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Polychlorinated biphenyls (PCBs): mutagenicity and carcinogenicity

Stephen Safe

Department of Physiology and Pharmacology, College of Veterinary Medicine, Texas A & M University, College Station, TX 77840 (U.S.A.)

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Contents

(1) Introduction

Commercial polychlorinated biphenyls (PCBs) (Fig. 1) were widely used as industrial compounds with such diverse applications as plasticizers, heat transfer fluids, organic diluents, cutting oils, wax extenders, adhesives, flame retardants and dielectric fluids for capacitors and transformers (Hutzinger et al., 1974; Pomerantz et al., 1978). It has been estimated that up to 1.4×10^9 pounds of PCBs were produced in the U.S.A. PCBs were detected in the environment in the late 1960s (Risebrough et al., 1968) and within a short time these compounds were reported as contaminants in almost every component of the global ecosystem including air, water, fish, wildlife and human blood, adipose tissue and milk (Bush et al., 1985, 1986; Buckley, 1982; Ballschmiter et al., 1981; Wasserman et al., 1979; Safe, 1982, Holdrinet et al., 1977; Kannan et al., 1988; Tanabe, 1988). In the 1970s, all 'open' uses for PCBs were discontinued, however, the 'closed' applications of PCBs as dielectric fluids in capacitors and transformers were continued until 1978. New transformers and capacitors now contain alternative dielectric fluids and as older PCB-containing electrical equipment is withdrawn from service or repaired, the PCB fluids are replaced.

Commercial PCBs are prepared by the chlorination of biphenyl and the products are graded and sold according to their chlorine content. The

Correspondence: Dr. Stephen Safe, Department of Physiology and Pharmacology, College of Veterinary Medicine, Texas A&M University, College Station, TX 77840 (U.S.A.).

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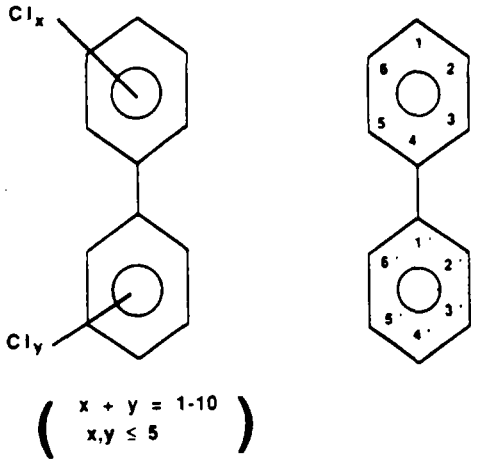

Fig. 1. The structure of polychlorinated biphenyls and the numbering system.

lower chlorinated PCBs typified by Aroclor 1221 (21% by weight of Cl; 1.15 Cl/biphenyl) and the higher chlorinated products typified by Aroclor 1260 (60% by weight of Cl; 6.30 Cl/biphenyl) exhibit markedly different physical chemical properties and use patterns (Hutzinger et al., 1974). Moreover, it is apparent from gas chromatographic analysis of the commercial products that PCB mixtures also differ with respect to the individual congeners present in these mixtures and their relative concentrations (Mullin et al., 1984; Safe et al., 1985a; Albro et al., 1981; Alford-Stevens et al., 1986; Jensen and Sundstrom, 1974; Ballschmiter and Zell, 1980). Obviously there is considerable overlap between the individual PCB congeners present in mixtures which contain similar % chlorine compositions and the extent of PCB congener overlap decreases with increasing differences in the degree of chlorination of the PCB mixtures.

The introduction of commercial PCBs into the ecosystem results in their subsequent translocation and uptake into different environmental components (Safe et al., 1985a). Since individual PCBs exhibit different physicochemical properties and susceptibilities to environmental breakdown, it is not surprising that the composition of most PCB extracts from environmental samples do not resemble the commercial PCB mixtures (Safe et al., 1985a; Wolff et al., 1982, 1986; Hansen et al., 1983; Brown et al., 1985, 1987). Conventional analysis of these environmental mixtures usually estimates 'total PCBs' using an appropriate commercial PCB cocktail as a surrogate quantitative standard (Webb and McCall, 1973). However, it is apparent from high-resolution gas chromatographic analyses that the congener composition and relative concentrations of the individual components in many PCB extracts from environmental samples differ markedly from the commercial PCBs (Safe et al., 1985a; Wolff et al., 1985, 1986; Jensen and Sundstrom, 1974). The differences in the composition of PCB mixtures are reflected in toxicity differences since the higher chlorinated products such as Aroclor 1254 and Aroclor 1260 are more toxic than the lower chlorinated PCBs (Safe, 1984; Fishbein, 1974; Nelson et al., 1972). This is not surprising since extensive structure–activity (including toxicity) studies with individual PCB congeners have demonstrated that the most toxic PCB congeners contain 5 or 6 Cl groups/biphenyl (Safe, 1984, 1985b; Parkinson et al., 1983; Leece et al., 1985). Since congener-specific analyses of few environmental mixtures have been determined, their composition and potential toxicities are therefore largely unknown.

(2) Mutagenic activity of PCBs

(i) Metabolism and macromolecular binding

A large number of PCB metabolites have been identified in both in vivo and in vitro studies in several animal species, microorganisms and also with microsome preparations (reviewed in Matthews and Dedrick, 1984; Safe, 1980; Schnellmann et al., 1985; Sundstrom et al., 1976). The major metabolic products are invariably phenolic compounds however, dihydroxy, dihydrodiol, phenol conjugate and thioether metabolites have also been identified. In addition, several studies have also identified hydroxylated/dechlorinated products as PCB metabolites (Hass et al., 1977; Safe et al., 1975a,b, 1976; Sundstrom et al., 1976). The metabolic pathways associated with PCB metabolism have been investigated using specifically labeled substrates (Schnellmann et al., 1984; Safe et al., 1975a) and induced microsomal enzymes which exhibit different monooxygenase enzyme activities (Kennedy et al., 1980, 1981; Kaminsky et al., 1981). Fig. 2 summarizes the pathways

