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POLYCHLORINATED BIPHENYLS*

1. Chemical and Physical Data

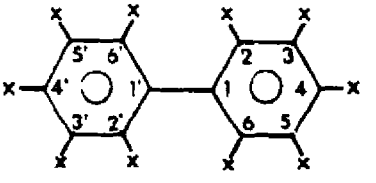
1.1 Synonyms and trade names

Chem. Abstr. No.: 13-36-36-3

Chlorinated biphenyl; chlorinated diphenyl; chlorinated diphenylene; chloro biphenyl, chloro 1,1-biphenyl; polychlorinated polyphenyls; polychlorobiphenyl

Aroclor, Clophen; Chlophen; Chlorextol; Dykanol; Fenclor; Inerteen, Kanechlor, Montar; Noflamol; Phenochlor; Phenoclor; Pyralene; Pyranol; Santotherm FR; Sovol; Therminol; Therminol FR-1

1.2 Chemical formula



In the above formula, X represents either a chlorine or a hydrogen atom.

* Considered by the Working Group in Lyon, June 1974

MONS 212257

1.3 Chemical and physical properties of the pure substance
(see also Tables 1 & 2)

(a) The melting- and boiling points of some chlorobiphenyls are given below*.

	MP °C	BP$_{(760)}$ °C	BP(mmHg)°C
2-chlorobiphenyl	54	267-268	154(12)
3-chlorobiphenyl	89	284-285	
2,2'-dichlorobiphenyl	59, 61-62		
4,4'-dichlorobiphenyl	148	315-319	
2,4,5-trichlorobiphenyl	78-79		
3,5,4'-trichlorobiphenyl	88		
3,4,3',4'-tetrachlorobiphenyl	172		230(50)
2,4,2',4'-tetrachlorobiphenyl	83		
2,4,5,3',4'-pentachlorobiphenyl	179		195-220/10)
3,4,5,3',4',5'-hexachlorobiphenyl	198		
2,3,4,5,2',4',5'-heptachlorobiphenyl			240-280(20)
2,3,4,5,6,2',3',4',5',6'-decachlorobiphenyl	310		

(b) Polychlorinated biphenyls are insoluble in water but soluble in most of the common organic solvents.

1.4 Technical products and impurities

Products vary from mobile oily liquids to white crystalline solids and hard non-crystalline resins. Technical products vary in composition, in the degree of chlorination and possibly according to batch. For example: Kanechlor 500 has an average content of 55.0% pentachlorobiphenyl, 26.5% tetrachlorobiphenyl, 12.8% hexachlorobiphenyl and 5.0% trichlorobiphenyl (lot 360). Kanechlor 400 has an average content of 43.8% tetrachlorbiphenyl, 32.8% trichlorobiphenyl, 15.8% pentachlorobiphenyl, 4.6% hexachlorobiphenyl

* Data from Hubbard (1964)

MONS 212258

TABLE 1

CHEMICAL AND PHYSICAL DATA ON KANECHLORS

Kanechlor		300	400	500
Appearance		colourless, gummy oil	colourless, gummy oil	colourless, gummy oil
Specific gravity	(at 15°C) (at 100°C)	1.337-1.339 1.310-1.322	1.453-1.468 1.376-1.389	1.460-1.475
Viscosity	(at 75°C)	3.5-4.4	5.4-7.3	12-19
Centistokes	(at 98°C)	2.1-2.6	2.8-3.7	5.0-6.6
Refractive index	(at 25°C)	1.6230-1.6260	1.6295-1.6325	1.6370-1.6390
Pour-point	(°C)	(-19)-(-15)	(-8)-(-5)	8-12
Acid value KOH	(mg/g)	0.005>	0.005>	0.005>
Distillation temperature range	(°C of 760 mm HG)	325-360	340-375	365-390

MONS 212259

TABLE 2

CHEMICAL AND PHYSICAL DATA ON AROCLORS

		Aroclor 1221	Aroclor 1242	Aroclor 1248	Aroclor 1254
Appearance		colourless, mobile oil*	almost colourless, mobile oil*	yellow-green-tinted, mobile oil*	light-yellow, viscous oil*
Density	(at 20°C)	1.18-1.19*	1.38-1.39**	1.45-1.47**	-
	(at 90°C)	-	-	-	1.47-1.49**
Refractive index	(at 20°C)	1.617-1.618*	1.625-1.627**	1.6305-1.6325**	1.638-1.640**
Pour-point	(°C)	+1*	-18 max**	-6 max**	+12 max**

* From Hubbard (1964)

** From Monsanto Co. (1973)

and 3.0% dichlorobiphenyl (lot 471). Kanechlor 300 has an average content of 59.8% trichlorobiphenyl, 23.0% tetrachlorobiphenyl, 16.6% dichlorobiphenyl and 0.6% pentachlorobiphenyl (lot 348). Monsanto, the only US manufacturer of these chemicals has produced a series of chlorinated biphenyls and chlorinated polyphenyls over the years which were numbered to identify each product. The first two digits indicated the type of material: 12 - chlorinated biphenyls; 25 - blend of chlorinated biphenyls and chlorinated triphenyls (75:25), 44 - blend of chlorinated biphenyls and chlorinated triphenyls (60.40), and 54 - chlorinated triphenyls. The last two digits indicated the approximate weight percentage of chlorine in the product. Thus, the product numbered Aroclor 1242 contains mainly trichlorobiphenyls, Aroclor 1248 contains mainly tetrachlorobiphenyls and Aroclor 1254 contains mainly pentachlorobiphenyls.

