
Diphenyl ether

(CAS No: 101-84-8)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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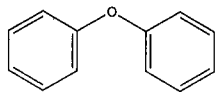
1 Introduction

The present document contains the assessment of the health hazard of diphenyl ether by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

The assessment of the toxicity of diphenyl ether was mainly based on the review by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in May 2000, literature was searched in the databases Medline, Toxline, and Chemical Abstracts, starting from 1981, 1966, and 1937, respectively, and using the following key words: diphenyl ether, phenoxybenzene, biphenyl oxide, diphenyl oxide, phenylether, oxydiphenyl, and 101-84-8. The final search was carried out in Toxline and Medline in October 2004.

In December 2004, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: E González-Fernández, Ph.D. (Instituto Nacional de Seguridad e Higiene en el Trabajo, Madrid, Spain). These comments were taken into account in deciding on the final version of the document.

2 Identity

name	: diphenyl ether
synonyms	: phenyl ether (vapor); phenyl oxide; diphenyl oxide; biphenyl oxide; phenoxy-benzene; 1,1'-oxybisbenzene
molecular formula	: C ₁₂ H ₁₀ O
structural formula	: 
CAS number	: 101-84-8

3 Physical and chemical properties

molecular weight	: 170.21
melting point	: 27°C
boiling point	: 257°C
flash point	: 96°C (open cup); 115°C (closed cup)
vapour pressure	: at 25°C: 2.8 Pa
solubility in water	: insoluble
log P _{octanol/water}	: 3.87-4.83 (experimental); 4.05 (estimated)
conversion factors	: at 20°C and 101.3 kPa: 1 ppm = 7.09 mg/m ³ 1 mg/m ³ = 0.14 ppm

Data from: ACG99, Gar71, NLM04, San89, http://www.syrres.com/esc/est_kowdemo.htm.

Diphenyl ether is a colourless liquid or solid with a somewhat disagreeable odour and low volatility (ACG99). Odour thresholds of 0.008 mg/m³ (0.0012 ppm) have been reported (Amo83, Rut86).

4 Uses

Diphenyl oxide is used as heat-transfer agent and is the major component of Dowtherm A[®] (an eutectic mixture of phenyl ether and biphenyl) and further as a chemical intermediate in the production of surface-active agents and high-temperature lubricants, and in perfumery due to its geranium-like odour (ACG99b).

5 Biotransformation and kinetics

Following 6-hour semi-occlusive applications of single doses of ca. 10, 100, and 1000 mg/kg bw of [¹⁴C]-diphenyl ether (as 0.5 to 50% solutions in diethyl phthalate) to the clipped skin of rats, about 18% of the dose administered was excreted in the urine and small amounts (1-4%) in the faeces over a 72-hour period. At 72 hour post-application, carcass and tissues contained about 0.2 and 0.4% of the dose, respectively, with the highest amounts found in the gastrointestinal tract (ca. 0.3%) (liver: ca. 0.04%; kidney: ca. 0.02%). Small amounts of radioactivity (0.2-2.8%) were found in cage wash and cage air, likely indicating volatilisation from the skin and/or excretion in exhaled air. About 60% of the dose was recovered from the occlusive dressings (Api03).

Rats given a single oral dose of 10 mg/kg bw of [¹⁴C]-diphenyl ether showed peak concentrations of diphenyl ether in blood at 15 hours after administration.

The half-life of elimination from the blood was about 1.5 hours. After administration of a single intraperitoneal injection of 5 mg/kg bw of [¹⁴C]-diphenyl ether to rats, radioactivity was found in all organs and tissues within one hour, reaching peak levels within 1 to 4 hours. Concentrations of diphenyl ether were twice as high in the liver, compared with blood, spleen, kidney, and lung, and about 10-fold the levels in the muscle, brain, heart, fat, and testes (Law83).

