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BIOASSAY OF AROCLOR 1254 FOR POSSIBLE CARCINOGENICITY (USED AS A REFERENCE IN OU1, OU4 AND OU5 RI REPORTS)

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REPORT

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National Cancer Inst, Bethesda, Md Carcinogenesis Program

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BIOASSAY OF AROCLOR® 1254 FOR POSSIBLE CARCINOGENICITY

CAS No. 27323-18-8

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16. Abstracts

A bioassay of Aroclor 1254 for possible carcinogenicity was conducted by administering the test chemical in feed to Fischer 344 rats. Groups of 24 rats of each sex were administered Aroclor 1254 at one of three doses, either 25, 50, or 100 ppm, for 104-105 weeks. Matched controls consisted of groups of 24 untreated rats of each sex.

Survival among males, but not among females, showed a significant dose-related trend. Adequate numbers of animals of both sexes survived for meaningful statistical analyses of the incidences of tumors. The combined incidences of lymphomas and leukemias showed a significant dose-related trend in males. However, the direct comparisons of each treated group with those of the matched controls were not significant, and the tumors cannot clearly be related to treatment with Aroclor 1254. Hepatocellular adenomas and carcinomas were found in the treated groups, but not in the controls. Although the incidences of tumors were not significant, the occurrence of the hyperplastic nodules appeared to be related to treatment. (continued on attached sheet)

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16. ...
It is concluded that under the conditions of this bioassay, Aroclor 1254 was not carcinogenic in Fischer 344 rats; however, a high incidence of a spectrum of proliferative lesions of the liver in both male and female rats was related to treatment. In addition, the carcinomas of the gastrointestinal tract may be associated with treatment in both males and females.

BIOASSAY OF

AROCLOR® 1254

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

DHEW Publication No. (NIH) 78-838

BIOASSAY OF
AROCLOR® 1254
FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health

CONTRIBUTORS: This report presents the results of the bioassay of Aroclor® 1254 for possible carcinogenicity, conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. The bioassay was conducted by Stanford Research Institute, Menlo Park, California, initially under direct contract to NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design and doses were determined by Drs. R. R. Bates[1,2], D. C. L. Jones[3], D. P. Sasmore[3], C. W. Newell[3], and R. M. Elashoff[4], and Mr. W. E. Davis[3]. The principal investigator was Dr. D. C. L. Jones; the technical supervisor of animal treatment, observation, and data handling was Mr. W. E. Davis; necropsy and tissue fixation were supervised by Dr. D. P. Sasmore.

Histopathologic examinations were performed by Dr. H. Elster[5] and the diagnoses included in this report represent his interpretation. Neoplasms and compound-related hyperplastic lesions were reviewed by Drs. W. M. Busey[6] and J. F. Hardisty[6], who also prepared the interpretive pathology summary included in this report.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute[7]. The statistical analyses were performed by Dr. J. R. Joiner[8], using methods selected for the bioassay program by Dr. J. J. Gart[9]. Chemicals used in this

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bioassay were analyzed at Stanford Research Institute, and the analytical results were reviewed by Dr. C. W. Jameson[8].

This report was prepared at Tracor Jitco[8] under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. Marshall Steinberg, Director of the Bioassay Program; Drs. J. F. Robens and R. W. Fogleman, toxicologists; Dr. R. L. Schueler, pathologist; Ms. L. A. Waitz and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley.

The statistical analysis was reviewed by members of the Mathematical Statistics and Applied Mathematics Section of NCI[9]: Dr. John J. Gart, Mr. Jun-mo Nam, Dr. Hugh M. Pettigrew, and Dr. Robert E. Tarone.

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SUMMARY

A bioassay of Aroclor® 1254 for possible carcinogenicity was conducted by administering the test chemical in feed to Fischer 344 rats.

Groups of 24 rats of each sex were administered Aroclor® 1254 at one of three doses, either 25, 50, or 100 ppm, for 104-105 weeks. Matched controls consisted of groups of 24 untreated rats of each sex. All surviving rats were killed at 104-105 weeks.

Mean body weights of males and females receiving mid and high doses and females receiving low doses of the chemical were consistently below those of the corresponding controls, beginning at about week 10 of the study. The decrease in survival among males, but not among females, showed a significant dose-related trend. Adequate numbers of animals of both sexes survived for meaningful statistical analyses of the incidences of tumors.

The combined incidences of lymphomas and leukemias showed a significant dose-related trend in males (controls 3/24, low-dose 2/24, mid-dose 5/24, high-dose 9/24, $P = 0.009$). However, the direct comparisons of each dosed group with those of the matched controls were not statistically significant, and the tumors cannot clearly be related to administration of with Aroclor® 1254.

Hepatocellular adenomas and carcinomas were found in the dosed groups, but not in the controls (males: mid-dose 1/24, high-dose 3/24; females: mid-dose 1/24, high-dose 2/24). Additionally, a high incidence of nonneoplastic hyperplastic nodules was noted in the dosed animals (males: controls 0/24, low-dose 5/24, mid-dose 8/24, high-dose 12/24; females: controls 0/23, low-dose 6/24, mid-dose 9/22, high-dose 17/24). Although the incidences of tumors were not significant, the occurrence of the hyperplastic nodules appeared to be related to administration of the chemical.

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In the stomach, jejunum, or cecum, adenocarcinomas were observed in two dosed males and in two dosed females as well as a carcinoma in one dosed male. None of these lesions was found in control animals in this study. Historical incidences of these tumors at this laboratory (6/500 males [1%], 2/600 females [0.3%] suggest that the lesions -- although not statistically significant -- may be related to the administration of Aroclor® 1254.

It is concluded that under the conditions of this bioassay, Aroclor® 1254 was not carcinogenic in Fischer 344 rats; however, a high incidence of hepatocellular proliferative lesions in both male and female rats was related to administration of the chemical. In addition, the carcinomas of the gastrointestinal tract may be associated with administration of Aroclor® 1254 in both males and females.

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I. INTRODUCTION

Aroclor® (CAS 27323-18-8; NCI C02664) is the registered trademark of the Monsanto Chemical Company for their polychlorinated biphenyls (PCBs). PCBs were developed in 1929 primarily for use as heat transfer fluids and dielectrics (insulators). Aroclor® 1254, a biphenyl containing approximately 54% chlorine, is a nonflammable heat transfer agent which functions in the range of 250-360°C (Hubbard, 1964; Poffenberger and Hubbard, 1965).

PCBs have been used in transformers and capacitors; as industrial fluids in hydraulic, gas turbine, and vacuum pumps; as lubricants and plasticizers (for flame retardation); and as additives in surface coatings, inks, papers, adhesives, sealants, pesticides, and dyes for carbonless duplicating paper (Hubbard, 1964; Broadhurst, 1972). These compounds tend to accummulate in the biosphere (Finklea et al., 1972). Because of direct and indirect human and animal exposure, food contamination, and environmental pollution from many of these uses, the marketing of PCBs has been markedly curtailed in recent years (EPA, 1977).

This bioassay of Aroclor® 1254 was conducted as a part of a larger study designed to assess the combined effects of a group of known or suspected carcinogens. Only the results of the study of the administration of Aroclor® 1254 are reported herein.

