Attachment IV

Chronic Toxicity of Three Polychlorinated Biphenyls[1] in Albino Rats

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ABSTRACT

The toxicology and reported ecologic effects of polychlorinated biphenyls are selectively reviewed as an introduction to the first of a series of toxicologic studies with Aroclors 1242, 1254 and 1260. Two-year toxicity studies were conducted with these materials in albino rats at dietary levels of 1, 10 and 100 ppm. Each of the 3 materials at the 100 ppm level caused liver changes characterized by increased liver weights and increased liver to body weight and liver to brain weight ratios. Liver weight effects were not observed at lower feeding levels. Histopathologic examination revealed treatment related hepatic changes in the case of each of the Aroclors. These changes were most pronounced at the 24-month sacrifice and consisted of an hepatocellular alteration beginning as focal hypertrophy and progressing to nodular foci of hyperplasia-hypertrophy and, in a few animals at the 100 ppm level, to hepatoma or cholangionepatoma. There was no evidence of metastasis, invasion, severe basophilia or mitosis which would permit classifying these neoplasms as malignant. The incidence and types of miscellaneous neoplasms seen in the liver and other organs of post-mortem animals and those sacrificed after treatment for 24 months provided no evidence of carcinogenicity.

INDEX TERMS

Polychlorinated biphenyls

Ecologic effects of

Toxicology of

Chronic toxicity of, in rats

Hepatotoxicity of, in rats

AROCLORS
AROCLOR 1242
AROCLOR 1254
AROCLOR 1260

MONS 211796

INTRODUCTION

The polychlorinated biphenyls (PCBs) comprise a family of compounds of variable chlorine content. In the case of the Aroclors, the last 2 digits of the numerical designation indicate the chlorine content in percent. Since the chlorine atoms are randomly distributed among the 10 ring positions available for substitution, each material is a mixture of isomers.

The PCBs are highly stable toward hydrolysis under either acidic or alkaline conditions and toward heat and oxidation. They do not support combustion, have high resistivity and dielectric strength, are non-drying, and retain adhesiveness and thermoplasticity under conditions of repeated stress.

Because of these properties, PCBs have been used in diverse applications since their commercial introduction in 1929. These have included a variety of dielectric applications, insulation impregnants, diffusion pump oils, liquid sealants, hydraulic fluids, heat exchange media, plasticizers for specialty inks, resins, rubbers and paints and adjuvants in pesticide formulations. In 1972, the manufacture of AROCLOR 1260 was discontinued in the United States and the sale of AROCLORS was restricted to a single use in closed systems, i.e., as dielectric fluids.

Questions were soon raised regarding the systemic toxicity and dermatologic effects which might be associated with industrial exposure to these materials. Jones and Alden (1936) reported a high incidence of acneform dermatitis among employees engaged in the manufacture of PCBs. Drinker et al. (1937) exposed rats to PCBs at a chamber concentration of 1 mg/m^3 for 16 weeks and produced liver damage. On the basis of these results and some additional observations, Drinker (1939) suggested a permissible concentration of

PCBs in the air of workrooms of 0.5 mg/m³. Bennett et al. (1938) reported morphologic changes in the livers of rats fed or injected with chlorinated biphenyls.

Greenberg et al. (1939) attributed the death of 3 young workers to exposure to chlorinated naphthalenes and biphenyls. Adams et al. (1941) demonstrated chloracneform responses in rabbits exposed to materials, including chlorinated biphenyls, which had been reported to cause acneform dermatitis in man. Miller (1944) reported on animal studies with a trichlorobiphenyl administered topically, by subcutaneous injection or by feeding to guinea pigs, rats and rabbits. The conspicuous pathologic finding consisted of liver damage characterized by degeneration of the centrilobular cells and by fatty degeneration. The greatest degree of liver damage was found in the guinea pig and the least in the rat.

