CHRONIC TOXICITY OF AROCLOR MIXTURES ADMINISTERED IN THE DIET TO SPRAGUE-DAWLEY RATS FOR TWELVE MONTHS.

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Abstract

A side-by-side evaluation of the chronic toxicity/ oncogenicity of the polychlorinated biphenyls (PCBs) Aroclors 1016, 1242, 1254 and 1260, at dose levels ranging from 25-200 ppm in diet, is ongoing in male (M) and female (F) Sprague-Dawley rats. The highly chlorinated PCB mixtures Aroclor 1260 and Clophen A 60 (60% Cl) have been demonstrated in previous chronic studies to induce hepatic tumors in rodents, while the less chlorinated PCB mixtures, Aroclor 1254 (54% Cl) and Clophen A 30 (42% Cl), have not produced tumorigenic responses. Interim evaluations have been conducted after 13 and 39 weeks (F only), and 26 and 52 weeks (M & F) for this 2-yr study. Parameters measured include feed consumption, body weight, serum chemistry, hematology, urinalysis and organ weights, as well as evaluations of appearance and behavior and macroscopic and histomorphologic lesions. Dose-related decreases in body weight gain were recorded for M receiving Aroclor 1254 and for F receiving Aroclors 1242, 1254 and 1260. Dose-related increases in aspartate aminotransferase were measured for F receiving Aroclors 1242 and 1254, and slight treatment-related increases in serum cholesterol were measured for M receiving Aroclors 1016, 1254 and 1260. Treatment-related increased relative (to brain) liver weight was measured for M (but not F) in all Aroclors, with dose-related increases evident for Aroclors 1254 and 1260. Histomorphologic evaluation of livers revealed treatment- and dose-related centrilobular hepatocellular hypertrophy in both M & F.

Introduction

Polychlorinated biphenyls (PCBs) are complex mixtures produced by iron-catalyzed chlorination of biphenyl resulting in the addition of 1-10 chlorines. There are 209 possible combinations for the number of chlorines and their distribution patterns around the biphenyl rings.

Commercial PCB mixtures were categorized and sold based upon their average chlorine content. In the United States, Aroclor was the principle commercial product. It was used in a host of applications including plasticizers, adhesives, cutting oils, flame retardants, heat exchange fluids, dielectric fluids, hydraulic fluids, microscope immersion oils, and carbonless paper. The dielectric properties, chemical stability, and non-combustibility of PCB fluids made them an attractive alternative to mineral oils for electrical equipment applications. The mixtures of choice for use in electrical capacitors were Aroclors 1016, 1242, and 1254, and for electrical transformers were Aroclors 1254 and 1260. These mixtures contain approximate chlorine contents of 41% (Aroclor 1016), 42% (Aroclor 1242), 54% (Aroclor 1254) and 60% (Aroclor 1260).

The realization in the mid-1960's that PCBs were accumulating in the environment resulted in a ban on their manufacture and sale in the late-1970's. Shortly thereafter, evidence mounted that PCBs were potentially hepatotumorigenic in rats[1,2,3,4] and mice[5,6] resulting in their designation by the EPA as probable human carcinogens (category B2). The limited information available for chronically exposed animals suggests that the

hepatotumorigenic response is a function of chlorine content, i.e., requiring $\geq 60\%$ Cl [7]. The dose levels producing this response in rats are less than that for mice, therefore, the data from rat (more sensitive species) studies are used to derive permissible human exposure levels.

This poster presents findings through 52-weeks from an ongoing 2-year chronic toxicity/carcinogenicity study in rats. Data from this study relating to the bioaccumulation and metabolism of Aroclors are presented in poster #1011.

Materials and Methods

Male and female Sprague-Dawley rats, 6-8 weeks old, were randomly assigned as follows:

Group Number	Aroclor Mixture	Dose (ppm)	Number/Sex at Necropsy Timepoints (Months)							
			3		6*		9		12*	
			M	F	M	F	M	F	M	F
1.	Control	0	-	6	6	6	-	6	6	6
2.	1016	50	-	6	6	6	-	6	6	6
3.	1016	100	-	6	6	6	-	6	6	6
4.	1016	200	-	6	6	6	-	6	6	6
5.	1242	50	-	6	6	6	-	6	6	6
6.	1242	100	-	6	6	6	-	6	6	6
7.	1254	25	-	6	6	6	-	6	6	6
8.	1254	50	-	6	6	6	-	6	6	6
9.	1254	100	-	6	6	6	-	6	6	6
10.	1260	25	-	6	6	6	-	6	6	6
11.	1260	50	-	6	6	6	-	6	6	6
12.	1260	100	-	6	6	6	-	6	6	6

*Serum chemistry, hematology and urinalysis performed on 10/sex/group from an associated oncogenicity study.

All test articles were administered in feed *ad libitum*. Body weights were recorded weekly, feed consumption was measured continuously, and clinical signs were monitored daily. At 13 and 39 weeks, 6 females/group, and at 26 and 52 weeks, 6 males and females/group were killed. Histomorphology was assessed for the following tissues and weighed (*) organs:

aorta	intestines	pituitary*	thymus*
adrenal glands*	kidneys*	prostate*	thyroid gland*
bone marrow	lacrimal glands	seminal vesicles*	trachea
brain*	liver*	skin	urinary bladder
epididymides*	lungs*	spinal cord	uterus*
esophagus	lymph nodes	spleen*	vagina
eyes	mammary gland	stomach	gross lesions
harderian gland	ovaries*	submaxillary glands*	
heart*	pancreas	testes*	

In addition, portions of adipose, brain and liver tissue were frozen for determination of tissue PCB concentrations.

