 ± 0.04 (−2.8%)	0.76 ± 0.02	0.75 ± 0.03 (+2.8)
Absolute brain weight (g)	1.9 ± 0.1	1.8 ± 0.1 (−5.3%)	1.8 ± 0.1 (−5.3%)	1.8 ± 0.1	1.8 ± 0.0 (0%)
Relative brain weight (g/100 g)	0.47 ± 0.03	0.49 ± 0.03 (+4.3%)	0.47 ± 0.03 (0%)	0.43 ± 0.01	0.47 ± 0.02* (+9.3%)
Rats (female)					
Mean body weight (mg)	Not tested	Not tested	Not tested	244.7 ± 12.3	246.3 ± 12.1 (+0.7%)
Absolute liver weight (mg)	Not tested	Not tested	Not tested	6.5 ± 0.4	6.6 ± 0.4 (+1.5%)
Relative liver weight (g/100 g)	Not tested	Not tested	Not tested	2.64 ± 0.19	2.65 ± 0.10 (+0.4%)
Absolute kidney weight (mg)	Not tested	Not tested	Not tested	1.8 ± 0.1	1.8 ± 0.1 (0%)
Relative kidney weight (g/100 g)	Not tested	Not tested	Not tested	0.74 ± 0.04	0.71 ± 0.05 (−4.1%)
Absolute brain weight (g)	Not tested	Not tested	Not tested	1.7 ± 0.0	1.7 ± 0.1 (0%)
Relative brain weight (g/100 g)	Not tested	Not tested	Not tested	0.68 ± 0.03	0.68 ± 0.03 (0%)

Table B-1. Mean Body and Organ Weights of Animals Exposed via Inhalation to Diphenyl Ether Vapor for 7 Hours/Day, 5 Days/Week for a Total of 20 Exposures[a]

Parameter[b]	Exposure Group, mg/m^3 ($HEC_{SYSTEMIC}$)[c]				
	0 (0)	34 (7.1)	69.5 (14.5)	0 (0)	140 (29)
Rabbits (male)					
Mean body weight (kg)	2.91 ± 0.15	2.57 ± 0.07 (+12%)	2.81 ± 0.32 (−3.4%)	Not tested	Not tested
Absolute liver weight (g)	84.1 ± 17.2	69.4 ± 7.9 (–17%)	85.6 ± 16.0 (+1.8%)	Not tested	Not tested
Relative liver weight (g/100 g)	2.91 ± 0.66	2.70 ± 0.27 (−7.2%)	3.04 ± 0.33 (+4.5%)	Not tested	Not tested
Absolute kidney weight (g)	15.1 ± 1.1	13.4 ± 1.7 (–11%)	13.7 ± 2.5 (–9.3%)	Not tested	Not tested
Relative kidney weight (g/100 g)	0.52 ± 0.05	0.52 ± 0.06 (0%)	0.49 ± 0.03 (−3.4%)	Not tested	Not tested
Absolute brain weight (g)	8.7 ± 0.4	8.6 ± 0.4 (−1.1%_	9.1 ± 0.5 (+4.6%)	Not tested	Not tested
Relative brain weight (g/100 g)	0.31 ± 0.02	0.34 ± 0.02 (+9.7%)	0.33 ± 0.02 (+6.5%)	Not tested	Not tested
Dogs (male)					
Mean body weight (kg)	12.25 ± 1.49	10.85 ± 0.64* (–11%)	12.95 ± 1.91 (+5.7%)	Not tested	Not tested
Absolute liver weight (g)	308.0 ± 23.7	288.9 ± 2.8 (–6.2%)	328.7 ± 37.2 (+6.7%)	Not tested	Not tested
Relative liver weight (g/100 g)	2.52 ± 0.11	2.67 ± 0.12 (+6.0%)	2.55 ± 0.09 (+1.2%)	Not tested	Not tested
Absolute kidney weight (g)	51.5 ± 2.6	61.6 ± 3.0 (+20%)	69.7 ± 11.0 (+35%)	Not tested	Not tested
Relative kidney weight (g/100 g)	0.42 ± 0.03	0.65 ± 0.14 (+55%)	0.48 ± 0.04 (+14%)	Not tested	Not tested
Absolute brain weight (g)	90.8 ± 1.6	81.7 ± 4.7 (−10%)	83.1 ± 0.9 (−8.5%)	Not tested	Not tested
Relative brain weight (g/100 g)	0.75 ± 0.78	0.75 ± 0.00 (0%)	0.71 ± 0.65 (−5.3%)	Not tested	Not tested

[a]Dow Chemical Co (1986a); Hefner et al. (1975).
[b]Mean ± SD (percent change from respective control).
[c]$HEC_{SYSTEMIC}$ = Concentration × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood-gas partition coefficient.
*Significantly different from respective control ($p < 0.05$).

