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## Polychlorinated Biphenyl (PCB) Partitioning Between Adipose Tissue and Serum

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It has been recently suggested that variabilities in the partitioning of chronically retained lipophilic xenobiotics between adipose tissue and serum may be related to variations in the lipid content of the serum (Eyster et al. 1983). Here, we present theoretical considerations and experimental data showing that this is indeed the case for polychlorinated biphenyls (PCBs) in humans

At equilibrium, in the absence of active transport, any lipophilic substance, X, must distribute itself among body tissues in such a way that its chemical activity,  $a_X$ , and also its chemical potential,  $\mu_X$ , are the same at all points. If we take the standard state as a solution of unit concentration in neutral lipid microphases, L, (e.g., fat droplets) and the standard potential as zero, we may write:

$$(1) \quad a_X = \exp(\mu_X/RT) = [X]_L$$

Then, for any fluid or tissue, T, in the body, containing neutral lipid content [L] and various types of assumedly non-saturated protein binding sites, P, each capable of binding X with affinity constant K, the total content of a water-insoluble X must be:

$$(2) \quad [X]_T = a_X[L]_T + \sum_i a_X K_i [P_i]_T$$

Therefore, when T be taken as adipose tissue, A, or serum, S, the partitioning constant,  $K_{AS}$ , should be of the form:

$$(3) \quad K_{AS} = \frac{[X]_A}{[X]_S} = \frac{[L]_A + \sum_i K_i [P_i]_A}{[L]_S + \sum_i K_i [P_i]_S}$$

where  $[L]_S$  denotes the effective X-carrying lipid microphase within the serum. In the event that binding to both adipose tissue and serum proteins be negligible, the terms involving  $K_i [P_i]$ 's in eq. (3) would drop out, and it would then take the very simple form:

$$(4) \quad K_{AS} = \frac{[X]_A}{[X]_S} = \frac{[L]_A}{[L]_S}$$

For bulky lipophilic molecules such as PCBs the effective X-carrying serum lipid microphase should consist of the disorganized interiors of the lipid-protein complexes known as the serum lipoproteins. This interior microphase is generally regarded as composed of the serum triglycerides, most or all of the cholesterol esters, some of the free cholesterol, and conceivably a little of the associated phospholipid (Smith et al. 1978). Thus, its magnitude  $[L]_S$ , should be equal to the serum content of triglycerides plus approximately 1.0 times that of cholesterol esters plus free cholesterol. The latter sum may be estimated from normal values (Henry 1968) as 1.50 times the clinically reported "cholesterol" equivalent weight. Thus,  $[L]_S$  should be described by the expression:

$$(5) \quad [L]_S = [\text{triglycerides}]_S + m [\text{"cholesterol"}]_S$$

where the precise value of  $m$  must be determined empirically from experimental data, but with the expectation that it should be approximately 1.5. In such a case, the effective X-carrying serum lipid microphase would become identical to the measurable value of the total serum neutral lipids, i.e., the sum of the serum triglycerides, free cholesterol, and cholesterol esters.

Applicability of eq. (4) and (5) to the adipose tissue/serum partitioning of PCBs is suggested by the findings that the predominant PCB carriers in human plasma are in the lipoprotein fraction (Matthews et al. 1977); and that PCB in rat serum is 94% carried on the low and high density lipoproteins, and only 5% on the albumin (Pepe 1982), in contrast to the findings for DDT and dieldrin, where nearly half is transported on the albumin (Skalsky, Guthrie 1978).

In order to verify the theoretical relationships and evaluate  $m$ , three sorts of data relating to serum PCB levels in a human population were examined.

#### MATERIALS AND METHODS

The population studied consisted of 173 capacitor workers who had had direct occupational exposure to Aroclors 1254, 1242, and 1016 for various periods of time up to June 1977. Fasting blood samples were drawn in November, 1979. Determinations of serum albumin, serum triglycerides, and serum "cholesterol" were performed as part of an SMA-26 analysis by Medpath, Inc., Teterboro, NJ. Analyses for serum Aroclors 1242, 1254, and 1260 were performed by Hazelton Raltech, Madison, WI. Statistical analyses were performed on a Honeywell 600/6000 computer using a statistical package, STATPAC, which incorporates programs for multiple step-wise regression (Nelson et al. 1977). Distributional assumptions were validated using the W-test (Hahn, Shapiro 1967).