II. MATERIALS AND METHODS

A. Chemical

Aroclor® 1254 was obtained in a single batch (Lot No. KB01-604) from the Monsanto Chemical Company, St. Louis, Missouri. The identity and relative purity of the test chemical were confirmed at Stanford Research Institute. Elemental analyses (C, H, Cl) indicated 54.67% chlorine. Gas-liquid chromatography and mass spectroscopy showed that the Aroclor® 1254 contained at least 18 isomers of polychlorinated biphenyls ranging from 4 to 7 chlorine atoms per molecule. Identity was confirmed by nuclear magnetic resonance, infrared, and ultraviolet spectra, which were in agreement with the structure. No attempt was made to identify or quantitate impurities.

The chemical was stored at room temperature in 1-gallon amber glass jars.

B. Dietary Preparation

All diets were formulated every 2 weeks using Low Fat Lab Chow® (Ralston Purina Co., St. Louis, Mo.). A stock diet was first prepared by hand mixing a weighed amount of the Aroclor® 1254 with corn oil (Staley Manufacturing Co., Orange, Calif.) and adding this mixture to a small amount of feed which was also mixed by

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hand. More corn oil and feed were then added to give a final concentration of 3,000 ppm Aroclor® 1254 and 3% corn oil and then machine mixed in a Hobart blender for 30 minutes. Each stock diet was analyzed for content of Aroclor® 1254 by a method involving extraction, Florisil® chromatography, and quantitation by gas-liquid chromatography. Concentrations of 3,000 ppm ± 10% were considered acceptable for use in preparing the test diets. Aroclor® 1254 at 3,000 ppm in the stock diet was found to be stable when held in rat feeders at room temperature for a 2-week period.

To obtain test diets having appropriate concentrations of Aroclor® 1254, the stock diet was diluted, as required, with control diet containing 3% corn oil and mixed in a Hobart blender. The stock and test diets were stored at room temperature in covered plastic containers.

C. Animals

Male and female Fischer 344 rats, obtained through contracts of the Division of Cancer Treatment, National Cancer Institute, were used in these bioassays. The rats were obtained from Simonsen Laboratory, Gilroy, California. On arrival at the laboratory, all animals were quarantined for 2 weeks as an acclimation period. Following this period, all males gaining less than 25

grams, all females gaining less than 15 grams, and all unhealthy animals were culled. The remaining animals were assigned to cages, one per cage, until each cage contained three animals. Cages were then numbered and assigned to control and treated groups using a computer-generated randomization table. Rats were ear-clipped for individual identification.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. The temperature was maintained at 22°C with a range of 21-24°C, and the relative humidity was maintained at approximately 45%. The room air was changed 10 times per hour and was maintained under positive pressure to the access halls. Fluorescent lighting provided illumination 12 hours per day. Food and water were available *ad libitum*. Drinking water was softened, filtered, sterilized with ultraviolet light, and supplied by means of an automatic watering system.

The rats were housed three per cage in polycarbonate cages equipped with disposable polyester woven filter tops. Autoclaved hardwood chips (Iso-Dri®, Becton, Dickinson, and Carworth, Warrensburg, N.Y.) were used as bedding. The cages were changed, washed, and provided with fresh bedding twice per week. Filter tops were replaced once per month.

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Rats fed Aroclor® 1254 were housed in the same room as rats treated with aflatoxin B_1 (CAS 1162-65-8), lead (II) acetate (CAS 301-04-2), hexachlorophene (CAS 70-30-4), or dieldrin (CAS 60-57-1) in the feed.

E. Subchronic Studies

Subchronic feeding studies were conducted with male and female Fischer 344 rats to estimate the maximum tolerated dose of Aroclor® 1254, on the basis of which low, mid, and high concentrations (hereinafter referred to as "low doses", "mid doses", and "high doses") were determined for administration in the chronic studies. In the subchronic studies, Aroclor® 1254 was added to feed in concentrations of 25, 50, 100, 200, or 400 ppm. Treated and control groups each consisted of 15 male and 15 female rats. The chemical was provided in feed to the treated groups for 8 weeks.

The animals receiving 400 ppm were inactive, had occasional diarrhea and tremors, and failed to gain weight. At this dose 4/15 males and 1/15 females died. Enlarged livers were observed on gross examination, and histologically atypical hyperplasia was observed. At 200 ppm, body weights for both males and females were approximately 70% of those of the controls, and mild hepatocellular pleomorphism was seen histologically in the livers.

Rats treated with 25 ppm Aroclor® 1254 had enlarged livers, but no evidence of histologic abnormalities. Weight gain in all animals treated at doses lower than 200 ppm was comparable to that in controls, and there was no mortality below 400 ppm. The low, mid, and high doses for the chronic studies were set at 25, 50, and 100 ppm.

F. Design of Chronic Studies

The design of the chronic studies is shown in table 1.

G. Clinical and Pathologic Examinations

All animals were observed daily for signs of toxicity and palpated for masses at each weighing. Animals were weighed individually every other week for 12 weeks, and once every fourth week for the remainder of the study. Animals that were moribund at the time of clinical examination were killed and necropsied.

The pathologic evaluation consisted of gross examination of major organs and tissues from killed animals and from animals found dead. The following tissues were routinely examined microscopically from both treated and control animals: lungs and bronchi, spleen, liver, testes, pituitary, kidney, and brain. In addition, sections of stomach, urinary bladder, thyroid, uterus, and ovary were examined in a majority of the controls; these

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Table 1. Design of Aroclor® 1254 Chronic Feeding Studies in Rats

Sex and Treatment Group	Initial No. of Animals[a]	Aroclor® 1254 in Diet[b] (ppm)	Time on Study	
			Treated[c] (weeks)	Untreated (weeks)
Males				
Matched-Control	24	0		105
Low-Dose	24	25	105	
Mid-Dose	24	50	105	
High-Dose	24	100	105	
Females				
Matched-Control	24	0		105
Low-Dose	24	25	104-105	
Mid-Dose	24	50	104-105	
High-Dose	24	100	105	

[a]All animals were 53 ± 2 days of age when placed on study.

[b]All diets contained 3% corn oil.

[c]All animals were started on study within 2 days of each other.

tissues were taken from treated rats only if a lesion was found at necropsy. Occasionally, additional tissues were examined microscopically. Gross lesions from all animals were also examined microscopically. The different tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Special staining techniques were utilized when indicated for more definitive diagnosis.

A few of the tissues selected by design from some animals were not examined, particularly from those animals that died early. Thus, the number of animals from which particular organs or tissues were microscopically examined varies, and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

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These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals necropsied (denominator).

The purpose of the statistical analyses of tumor incidence is t determine whether animals receiving the test chemical developed a

significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of treated animals at each dose level. When results for a number of treated groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the

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first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each treated group compared to its control was calculated

from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result ($P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit

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indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS

A. Body Weights and Clinical Signs

Beginning at about week 10 for the high-dose groups and about week 20 for the mid-dose groups, mean body weights of both male and female rats fed Aroclor® 1254 at the doses used in this bioassay were lower than those of the controls (figure 1). Mean body weights of low-dose males appeared comparable to those of controls throughout the study, while mean body weights of low-dose females were lower during the second year of the study. At week 30, an intercurrent respiratory infection in the colony caused weight loss, but no deaths; animals recovered within 30 days without treatment for the infection.