Some of the physical and chemical properties of Japanese and US products are given in Tables 1 and 2.

Specific data on the impurities in these products are not available, but colour is an indication of purity: the darker the product, the lower the purity (Monsanto Co., 1970). The raw materials used in the synthesis of polychlorinated biphenyls determine to a large degree the type of impurity or contaminant in the commercial product. Fractionated samples of some non-US products have shown them to contain the tetra- and pentachlorodibenzofurans and the hexa- and heptachloronaphthalenes as contaminants (Interdepartmental Task Force on PCBs, 1972).

2. Production, Use, Occurrence and Analysis

Several review articles on polychlorinated biphenyls have been published (Fishbein, 1973; Hubbard, 1964; Interdepartmental Task Force on PCBs, 1972).

2.1 Production and use[1]

The polychlorinated biphenyls were first described in the chemical

[1] Data from Chemical Information Services, Stanford Research Institute, USA

MONS 212261

literature in 1881. Commercial manufacture of these chemicals in the US is believed to have begun in 1929; and although a number of US companies have registered trademarks for polychlorinated biphenyls, recent information indicates that there is only one US producer of polychlorinated biphenyls. If these chemicals are sold at present by other companies, they are either manufactured by this one US producer or imported.

Polychlorinated bi-, ter- and polyphenyls are produced by chlorination of the appropriate aromatic hydrocarbon using either iron or ferric chloride as a catalyst. The composition of the end-product is determined by the quantity of chlorine present (Hubbard, 1964).

It was estimated in 1970 that since the commercial introduction of polychlorinated biphenyls in 1929, 454 million kg of these chemicals had been sold in North America. Between 1960 and 1970, production of polychlorinated biphenyls increased steadily from 17.3 million kg in 1960 to 85 million kg in 1970. In 1971 the US producer voluntarily agreed to restrict sale of polychlorinated biphenyls to those applications which minimize their introduction into the environment; thus, production dropped to 18.2 million kg, with an estimated output of 11.4-13.6 million kg for 1972. In general, the majority of these chemicals produced are the lower chlorinated grades (Interdepartmental Task Force on PCBs, 1972).

US imports of polychlorinated biphenyls were 290,836 kg in 1971 (US Tariff Commission, 1972) but only 160,985 kg in 1972 (US Tariff Commission, 1973). US exports of polychlorinated biphenyls increased steadily from 8% of production (1.6 million kg) in 1963 to 16% of production (6.2 million kg) in 1970. In 1971, 25% of total production was exported, but this amounted to only 4.4 million kg (Interdepartmental Task Force on PCBs, 1972).

It has been estimated that US production in 1971 represented roughly one half of the total world production of polychlorinated biphenyls. The following countries have also been reported to produce these chemicals: Czechoslovakia, the Federal Republic of Germany, France, Italy, Japan, Poland, Spain, the United Kingdom and USSR (Anon., 1973; Interdepartmental Task Force on PCBs, 1972). Argentina, Brazil and India have been reported to be possible producers (Anon., 1972).

MONS 212262

Production began in Japan in 1954, and by the end of 1971 approximately 55.4 million kg had been produced. Approximately 60% of Japan's total exports have gone to the US, with the remaining 40% going to Europe; between 1962 and 1971, exports of these chemicals totalled 4.5 million kg. Imports, solely from the US, totalled 0.6 million kg from 1967 to 1971. The production of polychlorinated biphenyls is now prohibited in Japan.

Prior to 1971, polychlorinated biphenyls were used in a variety of applications, primarily because of their excellent thermal and chemical stability. However, in 1971, Monsanto, the sole US producer of these chemicals, voluntarily decided to limit their use to those closed electrical applications from which possible release to the environment is minimized. Before that time about 40% of the polychlorinated biphenyls used in the US went into applications which led to loss into the environment, e.g., in plasticizers, hydraulic fluids and lubricants, surface coatings, inks, sealants, adhesives, pesticide extenders and microencapsulation of dyes for carbonless duplicating paper. The remaining 60% of US sales was used mainly in electrical transformers and capacitor applications; of all applications prior to 1971, the largest uses were in capacitors and transformers and in plasticizer applications, including carbonless duplicating paper. Today polychlorinated biphenyls are used in the US only in closed-system electrical applications which minimize introduction into the environment (Hubbard, 1964; Interdepartmental Task Force on PCBs, 1972).