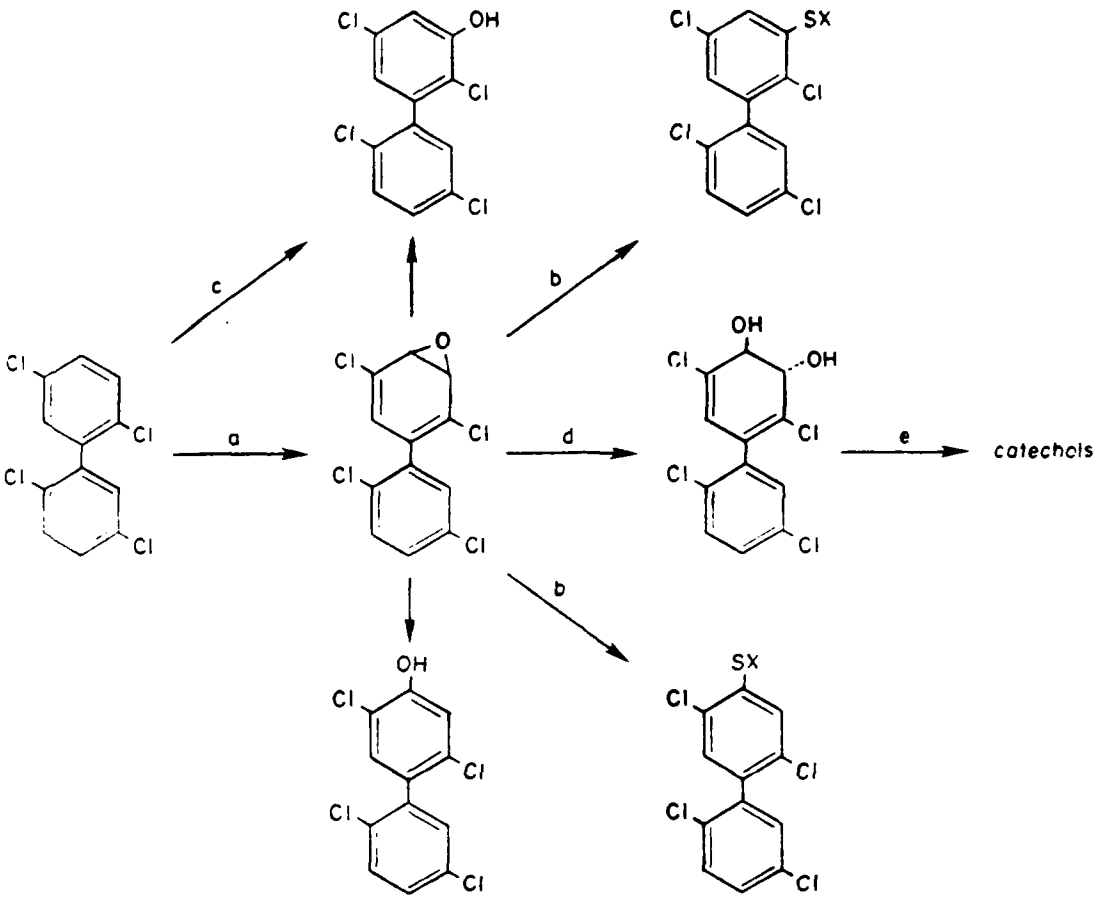

Fig. 2. Metabolism of 2,2′,5,5′-tetrachlorobiphenyl.

associated with the oxidative metabolism of 2,2′,5,5′-tetrachlorobiphenyl. The initial step involves the cytochrome P-450-dependent formation of an unstable arene oxide intermediate which can rearrange to form phenolic metabolites or undergo additional metabolic processing by phase I and phase II drug-metabolizing enzymes (Norback et al., 1976; Hsu et al., 1975; Gardner et al., 1973; Melancon and Lech, 1976). Incubation of radiolabeled 2,2′,5,5′-tetrachlorobiphenyl with microsome preparations has resulted in the identification of the arene oxide intermediate (Forgue and Allen, 1982) and it has also been reported that synthetic 3,4-oxo-2,2′,5,5′-tetrachlorobiphenyl (Riech et al., 1978) spontaneously rearranges in solution to give the phenolic products (Forgue and Allen, 1982) (Fig. 2). It has also been reported that non-arene oxide pathways are prevalent in the metabolism of 2,2′,5,5′-tetrachlorobiphenyl using phenobarbital-induced microsomes (Preston et al., 1984). However, data from most studies suggest that oxidative metabolism of PCBs results in the initial formation of arene oxide intermediates which are known to be strong electrophiles and alkylating agents.

In vivo and in vitro studies with individual PCBs and PCB mixtures have demonstrated that these hydrocarbons can undergo metabolic activation and alkylate cellular macromolecules (Wong et al., 1979; Wyndham and Safe, 1978; Morales et al., 1979; Hesse and Wolff, 1977; Hesse et al., 1978; Shimada and Sato, 1978; Hargraves and Allen, 1979; Wyndham et al., 1976). For example, incubation of [^{3}H]4-chlorobiphenyl with Aroclor 1248-induced rat liver microsomes resulted in the formation of protein, RNA and DNA adducts

with 4-chlorobiphenyl and incubation with homopolynucleotides indicated that poly G was more readily adducted than poly A, poly C or poly U (Wyndham and Safe, 1978). Comparable in vitro adduction of cellular macromolecules by other individual PCBs and PCB mixtures has also been reported. Morales and Matthews (1979) administered [^{14}C]2,2′,4,4′,5,5′- and [^{14}C]2,2′,3,3′,6,6′-hexachlorobiphenyl to mice and reported the in vitro incorporation of radioactivity into cellular protein and RNA for both compounds and into DNA only for the 2,2′,3,3′,6,6′-hexachlorobiphenyl isomer. The higher macromolecular binding (i.e., protein, RNA and DNA) by the latter isomer was consistent with its more rapid rate of metabolism (i.e., compared to the poorly metabolized 2,2′,4,4′,5,5′-hexachlorobiphenyl).

