CHRONIC TOXICITY OF HALOGENATED BIPHENYLS AND RELATED COMPOUNDS IN ANIMALS AND HEALTH EFFECTS IN HUMANS

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Some isomers and congeners of several aromatic halogenated hydrocarbons cause similar toxic syndromes (Kimbrough 1974). These are chlorinated and brominated biphenyls, naphthalenes, dibenzodioxins and dibenzofurans. The 3, 3', 4, 4' - tetrachloroazobenzene and 3, 3', 4, 4' - tetrachloroazoxybenzene cause similar effects but may be generally less toxic because they are more easily metabolized (Hsia et al. 1980). Of the compounds mentioned the chlorinated naphthalenes, the brominated biphenyls, and the chlorinated biphenyls have been used commercially while the halogenated dibenzofurans, dibenzodioxins and the chlorinated azobenzenes and azoxybenzenes are contaminants of commercial products.

Polychlorinated biphenyls may be contaminated with chlorinated dibenzofurans (Bowes et al. 1975). Pentachlorophenol may be contaminated with chlorinated dibenzodioxins and chlorinated dibenzofurans (Goldstein et al. 1977), and hexachlorobenzene (Villanueva et al. 1973), has been shown to contain the same compounds. The 2,3,7,8 -tetrachlorodibenzodioxin is a contaminant of 2,4,5 -trichlorophenol, and the derivatives made thereof, which include the herbicide 2,4,5-T and hexachlorophene. Furthermore, it has recently been shown that 2,4-D if made by the same company using the same equipment, that was used for the production of 2,4,5-T may then also be contaminated with 2,3,7,8-tetrachlorodibenzodioxin (Fed. Register 1979).

The commercial products are mixtures of isomers and congeners and as the different components of the mixture are studied more extensively it is recognized that they vary greatly in their toxicity (Table 1). The most toxic of the entire group of chemicals is the 2,3,7,8-tetrachlorodibenzodioxin. The amount of compound necessary to produce the same chronic toxic effect differs also, for different chemicals. A marked species variation exists in the response to these chemicals. Mink, guinea pigs and sub-human primates are more susceptible to the toxic effects than rats and mice. The types of diseases reported in different animals and the symptoms related to these different compounds in men are summarized in Tables 2, 3, and 4.

Although many of these compounds were introduced into commerce in the 1940s and some of them earlier than that, their toxicity was not studied extensively until the 1960s and 1970s. The first compounds of this entire group to cause illness in people were the chlorinated naphthalenes. During the first World War, chlorinated naphthalenes were used in the production of gas masks which resulted in outbreaks of occupational chloracne (Wauer, 1919). It was not until the second World War that it was recognized that mixtures of chlorinated napthalenes and chlorinated diphenyls may produce liver toxicity in workers (Jones, 1941; Sulzberger, 1934; Flinn et al. 1936). Such cases were isolated and it has been speculated that additional factors such as infectious viral hepatitis may have contributed to the disease.

In addition to the effects observed in laboratory animals, farm animals have also suffered a variety of illnesses from these different compounds. Among farm animals, cattle and chickens have primarily been affected. In cattle the so-called hyperkeratosis

or X disease is characterized by excessive lacrimation, diarrhea and discharge from the nostrils. In addition, such animals develop a chronic cough, poor appetite, numerous red maculae in the buccal mucosa, and hyperkeratosis of the skin. The abomasum may become inflamed with many superficial ulcers (Olafson, 1957; Sykes et al. 1952). After numerous investigations it was established that X disease could be produces in cattle by the ingestion of highly chlorinated naphthalenes.

In the late 1950s, outbreaks of a disease occurred among chickens which caused extensive losses throughout the southeastern part of the United States. One of the leading symptoms was fluid accumulation in the pericardial sac and the peritoneum. The disease was therefore called chick edema (Simpson et al. 1954; Sanger et al. 1958). Following extensive research it was finally determined in 1967 (Cantrell et al. 1967), that 1,2,3,7,8,9-hexachloro-dibenzodioxin was one chemical responsible for chick edema disease. The source of this compound was fat which had been obtained from fats and tallows of hides treated with chlorophenols. When these fats were heated to produce fatty acids some of the chlorophenols may have been converted to chlorinated dibenzodioxins. In addition, the chlorinated phenols were also contaminated with chlorinated dibenzodioxins and dibenzofurans. It was later established that chick edema could also occur following exposure of chickens to chlorinated naphthalenes and chlorinated biphenyls (Kimbough, 1974).