2.2 Occurrence

(a) Occupational exposure

Although polychlorinated biphenyls may have been used in pesticide formulations in conjunction with various pesticides, no information on human exposure during crop or forest spraying is available.

The US Occupational Safety and Health Administration health standards for air contaminants require that an employee's skin exposure to chlorodiphenyl (42% chlorine) and chlorodiphenyl (54% chlorine) does not exceed eight-hour time-weighted averages of 1 mg/m^3 and 0.5 mg/m^3, respectively, in the workplace air during any eight-hour workshift for a forty-hour work week (US Code of Federal Regulations, 1974).

MONS 212263

Masuda et al. (1972) reported that polychlorinated biphenyls occurred in carbonless copying paper in Japan; average amounts of 30 µg were found remaining on the skin after handling such paper. Lister & Bennett (1972) reported that the major manufacturers of this paper in the UK did not use polychlorinated biphenyls.

(b) Air and rain

Polychlorinated biphenyls may enter the air during the destruction of manufactured articles containing polychlorinated biphenyls in waste-disposal burners, through the gradual wear and weathering of polychlorinated biphenyl-containing products or through leaks from sealed systems. It has been estimated that some 400 thousand kg polychlorinated biphenyls were released into the atmosphere in 1970 in the US from waste-disposal burners (Nisbet & Sarofim, 1972) and that 1000-2000 thousand kg entered the atmosphere from the vaporization of plasticizers (Panel on Hazardous Trace Substances, 1972) In comparison, loss by evaporation or leakage from closed systems would appear to be insignificant. Carnes et al. (1973) have also demonstrated polychlorinated biphenyls in ash from industrial burners; in addition, some chlorinated dibenzofurans and dibenzodioxins may also be released through oxidation processes during incineration.

Measurement of the monthly airborne fallout of polychlorinated biphenyls in 8 sites in Sweden during 1970-71 revealed levels of 550-10,500 ng/m^2/month (Södergren, 1972). Air samples collected during February-April 1973 from a 20-metre high tower in Bermuda, or in June 1973 on the open sea off the island, contained polychlorinated biphenyl levels of 0.21-1.6 ng/m^3 in the vapour phase. Higher levels (2.1-9.4 ng/m^3) were found in Rhode Island where peaks resembled chromatograms of Arochlor 1242, which contains mainly tri-, tetra- and pentachlorobiphenyls (Bidleman & Olney, 1974).

Bevenue et al. (1972) reported levels of 60 ng/l polychlorinated biphenyls in rainwater in Hawaii during 1971-72.

(c) Soil and water

No data on polychlorinated biphenyl residues in various soils appear to be available. Holden (1970) reported concentrations of <0.1-14 ppm polychorinated biphenyls (wet weight) similar to Aroclor 1254 in 15 samples of

MONS 212264

sewage sludge intended for disposal in the sea off the Firth of Clyde in Scotland. Analyses by other laboratories of sewage sludge intended for disposal off the Thames and Mersey estuaries showed that 0.2 ppm and 0.1-5 ppm (wet weight) polychlorinated biphenyls were present, respectively (Holden, 1970). These figures are equivalent to a total discharge of about 1 thousand kg polychlorinated biphenyls per year. Analyses at 9 sewage treatment plants in California in 1970 revealed that concentrations of 0.2-12 ppb occurred in sewage pumped into the Pacific Ocean (Schmidt et al., 1971).

In the US, polychlorinated biphenyl concentrations of about 0.02-2.5 µg/l were reported in Milwaukee river water in 1969-70, the highest concentrations occurred near chemical plants (Veith & Lee, 1971). In Green Bay, Lake Michigan, Veith (1972) found concentrations of polychlorinated biphenyls (as Aroclor 1254) of <0.01-0.45 µg/l in various river waters entering the bay.

Measurements made during the summer of 1972 showed that the average concentrations of polychlorinated biphenyls in North Atlantic sea-water were 35 ng/l at the surface and 10 ng/l at a depth of 200 metres; the polychlorinated biphenyl concentration in Sargasso Sea surface waters averaged 27 ng/l (Harvey et al., 1973). However, Bidleman & Olney (1974) found lower values, <1-19.3 ng/l, in Sargasso Sea surface waters; the peaks resembled chromatograms of Aroclor 1254 or 1260, which contain mainly penta-, hexa- and heptachlorobiphenyls.

According to a review by the Panel on Hazardous Trace Substances (1972), polychlorinated biphenyls have been found at concentrations of 10-100 ng/l in drinking-water in Japan.

On July 5 1973, the US Environmental Protection Agency proposed a list of toxic pollutants which includes polychlorinated biphenyls (US Environmental Protection Agency, 1973). If this list is adopted, effluent standards restricting or prohibiting discharges of these chemicals into streams may come into effect.