Clinical chemical, hematologic and urinalyses evaluations at 26 and 52 weeks included:

Clinical Chemistry		Hematology	Urinalyses
AST	cholesterol	Hb	appearance
ALT	creatinine	Hct	bilirubin
ALP	glucose	RBC	blood
BUN	inorganic	WBC	color
CK	phosphate	MCH	glucose
γ-GT	potassium	MCV	ketones
LD	protein	MCHC	microscopic characteristics
albumin	sodium	differential count	pH
calcium	total bilirubin	platelet count	protein
chloride			urobilinogen
			specific gravity
			volume

Analyses of diet samples for test article concentrations, homogeneity and cross-contamination were conducted.

Parametric data were analyzed for treatment effects by analysis of variance, and pairwise comparisons between groups were made using Dunnett's t-Test. Nonparametric data were analyzed by Wilcoxon's Test for pairwise group comparisons.

Results

Clinical signs

No patterns of abnormal behavior or overt signs of toxicity were apparent for any treatment group. No treatment-related mortality was observed.

Feed consumption was similar between treatment groups and controls for both males and females.

Diet analyses indicated acceptable test article concentrations and homogeneity, and no evidence of cross-contamination.

Body weights

Group mean (includes all oncogenicity study animals) body weights for males in all treatment groups of Aroclors 1016, 1242 and 1260 were generally greater (≈6%) than control and was statistically significant only for 50 ppm Aroclor 1016 beginning at 4 months (Figures 1-4). Dose-related decreased group mean body weights were recorded for 50 and 100 ppm Aroclor 1254. The decreases from control at 12 months were 4 and 15%, respectively, and were statistically significant only in the 100 ppm Aroclor 1254 group, beginning at 1 month. Statistically significant body weight differences generally persisted.

Group mean (includes all oncogenicity study animals) body weights for females in all treatment groups of Aroclors 1016 and 1260 were similar to control. Dose-related decreased group mean body weights were recorded for 100 ppm Aroclor 1242, and for all treatment groups of Aroclor 1254. The decreases became statistically significant for the 100 ppm Aroclor 1242 group at 4 months, and for 25, 50 and 100 ppm Aroclor 1254 at 6, 3, and 1 months, respectively. At 12 months the differences from control were 10% for 100 ppm Aroclor 1242 and 9, 13, and 21% and 25, 50, and 100 ppm Aroclor 1254, respectively. As with males, statistically significant body weight differences generally persisted.

Serum chemistry, hematology and urinalysis

In males, treatment-related increases in serum AST (6 and 12 months) and GGT (6 months) activity were measured for Aroclor 1254 (Table 1). Serum cholesterol was increased in a dose-related manner at 6 months for Aroclor 1254 and in a treatment-related manner at 12 months for Aroclors 1016, 1254, and 1260. Treatment-related (but not dose-related) slight depressions in red blood cell parameters (i.e., MCH and MCHC) were measured at 12 months primarily for Aroclor 1254, and to a lesser extent for Aroclors 1242 and 1260.

In females, dose-related increases in serum AST activity were measured for Aroclor 1242 (12 months) and Aroclor 1254 (6 and 12 months). Dose-related increases in serum cholesterol were measured at 6 months for Aroclors 1254 and 1260, and although not statistically significant, similar numerical increases were measured at 12 months. Dose-related depressions in red blood cell parameters (i.e., Hb, Hct, MCV, MCH, and MCHC) were measured at 6 and 12 months, primarily for Aroclor 1254, and to a lesser extent for Aroclors 1242 and 1260.

Urine analyses did not reveal any treatment-related changes.

Organ weights

In males, there were consistent treatment- and dose-related increases only for liver/brain weight ratio. Increased liver weight ratios were calculated for 100 ppm Aroclor 1254 (6 months) and for 50 and 200 ppm Aroclor 1016, 100 ppm Aroclor 1242, and 25, 50, and 100 ppm Aroclors 1254 and 1260 at 12 months (Figure 5).

Consistent organ/brain weight ratio increases were similarly confined to liver for females. Weight ratio increases were calculated for 100 ppm Aroclor 1254 (3 and 6 months) and 50 and 100 ppm Aroclor 1260 (6 months) (Figure 6).

Pathology

Treatment-related lesions were found only in the liver. The most common change was centrilobular hepatocellular hypertrophy (with minimal necrosis), which was diagnosed in both males and females, with a trend toward increasing severity with increased duration of exposure and increasing %Cl (Aroclor 1016 < 1242 < 1254 ≈ 1260).

Additional hepatic lesions included cytoplasmic vacuolization, biliary duct hyperplasia, cytoplasmic pigment, and foci of cellular alteration. The sporadic incidence and severity of these lesions makes their relationship to treatment unclear.

Conclusions

Evidence of toxicity after 12 months of exposure to Aroclors 1016, 1242, 1254 or 1260 was minimal.

The decreased mean body weight gain recorded for some groups was not accompanied by clinical signs of toxicity, morbidity or mortality. The long-term effects of the weight depression will be evaluated during the final year of the study.

The depressed red blood cell parameters, more frequent and evident for females than males, were primarily confined to the 100 ppm groups in Aroclors 1242 and 1260, and all groups of Aroclor 1254. These changes are possibly the result of altered porphyrin metabolism [8,9,10].

The increased mean relative liver weight measured for some groups is presumably a result of enzyme induction (with corresponding increased endoplasmic reticulum), a reversible pharmacologic response, while the slight increases in hepatic leakage enzymes (e.g. AST and LDH) for Aroclor 1254 are consistent with minimal hepatocyte necrosis.

