Recommendation from the Scientific Committee on Occupational Exposure Limits for Diphenyl ether

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Employment, Social Affairs and Inclusion

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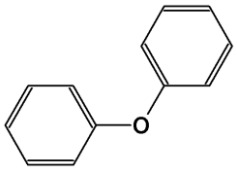
8-hour TWA:	1 ppm (7 mg/m^3)
STEL (15-minute):	2 ppm (14 mg/m^3)
BLV:	None
Notation:	None

1. Substance identification, physico-chemical properties

Name:	Diphenyl ether
Synonyms:	1,1'-Oxybis(benzene); biphenyl oxide; diphenyl oxide; phenyl oxide; phenyl ether; phenoxybenzene
Molecular formula:	$C_{12}H_{10}O$
Structural formula:	
EC No.:	202-981-2
CAS No.:	101-84-8
Molecular weight:	170.21 g/mol
Conversion factors: (20 °C, 101.3kPa)	1 ppm = 7.08 mg/m^3; 1 mg/m^3 = 0.141 ppm

EU classification: -

Diphenyl ether is a colourless organic compound, a liquid or solid with a disagreeable, geranium-like odour and a low volatility. The melting point of the substance is 27 °C, the boiling point is 257–258 °C and the vapour pressure is 2.8 Pa at 25 °C. Diphenyl ether is almost insoluble in water (21 mg/l at 25 °C) and the log P_{OW} is 3.87–4.83. The substance has a flash point of 96 °C (open cup) and a density of 1.07 g/cm^3 (ECB 2000, HCN 2005).

This evaluation is based on ACGIH (2001), ECB (2000), MAK (2004), HCN (2005), WHO (2004) and the references cited in these reviews.

2. Occurrence/use and occupational exposure

Diphenyl ether is widely used as a heat transfer agent (also as the main component of eutectic mixtures of diphenyl ether and biphenyl, i.e. the compounds are not miscible in the solid state, but fully miscible in the liquid state), as a chemical intermediate in the production of surface active agents and high temperature lubricants and

component of eutectic mixtures, and it is also used in perfumery (ACGIH 2001, HCN 2005).

In partially evaluated methods, diphenyl ether was sampled on charcoal tubes and measured by gas chromatography with flame ionisation detection (NIOSH 1994, OSHA 1988). Reported detection limits were 0.008 ppm for a 20-l air sample (OSHA 1988) and 0.1 ppm for a 10-l sample (NIOSH 1994).

3. Health significance

3.1. Toxicokinetics

3.1.1. Human data

No studies on toxicokinetics in humans were available.

3.1.2. Animal data

No quantitative data on the absorption following inhalation exposure were available. The occurrence of toxic effects after inhalation exposure shows the efficient absorption by this route.

The absorption of diphenyl ether after oral uptake is up to 90 % in rats and rabbits and is independent of the administered dose (MAK 2004, HCN 2005, WHO 2004). The data on dermal absorption are somewhat conflicting. After semi-occlusive application of 10–1 000 mg/kg to the clipped skin of rats, almost 20 % of the dose was absorbed as measured by the amount excreted in urine (Api and Ford 2003). However, in a diffusion experiment by Hotchkiss (1998), only 0.3 % (rat skin) or 0.2 % (human skin) of diphenyl ether penetrated the skin *in vitro*. The higher absorption in the *in vivo* experiment may have been caused by the vehicle (diethyl phthalate) and some oral uptake after removal of the occlusion plaster (Api and Ford 2003).

After intraperitoneal injection in rats, diphenyl ether was distributed into all organs and tissues within 1 hour with maximum concentrations in liver, lung, kidney and spleen. In mammals, the substance is mainly metabolised to hydroxylated derivatives regardless of the route of exposure (2- and 4-hydroxy-diphenyl ether, 4,4'-dihydroxy-diphenyl ether, in rats presumably also 4-methoxymonohydroxy- and 4-methoxydi-hydroxy derivatives) (MAK 2004, HCN 2005).

