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Pharmacokinetics of Polychlorinated Biphenyl Components in Swine and Sheep after a Single Oral Dose

R. E. BORCHARD [*], M. E. WELBORN, W. B. WIEKHORST, D. W. WILSON, and L. G. HANSEN [x]

Abstract □ Single-dose oral administration of a commercial polychlorinated biphenyl product containing 54% chlorine provided data with which to plot the time course of total polychlorinated biphenyl and individual components in the blood of swine and sheep. Pharmacokinetic parameters describing absorption from the gut and elimination from a two-compartment body system were determined for the components in swine and sheep. The absorption half-time for total polychlorinated biphenyl in swine was 1.13 hr while that for sheep was 3.83 hr. The half-time for disposition of total polychlorinated biphenyl from the central compartment was 4.4 hr in swine and 7.7 hr in sheep; the apparent biological half-life was 62.4 hr in swine and 78.8 hr in sheep. Individual components varied significantly from each other and from total polychlorinated biphenyl in all parameters.

Keyphrases □ Polychlorinated biphenyl components—pharmacokinetics in swine and sheep after single oral dose □ Pharmacokinetics—polychlorinated biphenyls in swine and sheep after single oral dose

The ecological persistence of polychlorinated biphenyls and their continual release into the environment in recent years have created a situation in which contamination of animal feed as well as human food is a constant threat. Since commercial preparations are mixtures of some 200 possible isomers and any given residue probably represents more than a single polychlorinated biphenyl mixture, it becomes important to evaluate the individual components as well as total polychlorinated biphenyl. Furthermore, such a mixture permits the simultaneous comparison of several different compounds in the same animal, and studies using single purified components can be used to assess the extent of interactions within the mixture.

One means of assessing exposure to polychlorinated biphenyls and persistence of the chemicals in the body is by way of blood sampling. Previous studies characterized the polychlorinated biphenyl mixture used (1), developed and refined methods of extraction and analysis (2), and determined pharmacokinetic parameters of individual components in swine and sheep after intravenous administration (3). Reports of investigations of pharmacokinetic parameters after feeding contaminated feed are in preparation.

This paper deals with the time course of polychlorinated biphenyls in the animal body as determined by blood sampling after a single oral dose of a commercial polychlorinated biphenyl containing 54% chlorine[1] to swine and sheep.

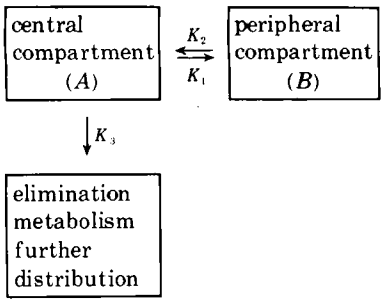
EXPERIMENTAL

Three sheep and three swine were given a calculated oral dose of a polychlorinated biphenyl containing 54% chlorine by weight[1] in a gelatin capsule. The dosage was 30 mg/kg for the sheep and 15 mg/kg for the swine; pilot studies indicated that these levels were necessary to provide adequate blood concentrations for analysis.

The sheep were mature ewes of mixed mutton-type breeding and weighed 53.5, 57.0, and 66.5 kg; the swine were of Hampshire-Yorkshire breeding and weighed 48.0, 59.5, and 57.2 kg. Both sheep and swine were maintained in individual steel cages with slot floors. Blood samples were obtained from the sheep by jugular puncture for 7 days and from the swine by femoral venous cannulas, fitted 24 hr prior to dosing, for 2 days.

The levels in swine blood collected after 48 hr were not adequate to permit accurate quantitation, and most of the β values were estimated from only one or two points along with the computer-generated tangent; therefore, the parameters for elimination from the tissue compartment in swine should be viewed with reservation. Further investigations will be conducted to determine these values more accurately.

[1] Aroclor 1254, Monsanto electrical grade No. KB-05-612.



Scheme I

Blood samples were extracted with hexane-saturated acetonitrile and analyzed for polychlorinated biphenyls by electron-capture GLC as previously described (2).