Treon et al. (1956) determined that cats, mice, rabbits, rats and guinea pigs were unaffected by exposure to a PCB containing 42% chlorine for 7 hours/day, 5 days/week, at concentrations of 1.9 mg/m³ for 150 exposures and 6.83 mg/m³ for 82 exposures. At 8.6 mg/m³ for 17 exposures, no effect was observed except for a slight weight depression in guinea pigs. With a PCB containing 54% chlorine, 150 exposures at 1.5 mg/m³ caused no ill effects but 83 exposures to 5.4 mg/m³ resulted in injury to liver cells and increased liver weights in rats. On the basis of these data, Threshold Limit Values of 1 and 0.5 mg/m³ respectively were established in 1962 (Am. Conf. Gov. Ind. Hyg.).

During succeeding years, little information was reported concerning the toxicology of the PCBs until McLaughlin et al. (1963) judged AROCLOR 1242 to

be toxic in the chick embryo test at levels of 10 or 25 mg/egg. Hatched chicks, which later died, showed some beak deformities and growth retardation.

Questions have been raised as to the causative toxic constituents of the PCBs. Tetra- and pentachlorodibenzofurans have been analytically demonstrated to be present in CLOPHEN A60 (Bayer AG, Leverkusen) and PHENOCLOR DP6 (Prodelec S.A., France) but were not detected in AROCLOR 1260 (Monsanto Co., St. Louis, Mo.). The chlorinated dibenzofurans are known to be potent chloracnegens, being somewhat weaker in this regard than the chlorinated dibenzodioxins (Bauer et al., 1961).

Vos et al. (1970) studied samples of these 3 PCBs, each containing 60 percent chlorine. Using the chick embryo test method and a dose level of 3.5 mg (in 0.05 ml of ethanol)/egg, it was demonstrated that AROCLOR 1260 was less toxic than the other 2 materials. Fewer deaths and only an occassional hydropericardium were observed following treatment with AROCLOR 1260, while CLOPHEN A60 and PHENOCLOR DP6 also produced centrilobular liver necrosis and subcutaneous and abdominal edema.

The PCBs remained inconspicuous as possible environmental contaminants until Jensen (1966) assigned a series of hitherto unidentified peaks in chromatograms of wildlife residues to these materials. Holmes et al. (1967) confirmed the presence of PCBs in the eggs and livers of birds in Britain, occurring most frequently and in the highest concentrations in samples from terrestrial predators and marine feeders. Hickey and Anderson (1968) related the drastic decline in populations of peregrine falcons, bald eagles and ospreys to increases

in chlorinated hydrocarbon residues. Reproductive failures were associated with effects on calcium metabolism and decreases in eggshell thickness. It was suggested that derangement of calcium metabolism might result from induction by the chlorinated hydrocarbons of the microsomal enzymes involved in the metabolism of steroidal hormones. The samples in this study were analyzed for chlorinated hydrocarbons but not for PCBs as such.

Risebrough et al. (1968) determined that PCB residues were present in significant quantities in samples from a variety of raptorial and fish-eating birds and also related population declines to derangements in calcium and steroid metabolism induced by the chlorinated hydrocarbons. They showed that a PCB (AROCLOR 1262) was more active than DDE or DDT in increasing polar metabolites of oestradiol by pigeon liver homogenates.

Koeman et al. (1969) reported the presence of PCBs in fish and birds from the Rhine and the Netherlands coastal areas. They observed that the lower chlorinated PCBs occurred more frequently in fish than in sea birds. This suggested that the lower chlorinated compounds are metabolizable and less persistent than compounds of higher chlorine content.

Many additional reports relating to the ecologic impact of the PCBs have continued to appear. Most of these include literature reviews which need not be redetailed here. Pertinent references include Presst et al. (1970), Duke et al. (1970), Peakall and Lincer (1970), Heath et al. (1970), Hansen et al. (1971) and Edwards (1971).