Thus far the only extensive outbreak of acute illness among the general population following exposure to these types of chemicals occured in Japan in 1968. There rice oil became contaminated with chlorinated biphenyls and also chlorinated dibenzofurans

and quarter-phenyls. Since the disease was caused by rice oil it was termed Yusho the Japanese word for rice oil (Kimbrough, 1974; Cordell et al. 1978).

Another group of compounds, 3,3',4, 4'-tetrachloroazobenzene and the tetrachloroazoxybenzene are contaminants of 3,4-dichloroaniline and its derivatives, (Sundstrom et al. 1978). The only illness linked to human exposure to 3,3',4, 4'-tetrachloroazobenzene and 3, 3',4, 4'-tetrachloroazoxybenzene is chloracne (Taylor et al. 1979; Morse et al. 1979). One such chloracne outbreak was investigated by the Center for Disease Control (Morse et al. 1979). A particular chemical company made propanil, N-(3,4-dichlorophenyl) propanamide, from 3,4-dichloroaniline. The 3,4-dichloroaniline used in this factory contained 51 mg/kg tetrachloroazobenzene and the propanil contained over 1000 mg/kg tetrachloroazobenzene. Other commercial herbicides that are also made from 3,4-dichloroaniline usually contain 3,3',4,4'-tetrachloroazobenzene at concentrations of less than 100 mg/kg (Hill et al. Arch. Environ. Health in press).

Most of these chemicals are not readily metabolized and excreted. Since they are all lipophilic they are stored in adipose tissue and may be excreted in milk. Certain isomers of chlorinated and brominated biphenyls are the most persistent in this group. When rats were given a single dose of a polybrominated biphenyl mixture (Kimbrough et al. 1978), the polybrominated biphenyls did not decline appreciably in blood and adipose tissue over a 14 month period once they were equilibrated in the different tissue compartments.

Similarly certain congeners of the polychlorinated biphenyls are not excreted. Rats fed Aroclor 1254 for 6 months (daily dietary intake about 5 mg/kg b.w.) after a 10 month recovery period still had 152 ppm polychlorinated biphenyls in their adipose tissue. The PCB congeners retained this long were the more highly chlorinated ones.

The 3,3',4,4'-tetrachloroazoxybenzene and 3,3',4,4'-tetrachlorobenzene seem to be more rapidly metabolized (Hala et al. 1980).

Not much information is available on the pharmakokinetics of halogenated dibenzodioxins, dibenzofurans and naphthalenes. The half life for 2,3,7,8-tetrachlorodibenzodioxin (TCDD), is 3-4 weeks (Rose et al. 1976). In rats, more TCDD is stored in the liver than in adipose tissue (Kociba et al. 1978), while in monkeys and humans, the opposite is true.

Polychlorinated biphenyls and 2,3,7,8-tetrachlorodibenzodioxins are animal carcinogens. At daily dietary levels of 0.1 µg/kg b.w. 2,3,7,8-tetrachlorodibenzodioxin an increased incidence of hepatocellular carcinomas of the liver and squamous cell carcinomas of the lung, hard palate/nasal turbinate or tongue was noticed (Kociba et al. 1978). Hepatocellular carcinomas have also been produced in rodents by feeding chlorinated biphenyls (Kimbrough et al. 1975), but tumors of the lungs and upper respiratory system were not noted.

In earlier studies in our laboratory, hepatic neoplastic nodules were observed in a preliminary study with polybrominated biphenyls (Kimbrough et al. 1978). Therefore, additional studies were conducted with larger numbers of rats. It was determined

that a single dose of 1000 mg/kg of PBB in corn oil given to eight-week-old female Sherman strain rats produced a 41% incidence of hepatocellular carcinomas. In addition most of these rats had hepatic neoplastic nodules, a tumor considered to represent part of the response of the rodent liver to carcinogens (ILAR 1980). Many of them also had hepatic pophyria. Repeated doses of 100 mg/kg twice a week for a total of 12 doses given to young rats produced a 67% incidence of hepatocellular carcinoma. At the end of the study these rats still had appreciable amounts of PBB in their adipose tissue and in the liver (Table 5). A lower single oral dose of 200 mg/kg given to female rats at the age of 4 months produced neoplastic nodules but no hepatocellular carcinomas (Kimbrough et al. manuscript in preparation).

