Chlorinated diphenyl oxides

Health-based Reassessment of Administrative Occupational Exposure Limits

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

No. 2000/15OSH/078, The Hague, 22 October 2003

Preferred citation:
Health Council of the Netherlands: Committee on Updating of Occupational Exposure Limits. Chlorinated diphenyl oxides; Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, 2003; 2000/15OSH/078.

1 Introduction

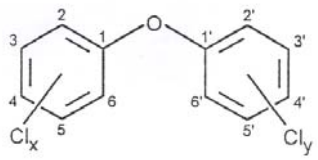
The present document contains the assessment of the health hazard of chlorinated diphenyl oxides (ethers) by the committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands.The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen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

The evaluation of the toxicity of chlorinated diphenyl oxides has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99) and on reviews published in 'Patty's Industrial Hygiene and Toxicology' (Ben94, Kir93). 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 Toxline, Medline, and Chemical Abstracts covering the periods of 1981 to May 2000, 1966 to May 2000, and 1937 to April 2000, respectively, and using the following key words: chlorinated diphenyl oxide; hexachlorodiphenyl oxide; chlorinated difenyl oxide; hexachlorodifenyl oxide; chlorinated diphenyl ether; chlorinated difenyl ether; benzene, 1,1'-oxy*bis*-, chloro derivatives; phenyl ether, derivatives; and 55720-99-5. The final search was carried out in Toxline and Medline in January 2003.

In April 2003, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	chlorinated diphenyl oxides
synonyms	:	chlorinated diphenyl ethers
molecular formula	:	$C_{12}H_{10-n}Cl_nO$, where n = 1-10
structural formula	:	



CAS number	:	each of the 209 congeners has a specific CAS number.

Data from ACG99.

3 Physical and chemical properties

There are 209 possible chlorinated diphenyl oxides (Ben94, Kur99). The molecular weights range from 204.7 for the monochlorodiphenyl oxides ($C_{12}H_9ClO$) to 514.7 for the decachloro congeners ($C_{12}Cl_{10}O$). A few physical properties of 106 chlorinated diphenyl oxides were calculated (Kur99). The data will not be presented here, but generally speaking, the congeners have:

- a low vapour pressure (for sub-cooled liquids), ranging from 0.54 Pa for 2-chlorodiphenyl oxide to 1.6 x 10^{-6} Pa for the decachloro congener.
- a low aqueous solubility, ranging from 12.7 mg/L for 2-chlorodiphenyl ether to 0.06 ng/L for the decachloro congener.
- a high *n*-octanol/water partition coefficient, the experimental log $P_{octanol/water}$ ranging from 4.45 for 2-chlorodiphenyl oxide to 8.16 for the decachloro congener (Kur99).

For the following chlorinated diphenyl oxides, specific physical and chemical properties were found (Isn88, Kir93, Lid99):

	monochloro diphenyl	4-chlorodiphenyl oxide	dichlorodiphenyl oxides	4,4'-dichlorodiphenyl	hexachlorodiphenyl oxides
CAS number	55398-86-2	7005-72-3	28675-08-3 or 86366-09-8	2444-89-5	31242-93-0 or 55720-99-5
molecular weight	204.7	204.7	239.1	239.1	376.9
melting point	-	-	-	30°C	-
boiling point	at 1.1 kPa: 153°C	285.5°C	at 1.1 kPa: 168.2°C	313°C	at 1.1 kPa: 230-260°C
conversion factors	not applicable				

Chlorinated diphenyl oxides, comprising 54% and 57% chlorine, are white to yellowish, waxy semisolids (ACG99).

4 Uses

Chlorinated diphenyl oxides are used as chemical intermediates in the manufacture of flame-inhibiting polymers, as corrosion inhibitors, dry-cleaning detergents, and thermal lubricants, as additives for soaps and lotions, and in the

manufacture of hydraulic fluids, pesticides, wood preservatives, and electric insulators (ACG99).

5 Biotransformation and kinetics

Human data

Measurement of chlorinated diphenyl ethers in adipose tissue of a Canadian population revealed the presence of detectable amounts of nonachlorodiphenyl oxide and decachlorodiphenyl oxide, at mean values of 1.53 and 0.38 ng/g, respectively (Wil91).

Animal data

The metabolism and excretion of ^{14}C-2,2',4,4',5-pentachlorodiphenyl oxide (PCDE) was investigated in male Sprague-Dawley rats after a single oral dose of 10 mg/kg bw. Within 7 days, 55% and 1.3% of the radioactivity were excreted in the faeces and urine, respectively. Faecal excretion products were identified as unchanged and hydroxylated PCDE (more than 64% and 23% of the faecal radioactivity, respectively) (Kom88). The metabolism of 4 chlorinated diphenyl oxides, viz., 4,4'-dichloro-, 2',3,4-trichloro-, 2,4, 4',5-tetrachloro-, and 3,3',4,4'-tetrachlorodiphenyl oxide was investigated in male Wistar rats, following administration of a single oral dose of 250 mg/kg bw of each congener in separate experiments. Metabolism predominantly occurred by aromatic hydroxylation, while scission of the ether bond was a minor metabolic process. Mono-and dihydroxy derivatives, either in the *ortho* or *meta* position, were major metabolites in the urine and/or faeces for all 4 compounds. In addition, trihydroxy derivatives were found as minor metabolites for both the 4,4'-dichloro and 2',3,4-trichloro congeners. No quantitative data were given. Neither in the case of the 2',3,4-trichloro-, nor in that of the 2,4,4',5-tetrachlorodiphenyl oxide, both possessing an *ortho* chlorine atom, could metabolic cyclisation to chlorodibenzo-*p*-dioxins, chlorodibenzofurans, or their hydroxylated derivatives be detected (Tul79).