References

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Figure 1

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Aroclor 1016

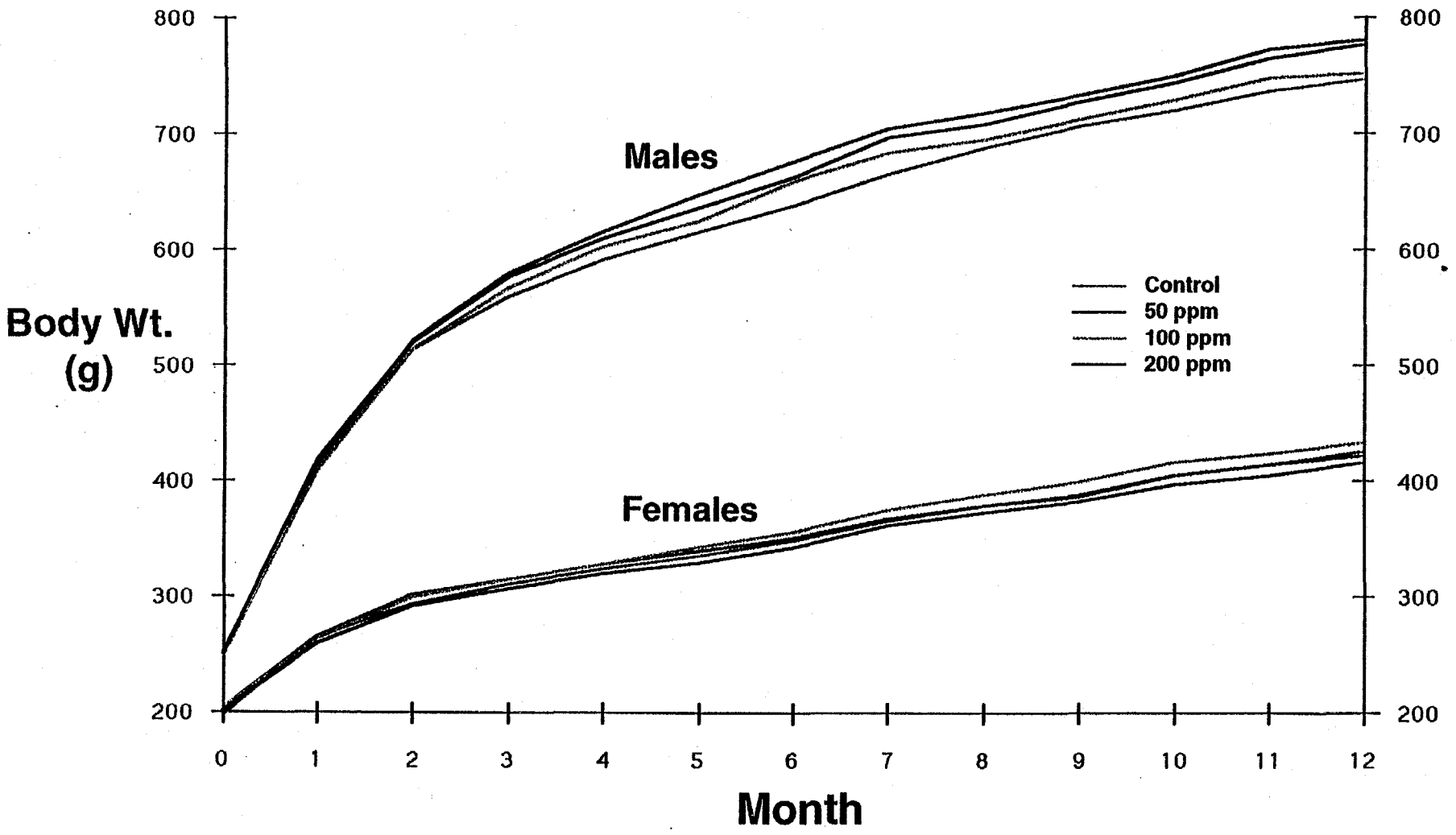

Figure 2

Aroclor 1242

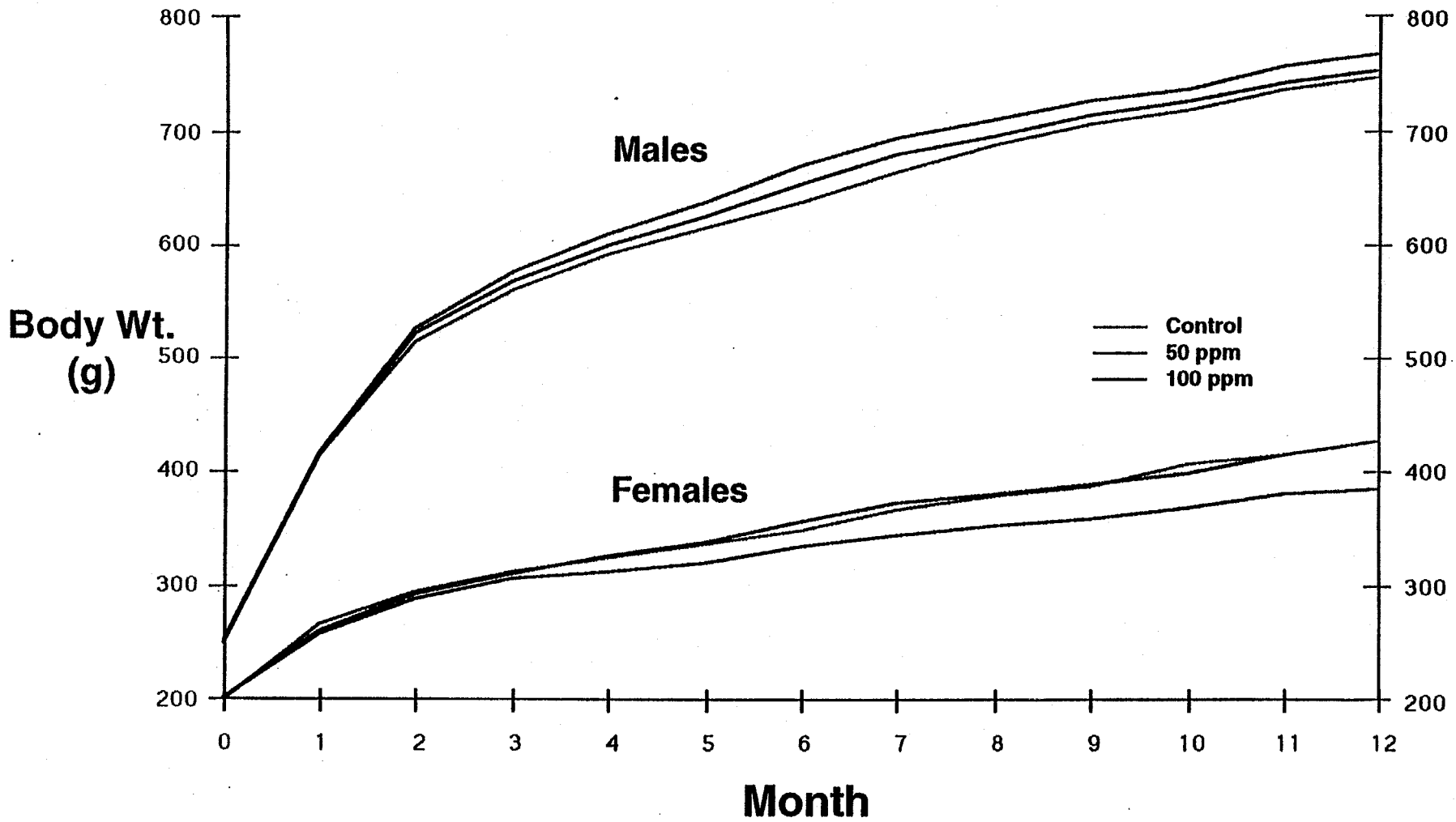

Figure 3

Aroclor 1254

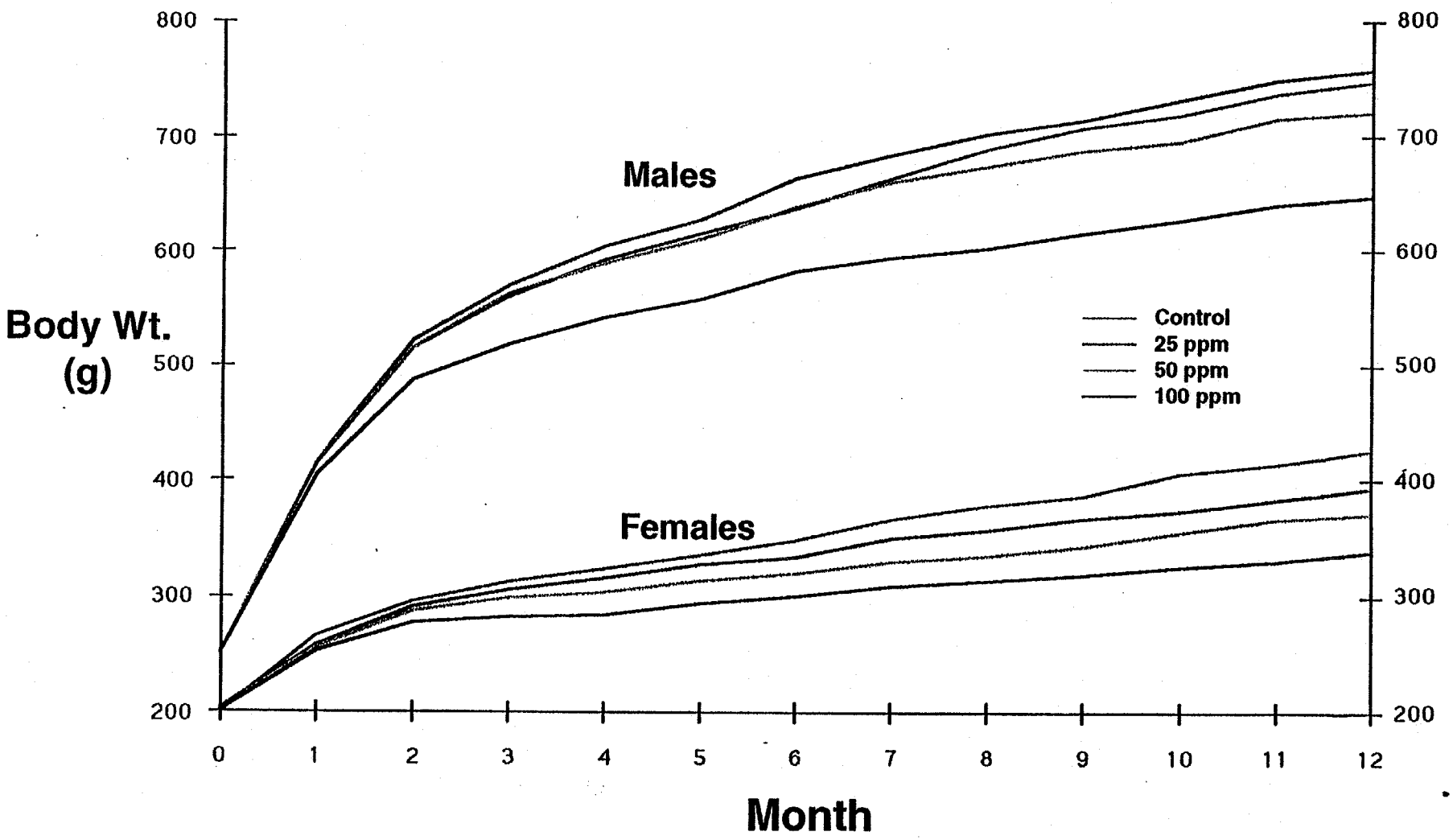

Figure 4

Aroclor 1260

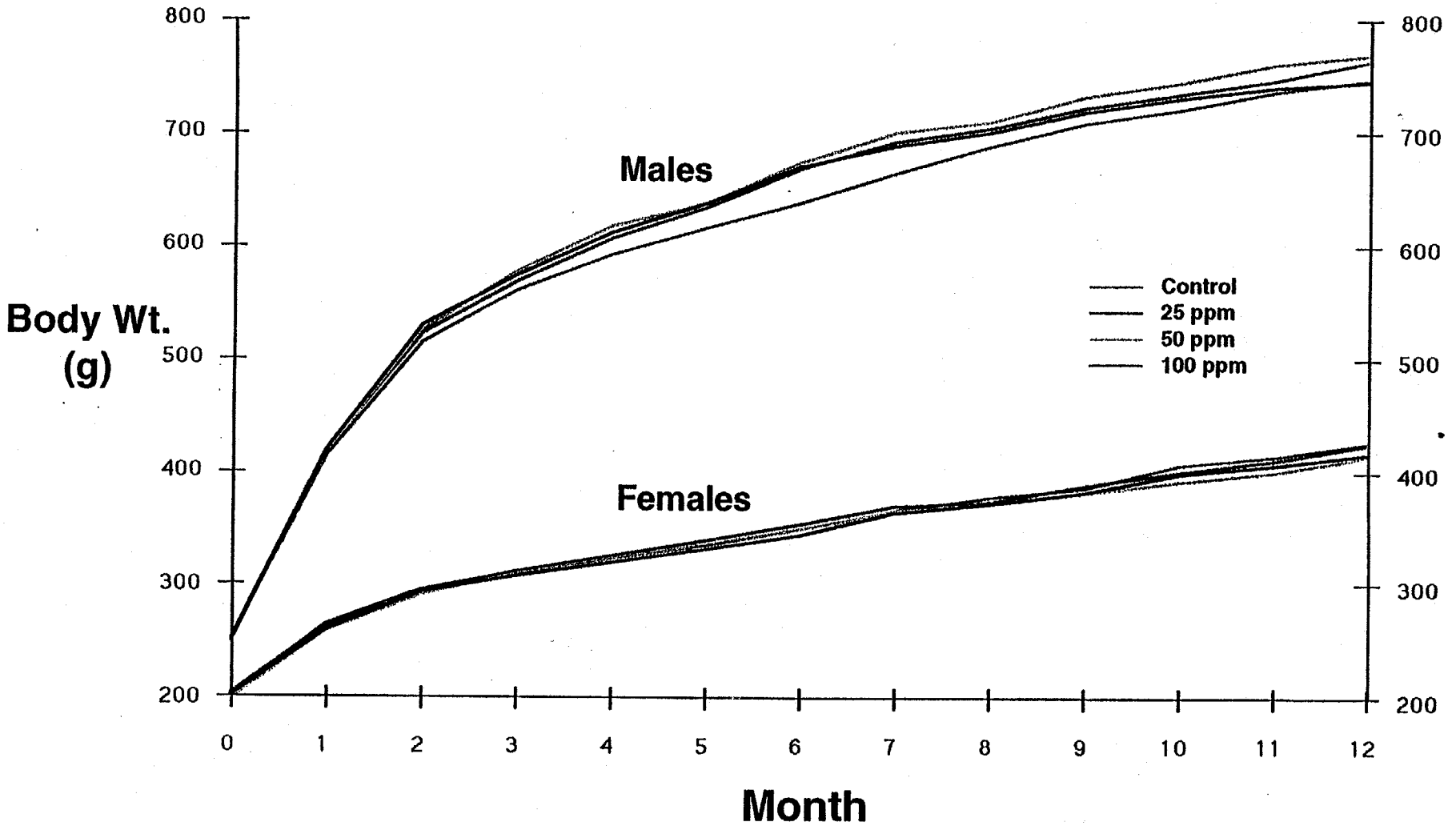

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Figure 5

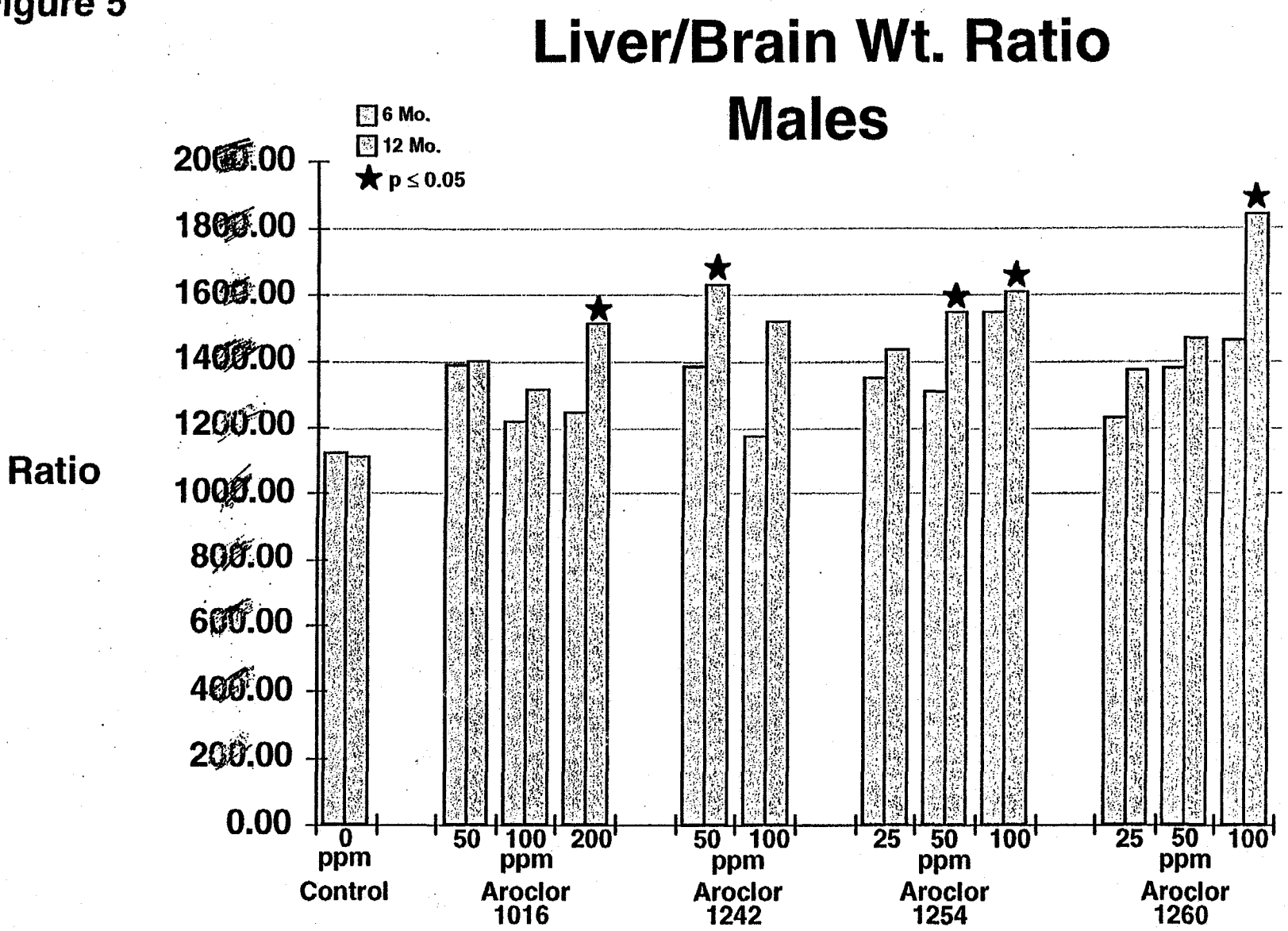

Figure 6

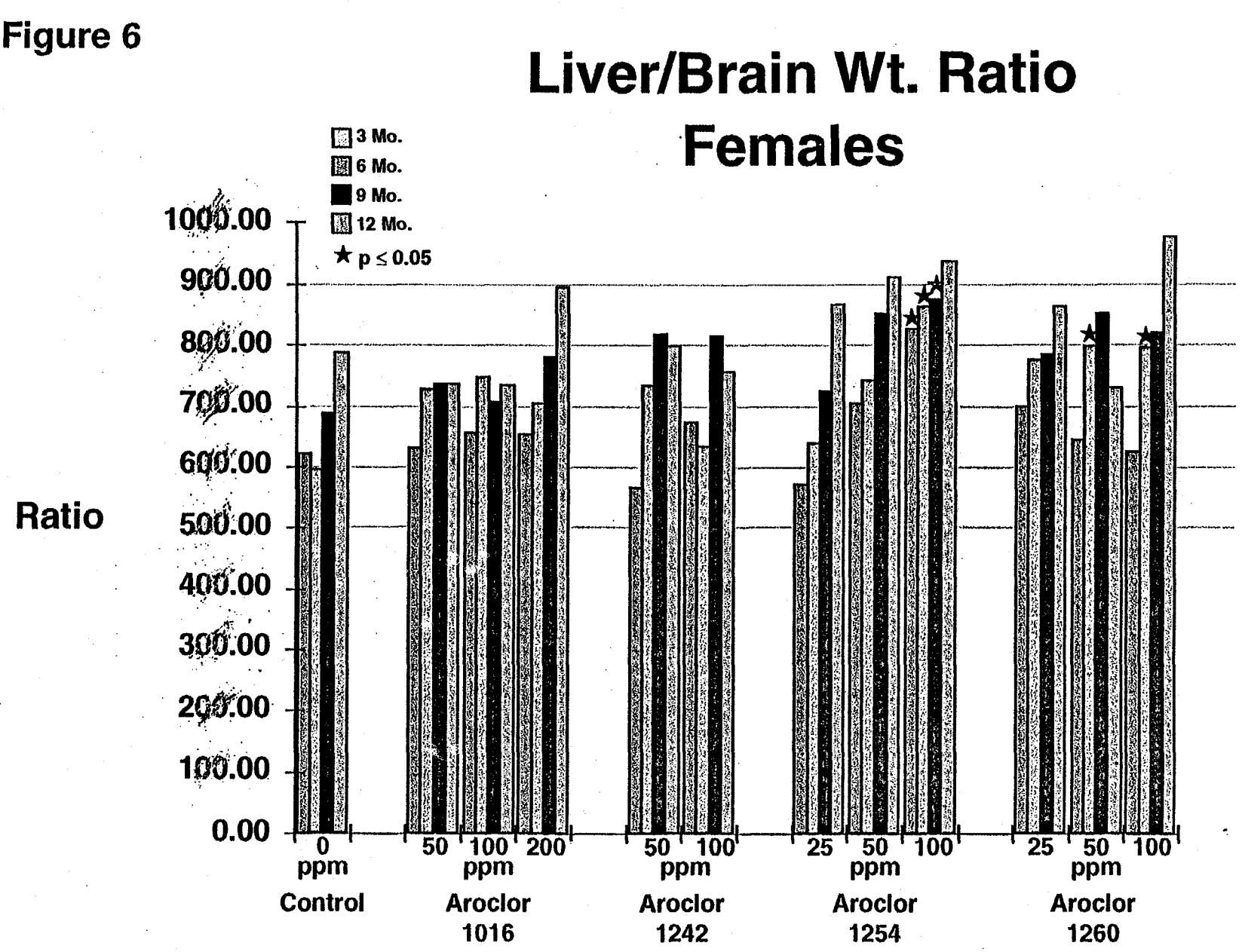

Table 1

Serum Chemistries and Hematology

Males

GROUP	Control		Aroclor 1016 50 ppm		Aroclor 1016 100 ppm		Aroclor 1016 200 ppm		Aroclor 1242 50 ppm		Aroclor 1242 100 ppm		Aroclor 1254 25 ppm		Aroclor 1254 50 ppm		Aroclor 1254 100 ppm		Aroclor 1260 25 ppm		Aroclor 1260 50 ppm		Aroclor 1260 100 ppm	
Month	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12
AST	90	90	***71***	77	101	98	86	93	90	117	80	98	112	119	137	***112***	128	***138***	79	100	***72***	82	87	107
ALT	43	45	39	36	56	40	41	42	48	48	4[illegible]	49	42	47	85	48	49	45	41	41	41	41	42	49