Attempts to induce cancer of the skin in rodents by dermal exposure to these compounds have not been very successful. It has been suggested that most of these compounds are promoters of cancer instead of intiators of cancer (Berry, et al. 1979).

A number of reports in the scientific as well as public press have associated exposure to these compounds with an increased incidence of cancer in people. Some of these reports have raised auspicions but thus far no studies have been reported suggesting a definite link between cancer and exposure to these compounds. One reason for the lack of such evidence is that groups of workers exposed to these compounds are usually small and studying them would not necessarily demonstrate slight increases in cancer rates.

Unfortunately, these negative findings may create a false sense of security.

However, other human health effects have been reported for some of these chemicals. In addition, to chloroacne, increased triglyceride and cholesterol serum levels have been associated with exposure to these types of compounds. Abnormal liver functions tests and a sensory neuropathy have also been reported (Kimbrough 1974). Workers exposed to high concentrations of TCDD have developed porphyria cutanea tarda (Jirasek,1976).

Recently the Center for Disease Control studied a population of about 600 inhabitants of a small rural town in the South Eastern United States. A source of protein was fish caught in a near by river system. When it was discovered that this fish contained high concentrations of DDT residues, DDT serum levels were determined in 1978 on a few fish eaters and found to be extremely high. Subsequently a study was conducted of the entire population (Kreiss et al. manuscript in preparation). This study consisted of the administration of a questionnaire, measurement of height, weight, blood preasure, clinical chemistry tests and analysis of serum for DDT levels. During the course of the serum DDT analyses it was discovered that PCB levels also seemed to be high in a number of the sera. The sera were subsequently also analyzed for PCB. Several interesting findings were made in this study. First DDT and PCB residue levels increased with age and correlated well with fish consumption. Although DDT

residue levels in the fish were high, the PCB levels in fish were below or close to the present FDA guidelines, suggesting that heavy fish eaters can build up substantial PCB levels.

For instance, a composite sample of 6 catfish from the area averaged 3.64 mg/kg and 4 cataco creek catfish had 4.34 mg/kg PCB. Catfish from other sites in the river system averaged 0.59 mg/kg. In spite of extensive environmental sampling by the EPA no point source for PCB could be uncovered. For the 458 individual PCB measurements the geometric mean serum PCB level was 17.2 µg/L and the range was 3.2-157.9 µg/L. This mean PCB blood level is within the same range of blood levels of the general population. Serum PCB levels correlated well with fish consumption. Of the health indices measured in this population only cholesterol, hypertension and one liver enzyme test, Y-glutamyl-transpeptidase, were positively associated with PCB serum levels, all independent of major confounding variables. Although there was a good correlation between total DDT and PCB blood levels there was no positive association between DDT serum levels and hypertension.

Many factors affect blood pressure and cardiovascular disease such as: smoking, diet, excercise, excessive salt intake and genetic make up. These factors are probably of greater importance than exposure to PCBs. Similar studies in other exposed groups are needed to study these various confounding variables.

Table I Acute Oral LD_{50} in Rats

Compound	LD_{50}	Reference
Aroclor 1240	4.25 g/Kg	Kimbrough et al, 1978
Aroclor 1260	4-10 g/Kg	Kimbrough et al, 1978
Aroclor 1254	4-10 g/Kg	Kimbrough et al, 1978
TCDD	44.7 µg/Kg	Rowe et al, 1971
2,3,6,7-Tetrachloronaphthalene	>11.3 mg/Kg	McConnell, in press
1-chloronaphthalene	1540 mg/Kg	NTIS PB 225-283
2-chloronaphthalene	2078 mg/Kg	NTIS PB 225-283
Brominated biphenyls (Firemaster BP-6)	21.5 g/Kg	Michigan Chemical Corp., 1974

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Table II. Examples of Effects Produced by Compounds in Animals