When male Sprague-Dawley rats were given a single intravenous injection of ^{14}C-4-chlorodiphenyl oxide (174 µg /kg bw), the concentration of the parent compound in the blood declined biphasically with time, and was not detectable anymore beyond 2 hours after administration. About 33% and 41% of the administered radioactivity was excreted in the faeces and urine, respectively, within 7 days. In bile, about 5% of the administered radioactivity was excreted

within 1 hour. The major metabolite in urine was identified as 4'-hydroxy-4-chlorodiphenyl oxide, which accounted for 90% of the urinary radioactivity (Chu87).

Following a single intravenous injection of ^{14}C-2,2',4,4',5-pentachlorodiphenyl oxide (PCDE) at a dose of 10 mg/kg bw, the highest concentrations of radioactivity were already found at 1 hour after administration in the liver, followed by the kidney, brain, spleen, muscle, and blood. Radioactivity levels in skin and adipose tissue peaked at 1 and 4 days after administration, respectively. At 21 days after administration, levels of radioactivity in most tissues (except adipose tissue) declined almost to background levels. Unchanged compound accounted for most of the radioactivity found in the tissues. Decay of PCDE in the blood was fitted to a 4-compartment pharmacokinetic model, and the half-life of PCDE in the last compartment was 5.8 days (Kom88).

In another study, the tissue distribution and relative rates of elimination of a mixture of chlorodiphenyl oxides in male Sprague-Dawley rats were studied following administration of a single oral dose of 2.1 mg of the mixture/kg bw by gavage. The mixture contained 5 hepta-, 4 octa-, and 2 nonachlororodiphenyl oxides, in the approximate proportion of 47%, 33%, and 18%, respectively. The uptake of total chlorodiphenyl oxide was rapid in blood, liver, and muscle, reaching peak values after approximately 8 hours. The highest levels were found in adipose tissue, followed by skin, liver, muscle, and blood. Half-lives of disappearance of the various chlorinated diphenyl oxides were similar in all tissues (with the exception of the adipose tissue), and ranged from 5.7-7.4, 8.9-10.4, and 9.8-13.4 days in liver, blood, and skin, respectively. No half-life in adipose tissue could be calculated in view of the slow removal of all isomers. Within 7 days, faecal and urinary excretion accounted for 20% and 0.04% of the administered dose, respectively. Comparison of the isomer distribution in tissues, determined 14 days after dosing with that of the original dosing solution revealed that the proportion of total hepta-, octa-, or nonachloro isomers remained relatively constant for all tissues except liver. In liver, the proportion of hepta- and octachloro isomers was decreased, but that of the nonachloro isomers increased. According to the authors, this increase of the nonachloro congener was thought to be a reflection of an increased uptake by the liver rather than a decreased elimination rate, since the half-lives of the hepta-, octa- and nonachloro congeners were similar (New83).

Groups of Sprague-Dawley rats (n=10/sex/congener) were given 6 chlorinated diphenyl oxides, containing 5, 6, or 7 chlorine atoms, either by gavage or via the food, for 28 days. At the end of the study, the animals were

sacrificed and concentrations of each chlorinated diphenyl oxide were measured in the liver and adipose tissue. The levels of the 6 congeners in both tissues were dose dependent, with the adipose tissue having concentrations between 1 and 2 orders of magnitude higher than the liver. The hexachloro congeners appeared to accumulate to a greater extent in the adipose tissue, but not in the liver, than the penta- or heptachloro congener (Chu89, Chu90). The committee concludes that the number of chlorine atoms and their position (i.e., *ortho* or *meta*) are less important in the biotransformation of chlorinated diphenyl oxides than in polychlorinated biphenyls (PCBs).

In vitro data
In *in vitro* studies, ^{14}C-4-chlorodiphenyl oxide was converted into ^{14}C-4'-hydroxy-4-chlorodiphenyl oxide by liver microsomes of rats. In addition, radioactivity was bound irreversibly to microsomal protein, indicating that ^{14}C-4-chlorodiphenyl oxide was converted by liver microsomes to protein-reactive metabolites (Chu87).

6 Effects and mechanism of action

Human data

Exposure to small amounts of hexachlorodiphenyl oxide (not further specified) was reported to induce appreciable acneiform dermatitis (Kir93). It has also been reported that following exposure to the more highly chlorinated diphenyl oxides, dermatitis may develop at the site of exposure, generally from prolonged skin contact. The dermatitis resembles common acne in appearance, and may be accompanied by intensive itching. Systemic toxicity has not been reported among workers handling the chlorinated diphenyl oxides (ACG99, Kir93).

Animal data

Irritation and sensitisation

When applied to the skin of rabbits, chlorinated diphenyl oxides were irritating, producing necrosis and sloughing (no experimental details given). The ability to cause the necrotic type of reaction increased with chlorine content, apparently reaching the maximum at 4 chlorine atoms, and then declining. Hexachlorodiphenyl oxide (not further specified) produced a marked irritation, but never definite necrosis. The ability to induce epithelial hyperplasia also

increased with increasing degree of chlorination, in particular from 3 to 4 or more chlorine atoms (Kir93).

The committee could not find data on eye irritation or on skin sensitisation of chlorinated diphenyl oxides.

Acute toxicity

The acute lethal oral toxicity data found in guinea pigs are summarised in Table 1.

Table 1 Acute lethal oral toxicity data of chlorinated diphenyl oxides in guinea pigs (Kir93).

compound	lethal dose
monochlorodiphenyl oxide	600 mg/kg bw
dichlorodiphenyl oxide	1000 mg/kg bw
trichlorodiphenyl oxide	1200 mg/kg bw
tetrachlorodiphenyl oxide	50 mg/kg bw
pentachlorodiphenyl oxide	100 mg/kg bw
hexachlorodiphenyl oxide	50 mg/kg bw

Except that the observation period was 30 days, no details were given on the tested isomer(s) or on the experimental method used for the determination of the lethal dose (Kir93).