GGT	0	1	0	0	1	1	0	1	0	0	0	0	***7***	1	***8***	1	***1***	2	***1***	1	5	0	3	1
LDH	818	360	423	503	665	730	526	606	712	***762***	***395***	588	1082	812	1075	710	1157	1130	517	***985***	436	445	660	752
Cholesterol	96	110	123	***168***	117	***153***	114	***136***	108	125	127	142	123	***160***	128	***151***	***164***	***194***	98	119	111	160	120	***143***
RBC	7.94	7.78	8.32	7.95	***8.47***	8.16	8.09	7.90	8.16	***8.48***	7.85	7.99	8.18	8.09	8.03	8.20	8.04	7.98	8.12	7.74	8.27	8.03	8.29	7.93
Hb	15.1	15.4	15.4	15.1	15.7	15.4	15.4	15.2	15.1	15.8	14.8	15.3	14.7	14.8	14.8	15.1	14.6	14.3	15.3	14.8	15.2	15.4	15.1	14.7
Hct	45.5	43.8	45.4	44.0	45.8	44.7	45.4	44.3	45.4	46.4	44.9	45.5	45.0	44.4	45.3	45.8	44.6	43.3	45.9	43.1	45.6	44.5	45.8	43.1
MCV	57	56	***55***	55	***54***	55	56	56	56	56	57	57	55	55	57	56	56	54	57	56	55	55	55	55
MCH	19.1	19.8	18.6	19.0	18.6	18.9	19.1	19.3	18.5	18.7	18.9	19.2	***18.0***	***18.3***	18.4	***18.4***	18.1	***17.9***	18.8	19.2	18.4	19.1	18.2	***18.6***
MCHC	33.3	35.0	34.0	34.3	***34.3***	34.4	34.0	34.4	33.3	***34.1***	33.0	***33.8***	32.7	***33.3***	32.5	***33.0***	32.7	***32.9***	33.3	34.4	33.4	34.6	32.9	***34.1***

Table 1