The metabolites are mainly excreted in the urine in free or conjugated forms. Following oral exposure, rabbits excreted 90 % of the administered dose in urine, 90 % of which as 4-hydroxy-diphenyl ether (15 % as free compound, 63 % as glucuronide and 12 % as sulphate) and 10 % as 4,4'-dihydroxy-diphenyl ether. In rats, 80 % and 10 % of an oral dose were excreted in urine and faeces, respectively. The metabolites identified in urine (in free or conjugated form) were 2- and 4-hydroxy-diphenyl ether, 4,4'-dihydroxy-diphenyl ether and presumably also 4-methoxymonohydroxy- and 4-methoxydihydroxy derivates. Because protein adducts in liver, lung and kidney were observed after intraperitoneal administration of the radiolabelled compound, the formation of arene oxides *in vivo* cannot be excluded (MAK 2004, HCN 2005, WHO 2004).

3.1.3. Biological monitoring

There were no data available.

3.2. Acute toxicity

3.2.1. Human data

Inhalation exposure of subjects to 7–10 ppm (50–71 mg/m^3) of an eutectic mixture of biphenyl and diphenyl ether produced a strong emetic effect and irritation (Kirwin and Sandmeyer 1981). The emetic response is presumably due to the presence of biphenyl because short-term exposure to 5 ppm of perfume-grade diphenyl ether (99.9 % pure) was "well tolerated" (Hefner *et al* 1975).

3.2.2. Animal data

The inhalation LC_{50} of Therminol VP-1 (a mixture of 73.5 % diphenyl ether and 26.5 % biphenyl) in rats was 2 660 mg/m^3 (no exposure duration stated). No toxicity was observed in rats after inhalation of a saturated atmosphere of 28 ppm (199 mg/m^3, the saturated concentration at 25 °C) of diphenyl ether for 6 hours (no further details). The oral LD_{50} in rats was 2 450–3 990 mg/kg. The dermal LD_{50} was > 5 000 mg/kg in rabbits and > 7 490 mg/kg in rats. Acute symptoms after high oral doses were piloerection, hypoactivity, loss of appetite, increasing weakness and collapse. The exposed animals showed congestion of lung and liver as well as lesions of the liver, spleen, kidneys, thyroid and irritation of the gastrointestinal tract (ACGIH 2001, MAK 2004, ECB 2000).

3.3. Irritation and corrosivity

3.3.1. Human data

Odour thresholds in the range of 0.0012–0.1 ppm (0.009–0.7 mg/m^3) have been reported (Amoore and Hautala 1983, Ruth 1986).

Exposure to 7–10 ppm (50–71 mg/m^3) of an eutectic mixture of biphenyl and diphenyl ether were painful to the eyes and upper respiratory tract (Kirwin and Sandmeyer 1981). These effects are presumably due to the presence of biphenyl because short-term and prolonged, repeated exposure to 5 ppm (35 mg/m^3) of diphenyl ether (99.9 % pure) was "well tolerated" (Hefner *et al* 1975). Exposure to 10 ppm (71 mg/m^3) might be unacceptable because of taste and upper respiratory tract irritation (Dow Chemical 1973, no further details). All these human data have been insufficiently reported.

3.3.2. Animal data

Undiluted diphenyl ether is slightly irritating to the intact or abraded skin of rabbits. Older studies showed stronger skin irritation, but the effects may have been caused by impurities (MAK 2004, HCN 2005).

Repeated dermal exposure of rats to diphenyl ether in diethyl phthalate (0, 10, 100, 300 and 1 000 mg/kg/day, semi-occlusive, 6 hours/day, 13 weeks) caused a dose-dependent increase in the incidence of desquamation and erythema of the skin. Skin thickening and oedema were observed in some animals treated with 1 000 mg/kg/day (Api and Ford 2003).

Eyes

Undiluted diphenyl ether produced reversible corneal effects and slight conjunctival irritation in the eyes of rabbits (MAK 2004, HCN 2005).

