Unusual Congener Selection Patterns for PCB Metabolism and Distribution in the Rhesus Monkey

Brown, J. F., Jr.

General Electric Corporate R&D, P.O. Box 8, Schenectady, NY 12301-0008, USA

Introduction. It has long been known that the PCB residues in chloracne patients who had ingested either Japanese rice oil (yusho) or Taiwanese rice oil (yucheng) that was contaminated with mixtures of polychlorinated biphenyls (PCBs), polychlorinated quaterphenyls (PCQs) and polychlorinated dibenzofurans (PCDFs) exhibit an unusual gas chromatographic (GC) pattern ("Pattern A") that is quite different from that exhibited by normal (i.e., non-chloracnegenic) persons,[1-2] including workers with occupational exposure to PCBs alone.[3] The chloracne-associated "Pattern A" arises from the accelerated metabolism of mono-*ortho* tetra-, penta-, and some hexachlorobiphenyl congeners. This is mediated by the PCDF-induced P450 cytochromes of group 1A, whereas PCB metabolism in the normal human (and many other higher animals as well) is mediated instead by agents with P4502B-like congener selection patterns.[3]

Rhesus monkeys that were dosed with either Aroclor 1248,[4] Aroclor 1016 with inadvertent additions of 1248,[5] or Aroclor 1254 at 280 μg/kg/day,[6] or at 5, 20, 40, or 80 μg/kg/day[7] (5 days per week) have been reported to show a variety of the symptoms previously reported for the PCDF-poisoned Japanese and Taiwanese chloracne patients, including characteristic alterations and losses of fingernails, increased meibomian gland secretion, follicular hyperpigmentation, dermal keratosis or chloracne, alterations in indicators of immune function, reproductive failure, and neurodevelopmental impairment.[4,5,8] However, the reported packed column GCs[5-7] all differed sharply from "Pattern A" in showing increased, rather than decreased, relative heights of peaks associated with mono-*ortho* PCB congeners.

In order to confirm the identities of the PCB congeners giving the packed column GC peaks, and to better define the metabolic alteration patterns exhibited by the monkey, we obtained from Dr. D. L. Arnold of Health Canada (Ottawa, Canada K1A OL2) archived analytical extracts and tissue specimens from monkeys that had been given Aroclor 1254 at the 40 μg/kg/day level[7] for 316 weeks and then allowed to recover for up to 189 weeks before sacrifice. These were submitted for

high resolution DB-1 capillary GC analysis by Northeast Analytical, Inc. (Schenectady, New York). The GC data were then analyzed to identify coherent patterns of changes in relative peak heights.

Metabolic Changes Observed in Adipose Tissue PCBs. The most commonly seen adipose tissue pattern, shown in an advanced stage in Figure 1 (top), featured a remarkable depletion in all di-and tri-*ortho*-substituted penta- and hexachlorobiphenyls, including the normally highly persistent congeners 138 (234-245 CB) and 153 (245-245 CB), all relative to the mono-*ortho's* 118 (245-34 CB), 105 (234-34 CB), 156 (2345-34 CB), etc. Congeners such as 146 (235-245 CB), and 187 (2356-245 CB), which are more persistent than 153 in the rat or human, were less so in the monkey; whereas PCB 110 (236-34 CB), which is very rapidly cleared by the P4502B-like metabolic activity present in most animals, tended to linger, and was easily seen (as Peak No. 6), even in the published packed column GCs.[6-7] Accordingly, we concluded that most PCB metabolism in the rhesus monkey was being mediated by some type of CYP450 other than 1A or 2B, and have provisionally designated this agent as "P450RH." It is known that the main CYP450 subtypes induced in the closely related cynomolgus monkey are 2C, 2E, and 3A;[9] however, it is not known which of these would exhibit a P450RH-like congener selection pattern for PCB metabolism.

Figure 1 (bottom) shows a pattern less commonly exhibited by monkey adipose tissue but somewhat more reminiscent of that seen in human chloracne patients or Aroclor 1254-dosed rats in showing reduced ratios of mono-*ortho* to di-*ortho* pentachlorobiphenyls, thus implying a significant contribution of P4501A-like activity to the PCB metabolism. Other evidence for P4501A induction in these monkeys will be reported elsewhere. In the cynomolgus monkey, induction of P4501A-like activity by dosing with either Aroclors 1248 or 1254 has been reported.[10] It would thus appear that in both macaques, as in the human and many other animals, induction of dioxin-like toxic responses is accompanied by that of P4501A cytochromes. However, it would appear that in the rhesus the induction of 1A is relatively modest and its effects on residual PCB congener distribution are easily obscured by those of P450RH.

