

Carcinogenicity/tumour promotion by NDL PCB

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Introduction

Polychlorinated biphenyls (PCBs) belong to the group of persistent environmental pollutants exhibiting neurotoxic, teratogenic and tumour-promoting effects in experimental animal models^{1,2,3}. PCB congeners can be divided into 'dioxinlike' and 'non-dioxinlike' congeners on the basis of their ability to act as aryl hydrocarbon receptor (AhR) agonists. Like the most toxic dioxin congener 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) 'dioxinlike' PCBs bind to the AhR and show characteristic effects on the expression of AhR-regulated genes including the induction of cytochrome P450 (CYP) 1A1³. On the other hand, 'non-dioxinlike' PCB congeners have a lower or no binding affinity to the AhR, but exhibit a 'phenobarbital-type' induction of CYP 2B1/2 activity^{3,4}.

A carcinogenic potential of PCBs has been demonstrated with technical mixtures such as Aroclors or Clophens. In these studies the liver and the thyroid gland were found to be the principal target organs of PCB-mediated carcinogenesis in rodents. No studies have been published, however, on the carcinogenicity of individual congeners.

In two-stage initiation-promotion protocols in rats, both technical mixtures and individual 'dioxinlike' and 'non-dioxinlike' congeners were reported to act as liver tumour promoters.

Carcinogenicity of technical PCB mixtures

A carcinogenic activity of PCBs was first reported in the early 1970s. Nagasaki et al.⁵ found that male mice, fed in the diet with Kanechlor 500, developed hepatic tumors. No hepatic tumors were reported when mice were fed in the diet with the lower chlorinated Kanechlor 400 and Kanechlor 300. These results and further investigations were validated by Ito et al.⁶ The arising neoplasms, produced by Kanechlor 500 were classified as nodular hyperplasia or hepatocellular carcinoma. Later studies with technical PCB mixtures revealed adenofibrosis and hepatoma of the liver in mice and rats^{7,8}. In comparison to Clophen A60, carcinogenic effects caused by the lower chlorinated Clophen A30 were weaker⁹. The incidence of carcinoma in PCB-treated female but not in male rats was significantly higher than in controls. The striking sex-differences were suggested to be related to either sex-linked enzymatic differences or endocrine effects¹⁰. Carcinogenic effects of PCB mixtures in mice were also described by Anderson et al.¹¹, in rats by Rao and Banerji¹².

In the study conducted by the National Cancer Institute (NCI) in 1978⁸, male and female rats were fed with Aroclor 1254 in estimated doses of 1.25, 2.5 or 5 mg/kg/day for 104 to 105 weeks. The

purity of Aroclor 1254 was not determined. In the treated animals low incidences of hepatocellular carcinoma and unspecified adenoma occurred in the middle and high dosed groups. In none of the control or low dosed group (24 rats each) incidences of hepatocellular carcinoma or unspecified adenoma were found. Reexamination and reclassification of the NCI liver data by Ward¹³ seven found that the total tumor incidence (hepatocellular adenoma and carcinoma) was significantly increased in the high dosed male rats.

A further carcinogenicity study in rats¹⁴ provides comparative data on the four most widely used commercial Aroclor mixtures (1016, 1242, 1254, 1260). Groups of 50 male and 50 female rats were fed in the diet with Aroclor 1016, 1242, 1254 or 1260 for 24 month. The dose levels were estimated based on feed consumption. The control group consisted of 100 male and female rats each. At the end of the study after 24 month, comprehensive histological examinations were performed. Evaluations included liver, mammary gland, brain, gross lesions and thyroid (males only). In the liver, tumor incidences were statistically increased, in the mammary gland the incidences were significantly decreased. Thyroid follicular cell adenomas were significantly increased in male rats with various Aroclors.

Additional tumour localizations were also reported by others. Morgan et al.¹⁵ reexamined the NCI gastrointestinal data and found increased incidences of dose-related stomach neoplasia and stomach adenocarcinoma. Preneoplastic lesions in the biliary tract (cholangioma) occurring at a higher incidence in Aroclor-treated male (14%) and female (21%) rats than in the controls (2 and 2%, respectively) were reported by Norback and Weltman¹⁰.

The carcinogenic potency of different commercial PCB mixtures varies greatly, one determinant being the percentage of chlorination or mean chlorine number. The group of Chase et al.¹⁶ used existing data and estimated tumourigenic potency factors (TPFs) for various Aroclor mixtures. It was found that Aroclor 1260 is approximately thirteen fold more potent in generating benign and malign tumors than Aroclor 1242 and over 2-fold more potent than Aroclor 1248 in rats and mice. Compared with TCDD the carcinogenic potency of Aroclor 1260 was estimated to be much lower.

Tumour promoting potency of PCBs

In the literature there are several papers addressing initiation/promotion of putative preneoplastic lesions by specific PCB congeners. Hayes et al.¹⁷ found that pure PCB 153, PCB 47, and PCB 52 did not initiate GGT-positive nodules in neonatal rats. A study by Buchmann et al.² found no enhanced formation of ATPase-deficient foci after treatment with either PCB 77 or PCB 153 in rats.