Biologic magnification of PCB concentrations by an early element of the food chain was shown to occur by Keil et al. (1971) who demonstrated magnification of Aroclor 1242 concentrations by a factor of 900 to 1000 by the marine diatom, Cylindrotheca closterium, which can also concentrate and metabolize DDT. A concentration of 0.1 ppm in water sharply retarded growth and RNA synthesis.

Biochemical studies relating to possible mechanisms of action of the PCBs have appeared. Using the 18-hour glycogen response of the immature rat uterus as the assay procedure, Bitman and Cecil (1970) demonstrated a low order of estrogenic activity for the lower chlorinated Aroclors. The minimum effective dose of Aroclors containing 48 percent chlorine or less was approximately twice that of p,p'-DDT whose activity in turn was less than that of diethylstilbesterol by a factor of 4×10^4. No activity was demonstrated for Aroclors containing 54 percent chlorine or more.

Villaneuve et al. (1971) demonstrated induction of carboxylesterase, aniline hydroxylase and aminopyrine N-demethylase in homogenates of liver from female rabbits treated through the gestation period with Aroclor 1254 at a level of 10 mg/kg/day. Reproduction was not affected, however, and no enzyme induction was demonstrated with Aroclor 1221.

Vos and Koeman (1970) found that a PCB could induce chemical porphyria in chickens, Japanese quail and rats. Vos et al. (1971) later showed that porphyria in Japanese quail was associated with induction of liver mitochondrial ALA-synthetase, leading to increased production of δ-aminolevulinic acid, an obligatory precursor for porphyrin synthesis. This induction was brought

about by Aroclor 1260 in which chlorinated dibenzofurans were not detected.

Westoo et al. (1970) reported the occurrence of PCB residues in all of 22 samples of human milk analyzed and Biros et al. (1970) demonstrated the presence of PCB residues in human adipose tissue. Nishizumi (1970) cited the occurrence of poisoning among the general population of western Japan as a result of contamination of rice bran oil by leakage of a chlorinated biphenyl (Kanechlor 400) used as a heat exchange medium in the manufacturing process.

Recent studies have emphasized the characterization of the hepatic changes induced by the polychlorinated biphenyls. Kimbrough (1972) fed Sherman rats Aroclors 1260 and 1254 at dietary levels up to 1000 ppm for 8 months and reported finding hypertrophy of liver cells, cytoplasmic inclusions, lipid accumulation and, at the higher dietary levels, adenofibrosis. Kimbrough and Linder (1974) reported hepatic adenofibrosis and hepatomas to occur in BALB/Cj male mice fed Aroclor 1254 at a level of 300 ppm for 11 months. The authors considered these lesions to be precancerous, but no evidence of malignancy was reported. Norbeck and Allen (1975) observed hepatocellular hypertrophy with proliferation of the endoplasmic reticulum following treatment of male rats with Aroclors 1248, 1254 or 1262 for up to 52 weeks at a dietary level of 100 ppm. They did not report any evidence of hepatocellular carcinoma.

Differences of opinion continue to exist as to the pathologic significance of hepatic changes such as adenofibrosis, cellular hypertrophy, hyperplastic nodules hepatomas, etc. and to the propriety of classifying such changes as hepatocellular carcinoma.

In order to define the toxicologic profile of the PCBs in terms of systems which have been traditionally used for assessment of the hazard of materials, the studies reported in papers which follow were initiated in 1969.

Summaries of this information have been published, Keplinger et al. (1971) and Jenkins et al. (1972).