(d) Animals and plants

A review of levels of polychlorinated biphenyls found in fish and birds

MONS 212265

in Japan has been published recently (Doguchi, 1973).

The concentrations of polychlorinated biphenyls in vertebrate food chains increases in such a way that the top predators (e.g., birds of prey, sharks and seals) may have total concentrations of polychlorinated biphenyls 10^7-10^8 times that in the ambient environment.

Studies of zooplankton from the North Atlantic shelf and slope areas revealed polychlorinated biphenyl concentrations in these organisms of 0.07-3 ppm (dry weight) and 0.02-0.64 ppm (wet weight) in the 2 areas, respectively (Risebrough et al., 1972). In the Gulf of Mexico, concentrations of <3-1000 µg/kg (wet weight) have been found in zooplankton (Giam et al., 1973); and, in plankton in the Gulf of St. Lawrence, concentrations of 0.09-3 mg/kg (wet weight) have been found (Ware & Addison, 1973).

In small predatory fish, polychlorinated biphenyl levels of 8 µg/kg were found in pike (fresh tissue) taken from an unpolluted lake in Finland, whereas 0.3 mg/kg were found in herring taken from the open sea (Hattula, 1972). Zitko (1971) found concentrations of 0.02-1 mg/kg polychlorinated biphenyls in eel, salmon, herring, mackerel, mussel, cod, hake and plaice, and traces in ocean perch, taken from the St John River system, New Brunswick, or from the Nova Scotia banks. Similar levels (0.36-1.54 mg/kg) were found in tuna from the Atlantic coast of North America (Zitko & Choi, 1971). Much higher levels (up to 7 mg/kg Aroclor 1254) have been found in shrimp and crab caught in accidentally-polluted bays, e.g., Escambia Bay, Florida (Duke et al., 1970) and in fish from inland lakes: for example, 26 mg/kg were found in a 12-year old trout caught in Cayuga Lake in Ithaca, New York (Bache et al., 1972) in which case the gas chromatogram was similar to that of Aroclor 1254. Stalling & Mayer (1972) have also reported high levels of polychlorinated biphenyls (>20 mg/kg) in inland lake and river fish in the US.

Numerous reports concerning polychlorinated biphenyl residues in predatory birds in Canada, Denmark, Finland, Sweden, the UK and the US have appeared. Jensen et al. (1969) reported the presence of up to 190 mg/kg polychlorinated biphenyls (whole body-weight) in 4 white-tailed eagles found between March-June in 1965 and in 1966. Risebrough et al. (1968)

MONS 212266

identified up to 65 mg/kg polychlorinated biphenyls (wet weight) in the carcasses of 4 peregrine falcons which died after having been trapped for falconry. Residues of 30 and 900 mg/kg were found in the livers of 2 herons in the UK (Prestt et al., 1970) Levels of 1.3-272 mg/kg polychlorinated biphenyls (wet weight) (comparable to Clophen A 60) were found in the livers of terrestrial predatory birds in Denmark (Jarlog et al., 1971), and levels of 93-470 mg/kg (wet weight) were found in the livers of cormorants found dead in 1970 in the Netherlands (Koeman, 1973).

Various concentrations of polychlorinated biphenyls have been recorded in birds' eggs. Concentrations in the eggs of cormorants, gulls and ducks from the Bay of Fundy, Canada, ranged from 6-44 mg/kg (Zitko & Choi, 1972). Lower levels, about 1-5 mg/kg (wet weight), have been reported in the UK (Prestt et al., 1970) and in the US (Greichus et al., 1973).

Polychlorinated biphenyl residues of up to 310 mg/kg have also been reported in the fat of seals living off the coast of Sweden (Jensen et al., 1969).

(e) Food

Sea-food or food packaged in grey cardboard packaging appear to have been the two main sources of dietary polychlorinated biphenyls. Small residues of polychlorinated biphenyls may also occur in milk and meat products, since silage stored in upright silos which have polychlorinated biphenyl wall sealants may contain about 0.1 mg/kg polychlorinated biphenyls (Savage et al., 1973). Fries (1972) detected 19 mg/kg in milk fat taken from cows at farms which had polychlorinated biphenyl-treated silos.

Cereals packed in cardboard containing 10 mg/kg polychlorinated biphenyls have been shown to contain about 0.2-0.3 mg/kg polychlorinated biphenyls (Trout, 1972). One sample of cashew nuts packaged in cardboard drums was reported to have contained 10 mg/kg polychlorinated biphenyls (Bailey et al., 1970), and analysis of various types of food packed in paperboard with or without a plastic barrier showed polychlorinated biphenyl levels of <0.1-4.3 mg/kg (Stanovick et al., 1973).