Quantitation of components as well as total polychlorinated biphenyl for each blood sample was accomplished by the methods previously utilized (1–3).

The blood concentrations of each component and total polychlorinated biphenyl were plotted and fit to a two-compartment model utilizing a computer program (4) for the elimination phase and a graphical method for the absorption phase. By using estimates obtained from data plots, the computer program generated four parameters (A, α, B, and β) which describe elimination for a two-compartment open model (Scheme I), where K_1 and K_2 are first-order distribution rate constants between the central compartment *(A)* and the peripheral compartment *(B)*; K_3 is the overall elimination rate constant.

The integrated mathematical equation for Scheme I is:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1)}$$

where:

C_t = blood concentration at time t
A = blood zero time concentration intercept for the rapid disposition curve
B = blood zero time concentration intercept for the slow disposition curve
α = first-order rate constant for disposition from the central compartment to the peripheral compartment
β = apparent elimination rate constant

It was established previously that the peripheral compartment consists, at least in part, of fatty tissues in sheep and swine[2].

With oral administration, one can modify the model as shown in Scheme II, where G is the enteric reservoir (gut) from where absorption occurs, and K_a is the rate constant of absorption from the gut.

The integrated mathematical model approximates:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} - C_0e^{-K_a t} \qquad \text{(Eq. 2)}$$

where $C_0 = A + B$ (generally determined from intravenous elimination data).

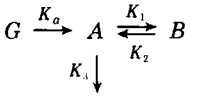
In this paper, the absorption rate constants, K_a, of the components and total polychlorinated biphenyl were determined by a method similar to the conventional one for one-compartment models. The value of K_a was determined from the slope[3] of the line when $(\bar{C}_t - C_t)$ is plotted semilogarithmically against time, where $(\bar{C}_t - C_t)$ = the difference between the predicted elimination line, extrapolated back to zero time, and the actual absorption data points.

The approximate integration of the mathematical model, as used here, then becomes:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} - Xe^{-K_a t} \qquad \text{(Eq. 3)}$$

where X = the zero time intercept of line $(\bar{C}_t - C_t)$ determined from oral elimination data.

[2] Unpublished data from this laboratory.
[3] Determined with a Wang 500 calculator exponential regression program.



Scheme II

Other parameters were calculated as follows:

$$t\tfrac{1}{2}\alpha = \frac{0.693}{\alpha} \qquad \text{(Eq. 4)}$$

$$t\tfrac{1}{2}\beta = \frac{0.693.}{\beta} \text{ (biological half-life)} \qquad \text{(Eq. 5)}$$

$$t\tfrac{1}{2} \text{ absorption} = 0.693/K_a \qquad \text{(Eq. 6)}$$

$$K_1 = \alpha + \beta - K_2 - K_3 \qquad \text{(Eq. 7)}$$

$$K_2 = \frac{A\beta + B\alpha}{A + B} \qquad \text{(Eq. 8)}$$

$$K_3 = \frac{\alpha\beta}{K_2} \qquad \text{(Eq. 9)}$$

Where applicable, component results were compared statistically by multiple-range and paired t tests (5).

RESULTS

The absolute blood concentrations for components and total polychlorinated biphenyl after a single oral dose are given in Table I for swine and in Table II for sheep. Absolute component concentrations were determined by utilizing the component percentage of the commercial mixture and concentrations relative to the standard mixture as previously discussed (3).

The components were first detected in swine blood at 0.5–1.0 hr after administration, and maximum blood concentrations were seen in 4–8 hr. As seen in Table III, components of a longer relative retention time and a larger percentage of chlorination (1) took longer to attain maximum concentrations. Component 286 attained a significantly greater ($p < 0.05$) relative blood concentration (and blood–dose ratio) than total polychlorinated biphenyl and all other components except Component 332.