While much of this data was presented at a conference sponsored by NIEHS at Rougemont, N.C. on December 20-21, 1971, it was unfortunately omitted from the published proceedings (Anon., 1972). Selection of dose levels was based on the permissible ambient air concentration of 0.5 mg/m^3 and the assumption of total absorption of the PCBs contained in an estimated daily inhalation volume of 15m^3 for man. This would result in a human exposure corresponding to 7.5 mg/day, or to approximately 0.1 mg/kg/day. Since a dietary level of 100 ppm would provide a dosage of approximately 10 mg/kg to rats, corresponding to a 100-fold safety factor over the estimated human intake, 100 ppm was selected as the high level for all chronic feeding studies. The human intake estimated from inhalation and complete absorption of PCB-containing air is considerably higher than the 0.001 mg/kg/day adopted by FDA as an acceptable intake for man based on subsequent human data used to establish tolerances for PCBs in food (Anon, 1973).

METHODS

For the chronic toxicity study in rats, weanling animals of the Charles River strain[4] were obtained and organized into a control group and 9 treatment groups each consisting of 50 males and 50 females with 3 treatment groups (designated as) for each of the 3 AROCLORS studied.

All diets were prepared fresh each week by mixing the appropriate AROCLOR at levels of 1, 10 and 100 ppm with a standard ration[5]. Each individually housed rat was offered an amount of food sufficient for ad libitum feeding for one week. Unconsumed food was weighed and food consumption was recorded for 5 rats of each sex from each group weekly for the first 3 months and once monthly for the next 9 months. Periodic spot checks were made thereafter. Water was freely available at all times.

Initially the body weight of each rat was determined. Individual weights were determined weekly for 13 weeks and monthly thereafter.

Hematologic studies, including determinations of hemoglobin concentration, hematocrit value, erythrocyte count and total and differential leukocyte counts, and urine analyses for the presence of glucose, albumin and microscopic elements and determinations of pH and specific gravity were conducted on specimens from 5 male and 5 female rats from the control group and from each of the high dose test groups after 3, 6, 9, 12, 18 and 24 months of treatment.

Clinical chemistry studies which included determinations of blood urea nitrogen concentration (BUN), serum alkaline phosphatase activity (SAP), fasting blood glucose concentration and serum glutamic pyruvic transaminase activity (SGPT) were conducted on the same animals at the same time intervals.

A complete gross autopsy examination was performed on each animal which died during the study and unless precluded by advanced postmortem autolysis all tissues were preserved in formalin for histopathologic study.

After 3, 6 and 12 months of testing, 5 animals of each sex from each group were sacrificed and subjected to complete gross pathologic examination. Organ weights were recorded for liver, kidneys, spleen, gonads, heart and brain, and organ to body weight and organ to brain weight ratios were calculated. These data were subjected to an Analysis of Variance and significant disclosures were further studied by "t"-tests.

Microscopic examinations were conducted on approximately 33 tissues from all control and high treatment level animals sacrificed after 3, 6 and 12 months of testing in which all tissues had been fixed in 10% formalin and stained with hematoxylin-eosin.

At termination of the study after 24 months of treatment, the remaining animals were sacrificed and all were subjected to gross and microscopic examination.

A tabulation of the incidence of tumor occurrence for each group was made at the conclusion of the investigation and data relative to location, weight, size and pathologic classification for each tumor were recorded.

Because of subsequent questions raised regarding the incidence and character of hepatic changes, additional liver sections from all animals at all dose levels were ~~subsequently~~ cut and examined by light microscopy after staining with hematoxylin and eosin.

RESULTS

Body Weights and Weight Gains:

Except for a statistically significant (99% confidence level) depression of weight gain at the 24-month point for female rats fed 100 ppm of AROCLOR 1254, no other effect was observed.

Food Consumption:

Food consumption measurements during the first 12 months of the study and periodic checks thereafter revealed no significant differences between the control group and any test group.

Mortality and Reactions:

The number of animals dying and the time frequency distribution of deaths did not differ among treatment and control groups.

Hematologic and Blood Chemistry Studies:

Values for all parameters were within the normal range for the albino rat. No significant differences between values for the control groups and those for any test group were observed.

Urinalysis

No differences from control data were observed for test animals of any group.