In rabbits, rats, and guinea pigs, orally or intraperitoneally administered diphenyl ether was metabolised into hydroxylated derivatives, i.e., mono- and dihydroxydiphenyl ethers and mono- and dihydroxymethoxydiphenyl ethers (Bra53, Law83, Poo86). Following a single oral dose of 500 mg/kg bw of diphenyl ether, rabbits excreted 90% of the dose as hydroxylated derivatives in the urine within 24 hours after administration, 90% of which as 4-hydroxydiphenyl ether and 10% as 4,4'-dihydroxydiphenyl ether. Of the 4-hydroxy derivative, 15% was excreted in free form, 63% as glucuronide and 12% as sulphate (Bra53). Rats given a single oral dose of 10 mg/kg bw of [¹⁴C]-diphenyl ether excreted approximately 80% of the radioactivity in the urine and about 10% in the faeces within 3 days after administration. About 50% of urinary radioactivity was excreted within 24 hours after application. Metabolites (free and conjugated) were identified as 2- and 4-hydroxy-, 4,4'-dihydroxy-, and mono- and dihydroxymethoxydiphenyl ether, but no quantitative data were given (Law83). The same metabolites, both free and conjugated, were identified in guinea pigs, given an intraperitoneal dose of 28 mg/kg bw of diphenyl ether. No quantitative data of excretion products were given (Poo86).

Based on physicochemical properties diphenyl ether has no potential for dermal absorption (Guy93).

6 Effects and mechanism of action

Human data

Short exposures (1 minute or less) of human subjects to 5 ppm of perfume-grade diphenyl ether (99.85% pure containing 0.01-0.04% biphenyl) were stated to be well tolerated (Hef75).

No skin sensitisation was observed when diphenyl ether was tested on 25 volunteers at a concentration of 4% in petrolatum (Opd74).

Animal data

Irritation and sensitisation

When 100 mg of diphenyl ether were placed into the conjunctival sac of the left eye, corneal effects persisted for more than 24 hours, but recovered within 21 days after treatment (Sug90). In another study, diphenyl ether induced slight conjunctival irritation in rabbits, which cleared in 72 hours (Opd74).

When applied undiluted to the intact or abraded skin of rabbits for 24 hours under occlusion, diphenyl ether was slightly irritating (Opd74). Application of 0.5 mL diphenyl ether to the rabbit skin under occlusion for 4 hours produced very slight erythema with little or no oedema at 0.5 hours after patch removal. By 24 or 48 hours after patch removal, most animals exhibited slight erythema (Bla88).

In a 13-week dermal toxicity in which doses of diphenyl ether solutions in diethyl phthalate of 100, 300, and 1000 mg/kg bw/day were applied daily under semi-occlusive conditions to the shaved back skin of rats (Sprague-Dawley; n=12/sex/group) for 6 hours, a dose-related increase in the incidence of desquamation (54, 83, and 96%, respectively, vs. 33% in vehicle-treated controls) and erythema (38, 42, and 67% vs. 0%) was observed. Skin thickening and oedema were seen in one and 2 high-dose animals, respectively. Api and Ford did not present information on the severity of the effects or the influence of repeating applications (Api03).

Acute toxicity

Results of acute lethal toxicity tests with diphenyl ether are summarised in Table 1.

Table 1 Summary of acute lethal toxicity studies in experimental animals.

exposure route	species (sex)	LD ₅₀	reference
oral	rat	3990 mg/kg bw	Kir93
oral	rat	3370 mg/kg bw	Opd74
oral	rat	2450 mg/kg bw	Bir77
oral	rat (female)	2830 mg/kg bw	Ram73
dermal	rabbit	>7940 mg/kg bw	Bir77

When undiluted diphenyl ether was applied to the skin of New Zealand albino rabbits at doses of 3160 (n=1 male), 5010 (n=1 female), or 7940 (n=1/sex) mg/kg bw, all animals survived. During the observation period, reduced appetite and

activity were seen. Upon gross post-mortem examination, there were no remarkable findings (Bir77).

Following single oral dosing of 2000, 2510, or 3160 mg/kg bw to Sprague-Dawley rats, signs of intoxication included reduced appetite and activity, increasing weakness, and collapse. All animals (2 males; 3 females) given 2000 mg/kg bw survived while administration of 2510 and 3160 mg/kg bw caused mortality in 2/3 males and 1/2 females and in 2/2 males and 3/3 females, respectively. Gross autopsy of the decedents showed lung and liver hyperaemia and acute gastrointestinal inflammation while the viscera of the animals surviving the 14-day observation period were not affected (Bir77).

In rats and guinea pigs surviving acute oral doses of 1000-2000 mg/kg bw, pathological examination revealed injury to the liver, spleen, kidneys, thyroid, and intestinal tract (Vog64).