Groups of male C57BL/6 mice (n=5/group) were given a single intraperitoneal injection of various doses of each of 12 chlorinated diphenyl oxides, containing 4, 5, 6, 9, or 10 chlorine atoms, to study their ability to induce hepatic drug metabolising enzyme activities and their immunosuppressive potencies (Har93, How90). Hepatic enzymes studied were 7-ethoxyresorufin-*O*-deethylase (EROD) and aryl hydrocarbon hydroxylase activity (AHH). The effects of the chlorinated diphenyl oxides on these enzymes are shown in Table 2.

The committee concludes that:

- All chlorinated diphenyl oxide congeners induced a dose-related increase in the activity of EROD.
- The induction of AHH activity was less marked than that of EROD
- The relative potencies of the tetra-, penta-, and hexachlorinated diphenyl oxides as inducers of AHH and EROD activities followed the order:

2,3’,4,4’,5-penta>3,3’,4,4’,5-penta>2,3,3’,4,4’,5-hexa>3,3’,4,4’-tetra>2,2’,4,4’,5,5’-hexa. Activities of the 2,2’,4,4’,5,6’-hexa, 2,2’,4,5,5'-pentachloro, or 2,3’,4,4’,5’,6-hexa congeners were much lower.

- For the 3 pentachloro isomers, the percentage induction of EROD activity decreased with increasing number of chlorine atoms at the *ortho* position. No relation between the degree of induction of EROD activity and the number of chlorine atoms at the *ortho* position could be found for the other chlorinated diphenyl oxide congeners.

Table 2 Percentage increase of hepatic enzymes EROD or AHH after a single intraperitoneal injection of various chlorinated diphenyl oxides in male C57BL/6 mice.

chlorinated diphenyl oxide congener	dose levels (mg/kg bw)	EROD activity	AHH activity	number of Cl atoms in *ortho* position	reference
3,3’,4,4'-tetrachloro	1.54	ns[a]	ns	0	How90
	3.08	534	ns		
	7.70	1252	ns		
	30.8	1180	595		
3,3’,4,4’,5-pentachloro	3.42	ns	ns	0	How90
	8.56	1154	523		
	34.2	2032	669		
2,3’,4,4’,5-pentachloro	8.56	511	728	1	How90
	34.2	704	1003		
	137	816	1167		
2,2’,4,5,5'-pentachloro	8.56	ns	ns	2	How90
	34.2	164	ns		
	137	352	ns		
2,3,3’,4,4’,5-hexachloro	3.77	283	ns	1	How90
	9.43	725	223		
	37.7	2318	536		
2,3’,4,4’,5,5'-hexachloro	9.43	ns	ns	1	How90
	37.7	256	ns		
	151	562	2327		
2,2’,4,4’,5,5'-hexachloro	9.43	176	ns	2	How90
	37.7	431	ns		
	151	1545	481		
2,2’,4,4’,5,6'-hexachloro	37.7	ns	ns	3	How90
	151	300	ns		

2,2',3,3',4,4',5,5',6-nonachloro	12	ns	-[b]	3	Har93
	48	225	-		
	192	1338	-		
2,2',3,3',4,5,5',6,6'-nonachloro	12	ns	-	4	Har93
	48	622	-		
	192	3364	-		
2,2',3,3',4,4',5,6,6'-nonachloro	4.8	ns	-	4	Har93
	12	459	-		
	48	1852	-		
	192	8643	-		
decachloro	5.15	ns	-	4	Har93
	12.9	273	-		
	51.5	504	-		
	206	8656	-		

[a] ns = not significant; differences are significant for the nona- and decachloro congeners at $p<0.05$ and for the tetra-, penta- and hexachloro congeners at $p<0.01$.

[b] - : not assayed.

The immunotoxic potency of each congener was determined by the inhibition of the splenic plaque-forming cell (PFC) response to sheep red blood cell antigen. The results are shown in Table 3.

The ED_{50} values show that the immunotoxicity of the higher chlorinated diphenyl oxides (nona and deca) are high compared to that of the lower chlorinated diphenyl oxides (tetra, penta, hexa). However, the committee concludes that overall the immunosuppressive potencies of chlorinated diphenyl oxides are not related to the degree of chlorination, or to the number of chlorine atoms in the *ortho* position. Harper et al. and Howie et al. suggested that the observed immunotoxicity of the lower chlorinated diphenyl oxides is caused through an aryl hydrocarbon (Ah) receptor-mediated mechanism. When the ED_{50} values for immunosuppression are combined with those for the induction of the hepatic EROD and AHH enzymes, they concluded that the lower chlorinated diphenyl oxides are more than 200 times less immunotoxic than TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) (How90). They also suggested that some of the immunosuppressive effects observed for the nona- and decachloro congeners may be Ah-receptor independent (Har93).

Table 3 Immunotoxic effects of various chlorinated diphenyl oxides after a single intraperitoneal injection in male C57BL/6.

chlorinated diphenyl oxide congener	dose level (mg/kg bw)	ED_{50} PFCs/spleen[a] (mg/kg bw)	ED_{50} PFCs/10^6 viable spleen cells (mg/kg bw)	number of Cl atoms in *ortho* position	reference
3,3',4,4'-tetrachloro	1.56 - 30.8	15.6 (8)	15.6 (8)	0	How90
3,3',4,4',5-pentachloro	3.42 - 34.2	3.01 (4)	1.74	0	
2,3',4,4',5-pentachloro	8.56 - 137	7.46 (7)	4.86	1	
2,2',4,5,5'-pentachloro	8.56 - 137	88.2 (10)	78.0	2	
2,3,3',4,4',5-hexachloro	3.77 - 37.7	0.174 (1)	0.829	1	
2,3',4,4',5,5'-hexachloro	9.43 - 151	0.264 (-)	nd	1	
2,2',4,4',5,5'-hexachloro	9.43 - 151	30.6 (9)	21.3	2	
2,2',4,4',5,6'-hexachloro	37.7 - 151	>151 (11)	>151	3	
2,3,3',4,4',5,5',6'-nonachloro	1.20 - 192	1.91 (3)	4.82	3	Har93
2,2',3,3',4,5,5',6,6'-nonachloro	1.20 - 192	1.30 (2)	1.37	4	
2,2',3,3',4,4',5,6,6'-nonachloro	1.20 - 192	4.18 (5)	7.88	4	
decachloro	1.29 - 206	5.20 (6)	14.2	4	

[a] The dose which elicits 50% reduction in response (ranking of immunosuppressive potency between parenthesis).
PFC = plaque forming cell.
nd = not determined due to inadequate correlation.