Respiratory tract

Rats and rabbits, which were exposed by inhalation to concentrations of 10 ppm (71 mg/m^3, 7 hours/day, up to 33 days), showed signs of irritation (not further specified) of the eyes and the upper respiratory tract. The NOAEL was 5 ppm (Hefner *et al* 1975, for more details and further effects, see Section 3.5).

3.4. Sensitisation

3.4.1. Human data

Diphenyl ether (4 % in petrolatum) did not produce skin sensitisation in a maximisation test on 25 volunteers (Kligman 1970).

3.4.2. Animal data

Studies on sensitisation in animals were not available.

3.5. Repeated dose toxicity

3.5.1. Human data

Adequate human data on the effects of repeated exposure were not available.

ACGIH (2001) stated there is no evidence that diphenyl ether is a human health hazard under normal conditions of manufacture, handling or use. No overt systemic toxicity was observed "at tolerable concentrations".

3.5.2. Animal data

Inhalation

In a study by Hefner *et al* (1975), male Sprague-Dawley rats (n = 20), New Zealand rabbits (n = 4) and Beagle dogs (n = 2) were exposed to diphenyl ether vapour at concentrations of 0, 5 and 10 ppm (35 and 71 mg/m^3) for 7 hours/day for a total of 20 exposures on 31 to 33 days. Another group of rats (10 males, 10 females) was similarly exposed to 20 ppm (142 mg/m^3) for an overall period of 27 days. The rats and rabbits, but not the dogs, exposed to 10 ppm (71 mg/m^3) exhibited mild irritation of the eyes and the nose. The rats exposed to 20 ppm showed irritation of these target organs (no further details given). Rabbits and dogs (both controls and exposed animals) suffered from infections, which produced inflammatory reactions of the lungs. Relevant substance-related systemic effects were restricted to a decreased body weight in male rats of the 20-ppm group (some observed organ weight changes and haematological alterations were not concentration-dependent). There were no other exposure-related gross or histopathological lesions. The NOAEL of this study is 5 ppm (35 mg/m^3).

Subchronic or chronic inhalation exposure studies with diphenyl ether were not available.

A subchronic inhalation study by Monsanto (1989) was conducted with an aerosol of Therminol VP-1 (a mixture of 73.5 % diphenyl ether and 26.5 % biphenyl). Sprague-Dawley rats (25 per sex and group) were exposed to 0, 10, 51 and 130 mg/m^3 for 6 hours/day with a total of at least 65 exposures within 14 weeks. A reddish nasal discharge was transiently observed in some animals at the lowest exposure concentration. Exposure to 51 mg/m^3 and above caused retarded body weight gain, salivation, lacrimation as well as reddish eyes and nasal discharge. The relevance of some haematological alterations (leuko- and lymphopenia) is unclear, since the effects

were not concentration-dependent. No NOAEL for irritating effects can be derived, but biphenyl may have contributed to the observed effects. The lowest exposure corresponds to a calculated concentration of 1.1 ppm (7.5 mg/m^3) diphenyl ether (MAK 2004).

Oral

Oral exposure of male Albino rats to 400 mg/kg/day of diphenyl ether for 2 months produced irritation of the gastrointestinal tract and degenerative changes in the liver and the kidneys as well as an increased function of the thyroid and parathyroids at 13 months. This study is insufficiently reported (MAK 2004).

Johnson *et al* (1992) exposed Sprague-Dawley rats (20 per sex and group) via the diet to diphenyl ether concentrations of 0, 200, 1 000 and 5 000 mg/kg diet (about 20, 100 and 500 mg/kg bw/day) for 13 weeks (OECD Guideline 408). Half of the animals per group were allowed to recover for 4 weeks. Males and females of the high-dose group as well as females of the 1 000-mg/kg group showed reduced food intake (probably caused by taste aversion) and reduced body weight gain. The observed organ weight changes were attributed to the reduced body weights. A NOAEL of 200 mg/kg food (20 mg/kg bw/day) is evident from this study (data presented as an abstract).