Preston et al.¹⁸ found that PCB 52 and PCB 47 promoted the formation of GGT+ foci in rats after initiation with DENA although the latter congener was approximately 10 times more potent. Deml and Oesterle and others also found PCB 47 and PCB 52 to have only weak promoting effects. PCB 15 was not effective as a promoter. After initiation with DENA, PCB 77 increased the number of enzyme-altered foci four- to six fold. The same group observed that both PCB 15 and PCB 52 are poor inducers of cytochromes P450 and also poor promoters. In contrast, technical mixtures of PCBs were found to be both strong inducers and promoters. A correlation between promoting potency and induction of CYPs was thus suggested^{19,20}.

In a study by Buchmann et al.² PCB 77 was a much more potent promoter than PCB 153. This result is important because of the known pharmacokinetic properties of the congeners, PCB 153 being less extensively metabolized in the rat than PCB 77. Thus it seems that persistence of the single PCB is not the only determinant of tumour-promoting ability. The authors speculate that the potency of PCB 77 as a promoter was possibly due to its toxicity rather than to its inducing

properties in the liver. Rose et al.²¹ found that PCB 153 increased the number and size of ATP-deficient foci in newborn rats, initiated by a single dose of DENA.

Discussion

PCBs occur in the environment and in food as mixtures. The patterns found in organisms differ from those in the technical mixtures, because of changes in the environment and after uptake in the organism. Bioaccumulated PCBs seem to be more persistent in humans. This is important, because it was found that bioaccumulated PCBs seem to be more toxic in animals than technical mixtures. An important research need is a cancer study comparing technical and bioaccumulated mixtures²².

In general, studies on *in vitro* and *in vivo* genotoxicity of PCBs were negative. Although the available data indicate that PCBs are not potent genotoxic or mutagenic agents, there is some experimental support for the possible involvement of genotoxic mechanisms in the development of PCB-induced cancer.

Various studies support the notion that technical PCB mixtures can cause cancer in experimental animals. Different mixtures seem to have different potencies. In animal studies Aroclors 1016, 1242, 1254 and 1260 induced liver tumors in female rats, while in male rats only Aroclor 1260 showed a certain potency to induce liver tumors. Gastrointestinal tumors were induced by mixtures containing 54 % chlorine. Furthermore, a significant increase in thyroid tumors was reported in male rats treated with various Aroclors.

Exposure to commercial mixtures with 42-60 % chlorine over less than lifetime induced preneoplastic liver lesions in rats and mice. A tumor-promoting activity in liver and lung was shown for Aroclor 1254 and some individual congeners (4 to 6 chlorine atoms), PCB 47, 49, 52, 77, 105, 118, 126 and 153 in rodents.

To address the question of a possible carcinogenicity of 'non-dioxinlike' congeners, long-term studies with these compounds are needed. The use of the available data on the carcinogenicity of technical PCB mixtures for risk assessment of 'non-dioxinlike' PCBs is hampered by the fact that the concentrations of the 'dioxinlike' congeners in technical mixtures are reported differently in various studies. Evidence is provided for significant lot-to-lot differences among similar mixtures^{22,23}. Analysis of the literature revealed that for none of the lots of technical mixtures used in carcinogenicity experiments, the exact chemical composition was available.

Analysis of the data published by Mayes et al.¹⁴ suggests that the carcinogenicity of technical mixtures in rats, is predominantly, if not exclusively, due to the 'dioxinlike' congeners. The authors found hepatic neoplasms after Aroclor treatment in female rats only, with the exception of one dose level of Aroclor 1260 which also caused liver neoplasms in males. Data on thyroid neoplasms were provided for male rats only. In Table 1 the dose regimen and the calculated TEQ doses based on data provided by Mayes et al. are shown. A non-linear correlation between the dose of TCDD equivalents (TEQ) present in the various Aroclors and the rate of female rats with neoplastic liver lesions is found. The lowest 'TEQ doses' resulted in incidences which were not significantly different from those in control animals. After log-probit transformation of the data a linear correlation was obtained. In a next step, data published by Kociba et al.²⁴ on the incidence of neoplastic liver lesions in female rats treated with TCDD are included. Kociba et al. found hepatic neoplasms after treatment of female rats only. Both in the non-transformed manner (not shown) and after log-probit transformation, these data seem to fit well into the data on Aroclor carcinogenesis (Fig. 1).

Table 1: Dose regimen and TEQ doses used by Mayes et al.¹⁴.