Pathologic Studies

Gross pathologic findings at the 3, 6 and 12 month sacrifices disclosed several randomly occurring intergroup differences in organ weights and organ to body weight and organ to brain weight ratios but no consistent dose-related response was apparent. At the 24-month sacrifice, it was determined that each of the 3 Aroclors led to increased liver weights and liver to body weight and liver to brain weight ratios, in females only in the case of Aroclor 1242. The data for liver weights and ratios are shown in Table 1. No other consistent, dose-related effects on organ weights were observed.

Histopathologic examination revealed treatment-related hepatic changes with each of the Aroclors. The liver effects, which were most pronounced at the time of the terminal (24-month) sacrifice, consisted of an hepatocellular alteration beginning as focal hypertrophy which progressed to nodular lesions of hyperplasia and hypertrophy. In a few animals at the 100 ppm level, benign liver tumors (hepatoma or cholangiohepatoma) were also present. The hypertrophic cells contained large amounts of light staining cytoplasm which is probably rich in glycogen, lipid, and smooth endoplasmic reticulum. In some sections, ring-shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells or they were marginated along the cytoplasmic membrane.

The nodules of hyperplastic to hypertrophic hepatocytes (designated as nodular hyperplasia) occupied larger areas which encompassed several lobules and often compressed the surrounding hepatocytes of the normal liver parenchyma.

Those lesions classified as hepatomas or cholangiohepatomas were usually larger nodular lesions which showed evidence of confluence of smaller nodules or some variation in cell size, shape, and staining. The latter neoplasm contained ductular structures which resembled bile ducts. In the absence of metastasis, invasion, severe basophilia, numerous mitoses, anaplasia or other evidence of malignancy, these lesions were classified as benign liver neoplasms rather than malignant neoplasms (hepatocellular carcinomas).

With the exception of the vacuolar changes in the cytoplasm of hepatocytes, identified as lipid by the Oil Red O staining method on frozen sections of formalin-fixed tissue, the more severe hepatocellular alterations were confined to animals sacrificed after 24 months with Aroclors 1242 and 1264. With Aroclor 1260, some hypertrophic and hyperplastic hepatocytes were observed after 12 months. Data relating to these hepatic alterations are shown in Tables 2 - 4.

Other minor degenerative lesions seen at terminal sacrifice in the livers of control and treated animals were judged to be unrelated to treatment.

Hyperplasia of the transitional epithelium of the urinary bladder, usually associated with calculi or cystitis, was observed in 1 control animal and in 1 or 2 animals of each group treated with Aroclors 1242 and 1254. This change was not observed among animals treated with Aroclor 1260. The absence of a dose correlation with regard to either incidence or severity makes it doubtful that these bladder lesions are related to treatment with the Aroclors.

No other significant histopathologic changes were observed. The incidence of all types of tumors for all groups, including the control group, was as would be expected for a random population of rats at the age of 2 years. The tumor findings are shown in Table 6 and summarized in Table 5. The predominant neoplasms were mammary fibroadenomas. Adenomas of the pituitary, thyroid, parathyroid, adrenals, pancreas and dermal fibromas occurred with much lower frequencies. Tumors judged to be malignant were of random occurrence and included adenocarcinoma of pancreas and mammary gland and lymphoreticular neoplasms (lymphosarcoma, reticulum cell sarcoma) arising in the lymph nodes and spleen.

DISCUSSION

From the results of this study it is concluded that 100 ppm is an effect level for each of the Aroclors investigated. The target organ is the liver, and the effect is characterized by increased liver weights and increased liver/body weight and liver/brain weight ratios accompanied by the hepatocellular alterations discussed above. These alterations were slow to develop, their incidence being related to both dose level and duration of treatment. There is no evidence that the proliferative or neoplastic changes in the liver are malignant or would progress to malignancy and the incidence and types of neoplasms provide no evidence of carcinogenicity of the Aroclors tested. The no-effect level is judged to be about 10 ppm.