Subacute toxicity

In 3 different studies, the potency of chlorinated diphenyl oxides to induce hepatic drug metabolising enzyme activities in Sprague-Dawley rats was investigated. In one study, 10 chlorinated diphenyl oxides, containing 2, 3, 4, 5, or 10 chlorine atoms, were tested in groups of 5 rats/congener, at doses varying between 2.39 and 5.15 mg/kg bw/day, for 3 consecutive days. The following 4 enzymes were measured: *O*-ethyl-*O*-p-nitrophenyl phenylphosphonothioate (EPN), cytochrome P450 (CYP450), aryl hydrocarbon hydroxylase (AHH), and NADPH cytochrome c reductase (CytC). No significant changes in the activity of any of these enzymes were found after administration of the dichloro- or trichloro congeners, and only of one enzyme with a tetrachloro congener. The higher chlorinated diphenyl oxides caused slightly increased activities (2.1- to 3.4-fold that of controls) of 2 or 3 enzymes (Car80).

In another oral study, 12 congeners containing 5, 6, 7, 8, or 10 chlorine atoms, were tested at doses of 5 mg/kg bw/day in groups of 3 rats/congener for 3

consecutive days. Enzymes measured were CYP450, EROD, and aminopyrine *N*-demethylase (APD). The tetra-, penta-, and hexachloro congeners induced a significant increase in EROD activity (5- to 69-fold), but not in APD, which was also seen after application of the reference compound 3-methylcholanthrene. In contrast, most of the higher chlorodiphenyl oxides induced a significant increase in APD activity (1.5- to 2-fold), but not in EROD, which was also seen after application of the reference compound phenobarbital. One compound (the 2,2',3,3',4,4',5-hexachloro congener) induced both enzymes, and one compound (the 2,2',3,4,4',5,5'-heptachloro congener) did not cause a statistically significant induction of either enzymes. CYP450 activity was slightly increased after administration of all congeners, independent of the degree of chlorination, and 9 of them statistically significant. The authors concluded that congeners having 0, 1, or 2 *ortho* substituents gave a 3-methylcholanthrene-type induction response, and compounds with 3 or more *ortho* substituents a phenobarbital-type induction (Ive87).

In a third study, rats were given intraperitoneal injections of each of 4 chlorinated diphenyl oxides, containing 1, 2, 3, or 4 chlorine atoms, at a dose of 100 mg/kg bw/day, for 3 consecutive days. Enzymes measured were CYP450, cytochrome b_5, APD, 7-ethoxycoumarin *O*-deethylase (ECOD), and benzo(*a*)pyrene hydroxylase (BPH). No statistically significant changes in the activity of any of these enzymes were found after administration of the monochloro congener. The trichloro congener induced a slight increase in CYP450 activity, but not in any of the other enzymes. The trichloro- and tetrachlorodiphenyl oxides induced a slight increase in the activity of all enzymes measured, in particular of ECOD (2.5- and 3.0-fold higher than the controls). In addition to enzyme induction, an increase of relative liver weight was found after application of the 2,4,4'-trichloro congener, but not with the other compounds (Chu85). The outcome of the 3 studies is shown in detail in Table 4.

Table 4 Percentage increase of several hepatic enzymes after a 3 daily oral or intraperitoneal doses of various chlorinated diphenyl oxides in male rats.

			increase in enzyme activity (% of control values)								
chlorinated diphenyl oxide congener	exposure route	dose (mg/kg bw/day)	EPN	CYP 450	Cytb	EROD	APD	BPH	AHH	CytC	reference
2,4'-dichloro	oral	2.39	ns	ns	-	-	-	-	ns	ns	Car80
4,4'-dichloro		2.39	ns	ns	-	-	-	-	ns	ns	Car80
2,4,4'-trichloro		2.74	ns	ns	-	-	-	-	ns	ns	Car80

2,2',4-trichloro		2.74	ns	ns	-	-	-	-	ns	ns	Car80
2',3,4-trichloro		2.74	ns	ns	-	-	-	-	ns	ns	Car80
2',3,4,4'-tetrachloro		3.08	ns	ns	-	-	-	-	210	ns	Car80
3,3',4,4'-tetrachloro		3.08	ns	ns	-	-	-	-	ns	ns	Car80
2,2',4,4',5-pentachloro		3.42	150	125	-	-	-	-	ns	ns	Car80
2,3',4,4',5-pentachloro		3.42	ns	155	-	-	-	-	240	ns	Car80
decachloro		5.15	340	260	-	-	-	-	ns	145	Car80
3,3',4,4'-tetrachloro		5.0	-	136	-	3018	ns	-	-	-	Ive87
3,3',4,4',5-pentachloro		5.0	-	161	-	6882	ns	-	-	-	Ive87
2,3,3',4,4'-pentachloro		5.0	-	129	-	1100	ns	-	-	-	Ive87
2,2',3,3',4,4'-hexachloro		5.0	-	ns	-	2632	ns	-	-	-	Ive87
2,3,3',4,4',5-hexachloro		5.0	-	ns	-	479	ns	-	-	-	Ive87
2,2',3,3',4,4',5-heptachloro		5.0	-	ns	-	536	146	-	-	-	Ive87
2,2',3,3',4',5,6-heptachloro		5.0	-	148	-	ns	207	-	-	-	Ive87
2,2',3,4,4',5,5-heptachloro		5.0	-	130	-	ns	NS	-	-	-	Ive87
2,'2',3,4',5,5',6-heptachloro		5.0	-	196	-	ns	239	-	-	-	Ive87
2,2',3,4,4',5,5',6-octachloro		5.0	-	189	-	ns	204	-	-	-	Ive87
2,2',3,3',4,4',5,6-octachloro		5.0	-	184	-	ns	242	-	-	-	Ive87
decachloro (commercial)		5.0	-	210	-	6740	ns	-	-	-	Ive87
decachloro (purified)		5.0	-	196	-	ns	195	-	-	-	Ive87
4-chloro	i.p.	100	-	ns	ns	ns *	ns	ns	-	-	Chu85
2,4-dichloro		100	-	129	ns	ns *	ns	ns	-	-	Chu85
2,4,4'-trichloro		100	-	146	237	246*	188	201			Chu85
2,4,4',5-tetrachloro		100	-	140	131	303*	171	171	-	-	Chu85