Aroclor	TEQ ^a (ng/mg)	level in the diet (mg/kg)	average dose (mg/kg b.w. per day)		average dose (ng TEQ/kg b.w. per day)	
			♂	♀	♂	♀
1016	0.11	50	2.0	2.7	0.22	0.30
		100	4.0	5.4	0.44	0.59
		200	8.0	11.2	0.88	1.23
1242	7.8	50	2.0	2.8	15.6	21.8
		100	4.0	5.7	31.2	44.5
1254	23.4	25	1.0	1.4	23.4	32.8
		50	2.0	2.9	46.8	67.9
		100	4.3	6.1	100.6	142.7
1260	7.2	25	1.0	1.4	7.2	10.1
		50	2.0	2.8	14.4	20.2
		100	4.1	5.8	29.5	41.8

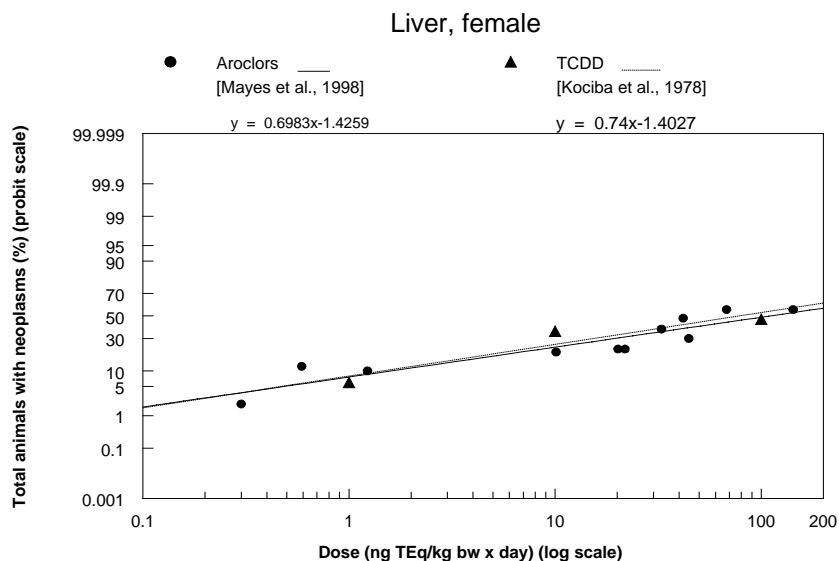
^aAccording to Table 1 in Mayes et al.¹⁴.

Fig. 1: Relationship between the total incidence of liver neoplasms in female rats and the dose of Aroclors (as TEQ)¹⁴ or TCDD²⁴, respectively, after log-probit transformation of the data. Straight lines and equations represent linear regression analyses.

For thyroid cancer which was detected in male rats after Aroclor treatment, it was evident that low TEQ doses calculated from Aroclor doses did not result in incidences significantly different from control animals. After log-probit transformation of the dosage levels and tumor incidence data, a linear correlation was obtained which seemed to exhibit a smaller slope than that for liver neoplasms in females (Fig. 2).

In summary, this analysis suggests that, in the experiments published by Mayes et al., the TEQ content of Aroclors was predominantly, if not exclusively, responsible for both the liver neoplasms observed in female rats and the thyroid neoplasms in male rats. This assumption is strongly supported by the fact that the correlation between the TCDD dose levels and incidences of hepatic neoplasms in female rats published by Kociba et al. were almost identical with those obtained for the TEQ portion of Aroclors.

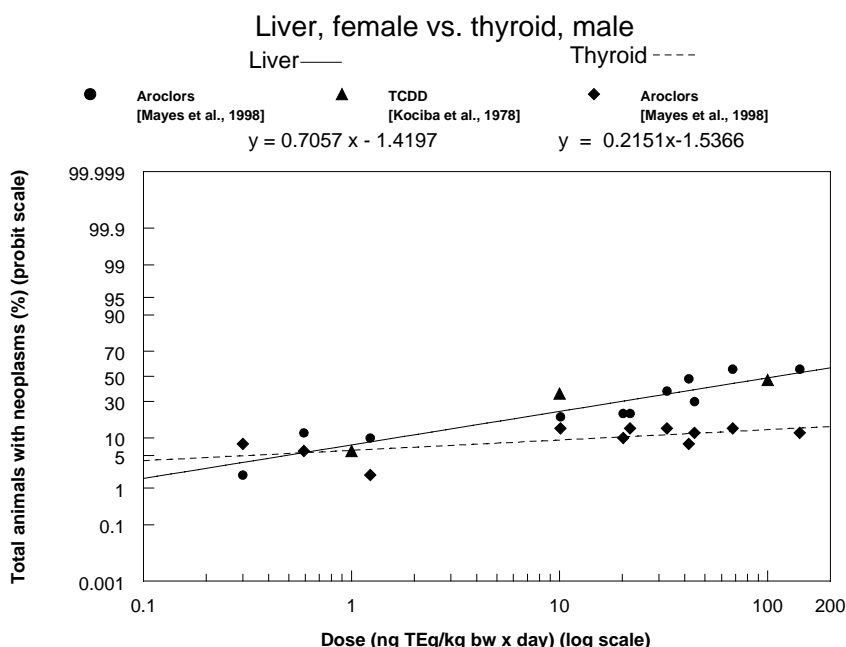


Fig. 2: Relationship between the total incidence of thyroid neoplasms in male, and of hepatic neoplasms in female rats, and the dose of Aroclors (as TEQ)¹⁴ after log-probit transformation of the data. The straight lines and equations represent linear regression analyses.

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