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Comparative Study on Accumulation and Elimination of Hexachlorobiphenyls and Decachlorobiphenyl in Mice

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In a previous paper we reported on the mode of accumulation and elimination of tetrachlorobiphenyl isomers in mice (MIZUTANI et al. 1977). The present work is an extension of this study and deals with all the possible isomers of symmetrically substituted hexachlorobiphenyl (HCB) and decachlorobiphenyl.

MATERIALS AND METHOD

Symmetric HCB's and decachlorobiphenyl were prepared by the methods previously described (MIZUTANI et al. 1978, WEBER & SÖLLSCHER 1883).

A group of 20 female mice weighing 20-22 g was fed ad libitum a diet containing 10 ppm of each of the chlorobiphenyl isomers listed in Table 1 for 20 days, during which time food intake was monitored. At the end of exposure period the experimental diets were replaced with a control diet. Each group of mice was randomly distributed into 4 subgroups of 5 mice and each subgroup was sacrificed at the intervals scheduled according to a preliminary experiment (Table 2). The whole body of mice was subjected to residue analysis.

Determination of chlorobiphenyl isomers was carried out as reported previously (MIZUTANI et al. 1977).

RESULTS AND DISCUSSION

Many reports have suggested that chlorobiphenyls might affect their own kinetics of accumulation and elimination processes through the alterations of hepatic drug-metabolizing activities (CHEN & DUBOIS 1973, IVERSON et al. 1975, BRUCKNER et al. 1977). In a separate experiment, therefore, the effects of dosage level employed in this experiment on the activities of drug-metabolizing enzymes were followed by measuring the pentobarbital-sleeping times of mice. All the chloro-

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TABLE 1

Physical data of chlorobiphenyl isomers

Compound	mp (°C)	Rt[a]	Rf[b]
2,3,4,2',3',4'-HCB	150-151	195	0.60
2,3,5,2',3',5'-HCB	128-129	134	0.81
2,3,6,2',3',6'-HCB	113-114	97	0.63
2,4,5,2',4',5'-HCB	97- 99	146	0.75
2,4,6,2',4',6'-HCB	112	85	0.77
3,4,5,3',4',5'-HCB	201	300	0.67
Decachlorobiphenyl	310-312	882	0.79

[a] relative to p,p'-DDE (=100) on an OV-1 column at 190°

[b] on commercially prepared TLC plate (Wakogel FM) developed with hexane

TABLE 2

Experimental schedule for sacrifice

Compound	Time between end of exposure and sacrifice (days)			
	Subgroup			
	i	ii	iii	iv
2,3,4,2',3',4'-HCB	1	16	36	61
2,3,5,2',3',5'-HCB	1	16	36	61
2,3,6,2',3',6'-HCB	1	3	5	7
2,4,5,2',4',5'-HCB	1	16	36	61
2,4,6,2',4',6'-HCB	1	11	31	51
3,4,5,3',4',5'-HCB	1	21	61	101
Decachlorobiphenyl	1	21	51	71

biphenyl isomers, except 2,3,5,2',3',5'- and 2,4,6,2',4',6'-HCB's, were ascertained not to alter significantly the pentobarbital-sleeping times. The pentobarbital-sleeping times were significantly ($P<0.01$) prolonged by 2,3,5,2',3',5'-HCB (150% of control value) and significantly shortened by 2,4,6,2',4',6'-HCB (63% of control value).

The residue levels of chlorobiphenyl isomers at various times after the end of exposure are shown in Table 3. These data were fitted by the method of least squares to the following first-order decline equation:

$$\log Y = -kX + \log Y_0 \qquad (1)$$

where Y is the concentration of chlorobiphenyl isomer at X days after the end of exposure, k is the rate constant for the decline of concentration, and Y_0 is the initial concentration. The results are shown in Table 4. Analysis of variance showed that there was no significant deviation from linearity in each case ($P<0.01$). The biological half-lives and the estimates of initial concentration calculated from the regression equations are also shown in Table 4. The biological half-lives for HCB isomers, except for 2,3,6,2',3',6'-HCB, are considerably greater than those for the tetrachlorobiphenyl isomers previously studied (MIZUTANI et al. 1977). 2,3,6,2',3',6'-HCB possesses chlorine atoms in neither the meta nor para positions to the phenyl-phenyl bond and this orientation of chlorine atoms may be responsible to its rapid metabolism and hence to its exceptionally short half-life. Previous study (MIZUTANI et al. 1977) has pointed out, however, that the biological half-lives of some tetrachlorobiphenyls seem to be determined by the rate of releasing from body fat mass rather than by the rate of metabolism. Therefore, another likely explanation for the rapid decline of 2,3,6,2',3',6'-HCB may be offered by a certain physicochemical nature which permits easy releasing of this isomer from the fatty compartment. The half-life of 2,4,5,2',4',5'-HCB, the most persistent isomer of the HCB's presently examined, was practically comparable to that of decachlorobiphenyl.