(ii) Mutagenicity

It was initially reported by Wyndham and coworkers (1976) that the 4-chlorobiphenyl and the lower chlorinated PCB mixture, Aroclor 1221, were mutagenic to *Salmonella typhimurium* strain TA1538 in the presence of an exogenous source of metabolic activation (S9). More highly chlorinated biphenyls (Aroclor 1254 and 2,2′,5,5′-tetrachlorobiphenyl) were not mutagenic; these results were consistent with the facile metabolic activation of lower chlorinated biphenyls and the activity of 4-chlorobiphenyl to cause unscheduled DNA synthesis in Chinese hamster ovary cells in culture (Wong et al., 1979). However, subsequent studies in the authors' laboratory (S. Safe, unpublished results) failed to reproduce the original observations. Moreover, Schoeny and coworkers (1979; Schoeny, 1982) have reported the lack of bacterial mutagenicity of Aroclor 1254, 4-chlorobiphenyl, 3,3′,4,4′- and 2,2′,4,4′-tetrachlorobiphenyl and 2,2′,4,4′,6,6′-hexachlorobiphenyl. Hsia et al. (1978) have also shown that 2,2′,5,5′-tetrachlorobiphenyl, 4-hydroxy-2,2′,5,5′-tetrachlorobiphenyl (a metabolite, see Fig. 2) and 3,4-oxo-2,2′,5,5′-tetrachlorobiphenyl (arene oxide intermediate, see Fig. 2) were inactive as bacterial mutagens in *Salmonella typhimurium* strain TA1537.

Heddle and Bruce (1977) reported that Aroclor 1254 did not cause cytogenic effects in mice (i.e., micronuclei and abnormal sperm production) and Aroclors 1242 and 1254 did not cause cytogenetic damage in the bone marrow of rats. It was also concluded that Clophens A-30 and A-60 did not exhibit clastogenic effects in *Drosophila melanogaster* (Nilsson and Ramel, 1974), however, Peakall and coworkers (1972) observed some chromosomal aberrations in ring dove embryos treated with Aroclor 1254. These results suggested possible clastogenic effects of PCBs in ring dove embryos.

(3) Carcinogenicity of PCBs — laboratory animal studies

(i) Cancer as a multi-stage process

The development of cellular neoplasia is a highly complex process which has been investigated using several different model systems (Farber, 1984a,b; Schulte-Hermann, 1985; Farber and Sarma, 1987; Pitot et al., 1987; Slaga, 1984). In the liver, a primary target organ for PCBs, several stages in the sequential development of hepatocellular cancer have been identified or proposed (Fig. 3). The initiation step in cancer development is in itself highly complex in which only one of the steps is presumed to involve irreversible cellular (DNA) damage. For chemical carcinogens, this step in the initiation process is believed to be associated with covalent adduction of DNA. Cellular damage such as the formation of carcinogen-DNA adducts is readily repaired in most tissues and, in the liver, the development of initiated hepatocytes requires a round of cell proliferation following the initial damage. The conversion of the initiated cell populations into focal proliferations such as nodules (liver), papillomas (skin) and polyps (colon) is a complex process known as promotion. Several classes of organ-specific promoters have been identified and have been utilized to study the biochemical and cellular process associated with the development of this altered cell population. The subsequent conversion of initiated cells which have been promoted into cancer cells is known as progression. The specific steps associated with this multi-stage process are not well defined, however Fig. 3 (adapted from Farber, 1986) summarized a proposed model which describes the sequential development of liver cancer in which several of the steps have either been identified or inferred from experimental

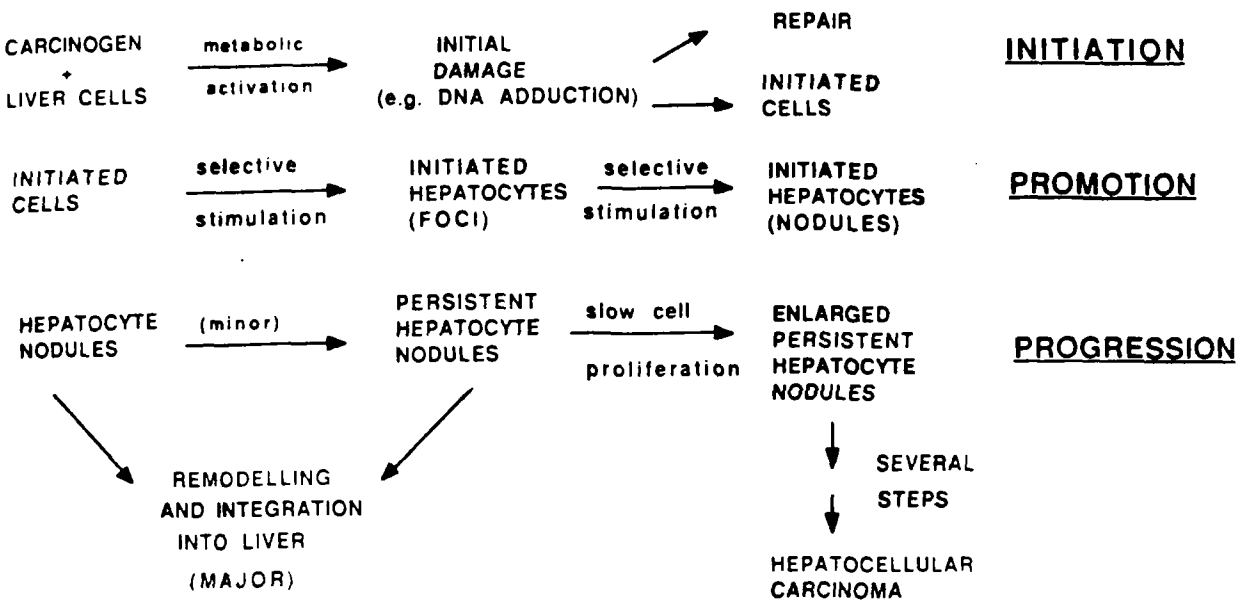

Fig. 3. Some of the proposed steps in the development of hepatic cancer (from Farber, 1986).

studies. Most studies on the role of chemicals in the development of cancer have focused on their activity as initiators or as tumor promoters. However, it is conceivable that chemicals such as PCBs, may act at more than one step in the highly complex conversion of normal cells into neoplastic cells and this possibility will be noted in this review and has been discussed in detail by Hayes (1987).