Compound	Effects	Reference
PCB	1. Decrease in liver vitamin A in Japanese quail and rats	Cecil et al, 1973
	2. Chick edema	Vos and Koeman, 1970
	3. Induction of liver microsomal enzymes in rats and other species	Johnstone et al, 1974
	4. Effect on chick embryo	Cecil et al, 1973
	5. Porphyria cutanea tarda (hepatic porphyria in rats chickens and quail)	Goldstein et al, 1975 Vos and Koeman, 1970 Vos et al, 1971
	6. Liver disease in rats, mice and chickens	Kimbrough et al, 1972 Kimbrough and Linder, 1974 Vos and Koeman, 1970
	7. Liver tumors in rats	Kimbrough et al, 1975 Ito et al, 1974
	8. Hyperkeratosis in rabbit ears	Vos and Notenboom-Ram, 1972
	9. Effects on embryo, neonatal and postnatal effects in rats and minks	Linder et al, 1974 Ringer et al, 1972
	10. Gastric mucosal ulceration in mink and rats. Hyperplasia gastric mucosa in subhuman primates	Kimbrough, 1974 Allen and Norback, 1973
TCDD	1. Effects on embryo, neonatal and postnatal in rats	Murray et al, 1978 Moore et al, 1973
	2. Porphyria cutanea tarda (Hepatic porphyria) in mice	Vos et al, 1974
	3. Liver disease in rats, mice and guinea pigs	Gupta et al, 1973
	4. Thymic atrophy in rat and guinea pig	Greig et al, 1973 Gupta et al, 1973

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Table II. (continued)

Compound	Effects	Reference
TCDD	5. Chick edema	Metcalfe, 1972
	6. Liver microsomal enzyme induction	Poland and Glover, 1974
	7. Hyperkeratosis in rabbit ears	Jones and Krizek, 1962
	8. Immunosuppression in mice	Thigpen et al, 1975
	9. Fatal liver necrosis in rabbits	Milnes, 1971
Chlorinated naphthalenes	1. X-disease in cattle	Sikes et al, 1952
	2. Chick edema	Pudelkiewicz et al, 1959
	3. Hyperkeratosis in rabbit ears and swine	Hambrick, 1957 Huber and Link, 1962
	4. Yellow atrophy of rabbit liver	Flinn and Jarvik, 1936
	5. Decreased vitamin A level in liver and plasma of cattle and swine	Olafson, 1947 Huber and Link, 1962
Brominated biphenyls	1. Liver disease in cattle, rats and minks	Jackson and Halbert, 1974 Kimbrough et al, 1978 Aulerich and Ringer, 1979
	2. Liver tumors in rats	Kimbrough et al, 1980
	3. Immunosuppression in rats, mice, chickens and guinea pigs	Luster et al, 1978 Vos and Van Genderen, 1973
	4. Porphyria cutanea tarda (Hepatic porphyria) in rats	Kimbrough et al, 1978
	5. Liver microsomal enzyme induction in rats and mice	Moore et al, 1978 Dent et al, 1976 Dent et al, 1977

Table II. (continued)

Compound	Effects	Reference
	6. Behavioral and neurological effects in rats and mice	Tilson et al, 1978
	7. Hyperkeratosis in rabbit ears	Kimbrough et al, 1977

Table III. Examples of Effects Produced by Compounds in Man

Compound	Effects	Reference
PCB	1. Chloracne	Umeda, 1972 Jones and Alden, 1936
	2. Mucoid discharge from eyes	Umeda, 1972
	3. Pigmentation of skin and nails	Umeda, 1972
	4. Induction of liver microsomal enzymes	Alvares et al, 1977
TCDD	1. Chloracne	Jirasek et al, 1976 Poland and Smith, 1971
	2. Porphyria cutanea tarda	Jirasek et al, 1976 Bleiberg et al, 1964
	3. Peripheral neuropathy	Goldman, 1972
	4. Elevated serum lipids	Jirasek et al, 1976
Chlorinated naphthalenes	1. Chloracne	Mayers and Silverberg, 1938 Hambrick, 1957
	2. Subacute yellow atrophy of liver	Von Wedel et al, 1943 McLetchie and Robertson, 1947
	3. Cable rash	Good and Pensky, 1943
Polybrominated biphenyls	1. Hypothyroidism?	Bahn et al, 1980

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Table IV. Examples of Fetotoxicity and/or Teratogenicity in Different Animal Species