HEC = human equivalent concentration; SD = standard deviation.

Table B-2. Selected Hematological or Serum Chemistry Effects on Animals Exposed via Inhalation to Diphenyl Ether Vapor for 7 Hours/Day, 5 Days/Week for a Total of 20 Exposures[a]

Endpoint[b]	Exposure Group, mg/m^3 ($HEC_{SYSTEMIC}$)[c]				
	0 (0)	**34 (7.1)**	**69.5 (14.5)**	**0 (0)**	**140 (29)**
Number of animals	20	20	20	10	10
Hemoglobin (g/100 mL) in male rats	17.2 ± 0.8	16.7 ± 0.4 (−3%)	16.2 ± 0.6* (−6%)	16.8 ± 0.7	17 ± 1.0 (+1%)
White blood cell count ($\times 10^3$/mm^3) in male rats	20.3 ± 2.7	12.6 ± 3.4* (−38%)	11.5 ± 1.7* (−43%)	15.1 ± 1.9	18.7 ± 3.7 (+24%)
BUN in male rabbits	21.3 ± 0.5	15.0 ± 1.4*	16.5 ± 1.0*	Not dosed	Not dosed
BUN in male rats	22.2 ± 4.8	21.9 ± 2.5	24.1 ± 4.1	Not measured	Not measured
BUN in male dogs	16.0 ± 0.7	12.0 ± 0.0*	15.0 ± 1.4	Not dosed	Not dosed

[a]Dow Chemical Co (1986a); Hefner et al. (1975).
[b]Mean ± SD (percent change from respective control).
[c]$HEC_{SYSTEMIC}$ = Concentration × (hours per day exposed ÷ 24) × (days per week exposed ÷ 7) × blood-gas partition coefficient.
*Significantly different from respective control ($p < 0.05$) by ANOVA and Dunnett's test, as reported by the study authors.

ANOVA = analysis of variance; BUN = blood urea nitrogen; HEC = human equivalent concentration; POD = point of departure; SD = standard deviation.

APPENDIX C. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2015). Phenyl ether. 2015 TLVs and BEIs. Based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices [TLV/BEI]. Cincinnati, OH. http://www.acgih.org/forms/store/ProductFormPublic/2015-tlvs-and-beis

ACGIH (American Conference of Governmental Industrial Hygienists). (2016). 2016 TLVs and BEIs: Based on documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH. https://www.acgih.org/forms/store/ProductFormPublic/2016-tlvs-and-beis

Api, AM; Ford, RA. (2003). Evaluation of the dermal subchronic toxicity of diphenyl ether in the rat. Food Chem Toxicol 41: 259-264.

ATSDR (Agency for Toxic Substances and Disease Registry). (2017). Minimal risk levels (MRLs). June 2017. Atlanta, GA: Agency for Toxic Substances and Disease Registry (ATSDR). Retrieved from http://www.atsdr.cdc.gov/mrls/index.asp

Biodynamics (Biodynamics Corp). (1987). Developmental toxicity study in rats with THERMINOL VP-1 heat transfer fluid with cover letter dated 011388. (TSCATS/305170, OTS0514002, Doc I.D. 86-880000112). St. Louis, MO: Monsanto Chemical Co.

Biodynamics (Biodynamics Corp). (1989). Chemical listing subject to submission and a developmental toxicity study in rats with therminol VP-1 heat transfer fluid (final report) with attachments and cover letter dated 060889. (TSCATS/403890). St Louis, MO: Monsanto.