## RESULTS AND DISCUSSION

In the population examined, the three reported measures of serum PCB level were lognormally distributed. Multiple stepwise regressions of  $\log[\text{Aroclor}]$  as the dependent variable against the various demographic and biochemical parameters showed significant associations (incremental  $F > 3.0$ ) only with  $\log[L]_S$  (calculated from eq. 5, taking  $m$  as 1.50) and age (which covaried with service time). For the specific model  $\log[\text{PCB}]_S = a + b \log[L]_S + c \log[\text{Albumin}]_S$  the incremental  $F$ 's and coefficients, indicating the dependencies on lipid and albumin were:

PCB Measure	5% - 95% Range (ppb)	N	Dep. on Lipid		Dep. on Alb'n	
			Incr. F*	b	Incr. F*	c
Aroclor 1242	12-392	173	29.2	1.48	0.04	0.19
Aroclor 1254	4-103	173	45.6	1.69	0.21	-0.38
Aroclor 1260	4-129	144	36.0	1.60	0.04	-0.20

\*  $F(2,173), 0.95 = 3.00$

When the  $m$ 's used in calculating the  $[L]_S$ 's in this model were varied, maxima in the Aroclor  $F$ 's were seen for  $m$ 's of 1.0, 1.5, and 2.2, and variations in the  $b$ 's over the range of 0.7-1.8. However, the maxima were too weak to permit significant determinations of either  $b$  or  $m$  values from the regressions.

The median adipose tissue fat/plasma distribution coefficients for 35 individual PCB isomers in a group of 26 workers drawn from the same plant population have already been reported (Wolff et al. 1982). From the weighted values for the persistent isomer peaks used by our analyst in calculating his reported Aroclor levels, we calculated the corresponding coefficients, i.e.,  $K_{AS}/[L]_A$  values, to be for Aroclor 1242, 210; for Aroclor 1254, 190; for Aroclor 1260, 200; weighted mean, 200. The latter indicates, according to eq. (4), a mean effective  $[L]_S$  of 500 mg./100g. For our population, the mean [triglyceride] $_S$  and ["cholesterol"] $_S$  values at the time of Wolff's sampling were 136 and 251 mg./100 ml., respectively, indicating from eq. (5) an effective  $m$  value of 1.45.

One individual in our population, who exhibited familial hyperlipidemia, went on a fat-free diet and exercise program. After 16 days, his weight dropped 4.5 kg. (5%), implying a fat loss of 2.7 kg., (9%); his serum triglycerides fell from 675 to 218 mg/100 ml. (68%); and his serum "cholesterol" went from 236 to 240 mg./100 ml. Presuming a constant PCB body burden (located almost entirely in adipose tissue fat) and an  $m$  of 1.45, eq. (4) and (5) predict serum PCB declines of 39%. The observed declines were for Aroclor 1242, from 1195 (+ 225) to 774 ppb (35%); for Aroclor 1254, from 57 (+ 1) to 33 ppb (42%); and for Aroclor 1260, from 30 (+ 3) to 19 ppb (37%).

The results show that in the human, the serum levels of PCBs are significantly dependent upon the level of lipids in the serum, but not that of albumin; that the apparent contribution of cholesterol and its esters to PCB transport (i.e., the  $m$  value) is nearly equal to their contribution to the total serum neutral lipids present; and that variations in the serum PCB levels can be accounted for within experimental uncertainty by eq. (4) and (5).

The demonstration of a simple relationship (eq. 4) for the partitioning of PCBs within the equilibrated human, along with an  $m$  value in eq. (5) like that for total serum neutral lipids, means that the level of serum lipid PCBs (as determined by dividing the serum PCB level by that of the total serum neutral lipids) must be equal to the adipose fat PCB level (as determined by dividing the adipose tissue PCB level by the neutral fat content of the tissues). Thus, if an estimate of the total body fat content be available, the total body burden of PCBs can be determined from measurements of serum PCBs and serum lipids alone.

These lipid PCB levels should also be the preferred measure of PCBs for use in studies of correlations with pharmacological effects, since, according to eq. (1), they provide a direct measure of the chemical, or thermodynamic activity  $a_{PCB}$ . For lipophilic xenobiotic agents, it has long been recognized (Ferguson, 1939) that this is the measure of xenobiotic level to which pharmacological response is proportional.

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