Tumor Responses, PCB Tissue Concentrations and PCB Hepatic Binding in S-D Rats Fed Aroclors 1016, 1242, 1254, or 1260.

J B Silkworth, B A Mayes, K M Fish, and J F Brown, Jr.. General Electric Corporate Research and Development, PO Box 8, Schenectady, NY, 12301

Abstract:

PCB congener specific analyses from a recent comparative toxicology and carcinogenicity study of four Aroclors in Sprague-Dawley (S-D) rats indicated that liver tumor risk was dependent on both sex and Aroclor composition. Evaluation of the PCB congener distribution in the target organ suggested that there were two mechanisms fundamental to rat liver carcinogenesis: one liver TEQ-dependent and predominant in the females of this strain, the other TEQ-independent, and predominant in the males. The relatively greater accumulation of TEQ-contributing PCB congeners in liver over body lipid raises the possibility of the induction of a binding protein that may modify the carcinogenic process.

Introduction:

In an effort to determine the relative carcinogenic potencies among the various PCB compositions, S-D rats were fed Aroclors 1016, 1242, 1254, or 1260 at concentrations ranging from 25-200 ppm for 2 years. These formerly commercial PCB compositions have sufficiently overlapping ranges of chemical composition to produce similar types of biological responses, but to extents that should be correlatable with the levels of particular subgroups of the PCB congeners. Accordingly, the accumulations of total PCB and individual PCB congeners were tracked during the dosing period using 118-peak analyses of adipose, brain and liver tissues. In addition, measurements of CYP 1A1 and CYP 2B1/2 protein induction and EROD, MROD, PROD, and BROD activities were made.

Results and Discussion:

No overt toxicological findings were evident for either males or females throughout the study. All Aroclors produced liver tumors in females resulting in potency rankings of Aroclor 1254 > 1260 ≈ 1242 > 1016[1,2]. A decrease in mammary tumor incidence was also observed in females. In males, a dose-independent increase in thyroid tumors was observed for Aroclors 1242, 1254, and 1260. Male liver tumor incidence was significant only for the highest Aroclor 1260 dose group and was correlated with time-averaged adipose (or liver) accumulation of total PCB but not with that of dioxin toxic equivalency (TEQ). Thus, the tumor incidence in males showed a roughly linear correlation with total lipid PCB accumulation. In females, however, liver tumor incidence was significantly increased in all groups except the Aroclor 1016 low dose group, and showed a marked positive departure

from that of the males for Aroclors 1242 and 1254, which departure clearly correlated with liver TEQ. These data suggest that two different processes may mediate hepato-tumorigenesis in this rat strain, one TEQ-dependent and one TEQ-independent. A mathematical expression (The Unisex Model) that relates tumor risk to rat sex, liver TEQ, and total lipid PCB was developed. This expression accurately (r^2=.935) predicted tumor risk in these highly dosed S-D rats[3].

During the mid-life period (6-18 mo.), the mean relative accumulations of total adipose PCBs in rats fed Aroclors 1016, 1242, 1254, and 1260, were 0.04, 0.05, 0.51, and 1.0, respectively, for both males and females. The female/male accumulation ratios of total adipose PCB in rats fed Aroclors 1016, 1242, 1254, and 1260, were 1.1, 2.0, 2.5, and 1.4, respectively. In some instances the lipid PCB concentrations reached 1%. The mean relative liver TEQs for Aroclors 1016, 1242, 1254, and 1260 were 0.0007, 0.21, 1.0, and 0.08 (based on WHO-1994 I-TEF values for PCB congeners), respectively.

The observation that a small subset of PCB congeners having reported TEQ activities accumulated preferentially in the liver and that this accumulation was correlated with tumor incidence suggests that there was a partitioning of these particular congeners in liver tissue and that they have a greater tumorigenic potency than the fraction that equilibrates with whole body lipid. To characterize this subset, the relative binding affinity (RBA) was determined for each PCB congener by calculating the difference between the ratio of its liver lipid-normalized concentration to its adipose lipid-normalized concentration and the same ratio for a chosen reference congener that clearly equilibrates throughout all lipid. PCB 28 was chosen for Aroclor 1016 and PCB 153 was chosen for the others.

Time averaged (6-18 mo) analytical results for the 100 ppm groups showed that PCB 126 (3,3'4,4',5) contributed 0.01, 1.4, 0.5, and 0.02% of the total hepatic PCB and 93, 98, 89, and 71% of the hepatic TEQ in Aroclors 1016, 1242, 1254, and 1260, respectively. Preliminary results indicated that the approximate RBA of PCB 126 in rats fed Aroclor 1242 or 1254 averaged 27 or 8, respectively. The RBA in females was slightly greater than that in males. Differences between Aroclors and sexes in the observed RBAs may be due to the presence of different sets of competing congeners within the Aroclors or to the abilities of these different congeners to induce the binding factor. The mono-ortho tetra-, penta- and hexachlorobiphenyl, most of which also have listed I-TEF values, showed significant, but much smaller hepatic binding, with RBA values averaging 0.4.

In general, the dose-saturated inductions of hepatic CYP 1A1 proteins (8-64 fold) and the EROD (8-64 fold) and MROD (2-32 fold) enzymatic activities at six months were least with Aroclor 1254 but generally about twice as great in the males as in the females. The inductions of CYP 2B1/2 protein and PROD and BROD activities were all low. With time (12 mo), CYP 1A1 protein and EROD and MROD activities decreased in all Aroclors, remaining most elevated in Aroclors 1242- and 1254- dosed animals, and thus correlated with hepatic TEQ, implying that the TEQ-binding factor may be CYP 1A2, as it is for dioxin[4]. Conversely, CYP2B1/2, PROD, and BROD rose to highest levels in the 1016- or 1260-dosed animals, predominating in the males, implying a role of these enzymes in the metabolic clearance of the PCBs. At 18 months, all levels and activities were slightly lower than at 12 months, but exhibited the same general dependencies on Aroclor type.

Whether the tumor risks associated with elevated hepatic TEQ resulted from free TEQ-type PCBs, free CYP 1A enzyme, or PCB-CYP complexes is still under investigation. Interestingly, the risk is minimized in the male, thus any explanation must include a sex-specific factor to complete our understanding of the carcinogenic mechanism in these rats.

References:

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