Clinical signs associated with administration of Aroclor® 1254 included alopecia, amber-colored urine, facial edema, exophthalmos, and cyanosis. These signs were apparent among the high-dose groups beginning at week 72 and among the mid-dose groups at week 104 of the study.

B. Survival

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats fed Aroclor® 1254 in the diet

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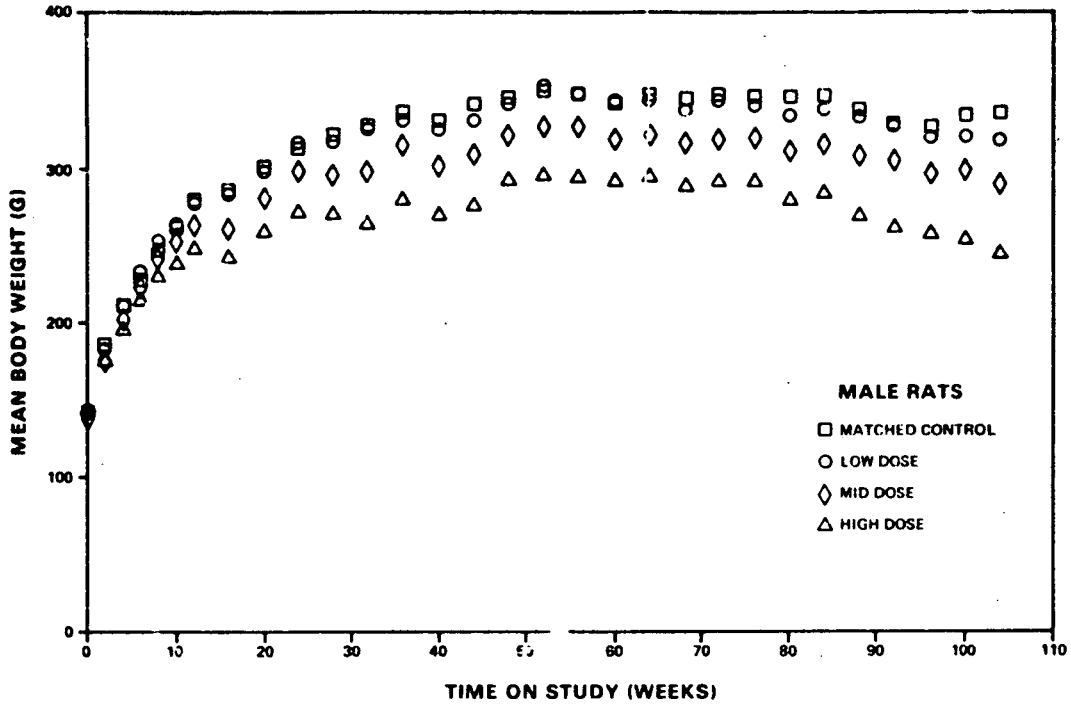


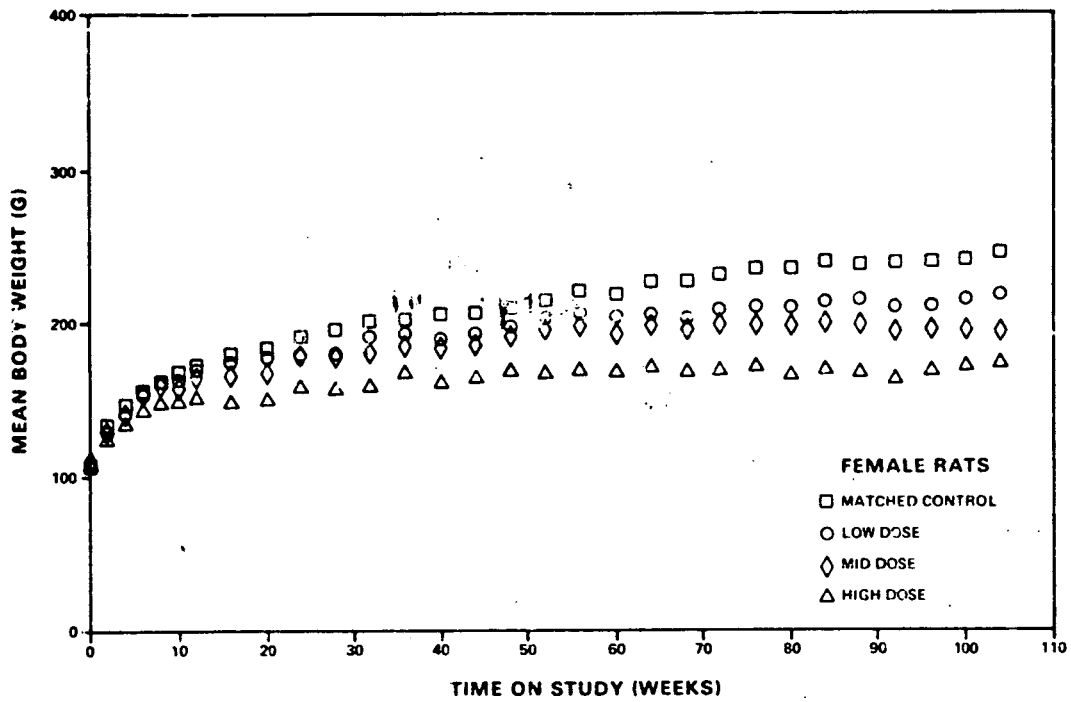
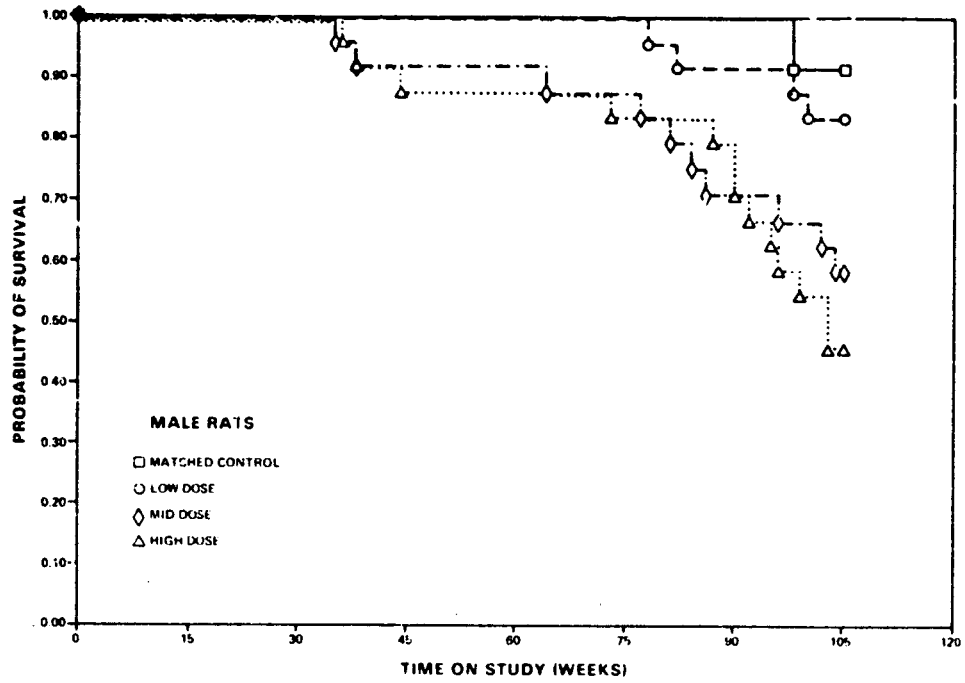