Abbreviations liver enzymes: NP = *O*-ethyl-*O*-p-nitrophenylphenylphosphothionate; CYP450 = cytochrome P450; Cytb = cytochrome b_5 ; EROD = 7-ethoxyresorufin *O*-deethylase; APD = aminopyrine *N*-demethylase; BPH = benzo(*a*)pyrene hydroxylase; AHH = aryl hydrocarbon hydroxylase; cytC = NADPH cytochrome c reductase.
ns = not statistically significant.
- = not determined.
* In this study, 7-ethoxycoumarin *O*-deethylase (ECOD) was measured, instead of EROD.

The committee concludes:

- All chlorinated diphenyl oxides, except the mono- and dichloro congeners, have the potency to induce one or more liver drug metabolising enzymes.
- Hepatic EROD and/or ECOD activity increased from trichloro to hexachloro congeners, and declined again from heptachloro to decachloro congeners.
- The induction of other enzymes was not related to the degree of chlorination.
- The trichloro congeners induced several liver enzymes after intraperitoneal injection, but not after oral dosing. The difference was considered to be the result of dose and route.
- No relation could be found between the number of chlorine atoms at the *ortho* position and the degree of enzyme induction. However, compounds having 0, 1, or 2 *ortho* substituents gave a 3-methylcholanthrene-type induction response, and compounds with 3 or more *ortho* substituents a phenobarbital-type induction.

Short-term toxicity

In a dermal study, the inner surface of one ear of 4 New Zealand White rabbits was treated with 0.2 mL of a 10% emulsion of a hexachlorodiphenyl oxide (no specification given of the used isomer) in olive oil, once a week, for 4 consecutive weeks. Beginning at week 3, gross follicular enlargement characteristic of chloracne developed. By week 4, the follicles were much enlarged, thickened, and hard. Severe scaling and exfoliation were evident. Epidermal biopsy showed severe acanthosis and follicular hyperkeratosis with distension of the follicles with keratin. During the 4 weeks after cessation of exposure, all animals showed body weight loss, and 2 out of 4 animals died. Gross macroscopic examination revealed rough, granular, tough, yellowish-brown livers in 2 animals. Microscopic examination revealed hepatic damage in all animals, characterised by focal hepatocyte hypertrophy, focal necrosis, fibrosis and bile statis, tubular degeneration of the kidney in 1 rabbit, lymphoid atrophy of the spleen in 1 animal, and hypoplasia of the bone marrow in all animals (Pow75).

Groups of 10 male and 10 female Sprague-Dawley rats were given chlorinated diphenyl oxides containing 5, 6, or 7 chlorine atoms, either by gavage or via the food for 28 days. At the end of the study, the animals were sacrificed and standard haematology and clinical chemistry, organ weight, and macroscopic and macroscopic examinations were conducted. In addition, the activity of the liver microsomal enzymes aniline hydroxylase (AH), APD, and

EROD were measured. The tested chlorinated diphenyl oxides, the doses given to the rats, and the observed effects are summarised in Table 5 (Chu89, Chu90).

Table 5 28-day oral toxicity studies with several chlorinated diphenyl oxides in Sprague-Dawley rats.

chlorinated diphenyl oxide congener	dose levels (mg/kg bw/day)	effects[a]	NOAEL (mg/kg bw/day)
administration via gavage (Chu89)			
2,2',4,4',6-pentachloro[b]	0, 0.04, 0.4, 4.0, 40	males/females: mild histological changes in liver and thyroid at the high dose[c]. males: increased serum glucose, calcium, total protein, and urea at all dose levels[d]; increased relative liver weight at the high dose.	4.0
2,2',4,4',5,6- hexachloro[b]	0, 0.04, 0.4, 4.0, 40	males/females: mild histological changes in liver and thyroid at the high dose[c]. males: increased APD activity at high dose. females: increased relative liver weight and AH activity at high dose.	4.0
2,2',3,3',4,6'- hexachloro[b]	0, 0.04, 0.4, 4.0, 40	males/females: increased relative liver weight and mild histological changes in liver and thyroid at the high dose[c]. females: increased serum LDH, K, and uric acid at the high dose[d].	4.0
administration via the food (Chu90)			
2,2',4,4',5-pentachloro[e]	males: 0, 0.07, 0.70, 7.2, 69 females: 0.06, 0.62, 6.1, 60	males/females: at the high dose, increased relative liver weight, increased APD activity, mild histological changes in liver and thyroid[c]. males: at the high dose: increased AH activity; at 7.2 mg/kg bw, increased APD activity.	males: 0.70 females: 6.1
2,2',4,4',5,5'- hexachloro[e]	males: 0, 0.03, 0.31, 3.0, 29 females: 0, 0.03, 0.34, 3.5, 32	males/females: at the 2 highest doses: increased serum inorganic phosphate concentrations[d]. At the high dose: increased relative liver weight; increased EROD activity, mild histological changes in liver and thyroid[c]. females: at the high dose: increased APD and AH activity.	males: 3.0 females: 3.5