Polychlorinated biphenyls have also been demonstrated in human milk in

MONS 212267

Japan at concentrations of 0.03 mg/kg (whole milk) and 1.1 mg/kg (fat basis) (Oura et al., 1972), and in the Federal Republic of Germany concentrations of 0.1 mg/kg (whole milk) and 3 5 mg/kg (fat basis) (Tombergs, 1972) have been found. However, none could be detected in the milk of women in Texas and New Guinea (Dyment et al., 1971), although the mean polychlorinated biphenyl level in samples of human milk in California was 60 µg/kg (Risebrough & Brodine, 1970). Thus, since the daily milk intake of breast-fed infants is 150 g/kg bw, the amount of polychlorinated biphenyls ingested would be in the order of 9 µg/kg bw/day. This figure is slightly above the maximum daily intake which would occur in adults eating 150 g/week of fish containing 15 mg/kg polychlorinated biphenyls (e.g., coho salmon from Lake Michigan) or 80 g of fish per day in Japan, where values of up to 5 mg/kg may be present (Panel on Hazardous Trace Substances, 1972).

The US Department of Agriculture has analyzed polychlorinated biphenyls in selected food commodities (US Department of Agriculture, 1972): fish contained from traces to 35.3 mg/kg (average, 1.87 with 54% positive samples), cheese contained from traces to 1.0 mg/kg (average, 0.25 and 6% positive samples); milk contained from traces to 27.8 mg/kg (average, 2.27 and 7% positive samples); whereas eggs contained from traces to 3.74 mg/kg (average, 0.55 and 29% positive samples). Of the total number of commodity samples examined, only 19% were positive with respect to contamination by polychlorinated biphenyls, reflecting an average concentration of 1.14 mg/kg of sample.

Twenty-two of 720 composite samples from the US Food and Drug Administration's (FDA) market-basket surveys have been found to contain polychlorinated biphenyls ranging in concentration from traces to 0.36 mg/kg. This maximum value was due to migration of polychlorinated biphenyls from greyboard containers and dividers for packaged shredded wheat. Estimates of the mean daily intake of polychlorinated biphenyls in the American diet range from 5-10 µg per day (National Environmental Research Center, 1974).

During the 'Yusho incident' in Japan, a poisoning accident caused by ingestion of rice oil contaminated with a commercial brand of polychlorinated biphenyl (Kanechlor 400), the minimum toxic intake for humans was estimated to be 200 µg/kg bw/day (Kuratsune et al., 1972).

MONS 212268

The FDA has established temporary tolerances for polychlorinated biphenyls in foods, animal feeds and food-packaging materials. These tolerances are as follows. 2.5 mg/kg (ppm) in milk (fat basis); 2.5 mg/kg (ppm) in manufactured dairy products (fat basis); 5 mg/kg (ppm) in poultry (fat basis); 0.5 mg/kg (ppm) in eggs; 0.2 mg/kg (ppm) in finished animal feed for food-producing animals (except in feed concentrates, feed supplements and feed premixes); 2 mg/kg (ppm) in animal feed components of animal origin, including fishmeal and other by-products of marine origin and in finished animal feed concentrates, supplements and premixes intended for food-producing animals; 5 mg/kg (ppm) in fish and shellfish (edible portion); 0.2 mg/kg (ppm) in infant and junior foods; 10 mg/kg (ppm) in paper food-packaging material intended for or used with human food, finished animal feed and any components intended for animal feeds (US Federal Register, 1973).

2.3 Analysis

This subject has been reviewed by Fishbein (1973) and by Jensen et al. (1973).

One of the main problems in the analysis of polychlorinated biphenyls is that during their extraction from the media, other organochlorine pesticides (which may have similar retention times on chromatographs) are also eluted. Simpler chromatograms can be obtained by using separation techniques prior to gas chromatography. Such clean-up methods include TLC, paper and column chromatography; and solvent partition or saponification and dechlorination of other compounds with alcoholic KOH have also been used. p,p'-DDE can be oxidized to 4,4'-dichlorobenzophenone without affecting the polychlorinated biphenyls (Collins et al., 1972).

Some widely-used methods and their modifications are described in the Pesticide Analytical Manual (US Department of Health, Education and Welfare, 1968), by Armour & Burke (1970) and by Porter et al. (1970). Volume III of the Pesticide Analytical Manual (US Department of Health, Education and Welfare, 1970) and Biros et al. (1970) give a method for analyzing residues in human tissues.

Quantitation of polychlorinated biphenyls from electron-capture

MONS 212269

chromatograms has been discussed by Zitko et al. (1971) However, for a fast, simple determination, the polychlorinated biphenyl sample can be converted to decachlorobiphenyl and compared with an Aroclor 1254 standard (National Environment Research Center, 1974). Some difficulties encountered with the use of standards in the quantification of polychlorinated biphenyls have been described by Beezhold & Stout (1973).