Dermal

In a study by Api and Ford (2003), rats were exposed dermally to diphenyl ether in diethyl phthalate (0, 10, 100, 300 and 1 000 mg/kg/day (d), semi-occlusive, 6 hours/day for 13 weeks (see also Section 3.3). The body weights of high-dose males were significantly reduced and the relative kidney and brain weights were increased. The relative liver weights were increased in animals of both sexes at 300 mg/kg/day and above. Males and females of the high-dose group showed an increase in serum phosphate and albumin and females also a decrease in serum cholesterol. The effect on the albumin concentration was also evident in females of the 300 mg/kg/day group. The NOAEL for systemic toxicity is 100 mg/kg/day (MAK 2004, HCN 2005).

Table 1. Summary of short-term toxicity studies in experimental animals.

Species, strain (sex;no)	Concentration	Exposure duration, days	Critical effect	NOAEL	Reference
Inhalation	mg/m^3			mg/m^3	
Rat, SD (20 males/group)	0, 35, 71, 142	27–33	Eye and nose irritation	35	Hefner 1975
Rabbit, N.Z. (4 males/group)	0, 35, 71	31–33	Eye and nose irritation	35	Hefner 1975
Dog, beagle (2 males/group)	0, 35, 71	31–33	None identified	71	Hefner 1975
Dermal	mg/kg bw			mg/kg bw	
Rat, SD (12/sex/group)	0, 100, 300, 1 000	90	Increase in liver weight	100	Api 2003

3.6. Genotoxicity

3.6.1. In vitro

Diphenyl ether was not mutagenic in the *Salmonella* strains TA98, TA100, TA1532, TA1535, TA1537, TA1538, TA1978 and TA2636, either with or without metabolic

activation. Diphenyl ether slightly increased the rate of gene conversion, mitotic recombination and gene reversion in yeast (*Saccharomyces cerevisiae* D7) with and without metabolic activation, but the increase was not statistically significant. It did not induce an increase in chromosomal aberrations in Chinese hamster ovary (CHO) cells or unscheduled DNA synthesis in primary rat hepatocytes (ECB 2000, MAK 2004, HCN 2005).

3.6.2. In vivo – Human data

Human data on genotoxic effects *in vivo* were not available.

3.6.3. In vivo – Animal data

Studies on genotoxic effects in animals *in vivo* were not available.

3.7. Carcinogenicity

3.7.1. Human data

Human data on carcinogenic effects were not available.

3.7.2. Animal data

Adequate studies on carcinogenic effects in animals were not available.

3.8. Reproductive toxicity

3.8.1. Human data

Human data on reproductive or developmental effects were not available.

3.8.2. Animal data

Reproductive toxicity studies with diphenyl ether were not available.

In the inhalation study by Hefner *et al* (1975), the oral study by Johnson *et al* (1992) and the dermal study by Api and Ford (2003), described in Section 3.5, the reproductive organs of the animals were examined. No histopathological changes of the reproductive organs were observed even at the highest concentration or doses tested (inhalation: up to 20 ppm, 142 mg/m^3, oral: up to 500 mg/kg/day, dermal: up to 1 000 mg/kg/day).

An unpublished developmental toxicity study by Monsanto (1989) was conducted with Therminol VP-1 (a mixture of 73.5 % diphenyl ether and 26.5 % biphenyl) according to OECD Guideline 414. Pregnant Charles-River-CD rats were exposed to doses of 0, 50, 200 and 500 mg/kg/day of the mixture on gestation days 6–15. There were signs of maternal toxicity at 200 mg/kg/day and above (reduced food intake, retarded body weight gain, alopecia and salivation; mortality at the highest dose), but no developmental effects.

Another unpublished study was performed by Farr (1987). Sprague-Dawley rats were exposed to Therminol VP-1 at oral doses of 0, 100, 200, 400, 800 and 1 500 mg/kg/day (mixture) on gestation days 6–15. Maternal deaths were reported at ≥ 400 mg/kg/day. Maternal food consumption was decreased at all doses when compared with that of the controls during days 6–15 of the treatment period. Maternal body weight gain was retarded in a dose-related manner in the groups receiving doses of

100, 200 and 800 mg/kg/day. Weight loss was reported in animals at 1 500 mg/kg/day. Rats receiving the mixture at doses of 400 mg/kg/day and above showed staining of the fur in the anogenital area and signs of excessive salivation. Significantly increased frequencies of uterine resorptions and significantly decreased numbers of viable foetuses per litter were reported at 800 mg/kg/day. Foetal weights at 1 500 mg/kg/day were significantly lower than those of controls. No treatment-related malformations were reported.