Serum Chemistries and Hematology

Males

GROUP	Control		Aroclor 1016 50 ppm		Aroclor 1016 100 ppm		Aroclor 1016 200 ppm		Aroclor 1242 50 ppm		Aroclor 1242 100 ppm		Aroclor 1254 25 ppm		Aroclor 1254 50 ppm		Aroclor 1254 100 ppm		Aroclor 1260 25 ppm		Aroclor 1260 50 ppm		Aroclor 1260 100 ppm	
Month	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12
AST	90	90	***71***	77	101	98	86	93	90	117	80	98	112	119	137	***112***	128	***138***	79	100	***72***	82	87	107
ALT	43	45	39	36	56	40	41	42	48	48	44	49	42	47	85	48	49	45	41	41	41	41	42	49
GGT	0	1	0	0	1	1	0	1	0	0	0	0	***7***	1	***8***	1	***1***	2	***1***	1	5	0	3	1
LDH	818	360	423	503	665	730	526	606	712	***762***	***395***	588	1082	812	1075	710	1157	1130	517	***985***	436	445	660	752
Cholesterol	96	110	123	***168***	117	***153***	114	***136***	108	125	127	142	123	***160***	128	***151***	***164***	***194***	98	119	111	160	120	***143***
RBC	7.94	7.78	8.32	7.95	***8.47***	8.16	8.09	7.90	8.16	***8.48***	7.85	7.99	8.18	8.09	8.03	8.20	8.04	7.98	8.12	7.74	8.27	8.03	8.29	7.93
Hb	15.1	15.4	15.4	15.1	15.7	15.4	15.4	15.2	15.1	15.8	14.8	15.3	14.7	14.8	14.8	15.1	14.6	14.3	15.3	14.8	15.2	15.4	15.1	14.7
