ASSESSING THE HUMAN HEALTH EFFECTS OF PCBs

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ABSTRACT

Toxic effects can be induced in experimental animals by high doses of pure PCBs, and in man by PCDF-contaminated PCB. In order to assess the effects of ordinary, uncontaminated PCB on man, a group of capacitor workers who had direct occupational exposure to Aroclors 1254, 1242, and 1016 during the period 1946 to 1977 has been under medical surveillance since 1976. This group presented some indications of non-AhR-mediated microsomal enzyme induction during the period of direct exposure, but no chloracne or increased cancer mortality. Multiple regression studies revealed no significant associations between lipid PCB levels and clinical indicators of hepatotoxicity, hypertension, or pulmonary impairment.

KEYWORDS

Polychlorinated biphenyls; PCBs; chloracne; health effects; cancer.

INTRODUCTION

Between 1930 and 1970, polychlorinated biphenyl (PCB) products, such as the Aroclors, Clophens, etc., were widely used in industry, with no evidence of adverse health effects except in rare situations where pyrolysis or contamination had occurred. By the 1970's, however, the PCBs were known to have become widespread in the human environment [1]. In industrialized countries, observed or estimated adipose tissue PCB levels ranged from a few (0.6-10.0) ppm in the population background up to hundreds of ppm in occupationally-exposed individuals. There was widespread popular feeling that such levels of a xenobiotic could not be entirely harmless. On the basis of toxicological responses seen in PCB-dosed laboratory animals, or in humans exposed to thermally-decomposed PCB, a variety of previously unobserved human health effects were postulated. These hypothesized effects of environmental PCB exposure provided the legal bases for extensive regulatory control programs and environmental remediation efforts.

In order to test the validity of these hypotheses, several studies of occupationally-exposed populations have been undertaken [2-6]. These include our continuing surveillance and study of a directly exposed GE capacitor worker population, which is now in its 15th year [5,6].

RESULTS

1. Chloracne. Chloracne, an acne-like skin disease characterized by follicular hyperkeratosis and other manifestations, has been known since 1899. It is an occasionally-observed human response to certain dioxin-like halogenated organic chemicals, all of which share the ability to bind to the cytosolic receptor (AhR) which activates the Ah gene locus [7]. In 1968, a chloracne outbreak associated with consumption of

rice bran oil ("yusho") occurred in southwestern Japan. The first contaminant of the oil to be identified was PCB from the overheated heat exchanger used in its manufacture. This led to the conclusion that PCB might be a powerful, though previously unrecognized, chloracnegen [8]. Subsequently, the major chloracnegen actually present was identified as a mixture of polychlorinated dibenzofurans (PCDFs) formed by the pyrolysis of the PCBs [9].

In the occupational health literature, all unequivocal observations of PCB-associated chloracne have involved exposures to pyrolysed or otherwise contaminated PCB. Our 194-person study population, which had received prolonged dermal exposure and had a geometric mean serum PCB level of about 431 ppb in 1976, presented no cases of chloracne at that time or subsequently [5].

Tracking the levels and distributions of individual PCB congeners in the sera of the study group over the 1976-1988 period showed that most of the lower (i.e., less highly chlorinated) PCB congeners are rapidly metabolized in man, probably by microsomal cytochromes of type P-450-IIB2, but that some of the higher congeners are more persistent, and can be used as near-permanent indicators of PCB exposure and response. Since individuals with PCDF-induced chloracne exhibit an altered PCB clearance pattern, which arises from AhR-mediated induction of cytochrome P-450-IA1, this altered pattern can be used as an indicator of a past chloracne episode [6]. None of the capacitor workers exhibited this evidence of P-450-IA1 induction, indicating no chloracne prior to the 1976 physical examination. Currently, it would appear that AhR-mediated enzymes and the associated toxic effects are considerably less easily induced in the human than in the rat.