The components were first detected in sheep blood at 2–4 hr after administration, and maximum blood concentrations occurred at 8–24 hr. As seen in Table IV, components of a longer retention time and a larger percentage of chlorination attained maximum concentrations later, just as in the swine. Components 286 and 332 attained significantly greater ($p < 0.05$) relative blood concentrations (and blood–dose ratios) than Components 70, 99, and 105 and total polychlorinated biphenyl. Component 286 was also greater than 84.

By comparing blood–dose ratios of swine to those of sheep (Table IV), one sees a significantly greater ratio for all components and total polychlorinated biphenyl in swine. Thus, for a given dose, one would expect to see higher blood concentrations in swine, which is consistent with results obtained after feeding a ration containing the same commercial mixture[2].

The blood concentrations of each commercial mixture component and total polychlorinated biphenyl were plotted as the mean concentration for swine and sheep at each sampling time. The data representing the elimination phase were fit to the two-compartment model for elimination, and the data representing the absorption phase were utilized for calculation of absorption rates, based on the extrapolated elimination curve. Examples of the data plots are given for both swine and sheep in Figs. 1–4 for Component 127. Figures 1 and 3 show the absorption phase of Component 127, and Figs. 2 and 4 show the complete elimination phase.

Fitted elimination curves for all components and total polychlorinated biphenyl are shown for swine in Fig. 5 and for sheep in Fig. 6. The slopes for each component in the figure for swine or sheep are the same as those resulting from plotting the data in Tables I and II; their positions on the graph vary depending on whether the values relative to the commercial mixture (Figs. 5 and 6) or the absolute values (Tables I and II) were used. For example, the relative concentration of Component 286 (Fig. 5) was greater than all others, but the absolute concentration (Table I) was only greater than Component 332.

Table I—Mean Absolute Blood Concentrations (Parts per Billion) of Polychlorinated Biphenyl Components after a Single Oral Dose in Swine

RRT[a]	Hours											
	1	2	3	4	5	6	8	12	18	24	30	48
70	8	59	158	202	185	120	79	45	13	10	6	4
84	15	58	169	241	261	217	176	111	49	39	27	22
99	6	32	90	120	144	116	92	63	30	22	15	12
105	5	37	101	121	149	118	101	54	18	12	9	6
127	8	61	184	255	297	253	213	133	55	31	20	16
149	7	47	134	195	219	196	186	120	63	41	23	14
176	5	22	71	114	122	130	145	93	46	30	24	16
208	1	5	15	25	34	32	36	23	12	7	5	4
253	1	4	16	23	31	32	37	24	12	8	6	5
286	3	3	8	8	11	13	19	15	10	7	5	3
332	1	3	5	6	10	12	14	10	6	4	3	2
Total polychlorinated biphenyl	60	331	951	1310	1463	1239	1098	691	314	211	143	104

[a] Aroclor 1254 component relative retention time; 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) = 100.