TABLE 1

Liver Weight and Ratio Data for Albino Rats Treated with Aroclors 1242, 1254 and 1260

Test Material	Dietary level (ppm)	Liver Weight (g) Males	Liver Weight (g) Females	Liver/Body Wgt. Ratio (g/100g) Males	Liver/Body Wgt. Ratio (g/100g) Females	Liver/Brain Wgt. Ratio (g/100g) Males	Liver/Brain Wgt. Ratio (g/100g) Females
None	-	22.0	16.3	3.5	3.1	10.1	8.4
Aroclor 1242	1	21.9	15.7	2.9	3.0	10.0	8.0
	10	22.3	17.1	3.2	3.2	10.2	8.5
	100	25.6	22.4[a]	4.0	4.8[a]	11.9	11.6[a]
Aroclor 1254	1	19.5	16.1	3.0	3.1	8.6[b]	8.3
	10	23.9	19.5	3.2	3.8[b]	11.4[b]	10.3
	100	30.2[a]	32.1[a]	4.8[a]	8.6[a]	14.1[a]	17.1[a]
Aroclor 1260	1	22.0	16.6	3.4	3.4	9.9	8.6
	10	24.1	18.1	3.7[b]	3.2	11.2	9.3
	100	29.9[a]	22.7[a]	4.7[a]	4.4[a]	13.4[a]	11.6[b]

[a] Statistically significant at the 99 percent confidence level

[b] Statistically significant at the 95 percent confidence level

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TABLE 2

Primary Liver Lesions Among Albino Rats Treated With

Aroclor 1242

Finding	3 Mo. Sacrifice				6 Mo. Sacrifice				12 Mo. Sacrifice				24 Mo. Sacrifice			
	Incidence of Finding at Dose Level (ppm) of															
	0	1	10	100	0	1	10	100	0	1	10	100	0	1	10	100
Vacuolar Change	2/10	0/8	2/10	1/9	1/10	0/10	0/8	0/9	1/10	2/10	4/10	0/9	1/23	7/31	8/30	9/20
Focal Hypertrophy	0	0	0	0	0	0	0	0	0	0	0	1	0	2	3	8
Nodular Hyperplasia	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	8
Hepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Ductular Hyperplasia	0	0	0	1	0	0	0	0	1	0	1	0	5	3	3	3
Cholangio-Hepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Hepatocellular Necrosis	0	1	0	0	1	1	0	0	0	0	0	0	1	1	1	0

—Denominator in each case indicates number of animals examined

MONS 211811

TABLE 3

Primary Liver Lesions Among Albino Rats Treated With

Aroclor 1254

Finding	3 Mo. Sacrifice				6 Mo. Sacrifice				12 Mo. Sacrifice				24 Mo. Sacrifice			
	Incidence of Finding at Dose Level (ppm) of															
	0	1	10	100	0	1	10	100	0	1	10	100	0	1	10	100
Number examined	10	10														
Vacuolar Change	2/10[a]	3/10	3/10	1/10	1/10	0/10	0/10	0/10	1/10	1/10	4/10	1/10	1/23	8/31	8/26	13/2
Focal Hypertrophy	0	0	0	0	0	0	0	4	0	0	4	2	0	3	4	13
Nodular Hyperplasia	0	0	0	0	0	0	0	0	0	0	0	0	1	0	3	13
Hepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4
Ductular Hyperplasia	0	0	0	0	0	0	0	0	1	1	1	0	5	6	3	4
Cholangiohepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Hepatocellular Necrosis	0	1	1	1	1	2	0	2	0	0	0	1	1	3	1	1

[a] Denominator in each case indicates number of animals examined.