Confirmation of identity can be made by combined gas chromatography-mass spectrometry, which, in addition, yields the number of chlorine atoms per molecule (Bagley et al., 1970; Biros et al., 1970; Widmark, 1967). However, rearrangement of the chlorine atoms or phenyl groups occurring in the electron-impact-induced fragmentation limits the use of mass-spectrometry for structural studies. Nuclear-magnetic-resonance (NMR) spectroscopy has been used to resolve the structure of some polychlorinated biphenyl isomers (Sissons & Welti, 1971). Characterization of the components of technical polychlorinated biphenyl mixtures has been reported by Tas & Kleipool (1972) using pure standards, GLC retention times on 3 different columns, infra-red spectra and NMR spectroscopy.

Methods for the determination of polychlorinated biphenyls in food, plant or animal tissue in Japan have been described by Wakimoto et al. (1973).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

(a) Oral administration

Mouse: Groups of 12 6-week old male dd mice were administered Kanechlor 300, 400 or 500 in the diet at concentrations of 100, 250 or 500 ppm for 32 weeks. Six control mice received the basal diet. Gross examination after 32 weeks of treatment showed that 7/12 mice given 500 ppm Kanechlor 500 developed liver nodules, and histopathological examination showed the presence of hepatocellular carcinomas in 5/12 mice. No metastases or tumours in other organs were seen. Amyloid degeneration of the liver was seen in the other groups, especially in those at the 100 ppm dosage level. No changes occurred in the 6 controls (Ito et al., 1973, Nagasaki et al., 1972). [See also Table 3.]

MONS 212270

TABLE 3

HISTOPATHOLOGICAL FINDINGS IN THE LIVERS OF MALE dd-MICE TREATED WITH PCBs FOR 32 WEEKS

PCBs in diet (ppm)		Effective no. of mice	Amyloid degeneration	Liver nodules	
				Nodular hyperplasia	Hepatocellular carcinoma
Kanechlor	500	12	0/12 -	7/12(58.3%)	5/12(41.7%)
500	250	12	2/12(16.7%)	0/12 -	0/12 -
	100	12	3/12(25.0%)	0/12 -	0/12 -
Kanechlor	500	12	0/12 -	0/12 -	0/12 -
400	250	12	3/12(25.0%)	0/12 -	0/12 -
	100	12	10/12(83.3%)	0/12 -	0/12 -
Kanechlor	500	12	1/12 (8.3%)	0/12 -	0/12 -
300	250	12	4/12(33.3%)	0/12 -	0/12 -
	100	12	10/12(83.3%)	0/12 -	0/12 -
Control		6	0/6 -	0/6 -	0/6 -

From Ito et al. (1973)

MONS 212271

Two groups of 50 male BALB/cJ mice were fed 300 ppm Aroclor 1254 in the diet for 11 months or for 6 months followed by the control diet for 5 months. Two additional groups of 50 mice were fed the basal diet. At the end of 11 months 1/24 surviving mice treated for 6 months with Aroclor 1254 had a hepatoma, while of the mice surviving the continuous treatment 9/22 developed hepatomas. In addition, adenofibrosis was observed in all 22 mice fed Aroclor 1254 continuously for 11 months (Kimbrough & Linder, 1974).

Rat: In groups of 10 male and 10 female Sherman rats fed 0, 20, 100, 500 or 1000 ppm Aroclor 1260, or 0, 20, 100 or 500 ppm Aroclor 1254, for 8 months, several rats died before 6 months at the 2 high-dose levels. Lesions described as adenofibrosis of the liver occurred in 2/10 males fed 1000 ppm Aroclor 1260 and in 1/10, 1/10 and 4/10 females fed 100, 500 and 1000 ppm Aroclor 1260. A higher incidence of this lesion occurred in rats fed Aroclor 1254, the incidences in males and females being 10/10 and 9/10 at 500 ppm and 1/10 and 7/10 at 100 ppm, respectively (Kimbrough et al., 1972).

A group of 10 male and 10 female Donryu rats was fed a diet containing 38.5-616 ppm Kanechlor 400 for 400 days. The initial concentration of 38.5 ppm was increased by factors of 2 in varying steps during the first 125 days until 616 ppm was reached. After 56 days at this level the concentration was reduced to 462 ppm for the remainder of the study except during two 28-day rest periods. A control group of 5 males and 5 females received a basal diet. In 6/10 treated females, multiple adenomatous nodules of the liver were observed; such lesions did not occur in male rats nor in the controls. No hepatocellular carcinomas were seen (Kimura & Baba, 1973).

Groups of 30 male Wistar rats were fed for 52 weeks on diets containing 100, 500 or 1000 ppm Kanechlor 300, 400 or 500. One group received a control diet. Each Kanechlor produced cholangiofibrosis in a proportion of the rats when fed at 1000 ppm in the diet, while lower dosage levels were ineffective. Hepatic nodular hyperplasia was found with all compounds, the incidence increasing with the degree of chlorination and with concentration in the diet (Ito et al., 1974). [See also Table 4.]

