



Grunnlag for fastsettelse av grenseverdi

Grunnlagsdokument for difenyleter
(C₁₂H₁₀O)

Kommisjonsdirektiv 2017/164/EU

Tittel: Grunnlag for fastsettelse av grenseverdi.
Grunnlagsdokument for difenyleter (C₁₂H₁₀O).

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Denne rapporten omhandler det toksikologiske grunnlaget og vurderinger, samt tekniske og økonomiske hensyn for fastsettelse av grenseverdi for difenyleter (C₁₂H₁₀O).



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Forord

Grunnlagsdokumenter for fastsettelse av grenseverdier utarbeides av Arbeidstilsynet i samarbeid med Statens arbeidsmiljøinstitutt (STAMI) og partene i arbeidslivet (Næringslivets hovedorganisasjon/Norsk Industri og Landsorganisasjonen i Norge) i henhold til *Strategi for utarbeidelse og fastsettelse av grenseverdier for forurensninger i arbeidsatmosfæren*. Dette dokumentet er utarbeidet ved implementering av kommisjonsdirektiv 2017/164/EU fastsatt 31. januar 2017.

EU-rådets direktiv 98/24/EC (Vern av helse og sikkerhet til arbeidstakere mot risiko i forbindelse med kjemiske agenser på arbeidsplassen) av 7. april 1998 stiller krav om at EU- kommisjonen skal legge frem forslag til indikative grenseverdier for eksponering av visse kjemikalier som medlemslandene må innføre på nasjonalt nivå. De nasjonale grenseverdiene kan være høyere enn de som står oppført i direktivet, dersom et medlemsland mener at det er nødvendig av tekniske og/eller økonomiske hensyn, men landene bør nærme seg den indikative grenseverdien. Direktivet stiller krav om at indikative grenseverdier vedtas gjennom kommisjonsdirektiv.

I Norge ble de indikative grenseverdiene innført som veiledende administrative normer. Da nye Arbeidsmiljøforskrifter trådte i kraft 1.1.2013 ble de veiledende administrative normene forskriftsfestet i forskrift om tiltaks- og grenseverdier og fikk betegnelsen tiltaksverdier. I 2015 ble begrepet «grenseverdi» for kjemikalier presisert og begrepet «tiltaksverdi» for kjemikalier ble opphevet i forskrift om tiltaks- og grenseverdier. I vedlegg 1 til forskriften ble det innført en tydeliggjøring av anmerkningene.

Arbeidstilsynet har ansvaret for revisjonsprosessen og utarbeidelse av grunnlagsdokumenter for stoffene som blir vurdert. Det toksikologiske grunnlaget for stoffene i denne revisjonen baserer seg i hovedsak på kriteriedokumenter fra EUs vitenskapskomité for fastsettelse av grenseverdier, Scientific Committee for Occupational Exposure Limits (SCOEL). SCOEL utarbeider de vitenskapelige vurderingene som danner grunnlaget for anbefalinger til helsebaserte grenseverdier, og disse legges fram for kommisjonen.

Statens arbeidsmiljøinstitutt (STAMI) ved Toksikologisk ekspertgruppe for administrative normer (TEAN) bidrar med faglige vurderinger i dette arbeidet. TEAN vurderer og evaluerer de aktuelle SCOEL dokumentene, presiserer kritiske effekter og vurderer behov for korttidsverdier ut i fra den foreliggende dokumentasjonen. Videre søker og evaluerer TEAN nyere litteratur etter utgivelsen av dokumentet. TEAN bruker kriteriene gitt i SCOEL's metodedokument, "Methodology for the derivation of occupational exposure limits: Key documentation (version 7, June 2013)". Dette er inkludert i TEANs Metodedokument del B (Prosedyre for utarbeidelse av toksikologiske vurderinger for stoffer som skal implementeres i det norske regelverket for grenseverdier etter direktiv fra EU-kommisjonen) utarbeidet for denne revisjonen.

Informasjon om bruk og eksponering i Norge innhentes fra Produktregisteret, EXPO databasen ved STAMI og eventuelle tilgjengelige måledata fra virksomheter/næringer. Beslutningsprosessen skjer gjennom drøftingsmøter der Arbeidstilsynet, Næringslivets hovedorganisasjon/Norsk Industri og Landsorganisasjonen i Norge deltar, samt orienteringsmøter og offentlig høring. Konklusjonene fra høringen med forskriftsendringer og nye grenseverdier forelegges Arbeids- og sosialdepartementet som tar den endelige beslutningen.