(ii) Chronic feeding studies

Several studies have reported the carcinogenic effects of commercial PCBs after chronic administration. In male and female Donryu rats, Kimura and Baba (1973) reported adenomatous nodule formation in the liver of female (6/10) but not male rats; however, it was apparent that the dose levels used in this study were toxic. Ito and coworkers (1974) investigated the effects of chronic feeding of several Kanechlor preparations to male Wistar rats and observed nodular hyperplasia in some of the treatment groups. Tables 1 and 2 summarize results of 2 studies in which Aroclor 1260 was utilized. Exposure of female Sherman rats to Aroclor 1260 (100 ppm) in the diet for approximately 21 months results in 14% (26/184) hepatocellular carcinoma and 78% neoplastic nodules (144/184) in the liver whereas only 0.58% (1/73) and 0% (0/173) were observed in the control animals (Kimbrough et al., 1975). In a second long-term study (Norback and Weltman, 1985) using Aroclor 1260 (Table 2), it was demonstrated that this PCB preparation caused hepatocellular trabecular carcinoma, adenocarcinoma and neoplastic nodules in Sprague–Dawley rats. Moreover, it was apparent that female rats were more highly susceptible than males to the hepatocarcinogenic effects of Aroclor 1260.

TABLE 1

THE INCIDENCE AND TYPE OF LIVER LESIONS IN SHERMAN STRAIN FEMALE RATS FED AROCLOR 1260 (1000 ppm) FOR APPROXIMATELY 21 MONTHS (Kimbrough et al., 1975)

Type of lesion	Incidence	
	Controls	PCB-treated
Hepatocellular carcinomas	1/173	26/184
Neoplastic nodules	0/173	144/184
Foci or areas of cytoplasmic alteration	28/173	182/184

The National Cancer Institute (1978) investigated the effects of dietary administration of Aroclor 1254 on male and female F344 rats at dose levels of 0, 25, 50 and 100 ppm in the diet for 105

TABLE 2

EFFECTS OF AROCLOR 1260 ON HEPATOCELLULAR NEOPLASM FORMATION IN MALE AND FEMALE SPRAGUE-DAWLEY RATS (Norback and Weltman, 1984) [a]

Response	Treatment	% Incidence		
		Total (*n*)	Female (*n*)	Male (*n*)
Trabecular carcinoma [a]	Aroclor 1260	23 (21)	40 (19)	4 (2)
	Corn oil	0	0	0
Adenocarcinoma [b,c]	Aroclor 1260	26 (24)	51 (24)	0
	Corn oil	0	0	0
Neoplastic nodule only	Aroclor 1260	8 (7)	4 (2)	11 (5)
	Corn oil	1 (1)	2 (1)	0
Negative	Aroclor 1260	44 (41)	4 (2)	85 (39)
	Corn oil	99 (80)	98 (48)	100
Total number of animals	Aroclor 126	93	47	46
	Control	81	49	32

[a] Included in the table are data from 8 male and 7 female rats in the group administered Aroclor 1260 and 8 male and 10 female rats in the control (corn oil) group that had received partial hepatectomy during the first 18 months of the study.

[b] Animals containing neoplastic nodules plus carcinoma were only included in the carcinoma category.

[c] Animals with trabecular carcinoma and adenocarcinoma were only placed in the adenocarcinoma category.

weeks. The results summarized in Table 3 illustrate a dose-dependent increase of hepatocellular carcinomas and hyperplastic nodules in male and female rats and a significant increase in intestinal metaplasia (male + female rats data combined) (Ward, 1985) at the 100 ppm dose level. In contrast to the results obtained using Aroclor 1260 (Norback and Weltman, 1985), Aroclor 1254 was equally carcinogenic in both male and female F344 rats. Moreover, the incidence of hepatocellular carcinomas was considerably lower in the Aroclor 1254-treated animals than in the rats treated with Aroclor 1260. These results suggest a possible difference in the carcinogenic potencies of the two PCB mixtures and this must be related to differences in their composition.

The hepatocarcinogenicities of Clophens A60 and A30 were determined in male Wistar rats maintained on diets containing 100 ppm of the commercial PCBs for up to 832 days (Schaeffer et al., 1984). Table 4 summarizes the frequencies of the major lesions observed in the rats at the end of

TABLE 3

EFFECTS OF LONG-TERM FEEDING OF AROCLOR 1254 TO F344 RATS (NCI, 1978; Ward, 1985)

Lesion	Sex	Number of rats with lesions/number treated Dose (ppm)			
		0	25	50	100
Hepatocellular carcinomas	M	0	0	1/24	3/24
	F	0	0	1/24	2/24
Hyperplastic nodules	M	0	5/34	8/24	12/24
	F	0	6/24	9/22	12/24
Intestinal metaplasia	M + F	3/47	4/48	5/48	15/48
Adenocarcinoma gastric	M + F	0/47	1/48	3/48	2/48

TABLE 4

COMPARATIVE EFFECTS OF CHRONIC FEEDING OF CLOPHEN A60 AND CLOPHEN A30 ON MALE WISTER RATS (Schaeffer et al., 1984)

Lesion	Number of rats with lesions/number treated (%)		
	Control	Clophen A30	Clophen A60
Hepatocellular carcinoma	1/53 (2)	3/87 (3)	52/85 (61) *
Neoplastic nodules	2/53 (4)	35/87 (40)	34/85 (40) *
Bile duct hyperplasia	7/53 (13)	28/87 (32)	62/85 (73)
Adenofibrosis	12/53 (23)	6/87 (7)	2/85 (2) *
Thymoma	9/53 (17)	12/87 (14)	0/85 (0) *
Other neoplastics	19/53 (36)	33/87 (38)	13/85 (15)
Wistar nephritis	21/53 (40)	7/87 (8)	0/85 (0) *

* Significantly different ($P < 0.05$) from control animals.

the study. Both Clophen A60 and Clophen A30 caused the formation of neoplastic nodules in the liver but only the former compound caused hepatocellular carcinomas. These results clearly demonstrated the markedly increased hepatocarcinogenic potency of the higher chlorinated Clophen A60 (60% by weight of Cl) compared to the lower chlorinated Clophen A30 (30% by weight of Cl). These differences must be related to the relative distribution and concentrations of the individual PCB isomers and congeners present in these mixtures (note: polychlorinated dibenzofurans were not detected in the Clophens used in this study).