MONS 211812

TABLE 4

Primary Liver Lesions Among Albino Rats Treated With

Aroclor 1260

Finding	3 Mo. Sacrifice				6 Mo. Sacrifice				12 Mo. Sacrifice				24 Mo. Sacrifice			
	Incidence of Finding at Dose Level (ppm) of															
	0	1	10	100	0	1	10	100	0	1	10	100	0	1	10	100
Vacuolar Change	2/10[a]	0/11	4/10	3/10	1/10	1/6	2/5	5/9	1/10	2/9	5/10	3/9	1/23	5/25	6/23	10/2
Focal Hypertrophy	0	0	0	2	0	0	0	3	0	0	0	4	0	3	9	11
Nodular Hyperplasia	0	0	0	0	0	0	0	0	0	0	0	1	1	0	4	7
Hepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5
Ductular Hyperplasia	0	0	0	0	0	0	0	0	1	1	0	2	5	6	5	14
Cholangiohepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Hepatocellular Necrosis	0	0	0	0	1	0	1	0	0	0	0	0	1	4	2	6

[a] Denominator in each case indicates number of animals examined

MONS 211813

TABLE 5

Tumor Findings Among Albino Rats Treated With

Aroclors 1242, 1254 and 1260

Test Material	Dietary Level (ppm)	No. of Animals Examined	Tumor of Incidence			No. of Animals with Tumors
			Benign	Malignant	Total[a]	
None	-	26	9	2	13	10
Aroclor 1242	1	29	17	2	19	14
	10	27	14	1	17	13
	100	21	4	0	6	5
Aroclor 1254	1	34	15	1	16	13
	10	24	13	0	13	11
	100	27	12	3	15	15
Aroclor 1260	1	28	10	0	10	7
	10	23	12	0	12	9
	100	28	9	3	12	11

[a] 90% of tumors occurred in animals sacrificed at 24 mo; 97% in animals treated for 22 - 24 mo

TABLE 6

Tumor Findings Among Albino Rats Treated with Aroclors 1242, 1254 and 1260

Incidence of Neoplasms after treatment with Aroclors (ppm)

Tumor Type and Tissue	Control	1242			1254			1260		
		1	10	100	1	10	100	1	10	100
Mammary Adenocarcinoma-Skin		1	1		1					
Mammary Fibroadenoma-Skin	8	13	8	1	9	7	10	5	6	4
Mammary Adenoma-Skin	1				1					
Islet Cell Adenoma-Pancreas			1	1		1	1		1	2
Follicular Adenoma-Thyroid						1				
Adenoma-Parathyroid			1		2	1				
Acinar Cell carcinoma-Pancreas	1						1			
Pheochromocytoma-Adrenal	1		1	1						
Granulosa Cell Tumor-Ovary		1		1				1		
Chromophobe Adenoma-Pituitary		2	3	1	2	2		4	3	2
Dermal Fibroma-Skin			1				1		2	1
Myofibroma-Uterus		1								
Dermal Lipoma-Skin					1					
Lymphosarcoma-Spleen		1								
Lymphosarcoma-Lymph Node							1			1
Lymphosarcoma-Liver										2
Reticulum Cell Sarcoma-Lymph Node	1						1			
Number Animals Examined	26	29	27	21	34	24	27	28	23	28
Number Benign Neoplasms	10	17	15	5	15	12	12	10	12	9
Number Malignant Neoplasms	2	2	1	0	1	0	3	0	0	3
Number Animals with Neoplasms[a]	10	14	13	5	13	11	15	7	9	11

[a] 90% of tumors occurred in animals sacrificed after 24 months; 97% in those surviving 22 - 24 months

FOOTNOTES

1. Aroclors® 1242, 1254 and 1260 ~~Monsanto Company, St. Louis, Missouri~~ Capacitor dielectrics
2. Present Address: 624 N. Abrego Dr., Green Valley, Arizona 85614
3. ~~Medical~~ Dept.: Medical and Environmental Health, Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, Missouri 63166
4. Charles River Breeding Laboratories, North Wilmington, Massachusetts
5. Purina Rat Chow, Ralston Purina Co., St. Louis, Missouri

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