4. Recommendations

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 were 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.

Based on the results of acute lethal dermal (LD_{50} > 5 000 mg/kg bw) or oral (LD_{50} = 2 450–3 990 mg/kg bw) toxicity studies, SCOEL considers the compound not to present an acute health hazard.

The critical effect of inhalation exposure to diphenyl ether is irritation to the eyes and the upper respiratory tract. No qualified human data for deriving an OEL were available. There is an insufficiently documented human NOAEL of 5 ppm (35 mg/m^3) for repeated inhalation exposure (no details on duration given). In this study, exposure to 10 ppm (71 mg/m^3) was not tolerable for longer duration (Dow Chemical 1973). In addition, nausea was produced in subjects exposed by inhalation to 7–10 ppm (50–71 mg/m^3) of an eutectic mixture of biphenyl and diphenyl ether (Kirwin and Sandmeyer 1981), but the emetic response is presumably due to the presence of biphenyl (Hefner *et al* 1975).

The study by Hefner *et al* (1975) with subacute exposure of rats, rabbits and dogs to diphenyl ether vapour reveals a LOAEL of 10 ppm (71 mg/m^3) and a NOAEL of 5 ppm (35 mg/m^3) in rats and rabbits for irritation of eyes and nose. For dogs, the NOAEL was 10 ppm (71 mg/m^3).

Qualified animal studies with subchronic or chronic inhalation exposure to diphenyl ether were not available.

In the study by Hefner *et al* (1975), the first unspecific signs of systemic toxicity (body weight reduction) were observed at an exposure concentration of 20 ppm (142 mg/m^3) for diphenyl ether (20 exposures of 7 hours/day in 31–33 days). Studies with oral exposure support the notion that systemic effects may only occur at concentrations above the irritating concentrations. Subchronic oral exposure reveals a NOAEL of 20 mg/kg/day corresponding to 140 mg/m^3 (20 x 70 (kg)/10 (m^3) (100 % absorption by inhalation) (Johnson *et al* 1992).

Application of the factor 4 to adjust for specific differences between rat and humans (allometric scaling according to caloric demand) results in 35 mg/m^3 for systemic toxicity. This value corresponds to the NAOEL for irritants which is used as point of departure (5 ppm, 35 mg/m^3) to derive the recommended OEL.

The fertility and developmental parameters evaluated in the sub-acute inhalation study performed by Hefner *et al* (1975), the sub-chronic study with an eutectic mixture by Monsanto (1989), the subchronic oral study conducted by Johnson *et al* (1992) and the subchronic dermal study of Api and Ford (2003) with diphenyl ether were not affected.

Specific reproduction toxicity studies with diphenyl ether were not available

The available genotoxicity tests *in vitro* yielded negative results. *In vivo* studies on the genotoxicity or carcinogenicity of diphenyl ether were not available.

Skin sensitisation was not observed in a study with 25 volunteers (Kligman 1970).

Using the NOAEL of 35 mg/m^3 (5 ppm) for irritation of the eyes and upper respiratory tract in rats and rabbits (Hefner et al 1975) as point of departure and taking into account the limited data available and the short duration of the studies available, *an OEL of 1 ppm (7 mg/m^3) is proposed.*

A STEL of 2 ppm is proposed. This is based on the NOAEL of 5 ppm for irritation in rats, rabbits and humans. Since this value is obtained at constant exposures and exposure to 10 ppm is reported to be unacceptable because of taste and upper respiratory tract irritation, a STEL of 5 ppm is too high, because it would include exposure to such levels.

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

At the recommended TWA, no analytical difficulties are foreseen.

The present Recommendation was adopted by SCOEL on 13 December 2012.

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