The carcinogenicity of commercial PCBs after chronic feeding to mice has also been reported. Administration of Kanechlors 500, 400 and 300 to male dd mice for 32 weeks at dietary levels of 500, 250 and 100 ppm indicated that at the 500 ppm level, Kanechlor 500 caused hepatocellular carcinomas (5/12, 417%) (Nagasaki et al., 1972; Ito et al., 1973). In a second study (Kimbrough and Linder, 1974) there was an increase in hepatomas (9/22, 40%) observed in male BALB/CJ mice maintained on a diet of Aroclor 1254 (300 ppm) for 11 months whereas this lesion was not observed in the control mice. Moreover, based on the data noted above and the results reported by Schaeffer and coworkers (1984) for Clophen A30 and Clophen A60, it is apparent that the lower chlorinated PCB mixtures were significantly less potent as carcinogens than the higher chlorinated commercial products.

(iii) PCBs as modulators of carcinogenesis

PCBs are known to interact with structurally diverse carcinogens (initiators) and modulate their mutagenic and carcinogenic potencies. For example, PCB mixtures induce several phase I and phase II drug-metabolizing enzymes including glutathione *S*-transferases, epoxide hydrolase, glucuronyl transferases and several cytochrome P-450-dependent monooxygenases (reviewed in Safe, 1984). Commercial PCBs such as Aroclor 1254 and individual isomers and congeners induce a spectrum of cytochrome P-450 isozymes (cytochromes P-450a, P-450b, P-450c, P-450d, P-450e and P-450p) (Parkinson et al., 1983; Ryan et al., 1979a,b, 1981, 1982; Scheutz et al., 1986; Thomas et al., 1981, 1983) which in turn catalyze the oxidation of diverse compounds; including carcinogens such as benzo[*a*]pyrene and related polynuclear aromatic hydrocarbons, aflatoxin B_1 and acetylaminofluorene (Astrom and DePierre, 1985; Yang, 1988; Goldstein et al., 1984; McManus et al., 1984; Yoshizawa et al., 1982). Not surprisingly, PCBs can act as cocarcinogens or anticarcinogens which enhance or inhibit the tumorigenic activity of other carcinogenic compounds. For example Kanechlor 500 decreased the incidence of hepatic tumors in rats treated with the hepatocarcinogens 3′-methyl-4-dimethylaminoazobenzene, 2-acetylaminofluorene and diethylnitrosamine in the diet (Makiura et al., 1974). In a similar experiment, Kanechlor 400 also decreased the incidence of 3′-methyl-4-dimethylaminoazobenzene-induced hepatocarcinomas in

rats (Kimura et al., 1976).

The effects of PCBs on aflatoxin B_1-mediated hepatocarcinoma formation in rainbow trout have been extensively investigated. When 6 ppb of aflatoxin B_1 and Aroclor 1254 are simultaneously fed to rainbow trout, the PCBs inhibit the incidence of liver tumors (Hendricks et al., 1977). Similarly, PCB administration prior to aflatoxin B_1 treatment also decreased the liver tumor incidence (Shelton et al., 1983) whereas if Aroclor 1254 is fed after exposure of trout embryo to aflatoxin B_1 there is no effect on the formation of liver tumors. Table 5 summarizes the incidence of hepatic tumors in rainbow trout fed different dietary levels of aflatoxin B_1 (1, 4 and 8 ppb), Aroclor 1254 (50 ppm) and aflatoxin B_1 plus Aroclor 1254 (Shelton et al., 1984). The inhibition of aflatoxin B_1-mediated carcinogenicity was also correlated with the decreased bacterial mutagenicity of this compound in the presence of an Aroclor 1254-induced drug-metabolizing enzyme fraction from fish. The potential mechanisms of this interaction were further investigated (Shelton et al., 1986) by studying the effects of Aroclor 1254 on aflatoxin B_1 distribution, metabolism and DNA adduct formation. The results from the in vivo studies showed that PCB treatment resulted in a marked increase in the metabolism of aflatoxin B_1 to aflatoxin M_1 and aflatoxicol M_1 and their glucuronide conjugates. Moreover, after 21 days, the DNA adduct levels in the PCB-treated fish were 48–69% lower than in the controls. The results strongly suggest that the anticarcinogenic activity of PCBs in the fish model using aflatoxin B_1 as the carcinogen is associated with the activity of Aroclor 1254 as an inducer of cytochrome P-450-dependent monooxygenases (e.g., such as aflatoxin-4-hydroxylase) (Shelton et al., 1986; Halvorson et al., 1985).