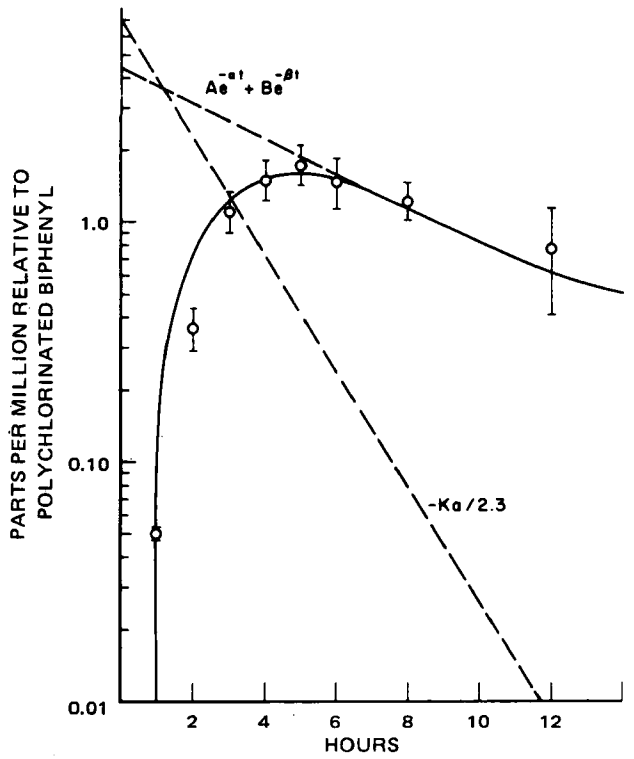


Figure 1—*Absorption phase of Component 127 in swine. The circles represent the mean blood concentrations relative to the standard mixture (concentration of standard necessary to cause the same detector response), the brackets around the circles represent the standard deviations of the means, the broken line designated by* $Ae^{-\alpha t} + Be^{-\beta t}$ *is the extrapolation of the fitted elimination curves, the broken line designated by* $-K_a/2.3$ *is the line describing absorption, and the solid line is the fitted curve for absorption and elimination.*

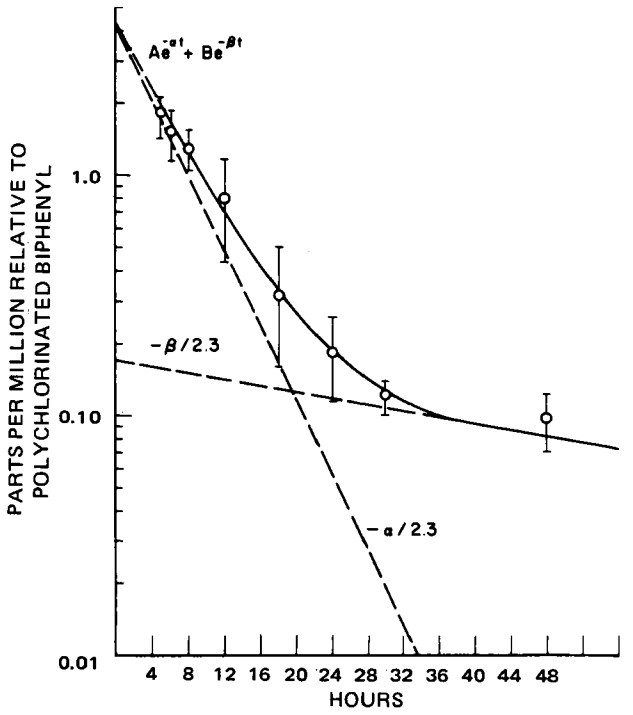


Figure 2—*Elimination phase of Component 127 in swine. The circles and brackets have the same designation as in Fig. 1, the broken line designated* $-\alpha/2.3$ *is the line describing distribution from the central compartment, and the broken line designated* $-\beta/2.3$ *is the extrapolated line describing the slower elimination phase.*

Pharmacokinetic parameters determined for components and total polychlorinated biphenyl after a single oral dose to swine and sheep are listed in Tables V and VI. Parameters A, α, B, and β were generated by the computer program from the elimination phase of the data plots. The parameters were determined as described under *Experimental.*

The pharmacokinetic parameters K_a, α, β, and K_3 were compared statistically. In swine, Component 70 was absorbed and eliminated at a faster rate ($p < 0.05$) than were most other components. In sheep, absorption of Components 70 and 105 was the most rapid, while the elimination of Components 99 and 105 was the most rapid; several components of longer retention time, as well as Component 84, were eliminated at a slow rate relative to the total polychlorinated biphenyl content.

The rate constants K_a, α, β, and K_3, in general, were greater for swine than for sheep. This comparison is consistent with results obtained from studies in which swine and sheep were fed a ration containing the commercial polychlorinated biphenyl.

DISCUSSION

This paper has attempted to provide some basic information on the time course of a polychlorinated biphenyl mixture when administered as a single oral dose to swine and sheep. Previously discussed methods (1–3) were utilized in sample and data analysis. A more precise method for the determination of absorption rate constants may be more desirable and may be adaptable in future studies when more basic information on the distribution of commercial polychlorinated biphenyl mixtures from the gut of swine and sheep is known.