Figure1. Growth Curves for Rats Fed Aroclor® 1254 in the Diet



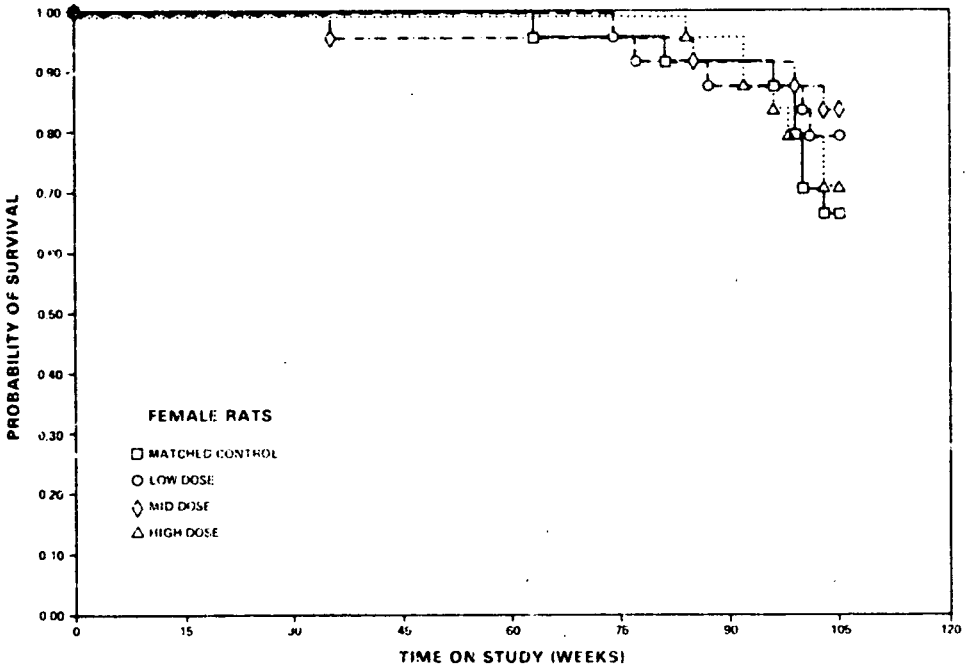


Figure 2. Survival Curves for Rats Fed Aroclor® 1254 in the Diet

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at the doses used in this study, together with those of the controls, are shown in figure 2.

For males, the result of the Tarone test for positive dose-related trend in mortality over the period is significant ($P < 0.001$); 92% of the control, 83% of the low-dose, 58% of the mid-dose, and 46% of the high-dose rats survived to the end of the study. Among females, the Tarone test showed a probability level greater than 0.05. In females, 67% of the control, 79% of the low-dose, 83% of the mid-dose, and 71% of the high-dose rats survived to termination of the study. Sufficient numbers of rats of both sexes were available for meaningful statistical analyses of the incidences of late-developing tumors.

C. Pathology

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix B, tables B1 and B2.

A variety of neoplastic processes were observed in both the control and treated rats, and, with the exception of the liver, the incidences of these neoplasms were comparable in the control and treated groups. Interstitial-cell tumors of the testes were present in the majority of control and treated males. The next most frequently observed neoplasm was leukemia of either the

granulocytic or lymphocytic type, and it involved multiple organs. The incidence of this neoplastic process was comparable in the control and treated groups. The following neoplasms were also present in some control and treated rats but without compound association: squamous-cell carcinomas of the skin, alveolar/bronchiolar adenomas of the lung, and uterine endometrial stromal polyps.

No proliferative lesions of the hepatocytes were found in the control animals in the study. The incidence of these proliferative lesions among treated animals was as follows:

	MALES			FEMALES		
	Low Dose	Mid Dose	High Dose	Low Dose	Mid Dose	High Dose
Number of Animals Necropsied	(24)	(24)	(24)	(24)	(22)	(24)
Nodular Hyperplasia	5	8	12	6	9	17
Adenoma, NOS*	0	0	1	0	1	2
Hepatocellular Carcinoma	0	1	2	0	0	0
Total Incidence	5	9	15	6	10	19

*Not otherwise specified

The areas of nodular hyperplasia appeared to be microscopically similar to what is currently termed "focal areas of cellular

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alteration" (Squire and Levitt, 1975). Neither this lesion nor any hepatocellular adenomas or carcinomas were diagnosed in the controls. The hepatocellular carcinomas were characterized microscopically by large foci of proliferating hepatocytes involving several lobules. These hepatocytes were bizarre in appearance, sometimes containing two or more nuclei. The sinusoidal architecture was lost, and frequently mitotic figures were present. These neoplasms compressed the surrounding normal liver tissue, and the cell plates usually were three to five cells in thickness. The hepatocellular adenomas were characterized by large foci involving several lobules of swollen, severely vacuolated hepatocytes still maintaining the general sinusoidal architecture of the liver. In general, the foci of nodular hyperplasia involved two or more hepatic lobules and contained hepatocytes whose tinctorial properties were distinctly different from those of the surrounding liver tissue. Occasionally, these foci would contain severely vacuolated hepatocytes, and in some instances, there were small foci of basophilic hepatocytes.

The results of the histopathologic examination indicate that the administration of Aroclor® 1254 at the three doses used in this study had an effect with respect to proliferative lesions of the liver and gastrointestinal tract. There were three hepatocellular carcinomas in male rats and a dose-related increase in

nodular hyperplasia in both the male and female animals. There was one carcinoma and four adenocarcinomas in the gastrointestinal tract of treated rats. These neoplastic lesions are seen only sporadically and at a low incidence in the Fischer 344 rat; in this study no lesions of these types were diagnosed in either the male or female controls.

D. Statistical Analyses of Results

Tables C1 and C2 in Appendix C contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and with an incidence of at least 5% of one or more treated groups.

In male rats, the results of the Cochran-Armitage test for positive dose-related trend in the incidences of leukemia and of combined leukemia and lymphoma are significant ($P = 0.022$ and $P = 0.009$, respectively). The corresponding results of the Fisher exact test, however, are not significant in any treated group when compared with the controls. There is no other incidence of tumors at any specific site in either sex which is statistically significant. A significant Cochran-Armitage trend in the negative direction is observed in the incidence of interstitial-cell tumor of the testis, where the incidence in the controls exceeds those in the mid- and high-dose groups.