Short-term toxicity

Groups of male Sprague-Dawley rats (n=20/group) were exposed to diphenyl ether vapour concentrations of 0, 35, and 71 mg/m³, 7 hours/day, 5 days/week, for a total of 20 exposures in 31-33 days. In a second experiment, groups of rats (n=10/sex/group) were exposed to vapour concentrations of 0 or 142 mg/m³, 7 hours/day, 5 days/week, for a total of 20 exposures in 27 days. Effects at 142 and 71 mg/m³ were dose-related eye and nasal irritation. At 142 mg/m³, a significant decrease in body weight was observed in males only. Absolute and relative liver weights were increased at 71 and 35 mg/m³, but not at 142 mg/m³. In the first experiment, haemoglobin concentration was decreased at 71 mg/m³ and white blood cell count at 71 and 35 mg/m³. However, in the second experiment, no changes were observed in haematological parameters. Clinical chemical liver function tests and gross and microscopic examination did not reveal abnormalities in exposed animals, compared with controls. Hefner et al. did not consider the changes in organ and body weights and in haematological parameters, observed in the first experiment, of toxicological significance, since similar results were not obtained in the second, high-dose experiment. The NOAEL in rats was 35 mg/m³, based on eye and nasal irritation (Hef75). The same authors conducted experiments, in which beagle dogs (n=2), or New Zealand rabbits (n=4) were exposed to diphenyl ether vapour at concentrations of 0, 35, and 71 mg/m³, 7 hours/day, 5 days/week, for a total of 20 exposures in 31-33 days. Dogs did not show signs of toxicity or irritation or treatment-related changes in body weight, absolute or relative organ weights, liver function and haematological tests, or gross and microscopic examination. The NOAEL in

dogs was 71 mg/m³. The only effect observed in rabbits was mild eye and nasal irritation at the high concentration. The NOAEL in rabbits was 35 mg/m³ (Hef75).

Groups of Sprague-Dawley rats (n=12/sex/group) received semi-occluded daily dermal applications of solutions of diphenyl ether in diethyl phthalate at doses of 100, 300, and 1000 mg/kg bw/day for 13 weeks while controls were treated with vehicle only. Six hours after placing patches on the shaved back skin, they were removed and remaining test substance was washed off. No clinical signs of toxicity or mortality were observed in any of the treated groups. There was a dose-dependent increase in the incidence of skin reactions in all dosed groups (see Section 'Irritation and sensitisation'). Apart from small changes in levels of albumin (increase by 5-6%) in high-dose males and females and mid-dose females, of phosphate (increase by 10-15%) in high-dose males and females, and of cholesterol (decrease by 14%) in high-dose females, urinalysis, haematology, and clinical chemistry parameters (examined in blood sampled from 10 animals/sex/group during week 13) were not affected. Body weights of high-dose males were slightly reduced. Relative organ weight changes included increases in liver weights of males and females of the mid- and high-dose groups (by 10 and 18-19%, respectively) and in kidney weights (by 21%) of high-dose males. No gross or microscopic abnormalities were seen in any organ in any of the treated groups (Api03). The committee concludes that 100 mg/kg bw is the NOAEL for systemic toxicity in this 13-week dermal toxicity study, based on the slight dose-dependent increases in relative liver weights at the next higher doses.

Oral dosing of 170 mg/kg bw for 14 days (7 doses) did not increase the relative liver weights or the activities of liver enzymes in plasma of rats (Car80).

The results of short-term toxicity studies with diphenyl ether are summarised in Table 2.

Table 2 Summary of short-term toxicity studies in experimental animals.

exposure route	species (strain/sex/number)	concentration or dose levels	exposure duration	critical effect	NOAEL	reference
inhalation	rat (Sprague-Dawley; male; n=20/group)	0, 35, 71, 142 mg/m ³	27-33 days	eye and nose irritation	35 mg/m ³	Hef75
	rabbit (New Zealand; male; n=4/group)	0, 35, 71 mg/m ³	31-33 days	eye and nose irritation	35 mg/m ³	Hef75
	dog (beagle; n=2 males/group)	0, 35, 71 mg/m ³	31-33 days	none identified	71 mg/m ³	Hef75
dermal	rat (Sprague-Dawley; n=12/sex/group)	0, 100, 300, 1000 mg/kg bw	13 weeks	liver weight increase	100 mg/kg bw	Api03

The committee did not find data from long-term toxicity studies, including carcinogenicity, with diphenyl ether.