The anticarcinogenic activities of Aroclor 1254 and some PCB congeners have also been reported in the mouse skin model using polynuclear aromatic hydrocarbons as initiators (Berry et al., 1978; DiGiovanni et al., 1977, 1979, 1980). The results summarized in Table 6 show that Aroclor 1254 (100 μg/mouse) administered 18 h prior to the initiator, 7,12-dimethylbenz[*a*]anthracene (DMBA), significantly decreased the incidence of papilloma formation in female Charles River CD-1 mice. 2,2′,4,4′,5,5′-Hexachlorobiphenyl (625 μg/mouse), a PCB congener which resembles phenobarbital in its mode of incubation of drug-

TABLE 5

HEPATOCARCINOMA INCIDENCE FOLLOWING VARIOUS DIETARY CONCENTRATIONS OF AFB_1 AND AROCLOR 1254 (from Shelton et al., 1984)

Treatment diet	9-month sample		12-months sample	
	Hepatocarcinoma incidence [a]	%	Hepatocarcinoma incidence	%
1 ppb AFB_1 [b]	2/52	3.8	27/121	22.3
4 ppb AFB_1	5/51	9.8	68/126	54.0
8 ppb AFB_1	32/62	51.6	98/118	83.1
1 ppb AFB_1 + 50 ppm PCB [c,d]	–	–	14/120	11.7
4 ppb AFB_1 + 50 ppm PCB	3/59	5.1	38/122	31.2
8 ppb AFB_1 + 50 ppm PCB	12/58	20.7	88/118	74.6
4 ppb AFB_1 + 5 ppm PCB	10/67	14.9	56/119	47.1
50 ppm PCB	0/74	0	0/120	0
Control	0/70	1.1	0/120	0

[a] The 9- and 12-month samples show pooled data from duplicate tanks. Less than 80 fish at 9 months and 120 fish at 12 months reflect mortalities during the experiment.

[b] The 12-month AFB_1 dose–response curve was linear ($y = 8.60x + 15.84$, $r = 0.944$) with an ED_{50} of 4.0 ppb.

[c] The 12-month AFB_1 + 50 ppm PCB dose–response curve was linear ($y = 9.09x - 0.25$, $r = 0.0991$) with an ED_{50} of 5.5 ppb.

[d] Regression line for AFB_1 + PCB not significantly different from parallel ($0.75 > P > 0.5$) when compared with regression line for AFB_1 alone.

TABLE 6

EFFECTS OF 2,3,7,8-TCDD, AROCLOR 1254 AND POLYCHLORINATED BIPHENYL CONGENERS ON SKIN TUMOR INITIATION BY DMBA IN CD-1 MICE (from DiGiovanni et al., 1979) [a]

Pretreatment (μg/mouse)	Weeks of promotion	Initiator	Pretreatment time	Papillomas per mouse	Percent of control
Acetone	20	DMBA	5 min	3.80	100
Aroclor 1254 (100)	20	DMBA	5 min	3.60	85
Aroclor 1254 (100)	20	DMBA	18 h	2.1	55
Aroclor 1254 (100)	20	DMBA	3 days	3.3	88
Aroclor 1254 (625)	20	DMBA	18 h	2.70	71
Acetone	24	DMBA	3 days	3.83	100
3,4,3′,4′-TCB (625)	24	DMBA	3 days	0.40	10
2,4,5,2′,4′5′-HCB (625)	24	DMBA	3 days	3.36	88
Acetone	20	DMBA	5 min	3.80	100
TCDD (1)	20	DMBA	3 days	0.34	9

[a] Pretreated mice (30 per group) were initiated with DMBA as described (DiGiovanni et al., 1979).

metabolizing enzymes, did not act as an anticarcinogen, whereas 3,3′,4,4′-tetrachlorobiphenyl was more active than Aroclor 1254 as an inhibitor. Both 3,3′,4,4′-tetrachlorobiphenyl and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) resemble MC in their mode of cytochrome P-450 induction (Parkinson et al., 1983) and both halogenated aryl hydrocarbons significantly decreased the number of DMBA-initiated papillomas/mouse. Although the PCB treatment did not modulate the incidence of papillomas caused by B[*a*]P, it was suggested that the anticarcinogenic effects of PCBs on mouse skin tumors initiated by DMBA were due to altered metabolism and DNA binding of the carcinogen by the PCB-induced skin monooxygenases (DiGiovanni et al., 1979).

Several studies have investigated the activity of PCBs as cancer promoters using a number of different bioassays and target organs. Commercial PCBs promote hepatocarcinogenesis in rodents which have been initiated with carcinogens such as the isomeric hexachlorocyclohexanes, *N*-ethyl-*N*-hydroxyethylnitrosamine, diethylnitrosamine and 2-acetylaminofluorene (Ito et al., 1973; Hirose et al., 1981; Kimura et al., 1976; Periera et al., 1982; Tatematsu et al., 1979; Anderson et al., 1983, 1986). Table 7 summarizes the effects of treatment of male Sprague–Dawley rats with Aroclor 1254 for 18 weeks (100 ppm in the diet) following initiation with diethylnitrosamine (administered for 5 weeks in the drinking water). The results demonstrated that Aroclor 1254 treatment promoted diethylnitrosamine-initiated hepatocellular carcinomas in male rats. Moreover, the promoter activity was observed using either commer-

TABLE 7

INCIDENCE AND TYPE OF LIVER LESIONS IN MALE SPRAGUE–DAWLEY RATS TREATED WITH DIETHYLNITROSAMINE AND AROCLOR 1254 (Preston et al., 1981)

Treatment	Number of rats	Neoplastic nodules	Hepatocellular carcinoma (%)
Control	72	0	0 (9)
Diethylnitrosamine	32	6	5 (16)
Aroclor 1254 [a]	34	0	0 (9)
Diethylnitrosamine plus Aroclor 1254 [a]	33	10	21 (64)
Aroclor 1254-U [b]	34	0	0 (9)
Diethylnitrosamine plus Aroclor 1254-U [b]	33	5	27 (84)

[a] Aroclor 1254 cleaned up to remove polychlorinated dibenzofurans.

[b] Aroclor 1254-U not cleaned up as noted above.

cial Aroclor 1254 or a sample that had undergone cleanup to remove polychlorinated dibenzofuran impurities. Anderson and coworkers (1986) showed that a single dose of Aroclor 1254 enhanced *N*-nitrosodimethylamine-initiated lung tumors in male Swiss mice, however, the effects on liver tumor formation were variable. It was also reported that 2 higher chlorinated biphenyls 2,2′,4,4′,5,5′-hexachlorobiphenyl and 2,2′,3,4′,5,5′-hexachlorobiphenyl were the dominant congeners persisting in the tissues of the PCB-treated mice. It should be noted that only the more highly chlorinated commercial PCBs (> 50% by weight) were reported as promoters of hepatocarcinogenesis in rodents and the promoting effects of the lower chlorinated PCBs and individual PCB congeners have not been determined.