Innledning

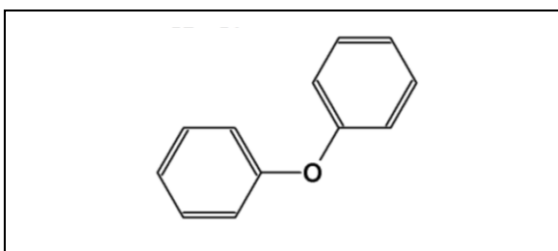
Dette grunnlagsdokumentet omhandler vurderingsgrunnlaget for fastsettelse av grenseverdi for difenyleter. Innholdet bygger spesielt på anbefalinger fra Scientific Committee on Occupational Exposure Limits (SCOEL) i EU for difenyleter (vedlegg 1), samt vurderinger og kommentarer fra Toksikologisk Ekspertgruppe for Administrative Normer (TEAN).

1. Stoffets identitet

Stoffet og dets molekylformel, synonymer av stoffets navn, stoffets identifikasjonsnummer i Chemical Abstract Service (CAS-nr.), European Inventory of Existing Commercial chemical Substances (EINECS-nr. og/eller EC-nr.) og indekseringsnummer (Indeks-nr.) i EINECS der disse er kjent er gitt i tabell 1. Strukturformel av stoffet er vist i figur 1.

Tabell 1. Stoffets navn og identitet.

Navn	Difenyleter
Molekylformel	C ₁₂ H ₁₀ O
Synonymer	1,1'-oxybis(benzen), bifenyloksid, difenyloksid, fenyloksid, fenyleter; phenoxybenzen
CAS-nr.	101-84-8
EC-nr.	202-981-2
Indeks-nr.	-



Figur 1. Strukturformel av difenyleter¹

¹ SCOEL/SUM/182 Desember 2012

2 Fysikalske og kjemiske data

Det vises til tabell 4 for fysikalske og kjemiske data for difenyleter.

Tabell 4. Fysikalske og kjemiske data for difenyleter (C₁₂H₁₀O).

Kjemisk formel	C ₁₂ H ₁₀ O
Molekylvekt (g/mol)	170,20
Fysisk tilstand	Fargeløs væske eller fast stoff med en geraniumliknende lukt.
Smeltepunkt (°C)	27
Kokepunkt (°C)	257
Flammepunkt (°C)	115 (closed cup)
Selvantennelsestemperatur (°C)	618
Tetthet (g/l ved 20 °C)	1,070
Damp tetthet (luft = 1):	5,86
Damptrykk (Pa, 20 °C):	2,7
Metningskonsentrasjon (ppm, 20 °C):	28
Fordelingskoeffisient n-oktanol/vann (log K_{ow}):	4,21
Løselighet i vann (25 °C)	Lite løselig i vann (21 mg/l)
Løselighet i andre løsemidler	Løselig i alkohol, benzen, eter
Eksplosjonsgrenser	Nedre (UEL): 0,8 % Øvre (LEL): 1,5 %
Lukterskel (ppm)	0,1
Omregningsfaktor (20 °C, 101 kPa)	1 ppm = 7,08 mg/m ³ , 1 mg/m ³ = 0,141 ppm

* <https://www.cdc.gov/niosh/ipcsneng/neng1249.html>

** <https://echa.europa.eu/registration-dossier/-/registered-dossier/15941/4/2>

2.1 Forekomst og bruk

Difenyleter brukes i stor utstrekning som varmeoverføringsmedium (også som hovedkomponent i eutektiske blandinger av difenyleter og bifenyl, det vil si at stoffene ikke er blandbare i fast form, men fullt blandbare i væskeform), som mellomprodukt i produksjon av overflateaktive midler og høytemperatur smøremidler og anvendes også i parfyme.



3 Grenseverdier

3.1 Nåværende grenseverdi

Nåværende grenseverdi i Norge for stoffet er: 1 ppm, 7 mg/m³

3.2 Grenseverdi fra EU

Den europeiske vitenskapskomiteen, SCOEL foreslår for difenyleter i sitt kriteriedokument fra 1994:

IOELV (Indicative Occupational Exposure Limit Value): 1 ppm, 7 mg/m³

STEL (Short Term Exposure Limit): 2 ppm, 14 mg/m³

Anmerkning: ingen

3.3 Grenseverdier fra andre land og organisasjoner

Tabell 2. Grenseverdier for stoffnavn fra andre land og organisasjoner. Land og organisasjoner som ikke har grenseverdier er merket -.

