# PCB Metabolism, Persistence, and Health Effects After Occupational Exposure: Implications for Risk Assessment

Brown, J.F. Jr., Lawton, R.W.
GE Corporate Research and Development, Schenectady, NY 12301-0008

**Introduction**. Formerly, direct human exposure to undiluted PCBs occurred in many PCB-using operations, resulting in serum PCB levels 10-100 times those arising from fish consumption or environmental exposure in the general population. During the 1970s and 1980s about 20 different clinical or epidemiological studies of the dozen-odd more easily identified PCB-exposed worker populations, including our own longitudinal clinical study of GE capacitor workers[1] were undertaken. These studies have resulted in the publication of several dozen reports in the scientific literature, and several critical reviews. Among the more recent studies and reviews[2-4] there has been a growing consensus that such PCB-exposed workers have exhibited no consistent clinical evidence of adverse effects on the liver, lungs, skin, nervous system, blood/immune system, cardiovascular system, G.I. or urinary tracts, or endocrine systems examined, nor any epidemiological evidence of increased mortality due to cardiovascular disease, pulmonary disease, or cancer.

The extraordinary contrast between the absence of clinically- or epidemiologically-demonstrable health effects in heavily-exposed worker groups and the numerous reports of toxicological and carcinogenic effects in laboratory animals has been repeatedly noted; however, there has remained uncertainty as to whether this arises from interspecies differences in susceptibility to PCBs or to differences in dosage or accumulation. Also unresolved has been the question of why statistical correlations between health abnormalities and PCB levels may exist even in population groups carrying PCBs at only background levels. To address such questions, we have been examining PCB metabolism and pharmacokinetics in the human, and comparing our findings with data reported for animals.

**PCB Metabolism**. The congener distribution in any partially metabolized PCB residue provides a highly characteristic indicator of the PCB-metabolizing system(s) present in the host organism or culture.[5, 6] The PCB residues in the

occupationally exposed workers thus far examined (>200) show only the congener distribution pattern that is produced by cytochrome P4502B (i.e., phenobarbital-induced) isozymes.[6,7] This is the pattern also exhibited by the chromatograms of PCB-dosed sheep and mice, as well as those of many wild birds, a few fish species, and some crustaceans.[5]

Conversely, the pattern seen in the yusho and yucheng chloracne patients, who were poisoned by PCDF + PCB mixtures, indicates PCB-metabolizing activities like those of cytochrome P4501A (i.e., dioxin-induced) as well as P4502B isozymes.[6] This is the pattern also seen in most PCB-dosed rats and probably monkeys, as well as in many species of wild birds and fish.[5] The rats and monkeys in which P4501A-like activities appeared carried tissue PCB concentrations that were the same or lower than those of PCB-exposed workers, showing that the absence of a dioxin-like response to PCB in the human arises from a physiological difference in the species, not one of lower dose.

**PCB Kinetics**. Following the 1977 cessation of PCB use in capacitor manufacturing, serum PCB levels in our study group dropped rapidly.[3] We now find that this decay in PCB levels occurred at rates that could be correlated with various physiological characteristics of the individuals involved, including age, sex, body fat, and serum iron, and that it followed approximately second order kinetics, indicating that the levels of the PCB-metabolizing P4502B-like isozymes must have diminished roughly proportionally with those of the PCBs. Earlier, PCB-mediated increases in P4502B-like isozymes over background levels in capacitor workers was suggested by antipyrine clearance times.[8] PCBs have also been observed to increase P4502B activities in rats, mice, and winter flounder, although apparently not in the rhesus monkey. Thus, the human would appear to be at least qualitatively similar to the rodents in its P4502B-induction response to PCBs.

In rodents, however, P4502B-inducing agents, such as the more heavily chlorinated PCBs, DDT, other chlorinated pesticides, and the barbiturate and hydantoin drugs, all appear to be either hepatotumorigenic or liver tumor promoters at high doses, whereas none of these agents have been found to be human carcinogens. Thus, there would also appear to be an interspecies difference between rat and man in the sequellae of hepatic P4502B induction.

**PCB Levels in Chronically Exposed Individuals**. Most PCB congeners are so rapidly metabolized by human P4502B as to be undetectable in the serum. A few are scarcely metabolized at all, and hence can serve as permanent records of PCB exposure events.[7] In between are the dozen or so congeners that account for most of a measured human PCB level, and which have half-lives in the 1-15 year range.[6] In adults who have been exposed for several years to a single PCB source, whether environmental or occupational, body PCB levels of those dominant

congeners will have approached a steady state level, where uptake is approximately balanced by metabolism. The kinetic behavior of PCBs in the human body indicates that in such individuals the serum PCB level will be approximately proportional to PCB intake rate and the level of serum neutral lipids, and inversely proportional to total body fat and P4502B activity.

Early failures to recognize such relationships in occupationally exposed workers led to several reports that elevated serum PCBs caused elevated serum lipids and the associated serum enzymes. The observed statistical associations disappeared, however, when the serum PCB levels were corrected for variations in serum lipids.[1,4] More recently, much weaker statistical associations with fetal neurodevelopmental deficiencies have been reported for PCB levels in background-exposed mothers; however, no corrections of the PCB levels for variations in serum lipids, body fat, or P4502B activity have yet been carried out, so the hypothesis that the developing fetus may represent an organ system that is orders of magnitude more sensitive to PCBs than any other in the human body (which is clearly not the case for the dioxin-like PCDFs) remains unproven.

**Relative Risks of Different PCB Compositions**. Currently, the assessed risks of all PCB compositions are regarded as equal, a presumption widely regarded as scientifically implausible, albeit administratively convenient.

One frequently discussed alternative has been to scale presumptions as to health risk on the basis of dioxin equivalency, a measure that may indeed be a plausible indicator of relative risk to some species of wildlife. As a measure of cancer risk to humans, however, it suffers the drawbacks (a) that PCBs do not seem to have appreciable dioxin-like activity in humans, as we have just noted, and (b) even in rats, where PCB compositions do have dioxin-like activity, that activity does not correlate with tumorigenic response.

An alternative suggested by the recent availability of metabolic rate data for the PCB congeners that are commonly detected in humans[6,7] would be to use the persistence, or accumulability, of the PCB composition as a measure of relative risk. This parameter, which is readily calculated from the rate data, does seem to track reported tumorigenicity in rats and immunotoxicity in mice, and probably also increased P4502B-like metabolic activity, which is currently the only demonstrable human response to elevated PCB loadings.

**Conclusions**. The metabolic and pharmacokinetic behavior of PCBs in capacitor workers supports earlier conclusions[2] that humans differ from rats and monkeys in their response to PCBs, just as various animal species differ from each other.[2,5] At present, the only unequivocally demonstrable pharmacological response of humans to PCBs at levels produced by direct occupational exposure, which are 10-100 times greater than those produced by fish consumption, has been increased induction of metabolic enzymes having activity profiles like that

of cytochrome P4502B. There is no evidence that this P4502B increase would occur at lower levels of exposure, nor is there any clinical or epidemiological data to indicate that this or any other pharmacological response has had deleterious effects on the health of the occupationally exposed individuals.
However, if concerns remain that there may still be real, though unmeasurable, health risks associated with any agent having a pharmacological activity in the human, then it would seem appropriate to regulate different PCB compositions according to their ability to accumulate to levels that would produce such a response. Institution of such an approach (e.g., regulation of fish on their content of "Aroclor 1260 equivalents" rather than that of "total PCBs") would not require any new analytical procedures, but merely the incorporation of available kinetic data into the mathematical programs used for computing a reportable analytical result.

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