Compound	Fetotoxic	Teratogenic	Reference
Aroclor 1248	2.5 ppm[1] (Monkey)	-	Barsotti et al, 1976
Aroclor 1260	35.4 mg/Kg/day[2] (Rat)	-	Linder et al, 1974
Aroclor 1254	1.5 mg/Kg/day[3] (Rat)	-	Linder et al, 1974
TCDD	0.01 µg/Kg/day[4] (Rat)	0.125 µg/Kg/day[5] (Rat)	Murray et al, 1979 Sparschu et al, 1971
	-	3 µg/Kg/day[6] (Mouse)	Courtney and Moore, 1971
		1.0 µg/Kg (Monkey)[7]	Zingeser, 1979
Hexachloro-dibenzodioxin	1 µg/Kg[8] (Rat)	100 µg/Kg[8] (Rat)	Schwetz et al, 1973
Brominated biphenyls	200 mg/Kg[9] (Rat)	800 mg/Kg[9] (Rat)	Beaudoin, 1977
	-	1000 ppm[10] (Mice)	Corbett et al, 1975

Footnotes

1. Monkeys fed Aroclor 1248 at 2.5 ppm in diet for 7 months prior to breeding.
2. Rats fed 500 ppm Aroclor 1260 in diet for 62 or 188 days before mating showed fetotoxicity in both F_{1a} and F_{1b} generations.
3. Rats fed 100 ppm Aroclor 1254 in diet for 62 or 186 or 129 days before mating showed fetotoxicity in the F_{1b} and F_{2a} generations but not in F_{1a}.
4. Rats fed 120-215 ppt TCDD to give 0.01 µg/Kg/day for 90 days prior to mating.
5. Rats dosed with 0.125 µg/Kg/day on days 6 to 15 of pregnancy by gavage.
6. Mice dosed subcutaneously with 3 µg/Kg/day of TCDD on days 6 through 15 of pregnancy.

Table IV. (continued)

7. Monkeys dosed nine times by gavage on days 20 through 40 after insemination.
8. Rats dosed day 6 through 15 of pregnancy by gavage.
9. Rats given a single dose by gavage at varying times during day 6 through 14 of pregnancy.
10. Mice were fed 1000 ppm Firemaster BP-6 days 7-18 of pregnancy.

Table V. PBB Concentrations Range (and mean) in Liver, Adipose Tissue and Liver Lesions of Rats given Single or Multiple Doses[1] at Given Times

Number of Rats	Number of Doses x(mg/Kg) per Dose	Recovery Period (Months)	Sex	Tissue (expressed as wet weight for liver and on lipid basis for adipose tissue)	PBB mg/Kg Concentration (ppm)	% Lipids
4	1 x 1000	10	M	Liver	21.0 - 100 (60.3)	5.60 - 9.90 (7.55)
				Adipose tissue	434 - 920 (714)	74.2 - 88.2 (81.3)
				Blood	0.55 - 1.35 (0.94)	- -
5	1 x 1000	14	M	Liver	32.0 - 105 (63.2)	3.60 - 11.6 (7.00)
				Adipose tissue	662-1170 (866)	80.8 - 86.6 (8.35)
				Blood	1.20 - 1.42 (1.34)	- -
4	1 x 1000	10	F	Liver	27.5 - 58.7 (37.4)	3.40 - 5.10 (4.10)
				Adipose tissue	857 - 1802 (1202)	75.1 - 88.7 (83.5)
				Blood	2.00 - 4.66 (2.90)	- -
5	1 x 1000	14	F	Liver	11.0 - 41.0 (22.0)	3.20 - 4.10 (3.80)
				Adipose tissue	479 - 1264 (783)	81.5 - 92.2 (85.5)
				Blood	1.64 - 3.63 (2.92)	- -
12	1 x 1000	26	F	Liver	8.77 - 25.8 (18.1)	1.90 - 7.30 (4.54)
6	1 x 1000	26	F	Hepatocellular carcinoma	8.99 - 22.3 (15.3)	1.60 - 6.80 (4.23)
7	12 x 100	26	F	Liver	23.8 - 74.5 (34.2)	2.53 - 4.38 (3.04)
5	1 x 200	22	F	Liver	1.85 - 4.07 (2.68)	0.92 - 2.66 (1.68)
				Adipose	136 - 441 (244)	87.4 - 91.7 (90.0)
				Blood	0.17 - 0.31 (0.22)	-

Footnote

1. PBB concentrations were determined for a number of control rats each time with negative results in all.

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