2,2',3,4,4',6,6'-heptachloro[f]	males: 0, 0.04, 0.40, 3.5 or 32 females: 0, 0.04, 0.36, 3.9 or 37	males/females: at the high dose: decreased food consumption, increased relative liver weight, increased EROD activity, mild histological changes in liver and thyroid[c], mild changes in thymus, bone marrow and spleen. males: at the 2 highest doses: decreased number of leucocytes. At the high dose: decreased number of lymphocytes; increased serum inorganic phosphate concentrations[d]. females: at the 2 highest doses: increased serum inorganic phosphate concentrations[d].	males: 0.40 females: 3.9

[a] Statistically significant effects only ($p<0.05$)
[b] 3 chlorine atoms at *ortho* position
[c] Liver changes: nuclear vesiculation, increased cytoplasmic volume, generally accompanied by increased hepatic enzyme activity; thyroid changes: increased epithelial height and follicular collapse.
[d] Not considered of toxicological significance by Chu et al.
Abbreviations: M = male; F = female; EROD = 7-ethoxyresorufin *O*-deethylase; APD = aminopyrine *N*-demethylase; AH = aniline hydroxylase.
[e] 2 chlorine atoms at *ortho* position
[f] 4 chlorine atoms at *ortho* position

The committee concludes that the NOAELs for the pentachloro congeners were similar for female rats when the compounds were given either by gavage or via the food. The NOAEL for male rats was a factor 10 lower after feeding, based on induction of APD. For the hexachloro isomers, NOAELs for both males and females were similar, when the compounds were given either by gavage or via the food. Male rats were more sensitive for the toxic effects caused by the heptachloro congener than female rats, based on a decreased number of white blood cells. All congeners caused mild liver and thyroid injury in the high-dose animals only. The number and position of the chlorine atoms was not related to the toxicity of the compounds.

In another study, rabbits were given oral (gavage) doses of commercial-grade chlorinated diphenyl oxides, containing 1,2,3,4,5, or 6 chlorine atoms, 5 days/ week, for 4 weeks, unless death intervened. The NOAEL for the monochloro congener was 100 mg/kg bw/day. At this dose level, the dichlorodiphenyl oxide caused mild liver injury, and the trichloro congener caused death. The NOAEL and LOAEL for the latter were 10 and 50 mg/kg bw/day (slight liver injury), respectively. When the tetrachloro congener was given, severe liver injury was reported at a daily dose of 5 mg/kg bw/day, and death at 50 mg/kg bw/day. Commercial-grade pentachlorodiphenyl oxide caused death at a dose of 50 mg/kg bw/day. When highly purified material was used, the NOAEL was 1 mg/kg bw/day while slight and moderate liver injury were produced at 10 and

100 mg/kg bw/day, respectively. No mortality was reported at any dose level, indicating that the purified product was appreciable less toxic than the commercial product. The NOAEL for commercial-grade hexachloro congener was 0.1 mg/kg bw/day. Repeated doses of 1 mg/kg bw/day caused severe liver injury, and 5 mg/kg bw caused death. The liver injury produced by the various compounds was characterised by congestion and varying degrees of fatty degeneration (Kir93, ACG99).

Long-term toxicity and carcinogenicity

The committee did not find data on the toxicity, including carcinogenicity following long-term exposure to chlorinated diphenyl oxides.

Mutagenicity and genotoxicity

Neither 2,4,5,4'-tetrachlorodiphenyl oxide, nor the 2,4,6,4'-tetrachloro congener induced forward mutations, mitotic crossing over, or mitotic gene conversion in *S. cerevisiae*, strain MP-1, at a concentration up to 1000 mg/L (Fah78).

Reproduction toxicity

The maternal and developmental toxicity of tetra-, penta- and hexachlorodiphenyl oxides (in total 9 congeners) were investigated in groups of pregnant Swiss Webster CD-1 mice (n=4-22/group), which received doses of ranging from 10 to 100 mg/kg bw of each of the chlorodiphenyl oxide by gavage during days 6 to 15 of gestation. The control group comprised 85 animals. In a second study, the following compounds were examined in groups of pregnant Sprague-Dawley rats (n=4-18/group): 2,6,3’,4’-tetrachloro, and 2,4,5,2',6'-pentachlorodiphenyl oxide, which appeared to be the most potent developmental toxicants in mice, and 2,4,5,2',4',5'-hexachlorodiphenyl oxide, which turned out to be a potent inducer of CYP450 in the liver of pregnant mice. The rats were given doses ranging from 25 to 100 mg/kg bw by gavage during days 6 to 15 of gestation. The control group comprised 31 animals. Developmental toxicity was evaluated using a modification of the Chernoff-Kavlock assay. The end points measured were maternal toxicity, number of litters born, number of pups born per female mated, number of pups born per litter born, and their survival and growth on postnatal days 1 and 5 pups. The results of these studies are shown in Table 6 (Ros97a).

From these results, the committee concludes that in pregnant mice prenatal toxicity occurred at lower doses as the number of chlorine substituents increased. Regarding post-natal toxicity, 1 of 2 hexachloro and 1 of 2 tetrachloro congeners induced a dose-related decrease in live pups per litter, and of mean pup weight on post-natal days 1 and 5. The developmental toxicity potency of both the pentachloro and the hexachloro congener was about similar in mice and rats. However, the developmental toxicity of the tetrachloro congener was much higher in mice than in rats. The committee could not find a correlation between the reproduction toxicity of the chlorinated diphenyl oxides and the number of chlorine atoms at the *ortho* position. Neither induction of cytochrome P450 in pregnant mice and rats, nor tissue residues in pregnant mice of individual congeners correlated well with developmental toxicity. None of the chlorinated diphenyl oxides caused absence or decreased size of the Harderian glands in 30-day-old pups, suggesting that the fetal thyroid, or thyroid hormone receptors were not affected (Ros97a). The committee is of the opinion that no definitive conclusions can be drawn from this study for the developmental toxicity of chlorinated diphenyl oxides.