Hct	45.5	43.8	45.4	44.0	45.8	44.7	45.4	44.3	45.4	46.4	44.9	45.5	45.0	44.4	45.3	45.8	44.6	43.3	45.9	43.1	45.6	44.5	45.8	43.1
MCV	57	56	***55***	55	***54***	55	56	56	56	56	57	57	55	55	57	56	56	54	57	56	55	55	55	55
MCH	19.1	19.8	18.6	19.0	18.6	18.9	19.1	19.3	18.5	18.7	18.9	19.2	***18.0***	***18.3***	18.4	***18.4***	18.1	***17.9***	18.8	19.2	18.4	19.1	18.2	***18.6***
MCHC	33.3	35.0	34.0	34.3	***34.3***	34.4	34.0	34.4	33.3	***34.1***	33.0	***33.8***	32.7	***33.3***	32.5	***33.0***	32.7	***32.9***	33.3	34.4	33.4	34.6	32.9	***34.1***

Females

GROUP	Control		Aroclor 1016 50 ppm		Aroclor 1016 100 ppm		Aroclor 1016 200 ppm		Aroclor 1242 50 ppm		Aroclor 1242 100 ppm		Aroclor 1254 25 ppm		Aroclor 1254 50 ppm		Aroclor 1254 100 ppm		Aroclor 1260 25 ppm		Aroclor 1260 50 ppm		Aroclor 1260 100 ppm	
Month	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12	6	12
AST	117	88	85	84	72	99	90	73	83	126	104	***178***	163	195	***194***	***197***	***244***	***334***	76	77	87	96	96	97
ALT	81	48	52	42	***42***	41	73	35	49	53	61	88	88	73	74	58	67	62	51	35	65	43	66	51
GGT	0	1	1	0	4	0	3	0	1	1	1	1	5	0	***9***	1	7	1	3	1	1	1	1	1