The activity of PCBs as promoters has also been investigated utilizing short-term in vivo assays in which the end points are preneoplastic lesions which are presumed to progress into cancer cells. Most of these studies demonstrate that the higher chlorinated commercial PCB mixtures promote the formation of putative preneoplastic lesions (Anderson et al., 1983, 1986; Ito et al., 1973; Nishizumi, 1976, 1979; Preston et al., 1981; Deml and Oesterle, 1982; Oesterle and Deml, 1983, 1984; Deml et al., 1983; Pereira et al., 1982; Buchmann et al., 1986). These studies were carried out using different initiators, commercial PCBs (usually Aroclor 1254 or Clophen A50) or PCB congeners and different treatment protocols; however, the results clearly demonstrate the activity of PCBs as promoters of preneoplastic lesions in rodent liver. Buchmann and coworkers (1976) reported the effects of 3,3′,4,4′-tetrachlorobiphenyl and 2,2′,4,4′,5,5′-hexachlorobiphenyl as promoters; although there were some problems with these studies (i.e., limited numbers of animals used and large standard deviations in some of the data) the results suggested that both congeners promoted diethylnitrosamine-initiated hepatocellular adenosine triphosphate-deficient focal lesions.

The effects of PCB mixtures and selected congeners have also been investigated (Hayes et al., 1985, 1986) using the resistant hepatocyte model developed by Farber and coworkers (Solt and Farber, 1976; Tsuda et al., 1980; Farber, 1984a,b, 1986). The PCBs used in these studies included Aroclor 1254, a reconstituted mixture of PCBs with a defined congener composition, 2,2′,5,5′-tetrachlorobiphenyl, 2,2′,4,4′-tetrachlorobiphenyl and 2,2′,4,4′,5,5′-hexachlorobiphenyl. None of these compounds exhibited activity as initiators in this model (Hayes et al., 1985). Subsequent studies (Hayes et al., 1986) using the aforementioned compounds and 3,3′,4,4′-tetrachlorobiphenyl (a prototypical MC-type inducer of cytochrome P-450-dependent monooxygenases) showed that these PCBs (50 μoles/kg) given 10 days after a dose of the initiator, diethylnitrosamine, and 7 days before 2-acetylaminofluorene, all reduced the size of the 2-acetylaminofluorene-selected γ-glutamyltranspeptidase-positive nodules. These results show that in contrast to the previous studies, noted above, PCBs also exhibit 'anti-promoting' activities in this model which utilizes 2-acetylaminofluorene as a mitoinhibitory toxin.

Poland and coworkers (1982) investigated the activities of 2,3,7,8-TCDD, Aroclor 1254 and other halogenated aryl hydrocarbons as promoters of DMBA and *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine-initiated papilloma formation in HRS/J hairless mice. The structure-dependent effects of these compounds as promoters correlated with their affinities for the aryl hydrocarbon (Ah) receptor and thus supported the role of the Ah receptor in mediating this process. With the exception of this study, the structure-dependent activities of PCBs as promoters of rodent hepatocarcinogenesis have not been investigated. However, like Aroclor 1254 and Aroclor 1260, the polybrominated biphenyl (PBB) mixture, FireMaster BP-6, exhibits comparable biologic and toxic effects (Safe, 1984; Parkinson et al., 1983) and is also a rodent hepatocarcinogen (Kimbrough et al., 1981; Gupta et al., 1983). Moreover, the structure–function relationships for PBB and PCB isomers and congeners are similar (Safe, 1984). Structure–activity studies utilizing 2,2′,4,4′,5,5′- and 3,3′,4,4′,5,5′-hexabromobiphenyl (HBB) as promoters of *N*-nitrosodiethylamine-initiated enhancement of γ-glutamyltranspeptidase-positive altered hepatic foci showed that 2,2′,4,4′,5,5′-HBB but not 3,3′,4,4′,5,5′-HBB enhanced the development of altered hepatic foci and hepatic nodules (Jensen and Sleight, 1986). A combination of the two congeners resulted in a synergistic tumor pro-

motion response. The significance and mechanism of these interactive effects require further investigation. The negative results obtained with the toxic halogenated biphenyls which exhibit high affinity for the Ah receptor (i.e., 3,3″,4,4′-tetrachlorobiphenyl and 3,3′,4,4′,5,5′-HBB) contrasted to the reported activity of 2,3,7,8-TCDD (Pitot et al., 1980), 2,3,4,7,8-pentachlorodibenzofuran and 1,2,3,4,7,8-hexachlorodibenzofuran (Nishizumi and Masuda, 1986) as promoters of hepatic preneoplastic lesions and tumors in rodents. The apparent dichotomy in these results may be due to the different model systems used and this should be further investigated.

Kerkvliet and Kimeldorf (1977) have reported the antitumor activity of Aroclor 1254 in rats inoculated with Walker 256 carcinosarcoma cells. Depending on the timing of the treatment with PCBs and the number of tumor cells used in the study, Aroclor 1254 inhibited tumor growth, increased the latency period for tumor development, increased the host survival time and caused tumor regression (if administered after the tumors were established). Additional studies on the effects of Aroclor 1254 on transplantable tumors have not been reported.