Table 6 Maternal and developmental toxicity of 9 chlorinated diphenyl oxides in Swiss Webster CD-1 mice and Sprague-Dawley rats (Ros97a).

chlorinated diphenyl oxide congener	dose (mg/kg bw)	effects[a]	NOAE[b] (mg/kg bw/day)
mice			
3,3',4,4'-tetrachloro	0, 100	none	100
2,3',4',6-tetrachloro	0, 10, 50, 100	maternal: decrease in maternal weight. developmental: decrease in number of litters born, in number of pups born per female mated, in number of pups per litter born, in live pups per litter at PND 1 and 5, in pup weight at PND 1 and 5.	maternal: 50 developmental: LOAEL 10
3,3',4,4',5-pentachloro	0, 100	developmental: increased pup weight at PND 1	100
2,3',4,4',5-pentachloro	0, 100	none	100
2,2',4,5,6'-pentachloro	0, 10, 50, 100	maternal: decrease in maternal weight developmental: decrease in number of litters born, in number of pups born per female mated	50
2,2',4,4',6-pentachloro	0, 10, 50, 100	none	100
2,2',4,4',5-pentachloro	0, 10, 50, 100	developmental: decrease in number of pups per litter born, in live pups/litter at PND 5.	maternal: 100 developmental:
2,2',4,4',5,5'-hexachloro	0, 10, 50, 100	developmental: decrease in number of pups born per female mated.	maternal: 100 developmental:

2,2',4,4',5,6'-hexachloro	0, 10, 50, 100	maternal: decrease in maternal weight. developmental: decrease in number of litters born, in number of pups born per female mated, in number of pups per litter born, in live pups per litter at PND 1 and 5, in pup weight at PND 1.	LOAEL: 10
rats			
2,3',4',6-tetrachloro	0, 50, 75, 100	maternal: not presented developmental: none	maternal: not given
2,2',4,5,6'-pentachloro	0, 25, 50, 100	maternal: not presented developmental: decrease in live pups per litter at PND 1 and 5, in mean pup weight at PND 1 and 5.	maternal: not given developmental: 25
2,2',4,4',5,5'-hexachloro	0, 25, 50, 100	maternal: not presented. developmental: decreased pup weight at PND 1 and 5.	maternal: not given

[a] Statistically significant effects only ($p<0.05$).
[b] For both maternal and developmental effects, unless otherwise noted.
PND = post-natal day.

In order to study the possible effects on the chlorinated diphenyl oxides on the thyroid, 3 congeners, i.e., the 2,3',4',6-tetrachloro, the 2,2',4,5,6'-pentachloro, and the 2,2',4,4',5,5'-hexachloro congener were investigated in pregnant rats and in 16-day-old offspring. Groups of 10 to 12 pregnant Sprague-Dawley rats received daily oral dosages of 25, 50, 75, or 100 mg/kg bw of each congener by gavage on gestational days 6 to 15 of gestation. On gestational day 16, 5 animals of the control and the high-dose group were killed and serum was collected for measurement of concentrations of triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH). The remaining dams were allowed to litter and nurse their offspring until post-natal day 16. Then, the offspring was killed and serum collected for T3 and T4 determination. Both the penta- and the tetrachloro congeners depressed T4 levels in the maternal rats, as well as in male and female pups. The hexachloro congener did not alter T4 levels in the pregnant females, but decreased juvenile T4 levels. None of the congeners studied significantly altered serum T3 or TSH levels in the dams or pups. Effects on thyroid hormones did not correlate with the congeners' induction of cytochrome P450 (Ros97b).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for chlorinated diphenyls in the Netherlands is 0.5 mg/m^3, 8-hour TWA.

Existing occupational exposure limits for chlorinated diphenyl oxides in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The group of chlorinated diphenyl oxides consists of 209 congeners, like the group of polychlorinated biphenyls, and, therefore, can have a variety of chemical, physical, and toxicological properties. The most likely route of exposure for workers engaged in the manufacture and use of chlorinated diphenyl oxides is by direct skin contact. Inhalation of vapours or fumes may occur when exposed to monochlorodiphenyl oxides, or to the higher chlorinated congeners when heated.

The toxicokinetics of individual chlorinated diphenyl oxides have been studied in rats after oral or intravenous administration, and of a mixture of 11 congeners after oral dosing. Following oral administration of 10 mg/kg bw of a pentachlorodiphenyl oxide, 1.3 and 55% of the dose were excreted in the urine and faeces, respectively, within 7 days. When injected intravenously, the half-life in blood was 5.8 days, and the highest amounts of residues were found in the fat and the skin. Following oral administration of dichloro, trichloro, or tetrachlorodiphenyl oxides, metabolites in faeces and urine were predominantly mono-and dihydroxy derivatives, either in the *ortho* or *meta* position for all congeners. When rats were given a single oral dose of 2.1 mg/kg bw of a mixture of hepta-, octa-, and nonachlorodiphenyl oxides, the peak blood level was reached after 8 hours. The highest amounts of residues were found in the fat followed by the skin and the liver. The half-life of disappearance from the blood varied from 8.9 to 10.4 days for the different congeners, and was similar for all tissues investigated, except the fat, in which the half-life was much more prolonged. Faecal and urinary excretion were 20% and 0.04%, respectively, within 7 days after application. The committee concludes that chlorinated diphenyl oxides accumulate in the body following prolonged exposure, and that bioaccumulation might be comparable with that of polychlorinated biphenyls (PCBs).

In humans, dermal exposure to chlorinated diphenyl oxides produced dermatitis at the site of contact, resembling common acne in appearance. The committee could not find other human toxicity data.