Land Organisasjon	Grenseverdi (8 timer)	Korttidsverdi (15 min)	Anmerkning Kommentar
Sverige ¹	-	-	
Danmark ²	1 ppm, 7 mg/m ³	-	
Finland ³	1 ppm, 7,1 mg/m ³	3 ppm, 21 mg/m ³	2016
Storbritannia ⁴	1 ppm, 7,1 mg/m ³	-	
Nederland ⁵	-	-	
ACGIH, USA ⁶	1 ppm, 7 mg/m ³	2 ppm, 14 mg/m ³	
NIOSH, USA ⁶	1 ppm, 7 mg/m ³	-	
Tyskland, MAK ⁶	1 ppm, 7,1 mg/m ³	I (1)	Overskridelsesfaktor I(1) Gjelder korttidsverdi
Tyskland, Myndighetene ⁷	1 ppm, 7,1 mg/m ³	-	Overskridelsesfaktor 1(I), Det er ingen risiko for skade på fosteret når man observerer grenseverdien for arbeidsplassen og den biologiske grenseverdien, Sum av damp og aerosol, 2013

Arbetsmiljøverkets Hygieniske gränsvärden AFS 2015:7,

<https://www.av.se/globalassets/filer/publikationer/foreskrifter/hygieniska-gransvarden-afs-2015-7.pdf>.

² At-vejledning, stoffer og materialer - C.0.1, 2007, <https://arbejdstilsynet.dk/da/regler/at-vejledninger/g/c-0-1-graensevaerdi-for-stoffer-og-mat>.

³ Social og hälsövärdministeriet, HTP-värden, Koncentrationer som befunnits skadliga, Helsingfors, 2016, http://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/79110/STM_9_2016_HTP-varden_2016_Ruotsi_22122016_NETTI.pdf.

⁴ EH40 andre utgave, 2013, <http://www.hse.gov.uk/pubns/priced/eh40.pdf>

⁵ http://www.ser.nl/en/oel_database.aspx;



⁶ Guide to occupational exposure values compiled by ACGIH, 2017.

⁷ Baua, TRGS 900, oppdatert 2016, https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/TRGS-900.pdf;jsessionid=439FFF321DF2323E60F868CD08E9CD3A.s1t2?_blob=publicationFile&v=2

3.4 Stoffets klassifisering

Difenyleter er ikke klassifisert i henhold til CLP (Annex VI Forordning (EC) Nr. 1272/2008).

3.5 Biologisk overvåking

For å vurdere grad av eksponering for forurensning i luften på arbeidsplassen kan man anvende konsentrasjonen av forurensningen i arbeidstakerens urin, blod eller utåndingsluft, eller annen respons på eksponeringen i kroppen. EU har satt verdier for dette kalt biologisk grenseverdi (BLV).

SCOEL fremmer ikke et forslag til biologisk grenseverdi for difenyleter.

4 Toksikologiske data og helseeffekter

4.1. Anbefaling fra SCOEL

EUs vitenskapskomite (SCOEL) har utarbeidet kriteriedokumentasjon for difenyleter datert 2012 hvor de anbefaler en grenseverdi for stoffet lik 1 ppm og en korttidsverdi lik 2 ppm, se vedlegg 1.

4.2. Kommentarer fra TEAN

SCOEL-dokumentet er fra desember 2012 og er basert på ACGIH (2001), ECB (2000), MAK (2004), HCN (2005) og WHO (2004).

Et nyere dokument om difenyleter fra EPA har også blitt brukt i utarbeidelsen av dette dokumentet (EPA, 2017). Det er søkt i TOXLINE og PubMed, men dette har ikke tilført nyere informasjon.

Det finnes begrenset informasjon om difenyleters effekt på mennesker og dyr. Flere av de rapporterte helseeffektene ved eksponering er basert på en blandingseksponering for difenyleter og bifenyyl. Dette gjør det vanskelig å uttale seg om effektene av difenyleter.

Den kritiske effekten av eksponering for difenyleter er irritasjon i øyne og de øvre luftveiene.

Dyrestudier viser irritasjon hos rotter, kaniner og hunder ved 10 ppm, med en NOEL på 5 ppm. Hos mennesker rapporteres det irritasjon i øyne og de øvre luftveiene ved en eksponering på 7 ppm. Det fins ingen data som tyder på en mulig sensibilisering eller kreftrisiko ved eksponering for difenyleter hos mennesker eller dyr.