(4) Carcinogenicity of PCBs — human studies

Analytical studies have confirmed that most individuals carry significant body burdens of PCBs in their adipose tissues (in the range of 0.1–1.0 ppm) and these residues are derived from multiple environmental pathways. The potential carcinogenic (or anticarcinogenic) effect of these background PCB levels has not been determined. In addition, there are 2 major groups which have experienced exposure to relatively high levels of PCBs, namely, individuals who consumed PCB-contaminated rice oil in the Yusho or Yu Cheng incidents (Kuratsune, 1980; Masuda et al., 1982) and occupationally exposed workers. There is insufficient data to assess the carcinogenic effects of exposure to the contaminated rice oil, moreover, this data may not be appropriate for assessing the human carcinogenic potential of PCBs. Several studies have reported that the PCB industrial fluid involved in the rice oil contamination contained relatively high levels of polychlorinated dibenzofurans (Chen et al., 1985; Buser et al., 1978) and these compounds are likely the major etiologic agents of Yusho/Yu Cheng poisoning (Bandiera et al., 1984; Kunita et al., 1985).

Zack and coworkers (1979) examined a small cohort of workers (89) with occupational exposure to PCBs. No liver cancer were reported among the 30 deaths which occurred in this group. Gustavsson and coworkers (1986) did not observe any excesses in either overall mortality or cancer in a group of 142 male Swedish workers exposed to PCBs during the manufacture of capacitors. Both of these studies are limited because of the small size of the sample population.

Bertazzi et al. (1981, 1987) examined a group of 1310 workers employed ($\geq$ 6 months) in a capacitor-manufacturing plant from 1946 to 1970. The updated study of these PCB-exposed individuals (Bertazzi et al., 1987) added 790 workers (total = 2100) and their data showed a statistically significant excess of cancer in males (14 observed vs. 7.6 expected) and females (12 observed vs. 5.3 expected). Excess (significant) lymphatic hematopoietic cancer (4 observed vs. 1.1 expected) was noted for females whereas significantly increased digestive cancers (6 observed vs. 2.2 expected) were seen in males. However, it was reported that there were no apparent correlations between cancer mortalities (individual or total cancers) and the duration of exposure and latency periods from the time of first exposure. The small number of deaths observed in this study do not yet permit any firm conclusions regarding the carcinogenicity of PCBs and additional follow-up studies on this group will be required.

The most comprehensive mortality and cancer studies of PCB-exposed workers were reported by Brown and Jones (1981) and Brown (1987). For the 2588 workers employed in 2 capacitor-manufacturing plants (Brown, 1987), the overall mortality of this group (295 deaths) was lower than expected (318) and the mortality for cancer deaths (62 observed) was also lower than expected (80). Inspection of the cancer mortality data among workers exposed to PCBs showed that the only category where there was a significant increase ($P < 0.05$) in deaths was associated with liver, gall bladder and biliary tract cancers (combined). A detailed analysis of the data with respect to latency

periods, length of employment and sex of the workers was carried out. There was a higher female susceptibility to these cancers in the PCB-exposed workers. Moreover, for the individuals employed in plant 2, the length of employment was also important and this correlated with potential exposure to the more highly chlorinated PCBs which were initially used in this plant. This observation also correlated with the animal data. It was interesting to note that based on pathology reports, it is likely that only 1 of the 5 individuals with liver/gall bladder/biliary tract cancer had primary liver cancer. Most of these neoplasms were originally bile duct or gall bladder cancers and PCB-mediated cancer at these sites has not been extensively investigated or reported in rodent cancer studies. Subsequent updates of the mortality data in this cohort and others will be useful in determining the potential role of PCBs as human carcinogens.

(5) Summary and conclusions

The potential mutagenicity and carcinogenicity of commercial PCBs has been investigated in both in vivo and in vitro systems and several conclusions can be drawn from these studies.

(1) PCBs can covalently adduct DNA both in vivo and in vitro (using a source of metabolic activation); the more highly chlorinated biphenyls are poorly metabolized and these compounds tend to exhibit very low binding to DNA. Based on the structure–activity relationships for PCBs (Safe, 1984) it is unlikely that the more toxic compounds such as 3,3′,4,4′,5-penta- and 3,3′,4,4′,5,5′-hexachlorobiphenyl, would form covalent adducts with DNA.

(2) PCB mixtures and individual compounds exhibit minimal mutagenic activity in most assay systems.

(3) The more highly chlorinated PCB mixtures (i.e. > 50% Cl by weight) are hepatocarcinogens in rodents whereas data from a limited number of studies suggest that the lower chlorinated mixtures are not carcinogenic.

(4) In some model systems, the higher chlorinated PCB mixtures act as promoters of preneoplastic lesions and hepatocellular carcinomas in rodents treated with a variety of initiators.

(5) Aroclor 1254 acts as a promoter of skin papilloma formation in HRS/J hairless mice and structure–activity and genetic studies suggest that the Ah receptor is necessary but not sufficient for the activity of halogenated aryl hydrocarbons as promoters in hairless mice.

(6) Individual PCB congeners and higher chlorinated commercial mixtures also exhibit anticarcinogenic activity in the CD-1 mouse skin cancer model.

(7) Results from occupational studies suggest that individuals exposed to PCBs may have an excess of cancer at some sites, however, the most comprehensive study (Brown, 1987) suggests that there are no significant increases in the overall cancer rate in workers exposed to PCBs. Follow-up and continuing epidemiological studies on the PCB-exposed workers are required to further clarify the potential carcinogenic effects of PCBs on humans.

In several strains of rats and mice, there is a high incidence of hepatic preneoplastic lesions and carcinomas and these lesions can be induced by diverse promoting agents (Schulte-Hermann et al., 1983; Weinstein, 1984). Since PCBs are not mutagenic and do not readily form covalent adducts with cellular DNA, it is likely that the higher chlorinated biphenyls are not genotoxic and act as promoters of carcinogenesis in rodents. A comparable mechanism has been suggested for 2,3,7,8-TCDD (Shu et al., 1987; Weinstein, 1984). For PCBs, the role of the Ah receptor in mediating their activity as promoters has not been delineated. It is conceivable that PCB congeners (e.g., 2,2′,4,4′,5,5′-hexachlorobiphenyl) which possess many properties similar to the promoter, phenobarbital, may also contribute to the development of cancer in rodents. Future studies should focus on the structure-dependent effects of PCBs and more accurately define the class of higher chlorinated biphenyl congeners which are carcinogenic.

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