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In each of the 95% confidence intervals of relative risk, shown in the tables, the value of one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by Aroclor® 1254, which could not be detected under the conditions of this test.

IV. DISCUSSION

At the doses used in this bioassay, Aroclor® 1254 was toxic to both male and female Fischer 344 rats, as shown by the dose-related depression of mean body weights and the clinical signs which occurred during the second year. Mean body weights of mid- and high-dose males and of all treated females were consistently lower than those of the corresponding controls after the initial growth phase. An intercurrent respiratory infection at week 30 resulted in temporary weight loss, but no deaths, in all groups including the controls; the animals later recovered without treatment. Clinical signs including alopecia, amber-colored urine, facial edema, exophthalmos, and cyanosis occurred in the high-dose groups beginning at week 72 and in the mid-dose groups at week 104. Survival among males, but not among females, showed a significant dose-related trend. Adequate numbers of animals of both sexes survived for meaningful statistical analyses of the incidences of tumors.

The combined incidences of lymphoma and leukemia in males were significant (controls 3/24, low-dose 2/24, mid-dose 5/24, high-dose 9/24, P = 0.009), using the Cochran-Armitage test for positive dose-related trend, but not in females (controls 4/24, low-dose 6/24, mid-dose 6/24, high-dose 6/24). Since the results of the Fisher exact test for increased incidence were not

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significant for any of these groups, the occurrence of these lesions cannot clearly be related to the administration of Aroclor® 1254.

Hepatocellular changes including hyperplastic nodules, adenomas, and carcinomas were found in treated animals, but none of these lesions were found in control animals in this study. Hepatocellular carcinomas were observed in one mid-dose and two high-dose males, and hepatocellular adenomas were observed in one high-dose male, one mid-dose female, and two high-dose females. Nodular hyperplasia was diagnosed with a dose-related frequency in the low-, mid-, and high-dose male and female rats. Although the incidences of the tumors were not significant, the occurrence of these proliferative lesions appeared to be related to treatment.

In the stomach, jejunum, or cecum, adenocarcinomas were observed in two treated males and in two treated females as well as a carcinoma in one treated male. None of these lesions was found in control animals in this study, suggesting that the lesions -- although not statistically significant -- may be related to the administration of Aroclor® 1254.

The toxicity of polychlorinated biphenyls (PCBs) has been reviewed by several groups, including the Environmental

Protection Agency (1976), National Research Council (1976), Panel on Hazardous Trace Substances (1972), and International Agency for Research on Cancer (1974). Kimbrough et al. (1972) demonstrated hepatic adenofibrosis in male and female Sherman rats fed Aroclor® 1254 at up to 500 ppm for 8 months. A similar PCB, Kanechlor® 500, fed for 12 months to male Wistar rats, induced nodular hyperplasia at doses of 100-1,000 ppm; at 1,000 ppm, cholangiofibrosis also was induced (Ito et al., 1974). Keplinger et al. (1971; see also EPA Critera Document PCBs, 1976) fed Charles River rats up to 100 ppm Aroclor® 1254 for 24 months and reported originally that there was no significant increase in hepatic tumors in this study; re-evaluation of the liver slides, however, indicated a significant incidence of nodular hyperplasia in treated rats, compared with controls. Ito et al. (1973) observed nodular hyperplasia and well-differentiated hepatocellular carcinoma in male strain dd mice fed 500 ppm Kanechlor® 500 for 8 months, and Kimbrough and Linder (1974) observed adenofibrosis and hepatomas in BALB/cJ mice fed 300 ppm Aroclor® 1254 for 11 months.

In a study of a closely related PCB, Kimbrough et al. (1975) observed hepatocellular carcinomas in female Sherman rats fed 100 ppm Aroclor® 1260 for 21 months.

It is concluded that under the conditions of this bioassay,

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Aroclor® 1254 was not carcinogenic in Fischer 344 rats; however, a high incidence of hepatocellular proliferative lesions in both male and female rats was related to treatment. In addition, the carcinomas of the gastrointestinal tract may be associated with treatment in both males and females.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS

IN RATS FED AROCLOR® 1254 IN THE DIET

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TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED AROCLOR® 1254 IN THE DIET

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS NECROPSIED	24	24	24	24
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	24
INTEGUMENTARY SYSTEM				
*SKIN	(24)	(24)	(24)	(24)
SQUAMOUS CELL PAPILLOMA	1 (4%)			
SQUAMOUS CELL CARCINOMA				1 (4%)
*SUBCUT TISSUE	(24)	(24)	(24)	(24)
SQUAMOUS CELL CARCINOMA	1 (4%)			1 (4%)
FIBROMA		1 (4%)	1 (4%)	
MYXOMA		1 (4%)		
RESPIRATORY SYSTEM				
*LUNG/BRONCHUS	(23)	(24)	(23)	(24)
PAPILLOMA, NOS		1 (4%)		
*LUNG	(23)	(24)	(23)	(24)
CARCINOMA, NOS, METASTATIC	1 (4%)			
ALVEOLAR/BRONCHIOLAR ADENOMA			2 (9%)	2 (8%)
HAMARTOMA		1 (4%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(24)	(24)	(24)	(24)
LYMPHOCYTIC LEUKEMIA				4 (17%)
GRANULOCYTIC LEUKEMIA	3 (13%)	2 (8%)	5 (21%)	4 (17%)
*LYMPH NODE	(3)	(3)	(4)	(5)
MALIGNANT LYMPHOMA, NOS				1 (20%)
CIRCULATORY SYSTEM				
NONE				

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
• NUMBER OF ANIMALS NECROPSIED

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TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#SALIVARY GLAND SARCOMA, NOS		(1)	(3) 1 (33%)	
#LIVER ADENOMA, NOS HEPATOCELLULAR CARCINOMA	(24)	(24)	(24) 1 (4%)	(24) 1 (4%) 2 (8%)
#STOMACH ADENOCARCINOMA, NOS	(21)		(2) 1 (50%)	(6)
#JEJUNUM CARCINOMA,NOS				(1) 1 (100%)
#CECUM ADENOCARCINOMA, NOS			(1) 1 (100%)	(4)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY ADENOMA, NOS	(23)	(24) 2 (8%)	(22)	(24)
#ADRENAL PHEOCHROMOCYTOMA	(1) 1 (100%)	(1)		
REPRODUCTIVE SYSTEM				
#TESTIS INTERSTITIAL-CELL TUMOR	(24) 24 (100%)	(24) 24 (100%)	(24) 20 (83%)	(24) 20 (83%)
#SCROTUM FIBROMA	(24) 1 (4%)	(24)	(24)	(24)
NERVOUS SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*TUNICA VAGINALIS	(24)	(24)	(24)	(24)
MESOTHELIOMA, MALIGNANT	1 (4%)			
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	24	24	24	24
NATURAL DEATH@	2		3	1
MORIBUND SACRIFICE		4	7	12
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	22	20	14	11
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	24	24	20	21
TOTAL PRIMARY TUMORS	32	32	32	37
TOTAL ANIMALS WITH BENIGN TUMORS	24	24	20	20
TOTAL BENIGN TUMORS	27	30	23	23
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	2	6	12
TOTAL MALIGNANT TUMORS	5	2	9	14
TOTAL ANIMALS WITH SECONDARY TUMORS#	1			
TOTAL SECONDARY TUMORS	1			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED AROCLOR® 1254 IN THE DIET

