PCB ACCUMULABILITY VERSUS TOXIC EQUIVALENCY AS QUANTITATIVE INDICATORS OF RELATIVE RISK

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Despite long concern over the tendency of some PCB compositions to accumulate in wildlife and man, little attention has been given to the problem of determining the chronic accumulation tendency, or accumulability, of such compositions nor to relating such accumulabilities to chronic toxicity.

The calculation of PCB accumulability from kinetic parameters describing the various metabolic and non-metabolic processes responsible for PCB clearance is simple in principle, but complicated in practice, because of the large number of individual PCB congener rate constants that must be determined from available chromatographic or kinetic data, and then brought into the calculation. Such calculations recognize that these kinetic parameters must be related to total accumulation by mass balance relationships such as eq (1) and (2), and integral forms such as eq (3) or its simplified versions:

$$(1) \qquad \frac{dA_s}{dt} = \sum^{i} c_i k_d - \sum^{j} A_i k_i \qquad \text{where}$$

$$(2) \qquad k_i = \sum^{j} (s_j k_{ij} + k_{in}) \qquad \text{whence}$$

$$(3) \qquad A_s(t) = \sum^{i} \frac{k_d c_i}{k_i}[1-\exp(-k_i t)] + \sum^{i} A_i(0)\exp(-k_i t).$$

In these equations $A_s(t)$ indicates the total PCB accumulation in the subject species at time t, A_i the accumulation of the i-th congener, c_i the fractional content of congener i in the PCB dose, k_d the total PCB dose rate, k_i the total clearance rate of congener i, k_{ij} the specific rate constant describing the contribution to k_i from metabolic process j, k_{in} the contribution from non-metabolic processes, and s_j the activity of the metabolic system j in the subject species relative to that in the standard system used for defining the k_{ij} terms. Familiar simplified forms of eq (3) arise where $k_d = 0$ (clearance only), $A_s(0) = 0$ (dosage-related accumulation only) or where $t \rightarrow \infty$ (steady state assumption; $\exp(-k_i t) = 0$).

With the PCBs, unlike most xenobiotics, it is possible to identify the metabolic systems contributing to clearance from the pattern of PCB congener depletion, as indicated by the gas chromatogram. Previous studies of such patterns in the human[1,2] and in various fish species,[3] as well as an ongoing review of published GC patterns for various species of wildlife and laboratory animals indicate that almost all PCB metabolism in higher animals consists of microsomal oxidation mediated by cytochrome P450 isozymes having P450IA-like and/or

P450IIB-like congener selectivity patterns. P450IA-like metabolism has been observed in some small cetaceans and in many species of teleost fish; P450IIB-like metabolism predominates in crustaceans, a few species of teleost fish, and many species of birds and mammals, including the sheep, mouse, very lightly dosed rats, and man; metabolism by both P450IA- and IIB-like isozymes is observed in many species of birds and mammals, including the dog, most PCB-dosed rats and monkeys, and PCDF-poisoned human chloracne patients. It would appear that PCB administration may induce cytochrome P450IA in the pig, rat, and monkey; but not in the mouse, rabbit, or human.[1,2,4]

Knowing which family, j, of metabolic enzymes was operative in any given system allowed us to determine either absolute or relative metabolic rate constants (k_{ij} values) from available kinetic or chromatographic data for whatever range of k_{ij} values was covered by that data set. Overlapping such k_{ij} data sets from different systems then permitted us to establish s_j values and cover the entire range (*ca.* 10^5) of k_{ij}'s for various PCB congeners. In so doing, we drew particularly upon data covering PCB congener clearance rates by purified P450 isozymes[5] or selectively induced rat liver microsomes[6] or fish[3] to define whole body metabolic clearance rates (s_jk_{ij} values) for the most rapidly cleared congeners, and clinically observed rates of clearance in PCB-exposed human populations[1,2,7] to define those for the more persistent congeners. As a result, we were able to determine or estimate s_jk_{ij} values for the PCB congeners responsible for all of the 100 to 140 resolved peaks now being reported out as results of DB-1 or DB-5 capillary GC or GC-MS analyses.