Bronzetti, G; Esposito, A; Pagano, G; Quinto, I. (1981). A comparative study on the toxicity and mutagenicity of biphenyl (BP) and diphenyl ether (DPE) in sea urchin, S. typhimurium and S. cerevisiae. Mutat Res Environ Mutagen Relat Subj 85: 233. http://dx.doi.org/10.1016/0165-1161(81)90076-5

Cal/EPA (California Environmental Protection Agency). (2011). Hot spots unit risk and cancer potency values. Appendix A. Sacramento, CA: Office of Environmental Health Hazard Assessment. http://standards.nsf.org/apps/group_public/download.php?document_id=19121

Cal/EPA (California Environmental Protection Agency). (2014). All OEHHA acute, 8-hour and chronic reference exposure levels (chRELs) as of June 2014. Sacramento, CA: Office of Health Hazard Assessment. http://www.oehha.ca.gov/air/allrels.html

Cal/EPA (California Environmental Protection Agency). (2017a). Chemicals known to the state to cause cancer or reproductive toxicity January 27, 2017. (Proposition 65 list). Sacramento, CA: Office of Environmental Health Hazard Assessment. http://oehha.ca.gov/proposition-65/proposition-65-list

Cal/EPA (California Environmental Protection Agency). (2017b). OEHHA toxicity criteria database [Database]: Office of Environmental Health Assessment. Retrieved from http://www.oehha.ca.gov/tcdb/index.asp

DOE (U.S. Department of Energy). (2016). Table 3: Protective Action Criteria (PAC) Rev. 28 based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. February 2016. Washington, DC. https://sp.eota.energy.gov/pac/teel/Revision_28A_Table3.pdf

Dow Chemical Co (Dow Chemical Company). (1935). Report on toxicity experiments in guinea pigs, rabbits and dogs (sanitized). (TSCATS/404188, OTS0520720, Doc I.D. 86-890001208S). East Lansing, MI.

Dow Chemical Co (Dow Chemical Company). (1936a). Toxicity of diphenyl oxide (sanitized). (TSCATS/404186, OTS0520718, Doc I.D. 86-890001206S).

Dow Chemical Co (Dow Chemical Company). (1936b). The toxicity of some chlordiphenyloxides (Progress report). (TSCATS/404189, OTS0520721, Doc I.D. 86-890001210). Washington, DC: U. S. Environmental Protection Agency.

Dow Chemical Co (Dow Chemical Company). (1973). Subjective response of volunteers to odors of diphenyl oxide (phenyl ether) at 3 to 20 parts per million concentrations (sanitized). Midland, MI.

Dow Chemical Co (Dow Chemical Company). (1986a). Repeated inhalation toxicity of diphenyl oxide (DPO) in experimental animals with attachment. Midland, MI.

Dow Chemical Co (Dow Chemical Company). (1986b). The toxicity of some chlorodiphenyloxides (sanitized). [Indexed in 1986]. (TSCATS/404191, OTS0520723, Doc I.D. 86-890001212S).

Dow Chemical Co (Dow Chemical Company). (2003). IUCLID data set: CAS No. 101-84-8; EINECS name: Diphenyl ether; TSCA name: Benzene, 1,1'oxybis. (201-14732A). Washington, DC: U.S. Environmental Protection Agency. https://iaspub.epa.gov/oppthpv/document_api.download?FILE=Revised_Summaries_c14164rr.pdf

Eastman Kodak (Eastman Kodak Company). (1979). Toxicity and health hazard summary, MSDS, and toxicity report for diphenyl oxide with cover letter dated 041989. (TSCATS/311584, OTS0516736, Doc I.D. 86-890000188). Rochester, NY: Eastman Kodak Co.

ECHA (European Chemicals Agency). (2016). Registered substances. Diphenyl ether. EC number 202-981-2. CAS number: 101-84-8. http://echa.europa.eu/registration-dossier/-/registered-dossier/14971

ECHA (European Chemicals Agency). (2017). Registered substances [Database]. Helsinki, Finland. Retrieved from https://echa.europa.eu/information-on-chemicals/registered-substances

Florin, I; Rutberg, L; Curvall, M; Enzell, CR. (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15: 219-232. http://dx.doi.org/10.1016/0300-483X(80)90055-4

Haworth, S; Lawlor, T; Mortelmans, K; Speck, W; Zeiger, E. (1983). Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 5: 3-142. http://dx.doi.org/10.1002/em.2860050703

Hefner, RE, Jr; Leong, BKJ; Kociba, RJ; Gehring, PJ. (1975). Repeated inhalation toxicity of diphenyl oxide in experimental animals. Toxicol Appl Pharmacol 33: 78-86. http://dx.doi.org/10.1016/0041-008X(75)90246-X

HSDB (Hazardous Substances Data Bank). (2015). Diphenyl ether. CASRN: 101-84-8 [Database]. Bethesda, MD: U.S. National Library of Medicine, Toxicology Data Network (TOXNET). Retrieved from https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm

IARC (International Agency for Research on Cancer). (2017). IARC Monographs on the evaluation of carcinogenic risk to humans. Geneva, Switzerland: International Agency for Research on Cancer, WHO. http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php

Johnson, WD; Ehrlich, JP; Hatoum, NS; Yermakoff, JK. (1992). Thirteen week oral (diet) toxicity study of diphenyl ether in rats [Abstract]. Toxicologist 12: 117.