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS NECROPSIED	24	24	24	24
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	24
INTEGUMENTARY SYSTEM				
*SKIN	(24)	(24)	(24)	(24)
SQUAMOUS CELL CARCINOMA			1 (4%)	
*SUBCUT TISSUE	(24)	(24)	(24)	(24)
FIBROMA		1 (4%)		
FIBROSARCOMA				1 (4%)
FIBROUS HISTIOCYTOMA, MALIGNANT				1 (4%)
LIPOSARCOMA		1 (4%)		
RESPIRATORY SYSTEM				
*LUNG	(22)	(24)	(24)	(24)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)		1 (4%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(24)	(24)	(24)	(24)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				1 (4%)
LYMPHOCYTIC LEUKEMIA	1 (4%)	2 (8%)	1 (4%)	
GRANULOCYTIC LEUKEMIA	3 (13%)	4 (17%)	4 (17%)	4 (17%)
*SPLEEN	(19)	(24)	(24)	(22)
GRANULOCYTIC LEUKEMIA			1 (4%)	
*LYMPH NODE	(4)	(1)	(3)	(1)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (100%)
CIRCULATORY SYSTEM				
NONE				

@ NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(23)	(24)	(22)	(24)
UNDIFFERENTIATED CARCINOMA METAS		1 (4%)		
ADENOMA, NOS			1 (5%)	2 (8%)
#STOMACH	(21)	(3)	(1)	(6)
ADENOMA, NOS				1 (17%)
ADENOCARCINOMA, NOS		1 (33%)	1 (100%)	
URINARY SYSTEM				
*GENITOURINARY TRACT	(24)	(24)	(24)	(24)
LIPOMA		1 (4%)		
#KIDNEY	(23)	(24)	(24)	(23)
UNDIFFERENTIATED CARCINOMA		1 (4%)		
ENDOCRINE SYSTEM				
#PITUITARY	(23)	(22)	(22)	(23)
ADENOMA, NOS	4 (17%)	1 (5%)	1 (5%)	1 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(24)	(24)	(24)	(24)
ALEMOMA, NOS	1 (4%)			
ADENOCARCINOMA, NOS		4 (17%)		
#UTERUS	(14)	(12)	(15)	(6)
ADENOCARCINOMA, NOS		1 (8%)		1 (17%)
ADENOCA IN ADENOMATOUS POLYP				1 (17%)
LEIOMYOMA		1 (8%)		
ENDOMETRIAL STROMAL POLYP	2 (14%)	5 (42%)	5 (33%)	3 (50%)
#OVARY	(20)	(1)	(3)	
GRANULOSA-CELL TUMOR		1 (100%)		
NERVOUS SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL SENSE ORGANS				
*EYE	(24)	(24)	(24)	(24)
SEBACEOUS ADENOCARCINOMA			1 (4%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	24	24	24	24
NATURAL DEATH@	1	1	1	
MORIBUND SACRIFICE	7	4	3	7
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	16	19	20	17
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	11	18	15	12
TOTAL PRIMARY TUMORS	12	24	17	17
TOTAL ANIMALS WITH BENIGN TUMORS	7	8	6	7
TOTAL BENIGN TUMORS	8	9	8	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	4	13	8	9
TOTAL MALIGNANT TUMORS	4	14	9	10
TOTAL ANIMALS WITH SECONDARY TUMORS#		1		
TOTAL SECONDARY TUMORS		1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1		
TOTAL UNCERTAIN TUMORS		1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS FED AROCLOR® 1254 IN THE DIET

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TABLE B1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED AROCLOR® 1254 IN THE DIET

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS NECROPSIED	24	24	24	24
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	24
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(24)	(24)	(24)	(24)
CYST, NOS	1 (4%)			
RESPIRATORY SYSTEM				
#TRACHEA	(19)		(1)	
INFLAMMATION, NOS	1 (5%)			
#LUNG/BRONCHUS	(23)	(24)	(23)	(24)
BRONCHIECTASIS	1 (4%)	4 (17%)	7 (30%)	1 (4%)
INFLAMMATION, NOS		1 (4%)		
#LUNG	(23)	(24)	(23)	(24)
EMPHYSEMA, NOS	1 (4%)			
ATELECTASIS		1 (4%)	2 (9%)	1 (4%)
CONGESTION, NOS	9 (39%)	12 (50%)	7 (30%)	4 (17%)
INFLAMMATION, NOS				1 (4%)
ABSCESS, NOS	2 (9%)	2 (8%)	3 (13%)	2 (8%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(23)	(24)	(23)	(24)
CONGESTION, NOS	1 (4%)	2 (8%)	1 (4%)	
FIBROSIS			2 (9%)	
HEMATOPOIESIS		1 (4%)		
#LYMPH NODE	(3)	(3)	(4)	(5)
CONGESTION, NOS			1 (25%)	
NECROSIS, NOS				1 (20%)
HYPERPLASIA, NOS			1 (25%)	
HISTIOCYTOSIS	2 (67%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

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TABLE B1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
*CELIAC LYMPH NODE	(3)	(3)	(4)	(5)
LYMPHANGIECTASIS				1 (20%)
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
*SALIVARY GLAND		(1)	(3)	
INFLAMMATION, NOS		1 (100%)		
*LIVER	(24)	(24)	(24)	(24)
CONGESTION, NOS	10 (42%)	18 (75%)	10 (42%)	4 (17%)
INFLAMMATION, GRANULOMATOUS				1 (4%)
GRANULOMA, NOS				1 (4%)
NECROSIS, NOS		1 (4%)		1 (4%)
NECROSIS, FOCAL				2 (8%)
NECROSIS, CENTRAL			1 (4%)	1 (4%)
HYPERPLASIA, NODULAR		5 (21%)	8 (33%)	12 (50%)
ANGIECTASIS	4 (17%)		2 (8%)	
*STOMACH	(21)		(2)	(6)
DIVERTICULUM				1 (17%)
HYPERPLASIA, LYMPHOID	1 (5%)			
*GASTRIC MUCOSA	(21)		(2)	(6)
CONGESTION, NOS				1 (17%)
HYPERPLASIA, NOS			1 (50%)	2 (33%)
*COLON			(1)	(4)
FIBROSIS				1 (25%)
PIGMENTATION, NOS				1 (25%)
*CECUM			(1)	(4)
NECROSIS, NOS				1 (25%)
URINARY SYSTEM				
*KIDNEY	(24)	(24)	(24)	(24)
CYST, NOS		2 (8%)		

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
# NUMBER OF ANIMALS NECROPSIED