PCB Accumulation in Rhesus Liver. In rats that were chronically dosed with Aroclors 1242 or 1254 there was a rather modest tendency for mono-*ortho* penta- and hexachlorobiphenyls to concentrate in the liver, and a strong tendency for their non-*ortho* substituted analogs to do likewise, both presumably as a result of binding to CYP4501A2.[11] However, the overall levels of PCBs in the rats' livers were little different than would be expected on the basis of their lipid content. By contrast, by the end of the recovery period, the monkeys' livers contained 36-106% as much total PCB as the adipose tissue on a wet weight basis, or

6-14 times as much on a lipid basis, indicating very extensive binding to non-lipoidal liver components. The retained PCB showed a distribution pattern (Figure 1, middle) markedly enriched in the di-*ortho* penta's and hexa's relative to their proportions in the adipose tissues of the same animal (Figure 1, top). Since the congener retention pattern resembled that for relative metabolizeability, it is possible that the rhesus liver constituent responsible for PCB binding was either P450RH itself, or some close relative. Still obscure, however, is the relationship of the unusual PCB metabolic and distribution patterns exhibited by the rhesus monkey to their unusual sensitivity to Aroclors 1248 and 1254.

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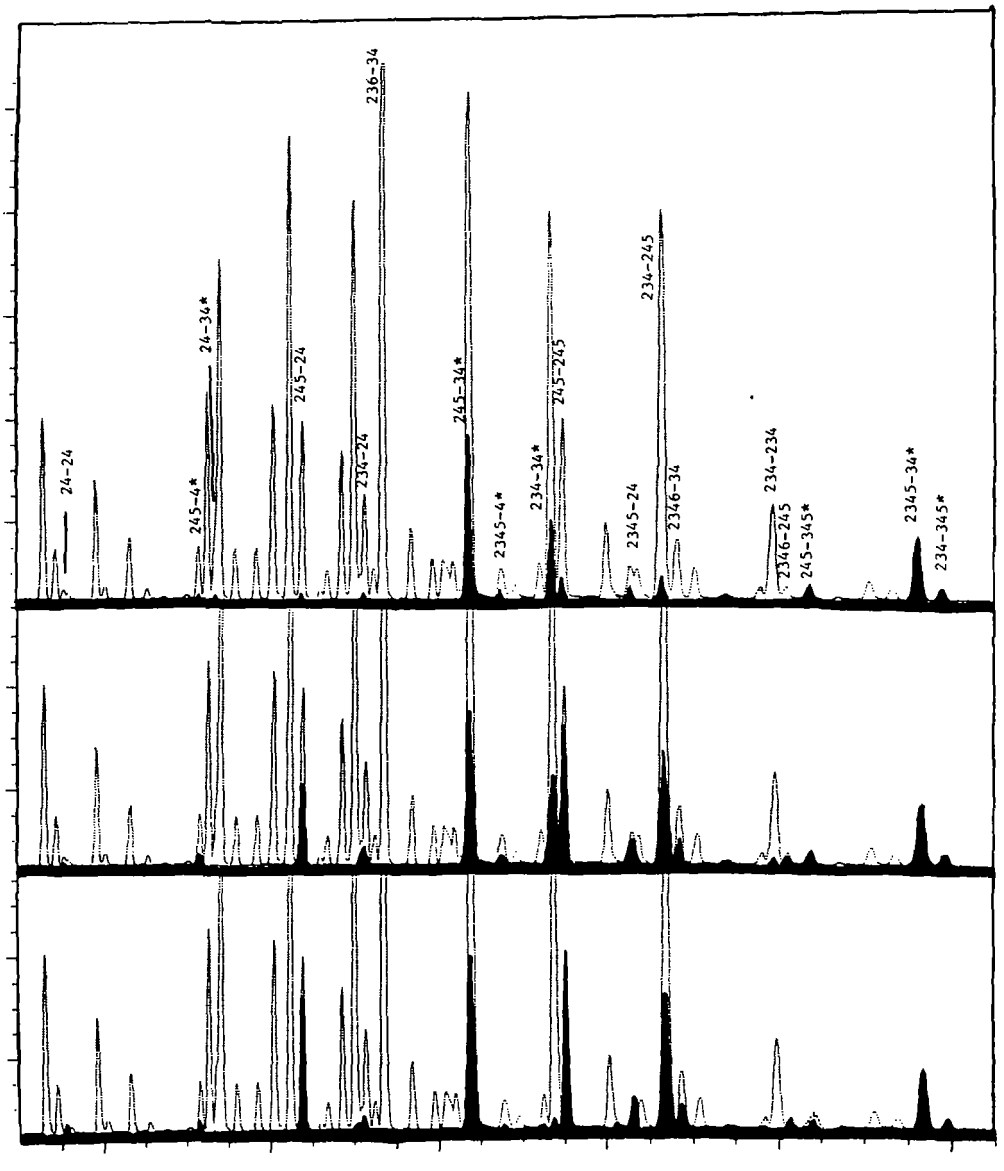

Figure 1. DB-1 gas chromatograms showing Aroclor 1254 (dotted lines) and PCB residues in rhesus monkeys (solid peaks) normalized to peak for 2345-34 CB (PCB 156). Top: PCBs in scapular adipose tissue from monkey FD015 after 316 wk dosing with Aroclor 1254 at 40 μg/kg/da and 189 wk recovery. Middle: PCBs in liver of same monkey, same time. Bottom: PCBs in scapular adipose tissue from monkey FD079, same dose but after 136 wk recovery. Mono-*ortho*-substituted congeners denoted by asterisks (*).