Law, FC; Chakrabarti, S. (1983). Irreversible binding of 14C-diphenyl ether-derived radioactivity to liver microsomes in vitro and tissue proteins in vivo. Drug Chem Toxicol 6: 285-294. http://dx.doi.org/10.3109/01480548309017819

Law, FC; Song, YY; Chakrabarti, S. (1983). Disposition and metabolism of diphenyl ether in rats. Xenobiotica 13: 627-633.

Lewis, RJ, Sr; Hawley, GG. (2007). Diphenyl oxide. In RJ Lewis, Sr.; GG Hawley (Eds.), Hawley's condensed chemical dictionary (15th ed., pp. 466). Hoboken, NJ: John Wiley & Sons. http://dx.doi.org/10.1002/9780470114735.hawley05974

Monsanto (Monsanto Company). (1977). Toxicity studies on diphenyl oxide with attachments and cover letter dated 060889. (TSCATS/402156, OTS0518143, Doc I.D. 86-890000346). St. Louis, MO. https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=86-890000346

Monsanto (Monsanto Company). (1986). Initial submission: Acute toxicity of therminol VP-1 administered by inhalation to Sprague-Dawley male and female rats with cover letter dated 080592. (TSCATS/450810, OTS0571522, Doc I.D. 88-9200096870). Washington, DC.

Monsanto (Monsanto Company). (1987a). Evaluation of the potential of Therminol R Vp-1 to induce unscheduled DNA synthesis in primary rat hepatocyte cultures (final report) with cover letter dated 042287. (TSCATS/302562, OTS0513056, Doc I.D. 86870000307). Washington, DC: Environmental Protection Agency, Washington, DC. Office of Toxic Substances. https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=86870000307

Monsanto (Monsanto Company). (1987b). Health and safety studies on monochlorobenzene and Therminol with cover letter dated 062287. (TSCATS/301586, OTS50513158, Doc I.D. 86870000410). St. Louis, MO.; Environmental Protection Agency, Washington, DC. Office of Toxic Substances.
: Office of Toxic Substances. https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=86870000410

Monsanto (Monsanto Company). (1989a). Chemical listing subject to submission & a 3-month study of Therminol VP-1 administered to male & female Sprague-Dawley rats by inhalation (final Report) W-attach & Letter 060889. (TSCATS/403891, OTS0520432, 86-890000353). Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=86-890000353

Monsanto (Monsanto Company). (1989b). In vitro chromosome aberration analysis in Chinese hamster ovary (cho) cells with attachments and cover letter dated 060889. (86-890000343; TSCATS/402150). https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=86-890000343

Monsanto (Monsanto Company). (1990a). AMES/salmonella mutagenicity assay of therminol Vpi (final report) with cover sheet and letter dated 021690. Washington, DC: U. S. Environmental Protection Agency.

Monsanto (Monsanto Company). (1990b). Micronucleus assay with therminol vp-1 with cover letter. (TSCATS/414448, OTS0530068). St. Louis, MO. https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=86-910000014

NIOSH (National Institute for Occupational Safety and Health). (2014). Phenyl ether (vapor). Immediately Dangerous to Life or Health Concentrations (IDLH). Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health, Education and Welfare. http://www.cdc.gov/niosh/idlh/101848.html

NIOSH (National Institute for Occupational Safety and Health). (2015). Phenyl ether (vapor). NIOSH pocket guide to chemical hazards. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health, Education and Welfare. http://www.cdc.gov/niosh/npg/npgd0496.html

NTP (National Toxicology Program). (2014). Report on carcinogens. Thirteenth edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service.