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TABLE B1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
PYELONEPHRITIS, NOS		1 (4%)		
SCLEROSIS		1 (4%)		
ENDOCRINE SYSTEM				
*PITUITARY	(23)	(24)	(22)	(24)
CYST, NOS	1 (4%)			
CONGESTION, NOS		1 (4%)	1 (5%)	2 (8%)
*PARATHYROID	(3)		(1)	
HYPERPLASIA, NOS	1 (33%)			
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
*BRAIN	(23)	(24)	(24)	(24)
CONGESTION, NOS			1 (4%)	
EDEMA, NOS			1 (4%)	
ABSCESS, NOS		1 (4%)		1 (4%)
INFARCT, NOS			1 (4%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*INGUINAL REGION	(24)	(24)	(24)	(24)
NECROSIS, FAT	6 (25%)	5 (21%)	3 (13%)	4 (17%)
ALL OTHER SYSTEMS				
NONE				

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
# NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY				
NONE				

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

000954

TABLE B2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS FED AROCLOR 1254 IN THE DIET

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	24	24	24	24
ANIMALS NECROPSIED	24	24	24	24
ANIMALS EXAMINED HISTOPATHOLOGICALLY	24	24	24	24
INTEGUMENTARY SYSTEM				
NONE				
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(22)	(24)	(24)	(24)
BRONCHIECTASIS			1 (4%)	1 (4%)
ABSCESS, NOS			1 (4%)	
#LUNG	(22)	(24)	(24)	(24)
ATELECTASIS		3 (13%)	3 (13%)	1 (4%)
CONGESTION, NOS	8 (36%)	10 (42%)	8 (33%)	10 (42%)
PETECHIA				1 (4%)
INFLAMMATION, NOS	2 (9%)	1 (4%)		1 (4%)
INFLAMMATION, INTERSTITIAL		1 (4%)		
ABSCESS, NOS	1 (5%)	1 (4%)	1 (4%)	1 (4%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(19)	(24)	(24)	(22)
CONGESTION, NOS			3 (13%)	
HEMATOPOIESIS		3 (13%)		
#LYMPH NODE	(4)	(1)	(3)	(1)
LYMPHANGIECTASIS	2 (50%)			
INFLAMMATION, NOS	1 (25%)			
CIRCULATORY SYSTEM				
#MYOCARDIUM		(1)		
INFLAMMATION, NOS		1 (100%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(23)	(24)	(22)	(24)
CONGESTION, NOS	6 (26%)	6 (25%)	4 (18%)	
INFLAMMATION, NOS			1 (5%)	
INFLAMMATION, GRANULOMATOUS		2 (8%)	3 (14%)	1 (4%)
GRANULOMA, NOS		1 (4%)	1 (5%)	
FIBROSIS		1 (4%)		
NECROSIS, FOCAL			1 (5%)	
HYPERPLASIA, NODULAR		6 (25%)	9 (41%)	17 (71%)
ANGIECTASIS	3 (13%)	2 (8%)	1 (5%)	1 (4%)
HEMATOPOIESIS		1 (4%)		
#LIVER/PERIVOCTAL	(23)	(24)	(22)	(24)
INFLAMMATION, NOS		2 (8%)		
*BILE DUCT	(24)	(24)	(24)	(24)
INFLAMMATION, NOS			4 (17%)	
#STOMACH	(21)	(3)	(1)	(6)
DIVERTICULUM				2 (33%)
EPIDERMAL INCLUSION CYST				1 (17%)
CONGESTION, NOS		1 (33%)		1 (17%)
#JEJUNUM	(1)			(1)
INFLAMMATION, NOS	1 (100%)			
#COLON	(1)	(1)		(1)
INFLAMMATION, NOS		1 (100%)		
#CECUM	(1)	(1)		(1)
INFLAMMATION, NOS	1 (100%)			
URINARY SYSTEM				
*GENITOURINARY TRACT	(24)	(24)	(24)	(24)
NECROSIS, FAT	1 (4%)	1 (4%)	1 (4%)	
#KIDNEY	(23)	(24)	(24)	(24)
HYDRONEPHROSIS		1 (4%)		
CYST, NOS	1 (4%)			1 (4%)
ENDOCRINE SYSTEM				
#PITUITARY	(23)	(22)	(22)	(24)
CYST, NOS	3 (13%)	1 (5%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

000956

TABLE B2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
CONGESTION, NOS	8 (35%)	3 (14%)	1 (5%)	1 (4%)
HEMORRHAGIC CYST	1 (4%)			
#ADRENAL	(2)		(4)	
CONGESTION, NOS	1 (50%)			
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(24)	(24)	(24)	(24)
HYPERPLASIA, CYSTIC		1 (4%)		
*VAGINA	(24)	(24)	(24)	(24)
INFARCT, NOS			1 (4%)	
#UTERUS	(14)	(12)	(15)	(6)
HYDROMETRA		1 (8%)	1 (7%)	
PYOMETRA	6 (43%)	1 (8%)	1 (7%)	
#UTERUS/ENDOMETRIUM	(14)	(12)	(15)	(6)
INFLAMMATION, NOS		1 (8%)		
HYPERPLASIA, NOS			1 (7%)	
HYPERPLASIA, CYSTIC	1 (7%)		4 (27%)	
#UTERUS/MYOMETRIUM	(14)	(12)	(15)	(6)
INFLAMMATION, FOCAL				1 (17%)
#OVARY/OVIDUCT	(14)	(12)	(15)	(6)
CYST, NOS	2 (14%)			
INFLAMMATION, NOS	1 (7%)			
#OVARY	(20)	(1)	(3)	
CYST, NOS	1 (5%)		2 (67%)	
FOLLICULAR CYST, NOS	1 (5%)			
PAROVARIAN CYST	1 (5%)			
CONGESTION, NOS			1 (33%)	
ABSCESS, NOS	1 (5%)			
NERVOUS SYSTEM				
#BRAIN	(23)	(23)	(24)	(22)
CONGESTION, NOS	1 (4%)			
SPECIAL SENSE ORGANS				
*EYE	(24)	(24)	(24)	(24)
HEMORRHAGE	1 (4%)	2 (8%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	MID DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*INGUINAL REGION	(24)	(24)	(24)	(24)
LIPOGRANULOMA		1 (4%)		
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED				1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

000058

APPENDIX C

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS FED AROCLOR® 1254 IN THE DIET

Table C1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Aroclor® 1254 in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma[b]	0/24 (0)	0/24 (0)	2/24 (8)	2/24 (8)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		--	Infinite	Infinite
Lower Limit		--	0.305	0.305
Upper Limit		--	Infinite	Infinite
Weeks to First Observed Tumor	--	--	105	90
Hematopoeitic System: Leukemia[b]	3/24 (13)	2/24 (8)	5/24 (21)	8/24 (33)
P Values[c,d]	P = 0.022	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.667	1.667	2.667
Lower Limit		0.060	0.369	0.739
Upper Limit		5.292	9.600	13.700
Weeks to First Observed Tumor	98	78	84	73