LDH	459	280	637	407	500	219	421	419	377	535	306	457	436	338	344	609	***201***	442	436	247	436	294	306	181
Cholesterol	118	180	106	136	123	153	127	167	110	146	128	211	145	176	***191***	223	***193***	226	127	157	151	200	***161***	244
RBC	7.17	7.14	7.28	7.14	7.12	7.02	7.07	7.05	7.08	7.11	7.49	7.03	7.40	7.29	7.24	6.70	7.21	6.93	7.31	7.08	7.23	7.20	7.35	7.28
Hb	14.7	15.0	14.6	15.1	14.2	14.6	14.2	14.4	14.3	14.5	14.4	***13.9***	14.2	14.5	***13.6***	***13.3***	***12.9***	***13.1***	14.5	14.4	14.3	14.6	14.1	14.4
Hct	42.7	42.0	43.9	42.8	42.9	41.5	42.0	41.1	41.5	41.2	42.5	40.6	42.8	41.6	41.0	***38.1***	***38.8***	***37.9***	43.2	41.7	42.5	42.0	41.6	41.6
MCV	60	59	60	60	60	59	59	58	59	58	57	58	58	57	***57***	57	***54***	***55***	59	59	59	58	***57***	57
MCH	20.6	21.0	20.1	21.1	20.0	20.8	20.1	20.5	20.2	20.3	***19.2***	***19.9***	***19.2***	***19.9***	***18.7***	***19.9***	***18.0***	***18.9***	19.9	20.4	19.8	20.4	***19.2***	***19.8***
MCHC	34.5	35.8	***33.4***	35.2	***33.1***	35.2	33.8	35.2	34.4	35.2	33.9	***34.3***	***33.2***	***34.9***	***33.1***	35.1	***33.4***	***34.5***	33.6	***34.6***	33.6	***34.8***	33.9	***34.5***