MONS 212272

TABLE 4

HISTOPATHOLIGICAL FINDINGS IN THE LIVERS OF MALE WISTAR RATS TREATED WITH PCBs

PCBs in diet (ppm)		Experimental period (weeks)	Effective no. of rats	Fibrosis	Cholangiofibrosis	Nodular hyperplasia	Amyloidosis
Kanechlor	1000	49.3	13/30	±	4/13(30.8%)	5/13(38.5%)	0/13 -
500	500	52	16/30	-	0/16 -	5/16(31.3%)	0/16 -
	100	52	25/30	-	0/25 -	3/25(12.0%)	0/25 -
Kanechlor	1000	40	10/30	++	2/10(20.0%)	3/10(30.0%)	0/10 -
400	500	27.8	8/30	-	0/8 -	0/8 -	0/8 -
	100	39.6	16/30	-	0/16 -	2/16(12.5%)	2/16(12.5%)
Kanechlor	1000	52	15/30	-	2/15(13.3%)	0/15(6.7%)	0/15 -
300	500	52	19/30	-	0/19 -	0/19 -	0/19 -
	100	52	22/30	-	0/22 -	1/22(4.5%)	0/22 -
Control		52	18/20	-	0/18 -	0/18 -	0/18 -

From Ito et al. (1974)

MONS 212273

3.2 Other relevant biological data

(a) Animals

The LD_{50}'s of orally administered Aroclor 1254 and 1260 in Sherman rats are 4-10 g/kg bw (Kimbrough et al , 1972) and that of Aroclor 1242 4.25 g/kg bw in male Wistar rats (Bruckner et al., 1973).

In DDD mice, the various components of a single oral dose of Kanechlor 400 were equally absorbed and distributed, mainly in the skin, liver and kidney. The tetrachlorobiphenyls, the major components of Kanechlor 400, were almost completely eliminated after 3-4 weeks; but the penta- and hexachlorobiphenyls, the minor components, were still retained after 9-10 weeks (Yoshimura & Oshima, 1971). In male Wistar King rats, 3 days after a single oral dose of 25 mg ^{3}H-Kanechlor 400, radioactivity was distributed mainly in the liver, skin and adipose tissue. During the first 4 weeks, 70% of the radioactivity was excreted in the faeces and 2% in the urine (Yoshimura et al., 1971).

Fifty male Sherman rats were fed 500 ppm Aroclor 1254 in the diet for 6 months, and 5 rats were killed 0, 1, 2, 3, 4, 6, 8 and 10 months after exposure to Aroclor 1254 had ceased. In the rats killed 10 months after the end of exposure, about 1200 ppm and 22 ppm polychlorinated biphenyls (PCBs) were present in the adipose tissue and liver, respectively. The compounds found were those containing mainly 5, 6 or 7 chlorine atoms (Kimbrough et al., 1973).

Preliminary work by Goto et al. (1973) on the metabolism of orally administered 2,2'-, 2,4-, 2,3-, 3,4-, 3,3'- and 4,4'-dichlorobiphenyls in male rats indicates that the main metabolites are dichlorodihydroxybiphenyls, which are excreted via the urine and faeces as such and not as conjugates.

In male Wistar rats 64% of a single oral dose of 25 mg 3,4,3',4'-tetrachlorobiphenyl (TCB) was excreted unchanged in the faeces during the first 14 days after dosing, and a metabolite thought to be the 2- or 5-hydroxy-3,4,3',4'-TCB was also found in small quantities (3%) (Yoshimura & Yamamoto, 1973). Similarly, the metabolites of 2,4,3'4,'-TCB were identified in the

MONS 212274

faeces of rats as free 5- or 3-hydroxy-2,4,3',4'-TCB (Yoshimura et al., 1973). Gardner et al. (1973) showed that in rabbits oral administration of 2,5,2',5'-TCB resulted in 3 urinary metabolites (3- and 4-hydroxy-2,5,2'5'-TCB and trans-3,4-dihydro-3,4-dihydroxy-2,5,2',5'-TCB), possibly formed through an arene oxide (epoxide).

Low levels of PCBs in the diet, or i.p. injections of PCBs, increase the microsomal mixed-function oxidase activity of the liver in rats (Bruckner et al., 1973; Norbach & Allen, 1972). PCBs can also be absorbed through the skin in rabbits (Vos & Beems, 1971).

In Sherman rats given doses of 10 or 50 mg/kg bw/day Aroclor 1254 on days 7-15 of pregnancy, the average PCB concentrations in foetuses taken by Caesarean section on day 20 of pregnancy were 0.63 and 1.38 mg/kg, respectively, compared with <0.12 mg/kg in controls (Curley et al., 1973a). Transplacental transfer was also demonstrated in rabbits (Grant et al., 1971).

Vos & de Roij (1972) demonstrated immunosuppressive activity of PCBs on both the humoral and cellular response of the immune system.