On the assumption that the accumulation follows first-order kinetics, the body burden (A_t) after t days of exposure is given by the equation:

$$A_t = (I_s/2.303k)(1 - e^{-2.303kt}) \qquad (2)$$

where I_s is the daily intake into the storage site. On substituting the numerical values of k and A_t (= A_{20})

TABLE 3

Concentrations of chlorobiphenyl isomers at various times after end of exposure

Compound	Concentration in mice, mean ± SEM, µg/g of wet tissue			
	Subgroup			
	i	ii	iii	iv
2,3,4,2',3',4'-HCB	15.94 ± 0.53	11.45 ± 1.75	5.58 ± 1.87	3.98 ± 1.13
2,3,5,2',3',5'-HCB	15.58 ± 0.64	15.32 ± 0.89	8.12 ± 1.82	6.08 ± 1.74
2,3,6,2',3',6'-HCB	1.83 ± 0.09	0.88 ± 0.20	0.52 ± 0.06	0.53 ± 0.03
2,4,5,2',4',5'-HCB	14.28 ± 0.22	15.04 ± 1.21	11.40 ± 0.96	9.92 ± 1.06
2,4,6,2',4',6'-HCB	6.40 ± 0.75	5.68 ± 1.29	2.88 ± 0.70	1.10 ± 0.05
3,4,5,3',4',5'-HCB	14.13 ± 1.30	13.22 ± 0.49	10.04 ± 2.39	4.14 ± 0.40
Decachlorobiphenyl	8.82 ± 0.63	7.46 ± 0.68	6.06 ± 0.81	5.71 ± 0.42

TABLE 4

Regression lines for relationship between concentrations of chlorobiphenyls and time after end of exposure

Compound	Regression line[a] $\log Y = -kX + \log Y_0$	$t_{1/2}$[b] (days)	Initial concn. ($\mu g/g$)
2,3,4,2',3',4'-HCB	log Y = -0.0116X + 1.1976	26 (20 - 39)	15.8
2,3,5,2',3',5'-HCB	log Y = -0.0093X + 1.2458	32 (22 - 61)	17.6
2,3,6,2',3',6'-HCB	log Y = -0.0930X + 0.1659	3.2 (2.1-6.9)	1.82
2,4,5,2',4',5'-HCB	log Y = -0.0032X + 1.1821	94 (63 -186)	15.3
2,4,6,2',4',6'-HCB	log Y = -0.0152X + 0.8436	20 (15 - 29)	6.97
3,4,5,3',4',5'-HCB	log Y = -0.0053X + 1.2019	57 (43 - 83)	16.1
Decachlorobiphenyl	log Y = -0.0028X + 0.9316	110 (68 -260)	8.54

[a] Y = concentration of chlorobiphenyl in $\mu g/g$, X = time in days after end of exposure

[b] 95% confidence intervals in parentheses

TABLE 5

Body burdens (A_{20}) at end of exposure, daily intakes into storage site (I_s), daily oral intakes (I_o), and storage ratios (I_s/I_o) of chlorobiphenyls

Compound	A_{20}[a] (μg)	I_s (μg/day)	I_o (μg/day)	I_s/I_o
2,3,4,2',3',4'-HCB	397.8	25.7	40	0.6
2,3,5,2',3',5'-HCB	467.4	28.8	41	0.7
2,3,6,2',3',6'-HCB	50.2	10.9	36	0.3
2,4,5,2',4',5'-HCB	373.6	20.1	38	0.5
2,4,6,2',4',6'-HCB	165.2	11.5	31	0.4
3,4,5,3',4',5'-HCB	389.6	22.0	36	0.6
Decachlorobiphenyl	188.9	10.1	34	0.3

[a] calculated by the formula: $A_{20} = w\ Y_0$, where w is the average body weight of mice at the end of exposure and numerical values for Y_0 are given in Table 4.

at the end of exposure into equation (2), the estimate of I_s and then the storage ratio defined as I_s/I_o (MIZUTANI et al. 1977), where I_o is the measured daily oral intake, were calculated and summarized in Table 5. In contrast to the case of the tetrachlorobiphenyl isomers, there were no striking differences in storage ratio among the HCB isomers, although the storage ratios for 2,3,6,2',3',6'- and 2,4,6,2',4',6'-HCB's were somewhat lower than those for the other isomers. This probably is a reflection of virtually the same metabolic rates of these isomers. The relatively low storage ratio for decachlorobiphenyl may be accounted for by the restricted intestinal absorption of this isomer.

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