Hudopptak: Det finnes motstridende data for hvor effektivt difenyleter tas opp gjennom huden. En studie har funnet at ved administrering av difenyleter (10-1000 mg/kg) på huden hos rotter gikk 20% av dosen igjennom huden. En annen studie har vist ved *in vitro* tester at gjennomtrengningen av hud var 0,3% for hud fra rotter og 0,2% for hud fra mennesker. Det bedømmes å være for tynt grunnlag for å gi difenyleter en hudmerking.



Basert på de irriterende effektene på øvre luftveier og øyne foreslår SCOEL at det, foruten en grenseverdi, innføres en korttidsverdi for difenyleter. TEAN har ingen bemerkninger til SCOELs vurdering.

5. Bruk og eksponering

5.1. Opplysning fra Produktregisteret

På grunn av sikkerhetsbestemmelsene i Produktregisteret kan vi ikke gi opplysninger om bruk av difenyleter.

5.2. Eksponering og måledokumentasjon

5.2.1. EXPO- data

Det foreligger ingen måledata for difenyleter i STAMIs eksponeringsdatabase EXPO.

5.2.2. Prøvetakings- og analysemetode

I tabell 5 er anbefalte metoder for prøvetaking og analyser av difenyleter presentert.

Tabell 5. Anbefalte metoder for prøvetaking og analyse av difenyleter.

Prøvetakingsmetode	Analysemetode	Referanse
Kullrør	Desorpsjon m/CS ₂ , GC-FID ¹	NIOSH-metode 1617 ²

¹ Gasskromatografi - Flammeionisasjonsdetektor

² <https://www.cdc.gov/niosh/docs/2003-154/pdfs/1617.pdf>

6. Vurdering

Den kritiske effekten av difenyleter er irritasjon i øyne og øvre luftveier. SCOEL begrunner sitt forslag til grenseverdi og korttidsverdi med en NOAEL for rotte, kanin og mennesker på 5 ppm.

Da det ikke foreligger måledata som sier noe om eksponeringsnivået i Norge, og heller det heller ikke foreligger data fra Produktregisteret, foreslår Arbeidstilsynet å følge anbefalingene fra SCOEL.



7. Konklusjon med forslag til korttidsverdi

På bakgrunn av foreliggende dokumentasjon foreslår Arbeidstilsynet å innføre korttidsverdi for difenyleter. Grenseverdien beholdes uendret.

Forslag til korttidsverdi og anmerkning for difenyleter:

Grenseverdi (8-timers TWA): 1 ppm, 7 mg/m³

Korttidsverdi (15 min): 2 ppm, 14 mg/m³

Anmerkning: E (EU har fastsatt grenseverdi for stoffet), S (korttidsverdi)

8. Ny grenseverdi

Dette kapitlet utarbeides etter at ASD har fastsatt den nye grenseverdien.



9. Referanser

EPA, 2017, Provisional Peer-Reviewed Toxicity Values for Diphenyl Ether, EPA/690/R-17/009





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

*SCOEL/SUM/182
December 2012*

Employment,
Social Affairs
and Inclusion



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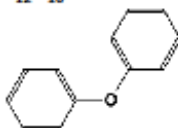
Recommendation from the Scientific Committee on Occupational Exposure Limits for Diphenyl ether

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: C₁₂H₁₀O

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/m³;
1 mg/m³ = 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/cm³ (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-methoxydihydroxy 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 derivatives. 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/m³) 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 LC₅₀ of Therminol VP-1 (a mixture of 73.5 % diphenyl ether and 26.5 % biphenyl) in rats was 2 660 mg/m³ (no exposure duration stated). No toxicity was observed in rats after inhalation of a saturated atmosphere of 28 ppm (199 mg/m³, the saturated concentration at 25 °C) of diphenyl ether for 6 hours (no further details). The oral LD₅₀ in rats was 2 450–3 990 mg/kg. The dermal LD₅₀ 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/m³) have been reported (Amoore and Hautala 1983, Ruth 1986).

Exposure to 7–10 ppm (50–71 mg/m³) 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/m³) of diphenyl ether (99.9 % pure) was "well tolerated" (Hefner *et al* 1975). Exposure to 10 ppm (71 mg/m³) 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/m³, 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/m³) 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/m³) for an overall period of 27 days. The rats and rabbits, but not the dogs, exposed to 10 ppm (71 mg/m³) 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/m³).