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000090

Table C1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Aroclor® 1254 in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia[b]	3/24 (13)	2/24 (8)	5/24 (21)	9/24 (38)
P Values[c,d]	P = 0.009	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.667	1.667	3.000
Lower Limit		0.060	0.369	0.871
Upper Limit		5.292	9.600	15.010
Weeks to First Observed Tumor	98	78	84	73
Pituitary: Adenoma, NOS[b]	0/24 (0)	2/24 (8)	0/24 (0)	0/24 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		Infinite	--	--
Lower Limit		0.305	--	--
Upper Limit		Infinite	--	--
Weeks to First Observed Tumor	--	105	--	--

000061

6091

Table C1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Aroclor® 1254 in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Liver: Hepatocellular Carcinoma[b]	0/24 (0)	0/24 (0)	1/24 (4)	2/24 (8)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		--	Infinite	Infinite
Lower Limit		--	0.055	0.305
Upper Limit		--	Infinite	Infinite
Weeks to First Observed Tumor	--	--	105	103
Testis: Interstitial-cell Tumor[b]	24/24 (100)	24/24 (100)	20/24 (83)	20/24 (83)
P Values[c,d]	P = 0.013 (N)	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]			0.833	0.833
Lower Limit			0.000	0.000
Upper Limit			1.200	1.200
Weeks to First Observed Tumor	98	78	77	87

[a]Treated groups received doses of 25, 50, or 100 ppm.

[b]Number of tumor-bearing animals/number of animals necropsied (percent).

000962

Table C1. Analyses of the Incidence of Primary Tumors in Male Rats Fed Aroclor® 1254 in the Diet[a]

(continued)

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in the control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the matched-control group.

000093

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Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Aroclor® 1254 in the Diet[a]

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Hematopoietic System: Leukemia[b]	4/24 (17)	6/24 (25)	6/24 (25)	4/24 (17)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.500	1.500	1.000
Lower Limit		0.411	0.411	0.211
Upper Limit		6.316	6.316	4.754
Weeks to First Observed Tumor	81	74	99	84
Hematopoietic System: Lymphoma or Leukemia[b]	4/24 (17)	6/24 (25)	6/24 (25)	6/24 (25)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		1.500	1.500	1.500
Lower Limit		0.411	0.411	0.411
Upper Limit		6.316	6.316	6.316
Weeks to First Observed Tumor	81	74	99	84

000064

Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Aroclor® 1254 in the Diet[a] (continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Pituitary: Adenoma, NOS[b]	4/24 (17)	1/24 (4)	1/24 (4)	1/24 (4)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		0.250	0.250	0.250
Lower Limit		0.005	0.005	0.005
Upper Limit		2.288	2.288	2.288
Weeks to First Observed Tumor	100	105	105	103
Liver: Adenoma, NOS[b]	0/24 (0)	0/24 (0)	1/24 (4)	2/24 (8)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		--	Infinite	Infinite
Lower Limit		--	0.055	0.305
Upper Limit		--	Infinite	Infinite
Weeks to First Observed Tumor	--	--	105	105

000065

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Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Aroclor® 1254 in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Mammary Gland: Adenocarcinoma, NOS[b]	0/24 (0)	4/24 (17)	0/24 (0)	0/24 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.003			
Relative Risk (Matched Control)[f]		Infinite	--	--
Lower Limit		0.961	--	--
Upper Limit		Infinite	--	--
Weeks to First Observed Tumor	--	105	--	--
Mammary Gland: Adenoma or Adenocarcinoma, NOS[b]	1/24 (4)	4/24 (17)	0/24 (0)	0/24 (0)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.031			
Relative Risk (Matched Control)[f]		4.000	0.000	0.000
Lower Limit		0.437	0.000	0.000
Upper Limit		187.475	18.289	18.289
Weeks to First Observed Tumor	105	105	--	--

000066

Table C2. Analyses of the Incidence of Primary Tumors in Female Rats Fed Aroclor® 1254 in the Diet[a]

(continued)

Topography: Morphology	Matched Control	Low Dose	Mid Dose	High Dose
Uterus: Endometrial Stromal Polyp[b]	2/24 (8)	5/24 (21)	5/24 (21)	3/24 (13)
P Values[c,d]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Matched Control)[f]		2.500	2.500	1.500
Lower Limit		0.459	0.459	0.188
Upper Limit		24.045	24.045	16.583
Weeks to First Observed Tumor	105	100	103	96

[a]Treated groups received doses of 25, 50, or 100 ppm.

[b]Number of tumor-bearing animals/number of animals necropsied (percent).

[c]Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when $P < 0.05$; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a treated group is the probability level for the Fisher exact test for the comparison of that treated group with the matched-control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated.

[d]A negative trend (N) indicates a lower incidence in a treated group than in the control group.

[e]The probability level for departure from linear trend is given when $P < 0.05$ for any comparison.

[f]The 95% confidence interval of the relative risk between each treated group and the matched-control group.

1609

Review of the Bioassay of Aroclor 1254* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

November 28, 1977

The Clearinghouse on Environmental Carcinogens was established in May, 1976 under the authority of the National Cancer Act of 1971 (P.L. 92-218). The purpose of the Clearinghouse is to advise on the National Cancer Institute's bioassay program to identify and evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in organic chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of NCI bioassay reports on chemicals studied for carcinogenicity. In this context, below is the edited excerpt from the minutes of the Subgroup's meeting at which Aroclor 1254 was reviewed.

(Aroclor 1254 was tested in rats as part of another study designed to investigate the combined effects of chemicals.) The primary reviewer briefly outlined the experimental design and findings. Although statistically significant increases in the incidence of tumors were not found in the treated rats, a high incidence of liver hyperplastic nodules was observed in both sexes.

The primary reviewer said that in published rat and mouse studies, Aroclor was reported to induce liver neoplasms, although in one rat study only hyperplastic nodules of the liver were found. In regard to the rat pathology, he said that after the proliferative stimulus is removed, the hyperplastic nodules regress and disappear. Stimuli of such liver nodules act more like tumor promoters than complete carcinogens. Based on reports in the literature, he concluded that Aroclor 1254 could pose a risk to the human population as a tumor promotor. A lengthy discussion followed as to whether the evidence was adequate to assess Aroclor's tumor promoting potential.

An NCI staff pathologist pointed out that a number of tumors also were found in the gastrointestinal tract of the treated rats. Although they did not occur in statistically significant numbers, none was observed among the control

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animals. A discussion ensued as to the appropriateness of combining tumors when they occur at different sites along the GI tract.

One Subgroup member opined that the study was deficient because of an inadequate number of animals per group. He suggested that the tumors of questionable significance may have been more meaningful had more animals been used.

A motion was made that the conclusion stated in the report summary be accepted with an addition that Aroclor 1254 may act as a tumor promoter. The motion thus read: It is concluded that, under the conditions of the bioassay, Aroclor 1254 was not carcinogenic in Fischer 344 rats; however, a high incidence of hepatocellular proliferative lesions in both male and female rats was related to treatment. In addition, the carcinomas of the gastrointestinal tract may be associated with treatment in both males and females. Based on the liver proliferative lesions in the treated rats and published reports, it is suggested that Aroclor 1254 may be a tumor promoter. The motion was seconded and accepted by Drs. Wogan, Pitot, Roush, Shimkin, Strong, and Weisburger. Mr. Garfinkel opposed the motion and Dr. Rowe abstained.

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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