Legend: Aspartate Aminotransferase (AST - U/l), Alanine Aminotransferase (ALT - U/l), Gamma Glutamyl Transferase (GGT - IU/l), Lactate Dehydrogenase (LDH - IU/l), Cholesterol (mg/dl), Red Blood Cells (RBC - $10^3/\mu l$), Hemoglobin (Hb - g/dl), Hematocrit (Hct - %), Mean Corpuscular Volume (MCV - fl), Mean Corpuscular Hemoglobin (MCH - pg), Mean Corpuscular Hemoglogin Concentration (MCHC - g/dl). ***P≤0.05.***

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
SOLID WASTE AND EMERGENCY
RESPONSE

March 17, 1995

MEMORANDUM

SUBJECT: Hudson River PCBs NPL Site/Material on PCBs

FROM: Dorothy Canter

TO: Marian Olsen

Per our conference call on March 9, 1995, regarding the Hudson River PCBs NPL site, I am attaching copies of the material from the two posters on the long-term carcinogenicity and chronic toxicity studies of four PCB mixtures presented by General Electric (G.E.) staff at the Society of Toxicology meeting last week. The first poster summarizes data on chronic toxicity of the four mixtures - Aroclor 1016, Aroclor 1242, Aroclor 1254, and Aroclor 1260 - in male and female Sprague-Dawley rats following 12 months of administration in the feed. The liver was the only site at which treatment-related lesions were found in rats sacrificed at 12 months and subjected to histopathological evaluation. The most common change was centrilobular hepatocellular hypertrophy, which was diagnosed in both sexes, with a trend toward increasing severity with increased exposure duration and with increasing percentage chlorination. Interestingly, treatment with Aroclor 1254 or Aroclor 1260 caused approximately the same effects in the liver at 12 months of this two-year study.

The second poster presents data from the same studies on sex differences in mammary adipose tissue accumulation and metabolic profiles of the four Aroclor mixtures. For each mixture tested there was a dose-related increase in total PCB in adipose mammary tissue. Female rats exhibited a greater accumulation of total PCBs at 18 months than did males for each of the PCB mixtures studied. Further, the cumulative PCB levels in mammary tissue was significantly higher in both sexes of rats treated with Aroclor 1254 or Aroclor 1260 than in rats treated with either Aroclor 1016 or Aroclor 1242. In female rats, the level was an order of magnitude higher at 18 months. The authors speculate that metabolizing activity of one of the cytochrome P450 isozzymes is greater in males than in females and is dose-dependent.

The two-year exposure phase of these studies was completed in February 1995 in both sexes of rats. Histopathological evaluation is currently underway. Following the development of the initial pathologic diagnoses by the contractor pathologist, G.E. will convene a pathology working group to review the slides and provide quality assurance/quality control. This group will follow the model of the National Toxicology Program Pathology Working Group. I suggest that we request an update on the status of these studies at our upcoming meeting with G.E. staff. The results of these studies may have some effect on the approach that EPA uses to assess carcinogenic potential of PCB congeners and mixtures. Therefore, the results could have some impact on decisions made at the Hudson River PCBs site, if available in time.

The data available to date from these carcinogenicity/toxicity studies are consistent with the liver being the target organ, as found in previous carcinogenicity studies in rats and mice. Whether the percentage chlorination of given PCB mixtures is the key determinant of carcinogenicity, as advanced several years ago by the Institute for Evaluating Health Risks, or the presence in certain mixtures of particular PCB congener(s), or some other factors, remains to be determined.

Also attached is a copy of a review paper by Stephen Safe entitled "Polychlorinated Biphenyls (PCBs): Environmental Impact, Biochemical and Toxic Responses, and Implications for Risk Assessment" which was published last year in Critical Reviews in Toxicology. It deals with the issue of developing toxic equivalency factors for PCBs. I am currently in the process of reviewing it. I hope that you find it useful.

With regard to the four reports submitted to Region 2 by G.E. for the forthcoming meeting, I suggest that at the meeting EPA staff discuss with them the possibility of performing studies in several species of fish found in the upper Hudson River in which PCB content is measured in one filet from the fish before cooking and in the other filet after cooking. For each fish species several methods of cooking could be used and compared. At least three fish per species per cooking method should be used to generate average PCB levels in tissue before and after cooking. We might also recommend that congener distribution studies be performed in some subset of the fish to determine whether the distribution seen in fish tissue corresponds to that in river sediments, etc.

I look forward to participating in the upcoming meeting and have blocked out the days May 9 -12, pending notification from you as to the confirmed date and time of the meeting. Please do not hesitate to call me if I can be of further assistance.

Attachments