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/m³ 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/m³ 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/m³) 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
<i>Inhalation</i>					
	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
<i>Dermal</i>					
	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/m³, 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 ($LD_{50} = 2\,450\text{--}3\,990$ 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/m³) for repeated inhalation exposure (no details on duration given). In this study, exposure to 10 ppm (71 mg/m³) 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/m³) 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/m³) and a NOAEL of 5 ppm (35 mg/m³) in rats and rabbits for irritation of eyes and nose. For dogs, the NOAEL was 10 ppm (71 mg/m³).

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/m³) 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/m³ (20 x 70 (kg)/10 (m³)) (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/m³ for systemic toxicity. This value corresponds to the NOAEL for irritants which is used as point of departure (5 ppm, 35 mg/m³) 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/m³ (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/m³) 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.

5. References

- ACGIH, American Conference of Governmental Industrial Hygienists (2001). Phenyl ether. In: ACGIH Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH.
- Amoore JE, Hautala, E (1983). Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 3:272-290.
- Api AM, Ford, RA (2003). Evaluation of the dermal subchronic toxicity of diphenyl ether in the rat. *Food Chem Toxicol* 41:259-264, cited in Greim 2004 and HCN 2005.
- Dow Chemical (1973). Subjective response of volunteers to odors of diphenyl oxide (phenyl ether) at 3 to 20 parts per million concentrations. EPA/OTS Doc 86-890001217S, NTIS/OTS 0520728. Springfield, VA, USA.
- ECB, European Chemicals Bureau (2000). IUCLID, International Uniform Chemical Information Database. Edition II. EUR 19559 EN, European Commission.
- Farr CH (1987). Range-finding teratology study in rats with Therminol VP-1. Submission to EPA. Unpublished report to the Flavor and Extract Manufacturers Association. Submitted to WHO by the Flavor and Extract Manufacturers Association of the United States, Washington DC, cited in WHO 2004.
- HCN, Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits (2005). Health-based reassessment of administrative occupational exposure limits - diphenyl ether. Publ. No. 2000/15OSH/147. Health Council of the Netherlands, The Hague.
- Hefner RE, Leong BKJ, Kociba RJ, Gehring PJ (1975). Repeated inhalation toxicity of diphenyl oxide in experimental animals. *Toxicol Appl Pharmacol* 33:78-86.
- Hotchkiss SAM (1998). Absorption of fragrance ingredients using in vitro models with human skin. In: Frosch PJ, White IR. *Fragrances: beneficial and adverse effects*. Springer Verlag Berlin, 125-135, cited in MAK 2004.
- Johnson WD, Ehrlich JP, Hatoum NS, Yermakoff JK (1992). Thirteen week oral (diet) toxicity study of diphenyl ether in rats. *The Toxicologist* 12:117, cited in MAK 2004.
- Kirwin CJ, Sandmeyer EE (1981). Ethers. In: Clayton GD, Clayton FE (eds.). *Patty's industrial hygiene and toxicology*, Vol. 2A, 3rd edition, 2541-2545. John Wiley and Sons, New York, cited in MAK 2004.
- Kligman AM (1970). Report to research institute for fragrance materials on the contact sensitizing potential of four fragrance materials. Ivy Research Laboratories Inc, Philadelphia, Pennsylvania, USA, cited in MAK 2004.
- MAK (2004). *Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, Loseblattsammlung*, 39. Lfg. DFG, Deutsche Forschungsgemeinschaft, Wiley-VCH Verlag, Weinheim.
- Monsanto (1989). A developmental toxicity study in rats with Therminol VP-1 heat transfer fluid (final report). NTIS/OTS 0520431, EPA/OTS Doc ID 86-890000352, Springfield, VA, USA, 1989, cited in MAK 2004.

NIOSH, National Institute for Occupational Safety and Health (1994). Phenyl ether: method 1617, issue 1. In: NIOSH manual of analytical methods (NMAM), fourth edition, 8/15/94. U.S. National Institute for Occupational Safety and Health, Centers for Disease Control & Prevention. Department of Health and Human Services.

OSHA, Occupational Safety & Health Administration (1988). Sampling and analysis methods: diphenyl and phenyl ether. Method no: PV2022. U.S. Department of Labor.

Pecchiani L, Saffiotti U (1957). Study of toxicity of diphenyl, oxydiphenyl, and their mixtures (Dowtherm). Med Lav 48:247-254, cited in WHO 2004.

Ruth JH (1986). Odor thresholds and irritation levels of several chemical substances: a review. Am Ind Hyg Assoc J 47:795-800.

WHO, World Health Organization (2004). WHO Food Additives Series 52: Aliphatic and aromatic ethers. <http://www.inchem.org/documents/jecfa/jecmono/v52je16.htm>.