Table II—Mean Absolute Blood Concentrations (Parts per Billion) of Polychlorinated Biphenyl Components after a Single Oral Dose in Sheep

	Hours													
RRT[a]	4	6	8	12	24	36	48	60	72	84	96	120	144	168
70	37	63	79	66	35	21	14	12	12	9	9	—	—	—
84	44	80	111	110	81	48	29	24	24	19	21	18	17	—
99	22	37	49	43	28	20	11	11	10	—	—	—	—	—
105	14	22	28	21	11	8	5	5	4	4	—	—	—	—
127	55	105	147	147	122	67	48	42	39	31	28	26	22	21
149	25	77	99	133	114	72	50	47	42	37	32	29	27	26
176	26	50	78	84	66	41	27	25	24	18	18	17	17	15
208	5	11	19	19	13	7	5	4	4	3	3	3	2	—
253	6	12	21	24	23	16	12	12	10	8	8	7	7	6
286	3	5	8	11	12	9	6	6	5	4	3	3	3	—
332	2	4	7	11	11	8	6	6	5	4	4	3	3	3
Total polychlorinated biphenyl	239	466	646	669	516	317	213	194	179	137	126	106	98	71

[a] Aroclor 1254 component relative retention time; 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) = 100.

Table III—Concentration of Polychlorinated Biphenyl Components in the Blood of Swine after a Single Oral Dose

		Maximum Concentration in Blood			
RRT[a]	Absolute Dose, mg/kg	Relative, ppm	Absolute, ppm	Hours	Blood[b] / Dose
70	2.41	1.260	0.202	4	0.084
84	2.46	1.587	0.261	5	0.106
99	1.51	1.423	0.144	5	0.095
105	1.51	1.477	0.149	5	0.099
127	2.50	1.780	0.297	5	0.119
149	2.05	1.600	0.219	5	0.107
176	1.24	1.760	0.145	8	0.117
208	0.31	1.707	0.036	8	0.116
253	0.29	1.900	0.037	8	0.128
286	0.10	2.960	0.019	8	0.190
332	0.10	2.207	0.014	8	0.140
Total polychlorinated biphenyl	15.00	1.463	1.463	5	0.098

[a] Aroclor 1254 component relative retention time; 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) = 100. [b] Absolute maximum concentration per dose.

Published methods for the determination of absorption rate constants exhibiting two-compartment open-model characteristics utilize at least two parameters generated from intravenous data

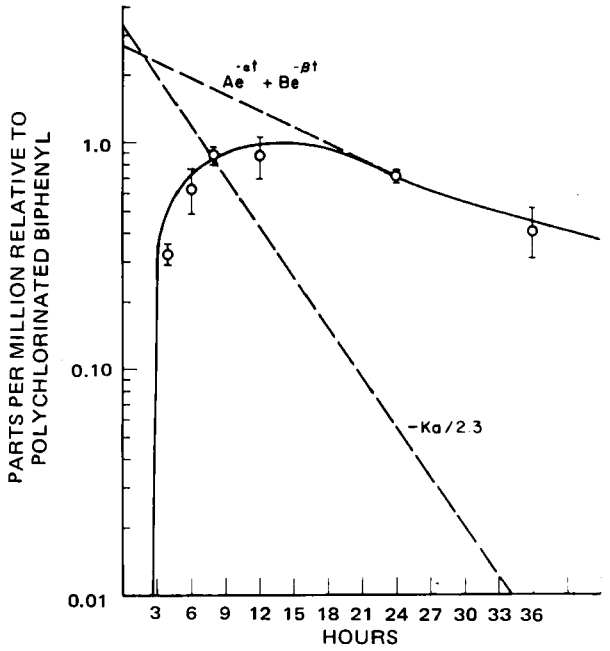


Figure 3—*Absorption phase of Component 127 in sheep. The circles, brackets, and lines have the same designations as in Fig. 1.*

Table IV—Concentration of Polychlorinated Biphenyl Components in the Blood of Sheep after a Single Oral Dose