2. Hepatotoxicity. Rats administered Aroclors 1242, 1260 or, especially, 1254, exhibit marked induction of hepatic microsomal enzymes of both the AhR-mediated and non-AhR-mediated types, but no immediate evidences of hepatotoxicity. After 6-8 months dietary dosage at 100-1,000 ppm levels those administered Aroclors 1254 or 1260 accumulated up to thousands of ppm in their adipose tissues and showed histopathological changes in their livers (e.g., cellular hypertrophy, cytoplasmic inclusions, pigmentation, adenofibrosis) similar to those produced by organochlorine pesticides [10]. Those administered Aroclors 1016 or 1242 accumulated up to about 200 ppm in their adipose tissues and showed only mild and reversible effects on their livers [11]. The Aroclor hepatotoxicities appeared to fall sharply in the sequence 1260 > 1254 > 1242 > 1016, which parallels the sequence for PCB persistence rather than that for AhR binding or activation. When the administration of Aroclor 1260 at the 100 ppm level was continued two years, female rats exhibited hepatic lesions described as neoplastic nodules and hepatocellular carcinoma [12].

Our capacitor worker study group, in which lipid PCB accumulations initially ranged above those in the 1016- or 1242-treated rats, exhibited indications of slight non-AhR-mediated microsomal enzyme induction (e.g., decreased levels of serum bilirubin; decreased antipyrene clearance time) when examined during the period of direct PCB exposure, but these effects were not seen in subsequent examinations [5]. At all times they, like other similar study populations [2,3], exhibited statistical associations between serum PCB levels and serum levels of certain liver-derived enzymes (SGPT GGTP, and alkaline phosphatase) and liver-regulated serum lipids (triglycerides and cholesterol). These associations were once thought to indicate that the PCBs were affecting liver function. Further examination showed, however, that the PCB levels in the serum may themselves be determined by the serum lipid levels, which are also covariant with those of the liver-derived serum enzymes cited. When the PCB levels were expressed as concentrations in serum (or adipose) neutral lipids to avoid this confounding effect, the 1976-1979 statistical associations of PCBs with serum lipids, SGPT and alkaline phosphatase disappeared [3,5], and the association with GGTP was gone by 1983.

3. Hypertension. There is one report showing statistical association between serum PCB levels and blood pressure in a black American group that had consumed fish contaminated with DDT and PCB [13]. This result is also believed to reflect the covariance of serum PCBs with serum lipids and confounding by obesity. No association between serum lipid PCB and blood pressure was seen in our or other occupationally-exposed study groups.

4. Pulmonary Effects. There is one report suggesting reduced vital capacity in 1976 in a PCB-exposed capacitor worker study population that partially overlapped ours [14]. We did not observe this effect in our group, but did note procedural errors in the earlier spirometric measurements [15]. In 1979, we found no correlations of spirometric variables with serum PCB levels or past PCB exposure, although 15% of the population had findings suggesting obstructive impairment.

5. Carcinogenesis. As noted earlier, the more heavily chlorinated PCBs (e.g., Aroclor 1260 and Clophen A60), like dioxin and a number of chlorinated pesticides, when administered to female rats at levels close to or slightly above the maximum tolerated dose (MTD), can increase the incidence of lesions described as hepatocellular carcinoma. Concomitantly, the incidence of other types of tumors in the Clophen A60-dosed animals was significantly decreased, and the animals' lifespan increased [16]. Clophen A30, a lower PCB, was found to be negative in the same bioassay [16]. All of the tumorigenic agents of this group, which are of diverse structural types, appear to be non-genotoxic, but capable of promoting rat liver tumors initiated by other agents by some undefined mechanism. Currently unresolved questions include whether the observed lesions represent true cancer, whether the MTD was exceeded, whether the lower PCBs also present cancer risk in rats, and whether the observed tumor-suppression or the tumor-promotion effect is more important in the human.

Thus far, epidemiological studies of a 2,567-person capacitor worker group (which includes our study population and others with PCB exposures extending back into the 1930's) have shown no type of cancer incidence that could be causally related to PCB exposure, and overall cancer mortality somewhat below that expected [4].

6. Impaired Neurological Development. Quite recently, there have been reports of personality and behavioral effects in children who had *in utero* exposure to PCDF/PCB-contaminated rice bran oil [18], and also in those whose mothers consumed Lake Michigan fish, which are contaminated with PCBs, chlordane, DDT metabolites, other pesticides and heavy metals [19], implying impairment of neurological development by one of these agents at some critical stage of fetal development, and hence need for further study.

A population of children born to PCB-exposed capacitor workers has been identified and shown to have had slightly reduced gestational age [17]. However, the appropriate approach to retrospective assessment of possible PCB effects on their personality development is still uncertain.

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