When Aroclor 1254 was fed to pheasants either as a single dose of 50 mg or as 17 weekly doses of 12.5 or 50 mg, up to 82% was absorbed from the gastrointestinal tract and up to 50 mg/kg (wet weight) were found in their eggs (Dahlgren et al., 1971). In cows fed 200 mg/day Aroclor 1254 for 60 days, the average concentration in milk fat was 60 mg/kg (measured between the 40th and 60th days of feeding) (Fries et al., 1973). PCBs are also excreted in human milk (see section 2.2 (e)).

Two-day old cockerels were given a diet containing 400 mg/kg Phenoclor DP 6, Clophen A60 or Aroclor 1260 for 60 days, and concentrations of 120-2900 mg/kg and 40-700 mg/kg PCBs were found in the liver and brain, respectively, between the 12th and 58th days (Vos & Koeman, 1970). A maximum of 50 mg/kg Aroclor 1254 was found in eggs of white Leghorn hens fed for 12 weeks on a diet containing 50 mg/kg PCBs (Platonow & Reinhart, 1973).

In a series of papers describing an outbreak of poisoning involving 2 million chickens in Northern Japan, Kohanawa et al. (1969a,b) first reported that a 'dark oil', a by-product of a rice bran, may have been involved.

MONS 212275

The pathological changes seen in the poisoned chickens included oedema of the subcutaneous tissue, liver, and lungs, hydropericardium, peritoneal ascites and yellowish mottling of the liver. Histologically, oedema of skeletal muscle, epicardium and lung and focal necrosis of the liver were observed. Similar pathological changes could be induced in 20 experimental chickens fed on a commercial diet made up by the manufacturer with the dark oil, which was shown to contain Kanechlor 40% (Koga et al., 1970, 1971, Shoya et al., 1969).

(b) Man

Storage in human adipose tissue of the general population

Two samples of human adipose tissue were found to contain 200 and 600 mg/kg PCBs, but the source of these samples was not reported (Biros et al., 1970). Price & Welch (1972) estimated that 36% of the general population had levels of 1-2 mg/kg (wet weight) PCBs, ranging from penta- to deca-chlorobiphenyls, in their adipose tissue. In a Human Monitoring Survey of the exposure to pesticides experienced by the general population, Yobs (1972) found measurable amounts of PCBs (1-2 mg/kg) in 26% and >2 mg/kg in 5% of 637 samples of human adipose tissue taken from the general population of 18 states in the U.S. and of Colombia. Bjerk (1972) reported average levels of 0.9 mg/kg (1.6 mg/kg fat basis) in adipose tissue taken from 40 humans dying in the Oslo area. In Japan, mean PCB concentrations in 25 samples were found to be 0.5 and 0.8 mg/kg, using 2 different separation techniques (Farley et al., 1974b). Slightly higher concentrations (averages, 2.6 mg/kg in males and 1.8 mg/kg in females) were reported in 98 adipose tissue samples taken from humans living in Tokyo. Maximums of 5.1 mg/kg occurred in 70-79-year old men and 2.4 mg/kg in 60-69-year old women (Noguchi, 1973).

3.3 Observations in man

Kuratsune et al. (1972) reported an incident of accidental poisoning by PCB involving 1057 persons in Japan who ingested rice-oil which had been contaminated by Kanechlor 400 during the manufacturing process. From that group, 4 autopsy reports, 3 in adults and 1 in a stillborn, are available.

The autopsy of one 48-year old Japanese female, who was diagnosed as

MONS 212276

having liver cirrhosis, showed multilobular cirrhotic changes in the liver and many nodules of hepatic-cell carcinoma (Kikuchi, 1972). In the other 3 cases, there were various skin lesions associated with exposure to PCB, and chromatographic analysis showed PCB to be present in the mesenteric fatty tissue and skin in all 4 cases (Kikuchi et al., 1969, 1971). The skin of the stillborn child from an exposed mother showed disturbances of pigmentation; histologically, the changes were the same as those of PCB poisoning. The presence of PCB in the tissues of this stillborn child demonstrates transplacental passage (Kikuchi et al., 1969), and further evidence of such passage was provided by Miller (1971) and by Kuratsune et al. (1972) who reported on several infants born to mothers included in these cases of poisoning.

4. Comments on Data Reported and Evaluation[1]

4.1 Animal data

A limited number of PCBs have been tested. Kanechlor 500 and Aroclor 1254 are carcinogenic in mice inducing benign and malignant liver-cell tumours following oral administration, the only route tested. In rats, Kanechlor 500, 400 and 300 induced multiple hyperplastic liver nodules following oral administration.

4.2 Human data

In the absence of epidemiological studies the available case report does not allow an evaluation to be made.

[1] See also the section, "Animal Data in Relation to the Evaluation of Risk to Man" in the introduction to this volume (p. 15).

MONS 212277

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