OSHA (Occupational Safety & Health Administration). (2006a). Safety and health regulations for construction: Occupational health and environmental controls - Gases, vapors, fumes, dusts, and mists. (1926.55 App A). Washington, DC: U.S. Department of Labor. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10629

OSHA (Occupational Safety & Health Administration). (2006b). Table Z-1: Limits for air contaminants. Occupational safety and health standards, subpart Z, toxic and hazardous substances. (OSHA standard 1910.1000, 29 CFR). Washington, DC: U.S. Department of Labor. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992

OSHA (Occupational Safety & Health Administration). (2011). Air contaminants: Occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. (OSHA Standard 1915.1000). Washington, DC: U.S. Department of Labor. https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286

Pagano, G; Esposito, A; Giordano, GG; Vamvakinos, E; Quinto, I; Bronzetti, G; Bauer, C; Corsi, C; Nieri, R; Ciajolo, A. (1983). Genotoxicity and teratogenicity of diphenyl and diphenyl ether: A study of sea urchins, yeast, and Salmonella typhimurium. Teratog Carcinog Mutagen 3: 377-393. http://dx.doi.org/10.1002/1520-6866(1990)3:4<377::AID-TCM1770030407>3.0.CO;2-6

Poon, G; Chui, YC; Law, FC. (1986). Biotransformation of diphenyl ether by trout and guinea-pigs after intraperitoneal administration. Xenobiotica 16: 795-800. http://dx.doi.org/10.3109/00498258609038960

SRI International. (1987). Evaluation of the potential of diphenyl oxide to induce unscheduled DNA synthesis in primary rat hepatocyte cultures (final report) with attachments and cover sheet dated 060889. (TSCATS/402148, OTS0518139, Doc I.D. 86-890000342). Washington, DC: U.S. Environmental Protection Agency. https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=86-890000342

U.S. APHC (U.S. Army Public Health Command). (2013). Environmental health risk assessment and chemical exposure guidelines for deployed military personnel. Technical guide 230, 2013 revision. Aberdeen Proving Ground, MD. http://phc.amedd.army.mil/PHC%20Resource%20Library/TG230.pdf

U.S. EPA (U.S. Environmental Protection Agency). (1988). Recommendations for and documentation of biological values for use in risk assessment (pp. 1-395). (EPA/600/6-87/008). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. EPA (U.S. Environmental Protection Agency). (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report] (pp. 1-409). (EPA/600/8-90/066F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=51174829&CFTOKEN=25006317

U.S. EPA (U.S. Environmental Protection Agency). (2002). A review of the reference dose and reference concentration processes (pp. 1-192). (EPA/630/P-02/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/osa/review-reference-dose-and-reference-concentration-processes

U.S. EPA (U.S. Environmental Protection Agency). (2011). Health effects assessment summary tables (HEAST). Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. http://epa-heast.ornl.gov/heast.php

U.S. EPA (U.S. Environmental Protection Agency). (2012a). 2012 Edition of the drinking water standards and health advisories [EPA Report]. (EPA/822/S-12/001). Washington, DC: U.S. Environmental Protection Agency, Office of Water. http://www.epa.gov/sites/production/files/2015-09/documents/dwstandards2012.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2012b). Estimation Programs Interface Suite for Microsoft Windows, v 4.11 [Computer Program]. Washington, DC. Retrieved from https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

U.S. EPA (U.S. Environmental Protection Agency). (2015). About the TSCA chemical substance inventory. Download the non-confidential TSCA inventory [Database]. Retrieved from http://www2.epa.gov/tsca-inventory/how-access-tsca-inventory

U.S. EPA (U.S. Environmental Protection Agency). (2016). Diphenyl ether. CASRN 101-84-8. HPVIS. Chemical Data Access Tool (CDAT). Washington, DC. https://java.epa.gov/oppt_chemical_search/

U.S. EPA (U.S. Environmental Protection Agency). (2017). Integrated risk information system. IRIS assessments [Database]. Washington, DC: Integrated Risk Information 'System. Retrieved from http://www.epa.gov/iris/

Westinghouse Electric Corporation. (1977). Potential carcinogenicity testing of PCB replacements using the Ames test with cover letter [TSCA Submission]. (TSCATS/021943, OTS0206616, Doc I.D. 878214672). Pittsburgh, PA. https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0206616

WHO (World Health Organization). (2003). Diphenyl ether. Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety. http://www.inchem.org/documents/jecfa/jeceval/jec_660.htm

WHO (World Health Organization). (2004a). Diphenyl ether. Evaluation of certain food additives and contaminants. Sixty-first report of the Joint FAO/WHO Expert Committee on food additives. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety. http://apps.who.int/iris/bitstream/10665/42849/1/WHO_TRS_922.pdf

WHO (World Health Organization). (2004b). Diphenyl ether. Safety evaluation of certain food additives and contaminants. Prepared by the sixty-first report of the Joint FAO/WHO Expert Committee on food additives. (WHO Food Additives Series: 52). Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety. http://apps.who.int/iris/bitstream/10665/43038/1/924166052X.pdf