Mutagenicity and genotoxicity

In vitro tests

- Gene mutation assays. Diphenyl ether did not induce reverse mutations in *S. typhimurium* strains TA98, TA100, TA1535, TA 1537, and TA1538, at concentrations up to 500 µg/plate, in the absence or presence of metabolic activation (Flo80, Haw83, Pag83).
- Cytogenicity assays. Diphenyl ether (concentrations not specified) did not induce an increase in the frequency of chromosomal aberrations in Chinese hamster ovary cells, with and without an S9 metabolic activation system (San87).
- Other assays. Diphenyl ether did not induce gene conversions/reversions in *S. cerevisiae* D7 at concentrations up to 154 µg/mL (Pag83). In cultured rat hepatocytes, diphenyl ether (concentrations not specified) did not induce unscheduled DNA synthesis (Bak87).

Reproduction toxicity

The committee did not find data from reproduction toxicity studies with diphenyl ether.

7 Existing guidelines

For diphenyl ether, no administrative occupational exposure limit (MAC) has been established in the Netherlands.

Existing occupational exposure limits for these compounds in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Occupational exposure to diphenyl ether most likely takes place through inhalation of vapour or by direct skin contact when handling eutectic mixtures of diphenyl ether and biphenyl. No quantitative data is available of the percentage of pulmonary or dermal absorption of the compound.

Following oral intake of diphenyl ether, rats excreted about 80% of the dose in the urine and 10% in the faeces within 3 days. About 50% of the dose was

excreted in the urine within 24 hours. The highest tissue levels of diphenyl ether were found in the liver.

Diphenyl ether is not a skin sensitiser in humans.

In test animals, diphenyl ether was slightly irritating to the eyes and the skin. Based on the results of acute lethal dermal ($LD_{50} >ca. 8000 \text{ mg/kg bw}$) or oral ($LD_{50} 2450 \text{ mg/kg bw}$) toxicity studies, the committee considers the compound not to present an acute health hazard. Short-term (4-week) inhalation studies were carried out in rats (NOAEL: 35 mg/m^3), rabbits (NOAEL: 35 mg/m^3), and dogs (NOAEL: 71 mg/m^3). At higher exposures (142 or 71 mg/m^3 in rats, or 71 mg/m^3 in rabbits), diphenyl ether induced nasal and eye irritation, but no other effects were noted.

Diphenyl ether did not induce gene mutations or cytogenetic effects in *in vitro* assays, in the presence or absence of a metabolic activation system.

Based on the above data, the committee concludes that local eye and nasal irritation is the critical effect in animal studies. The committee takes the NOAEL of 35 mg/m^3 derived from the subacute inhalation study in rats, rabbits, and dogs (Hef75) as a starting point in establishing a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to an HBROEL, an overall assessment factor of 3, covering intraspecies variation, is established. Thus, applying this factor of 3 and the preferred value approach, a health-based occupational exposure limit of 10 mg/m^3 is recommended for diphenyl ether.

The committee recommends a health-based occupational exposure limit for diphenyl ether of 10 mg/m^3 (1.4 ppm), as an 8-hour time-weighted average (TWA).

There are no indications that the compound is absorbed in significant amounts through the skin. Therefore, a skin notation is not necessary.

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Annex

Occupational exposure limits for diphenyl ether in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note ^a	reference ^b
	ppm	mg/m ³				
the Netherlands						
- Ministry of Social Affairs and Employment	-	-				SZW05
Germany						
- AGS	1	7	8 h			TRG04
- DFG MAK-Kommission	1	7.1	8 h		^d	DFG05
	2	14.2	15 min ^c			
Great Britain						
- HSE	1	7	8 h	OES		HSE02
Sweden	-	-				Swe00
Denmark	1	7	8 h			Arb02
USA						
- ACGIH	1	-	8 h	TLV		ACG05
	2	-	15 min	STEL		
- OSHA	1	7	8 h	PEL		ACG04
- NIOSH	1	7	10 h	REL		ACG04
European Union						
- SCOEL	-	-				EC05

^a S = skin notation; which means that skin absorption may contribute considerably to the body burden; sens = substance can cause sensitisation.

^b Reference to the most recent official publication of occupational exposure limits.

^c Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.

^d Classified in pregnancy risk group C, i.e., among substances for which there is no reason to fear a risk of damage to the embryo or fetus when MAK and BAT (Biological Tolerance Value for Working Materials) values are observed.