Normal human non-metabolic clearance of lipophiles via fecal excretion was estimated from polybrominated biphenyl data[8] as about 0.008 yr^{-1}; the non-metabolic clearance rate in chloracne patients was estimated from those of the most difficultly metabolizeable congeners[9] as 0.15 yr^{-1}, or 20-fold faster. Addition of these k_n values, presumed to be the same for all congeners, to the s_jk_{ij} values for the individual congeners gave the k_i values (eq 2) needed to set up a simple spreadsheet program for computing chronic accumulation values, $A_s(t)$, for any PCB composition via eq (3), given only the analytical data for the c_i's.

As an indicator of the chronic accumulability of such compositions we propose the relative human accumulation over a 70 year lifetime, or RHA(70) value, where RHA(70) is defined as the ratio of the $A_h(70)$ calculated for the PCB composition to that similarly calculated for Aroclor 1260. RHA(70) values for the formerly commercial Aroclors, which span the accumulability range observed in environmental specimens, are given in Table 1.

TABLE 1. Relative Human Lifetime Accumulability, RHA(70), for Aroclors

Aroclor No.	% 1957-77 USA Prod'n	RHA(70)	
		Normal Human	Chloracne Pt.
1221	0.96	0.0074	0.0064
1016	12.88	0.0263	0.0219
1232	0.24	0.0280	0.0303
1242	51.76	0.0485	0.0543
1248	6.76	0.1023	0.1346
1254	15.73	0.3096	0.4363
1260	10.61	1.0000[a]	1.0000[b]
1262	0.83	1.263	1.131
1268	0.33	2.323	1.698
mean	100.00	0.2085	0.2299

a. Calc $A_h(70)$ for ref 1 pop'n, 24.47% of cumulative dose
b. Calc $A_h(70)$ for ref 7 pop'n, 5.17% of cumulative dose

In order to relate PCB accumulability to chronic toxicity, we drew upon a recent study[10] that rescored, according to modern criteria, the hepatohistopathological findings of five earlier chronic (two-year) PCB bioassay studies in rats. These studies had employed four different PCB compositions: Clophen A30 (intermediate in composition between Aroclors 1016 and 1242), Aroclor 1254, Aroclor 1260, and Clophen A60 (essentially identical to Aroclor 1260). Various calculations of dioxin equivalency[11] indicated the relative TEQ values for A30, 1254, and 1260/A60 to be about 3:8:1. The new scorings[10] indicated somewhat reduced, but still sizeable tumorigenic and carcinogenic activities for Aroclor 1260 or Clophen A60 in three different strains of rats; possible slight, though statistically insignificant, activities for Aroclor 1254 in one strain; and a little tumorigenicity but no carcinogenicity for Clophen A30. These findings were unequivocally inconsistent with the hypotheses (a) that all PCB compositions have equal carcinogenic potency, or (b) that either the tumorigenic or carcinogenic potency of PCB compositions is proportional to dioxin toxic equivalency (TEQ). The alternative hypotheses that are consistent with the observations include (c) that tumor incidence may be directly proportional to total PCB accumulation and (d) that carcinogenicity may require exceeding some threshold level of PCB accumulation. In order to distinguish rigorously among the allowed interpretations it would be necessary to test a greater range of PCB compositions and dosages in the same strain of rat.

A possible mechanistic basis for the observed correlation between PCB accumulability and tumorigenicity may be that the tumorigenic effects of PCBs are linked to induction of cytochrome P450IIB rather than IA. The more persistent PCB congeners are all roughly equipotent as agents for P450IIB induction, which has been correlated with liver tumor promotion in rats.[12]

Whether or not this explanation be valid, hypothesis (c), which is the more conservative of the allowed interpretations of the tumorigenicity data, suggests that it would be possible to use the now readily calculated RHA(70) value for an environmental PCB composition as a quantitative measure of its Aroclor 1260 equivalency, i.e., the maximum human cancer risk (if any) posed by that composition relative to that presumed to be posed by the same concentration of Aroclor 1260.. Since most of the PCB compositions released into the environment were substantially less accumulable than Aroclor 1260 (Table 1), application of this procedure would reduce the numbers of environmental sites and fish populations currently being calculated as posing significant cancer risk.

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