		Maximum Concentration in Blood				
RRT[a]	Absolute Dose, mg/kg	Relative, ppm	Absolute, ppm	Hours	Blood[b] / Dose	Swine[c] / Sheep
70	4.82	0.493	0.079	8	0.016	5.25
84	4.92	0.673	0.111	8	0.023	4.61
99	3.02	0.487	0.049	8	0.016	5.94
105	3.02	0.273	0.028	8	0.009	11.00
127	5.00	0.880	0.147	8	0.029	4.10
149	4.10	0.973	0.133	12	0.032	3.34
176	2.48	1.020	0.084	12	0.034	3.44
208	0.62	0.893	0.019	12	0.031	3.74
253	0.58	1.233	0.024	12	0.041	3.12
286	0.20	1.833	0.012	24	0.060	3.17
332	0.20	1.720	0.011	24	0.055	2.55
Total polychlorinated biphenyl	30.00	0.667	0.667	12	0.022	4.45

[a] Aroclor 1254 component relative retention time; 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) = 100. [b] Absolute maximum blood concentration per dose. [c] Accumulation (*i.e.*, blood/dose) comparison.

Table V—Comparison of Pharmacokinetic Parameters for Polychlorinated Biphenyl Components in Swine

RRT[a]	A, ppm	α, hr^{-1}	B, ppm	β, hr^{-1}	$t_{1/2}\ \alpha$, hr	$t_{1/2}\ \beta$, hr	$t_{1/2}$ Absorption, hr	K_a, hr^{-1}	K_1, hr^{-1}	K_2, hr^{-1}	K_3, hr^{-1}
70	3.858	0.283	0.135	0.0405	2.45	17.11	0.62	1.112	0.040	0.049	0.234
84	3.054	0.151	0.138	0.0005	4.59	1386.00	1.01	0.685	0.134	0.007	0.011
99	2.949	0.180	0.220	0.0014	3.85	495.00	1.19	0.585	0.149	0.014	0.018
105	3.546	0.184	0.092	0.0080	3.77	86.63	1.26	0.552	0.062	0.012	0.118
127	4.124	0.175	0.170	0.0150	3.96	46.20	1.24	0.560	0.046	0.021	0.123
149	2.796	0.140	0.340	0.0260	4.95	26.45	1.20	0.580	0.032	0.039	0.094
176	5.390	0.161	0.333	0.0108	4.30	64.17	1.87	0.371	0.063	0.020	0.087
208	4.778	0.148	0.281	0.0110	4.68	63.00	1.80	0.386	0.053	0.019	0.086
253	5.422	0.151	0.310	0.0059	4.59	117.46	1.90	0.364	0.040	0.008	0.109
286	5.052	0.103	0.900	0.0145	6.73	47.79	2.96	0.234	0.036	0.028	0.053
332	4.808	0.126	0.540	0.0100	5.50	69.30	2.19	0.317	0.056	0.022	0.057
Total polychlorinated biphenyl	2.929	0.156	0.170	0.0110	4.44	62.43	1.13	0.611	0.057	0.019	0.090

[a] Aroclor 1254 component relative retention time; 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) = 100.

Table VI—Comparison of Pharmacokinetic Parameters for Polychlorinated Biphenyl Components in Sheep