In animal studies, chlorinated diphenyl oxides were irritating to the skin of rabbits. The severity of irritation depended on the degree of chlorination, apparently reaching the maximum at 4 chlorine atoms and then declining. Following repeated skin exposure, gross follicular enlargement characteristic of

chloracne developed in rabbits. The committee did not find data on eye irritation or on skin sensitisation of chlorinated diphenyl oxides. Based on the results of acute lethal oral toxicity studies in guinea pigs, the higher congeners are more toxic than the lower chlorinated diphenyl oxides. The committee did not find data of acute lethal toxicity studies in rats.

The ability of chlorinated diphenyl oxides to induce hepatic drug metabolising enzymes has been studied in mice and rats. A single intraperitoneal injection of chlorinated diphenyl oxides containing 4, 5, 6, 9, or 10 chlorine atoms caused a dose-related induction of 7-ethoxyresorufin *O*-deethylase (EROD), and of aryl hydrocarbon hydroxylase (AHH) in mice. Only for the 3 pentachloro congeners tested, EROD activity decreased with increasing number of chlorine atoms at the *ortho* position. Chloro diphenyl oxides containing 3, 4, 5, 6, 7, 8, or 10 chlorine atoms caused induction of several drug metabolising enzymes, i.e., EROD, AHH, aminopyrine-*N*-demethylase, and/or cytochrome P450, in rat liver after oral administration for 3 consecutive days. No enzyme induction could be demonstrated for mono-and dichlorodiphenyl oxides. The most sensitive enzyme was EROD; its activity increased from trichloro to hexachloro congeners, and then declined. The induction of other enzymes was not related to the degree of chlorination, and no relation could be found between the number of chlorine atoms at the *ortho* position and the degree of enzyme induction for any of the enzymes.

Several chlorinated diphenyl oxides showed immunosuppressive activity in mice, after a single intraperitoneal injection. The committee concludes that the immunotoxic potency of the congeners is not correlated with the degree of chlorination or with the number of chlorine atoms at the *ortho* position.

Effects of chlorinated diphenyl oxides in short-term studies in experimental animals included skin irritation, liver and kidney injury in a 4-week dermal study with a hexachloro congener in rabbits (LOAEL: ca. 20 mg/animal) and liver injury in 4-week oral studies with congeners containing 1 to 6 chlorine atoms in rabbits. The severity of liver injury increased with the degree of chlorination. NOAELs varied from 100 mg/kg bw/day for the monochloro to 0.1 mg/kg bw/day for the hexachloro congener; liver and thyroid changes in 4-week oral studies with a pentachloro congener (NOAEL: 0.7 and 6.1 mg/kg bw/day for males and females, respectively), a hexachloro congener (NOAEL: 3 mg/kg bw/day, or a hepta congener (NOAEL: 0.4 and 3.9 mg/kg bw/day for males and females, respectively). The number and position of the chlorine atoms was not related to the toxicity of the compounds. No mutagenicity of either of 2 tetrachloro congeners could be demonstrated in *S. cerevisae*.

The committee did not find data on the toxicity, including carcinogenicity of chlorinated diphenyl oxides following long-term exposure.

In developmental toxicity studies, 9 chlorinated diphenyl oxides (tetra, penta, or hexa congeners) were tested in pregnant mice and 3 congeners (tetra, penta, or hexa) in pregnant rats. Parameters for maternal toxicity and developmental toxicity showed that no compound-related changes occurred for 2 pentachloro congeners in mice, and 1 tetrachloro congener in rats. However, for some congeners prenatal and post-natal fetotoxicity was already observed at the lowest dose tested (10 mg/kg bw/day). Prenatal mortality occurred at lower doses as the number of chlorine atoms increased. The committee could not find a correlation between the reproduction toxicity of the chlorinated diphenyl oxides and the number of chlorine atoms at the *ortho* position. Thyroid hormone T4 levels were affected in pregnant and juvenile rats when given a tetrachloro or a pentachloro congener at 25-100 mg/kg bw. A hexachloro congener altered T4 levels in the juvenile rats only. Due to the variety of effects found in the few studies available, the committee cannot draw definitive conclusions on a possible reproduction toxic activity of all chlorinated diphenyl oxides.

Based on 28-day oral studies with 6 different congeners (penta-, hexa- and heptachloro), the committee considers the liver and the thyroid to be the target organs. However, due to the variety in effects caused by the individual congeners investigated, and the absence of data for the majority of the congeners, the committee considers the database too poor to justify recommendation of a health-based occupational exposure limit for the group of chlorinated diphenyl oxides.

The committee concludes that the present MAC level of 5 mg/m^3 may be too high, based on the acute immunotoxic effects found in mice with ED_{50}s as low as 0.174 mg/kg bw, on the liver effects found in 28-day oral toxicity study in rats with NOAELs as low as 0.4 mg/kg bw/day, or on the reproductive effects found in rats and mice with LOAELs as low as 10 mg/kg bw/day.

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Annex

Occupational exposure limits for chlorinated diphenyl oxide[a] in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[b]	reference[c]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	0.5	8 h	administrative		SZW03
Germany						
- AGS	-	0.5[d]	8 h		S	TRG00
- DFG MAK-Kommission	-	-[e]	8 h		S	DFG02
Great Britain						
- HSE	-	-	-			HSE02
Sweden	-	-	-			Swe00
Denmark	-	-	-			Arb02
USA						
- ACGIH	-	0.5	8 h	TLV		ACG03b
- OSHA	-	0.5	8 h	PEL		ACG03a
- NIOSH	-	0.5	10 h	REL		ACG03a
European Union						
- SCOEL	-	-				EC03

[a] i.e., congener with CAS number 31242-93-0 (formerly 55720-99-5) (molecular formula: $C_{12}H_4Cl_6O$).

[b] S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[c] Reference to the most recent official publication of occupational exposure limits.

[d] Measured as the inhalable fraction of the aerosol.

[e] Listed among substances for which studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values.