RRT[a]	A, ppm	α, hr^{-1}	B, ppm	β, hr^{-1}	$t_{1/2}\ \alpha$, hr	$t_{1/2}\ \beta$, hr	$t_{1/2}$ Absorption, hr	K_a, hr^{-1}	K_1, hr^{-1}	K_2, hr^{-1}	K_3, hr^{-1}
70	0.723	0.068	0.090	0.0057	10.19	121.58	0.78	0.883	0.031	0.013	0.030
84	2.664	0.084	0.152	0.0026	8.25	266.54	3.98	0.174	0.049	0.007	0.031
99	0.606	0.061	0.150	0.0082	11.36	84.51	1.02	0.681	0.024	0.019	0.026
105	0.379	0.079	0.069	0.0077	8.77	90.00	0.82	0.841	0.035	0.018	0.034
127	2.422	0.065	0.253	0.0043	10.66	161.16	4.10	0.169	0.031	0.010	0.028
149	2.141	0.057	0.309	0.0030	12.16	231.00	3.71	0.187	0.033	0.010	0.017
176	2.554	0.066	0.286	0.0025	10.50	277.20	3.57	0.194	0.042	0.009	0.018
208	1.643	0.051	0.133	0.0015	13.59	462.00	2.37	0.292	0.033	0.005	0.015
253	2.217	0.046	0.498	0.0028	15.07	247.50	4.03	0.172	0.026	0.011	0.012
286	2.772	0.036	0.730	0.0043	19.25	161.16	4.41	0.157	0.015	0.011	0.014
332	2.782	0.037	0.600	0.0027	18.73	256.67	4.15	0.167	0.020	0.009	0.011
Total polychlorinated biphenyl	2.347	0.090	0.302	0.0088	7.70	78.75	3.83	0.181	0.037	0.018	0.044

[a] Aroclor 1254 component relative retention time; 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) = 100.

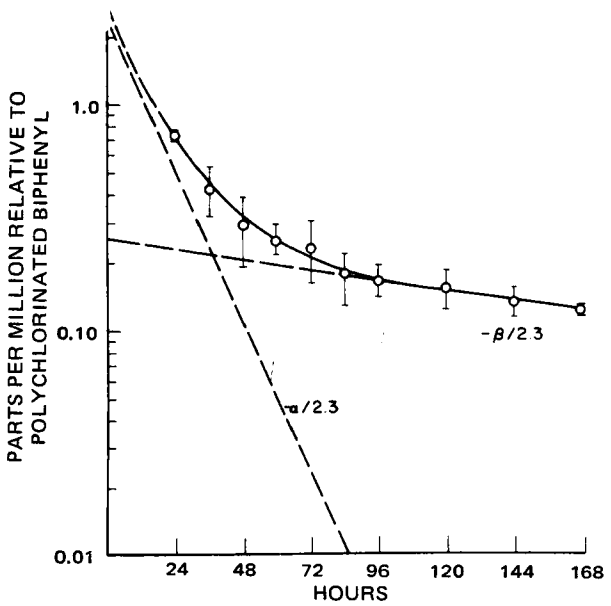


Figure 4—*Elimination phase of Component 127 in sheep. The circles and brackets have the same designations as in Fig. 1. The lines have the same designations as in Fig. 2.*

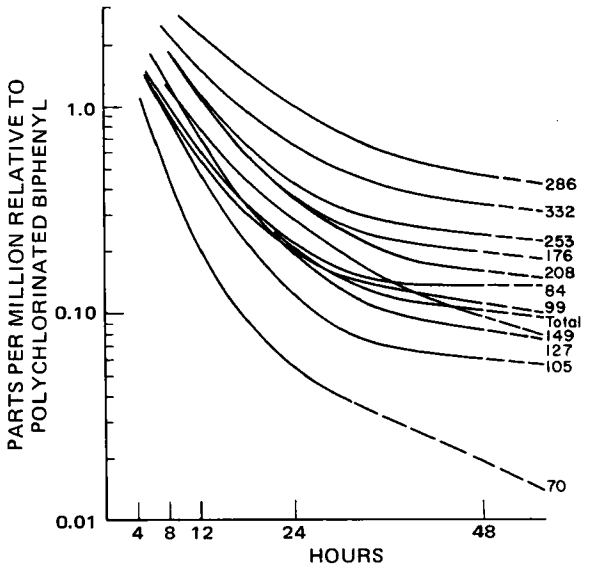


Figure 5—*Elimination of polychlorinated biphenyl components in swine (relative values).*

from the same animals (6, 7). Repeated experiments with a polychlorinated biphenyl mixture in the same animal are impractical because of slow excretion, tissue residues, and low metabolic conversion. Similar groups of animals can be utilized for the extrapolation of intravenous data to oral data if the intravenous and oral kinetics are well correlated in terms of dosage, compartmentalization, and extent of absorption. Since the correlation between intravenous and oral kinetics has not been well established for polychlorinated biphenyl mixtures, a method for the determination of absorption rate constants based only on oral dosage data seems to

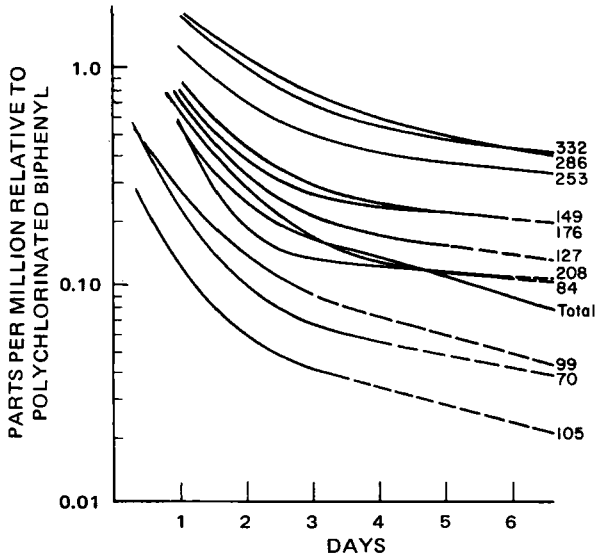


Figure 6—*Elimination of polychlorinated biphenyl components in sheep (relative values).*

be most appropriate, at least for comparison of the components within the commercial mixtures.

The comparisons made between swine and sheep are somewhat predictable, because of obvious species differences in GI physiology, and generally consistent with results obtained from other studies being prepared for publication. The components were absorbed faster, reached higher blood concentrations, and were eliminated faster in swine than sheep. There is a tendency for higher chlorinated components to be absorbed slower but to reach higher maximum concentrations relative to amounts present in the dose.

It is difficult at this time to attempt correlation of kinetic data within each species for each type of administration of the commercial mixture. Variations between intravenous parameters (3) and the oral parameters determined in this study pose questions concerning distribution and dose dependence. Although polychlorinated biphenyls are left intact after treatment with strong acids, their extractability from biological materials such as egg yolk is dependent on pH. Polychlorinated biphenyls, especially the higher chlorinated species, are not readily extractable from aqueous solutions at acid pH; neutralization of the acid can increase recovery up to 10-fold[2]. If this dependence applies to the gastric portions of the central compartment, the redistribution of polychlorinated biphenyl to the blood would reflect a lower K_3 and $t_{1/2}\,\beta$. Although a longer period of sampling after intravenous dosing might reveal closer half-lives, both areas will have to be investigated to resolve this discrepancy.

For total polychlorinated biphenyl, K_3 and $t_{1/2}$ *(B)* were 0.189 hr^{-1} and 15.1 hr, respectively, for swine administered 3 mg/kg iv; the same parameters for sheep were 0.194 hr^{-1} and 14.7 hr, respectively (3). In this study, the values were 0.091 hr^{-1} and 62.4 hr for swine receiving 15 mg/kg and 0.044 hr^{-1} and 78.8 hr for sheep receiving 30 mg/kg. In intravenous studies, however, the blood samples were collected for only 24 hr and the oral dose level in swine should have been followed for a longer duration in the present study. It is obvious that oral and intravenous investigations approximating the same C_0 are required and that the duration of the study needs to be expanded.

A previous report indicated similar poor absorption of the same mixture from the gut of growing pigs, but dilution rather than elimination was responsible for reducing tissue concentrations (8). It is difficult to compare these studies, however, since tissue concentrations were not determined at peak levels in the previous study and analytical methods limited results to an estimation of total polychlorinated biphenyls so that individual components were not assayed.

Accumulation of data from future studies along with analyses of data from studies already undertaken will undoubtedly help to assemble the total picture of polychlorinated biphenyl mixture distribution in the animal body.

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