COPY

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF TEXAS

BEAUMONT DIVISION

CECIL SCOTT, ET AL	]	
v.	]	No. B-84-1103-CA
MONSANTO COMPANY	]	

EXHIBITS TO

VIDEOTAPE DEPOSITION OF

DR. GEORGE LEVINSKAS

May 28, 1987

1300 Post Oak Boulevard

Houston, Texas

Wanda G. Kuhn, Court Reporter

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Monsanto TECHNOLOGY

DMEH
Toxicology Section/St. Louis
(CO./DIV./DEPT./LOCATION)

SPECIAL REPORT
(TYPE OF REPORT)

REPORT NO.: MSL-2002

JOB/PROJECT NO.:

DATE: October 14, 1981

TITLE: TOXICITY OF AROCLOR PRODUCTS 1242, 1254 AND 1260 TO THE LIVER OF ALBINO RATS

AUTHORS: George J. Levinskas, Ph.D.

ABSTRACT: This report is a tabulation of the results of microscopic evaluation of liver sections from rats fed AROCLOR 1242, AROCLOR 1254 or AROCLOR 1260 for two years.

AUTHORS: George J. Levinskas, Ph.D.
TITLE: TOXICITY OF AROCLOR PRODUCTS 1242, 1254 AND 1260 TO THE LIVER OF ALBINO RATS

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INTRODUCTION

The polychlorinated biphenyls (PCBs) comprise a family of compounds of variable chlorine content. PCBs manufactured by Monsanto (tradenamed "Aroclor") bear a four digit number, the '12' indicating biphenyl and the last two digits indicating the chlorine content by weight percent. Since the chlorine atoms are randomly distributed among the 10 ring positions available for substitution, each material is a mixture of isomers.

In 1969, Monsanto sponsored a series of animal studies at Industrial BIO-TEST Laboratories in Northbrook, Illinois, on Aroclor 1242, 1254, and 1260 for the assessment of the health and environmental hazards of these materials. This series consisted of 2-year chronic feeding studies to rats and dogs, a 3-generation rat reproduction study, a rat teratology study, a dominant lethal mutagenic study in mice and a toxicity/reproduction study in chickens on each of the 3 Aroclor products. Even though no such action was contemplated, such a broad battery of tests would have been adequate to support Food Additive Petitions for each of these materials. These studies were initiated by reports that PCBs had been detected in the environment. A report (Nelson, 1972b) by a Panel on Hazardous Trace Substances of an Ad Hoc Committee on Environmental Health Research covers the development of information on the environmental and biological effects of PCBs. There have been subsequent literature reviews which need not be recapitulated here [DHEW, 1978; EPA, 1976; IARC, 1978; NAS, 1979; Roberts, et al. (1978)].

Starting in 1969, while these studies still were in progress, information regarding them was made available to various government groups.[1] Subsequently, data from these studies were presented at a conference

sponsored by the National Institute of Environmental Health Sciences at Rougemont, N.C. on December 20-21, 1971, but the account of these studies was omitted from the published proceedings (Keplinger, et al., 1972; Nelson, 1972a).

Subsequently, it was reported that female Sherman strain rats developed hepatocellular carcinomas when fed Aroclor 1260[2] from Lot No. AK-3; the same lot used for the earlier Monsanto study with this material. As a result, Monsanto requested the contract laboratory's pathologists to review livers from all available rats from the 3 Aroclor studies. That review (which could have included new sections of liver from animals examined previously in addition to sections from animals not examined previously) was presented in the reports of Gordon and Richter (1975a,b,c).

In November 1975, reports containing evaluations of liver sections from the 2-year rat feeding studies (Gordon and Richter, 1975a,b,c) and the results of an independent evaluation of the same liver sections (Pour, 1975) were presented to and discussed with several federal regulatory agencies[3]. Later that month, a summary of data from all of the studies was presented at the National Conference on Polychlorinated Biphenyls sponsored by the Environmental Protection Agency and held in Chicago on November 19-21, 1975 (Calandra, 1976). Only summaries of data from these and other toxicity studies conducted over the years have been published (Jenkins, et al., 1972; Keplinger, et al., 1971; Monsanto, 1980). Knowledge of these efforts may have prompted the statement in a recent article that "...Monsanto, whose reaction to the possibility that polychlorinated biphenyls (PCBs) might be an ecological disaster was a classic of how such issues should be handled, says Ford[4]. Monsanto began to investigate the dangers as soon as they were

seriously voiced. It insisted on keeping an open mind about them. As soon as evidence appeared that there was a strong chance PCBs were a hazard, it published the results of its investigations, admitting the danger. It thus established a reputation of honesty even among the environmentalists." (Clutterbuck 1981).

At a later meeting in Bethesda, MD.[5], pathologists selected and reviewed some liver slides from the Monsanto-sponsored and Kimbrough studies. The pathologists differed in the terminology used to classify the lesions. They did conclude that the general incidence and severity of liver lesions (hyperplasia, nodular hyperplasia and neoplastic changes - carcinomas) were greater in the rats from the study subsequently published by Kimbrough, et al. (1975). No carcinomas were seen in the Monsanto-sponsored studies. It was noted that either the strain of rat or sex could have accounted for the differences. The spontaneous incidence of hyperplastic or neoplastic liver lesions in the Sherman strain rat was unknown, and the occurrence of such lesions appears to be higher in female rats and mice.

The different diagnoses were discussed with Dr. Philippe Shubik of the Eppley Institute for Research in Cancer at the University of Nebraska. Dr. Shubik suggested that the liver sections from these studies could be reviewed by Dr. Parvis Pour. This was done.

This publication is an effort to make readily available information in the Gordon and Richter reports (1975a,b,c) which are only summarized in the literature (Calandra, 1976).

METHODS

It appears that the Threshold Limit Value of 0.5 mg/m^3 for chlorobiphenyl with 54% chlorine (ACGIH, 1969) was used to estimate suitable dose levels for the rat feeding studies. For that purpose the following assumptions were made: if the ambient air concentration of PCBs is 0.5 mg/m^3, and if all of the inhaled PCBs are absorbed, and if 15 m^3 of air are inhaled during the working day, a person would receive a PCB dose of 7.5 mg/day. The corresponding dosage would be approximately 0.1 mg/kg/day for a 70-kilogram person. Consequently, dosages of 0.1, 1, and 10 mg/kg/day were decided upon, and the dietary concentrations were set at 1, 10, and 100 ppm. As it turned out, the assumptions used to set dosages for the feeding study resulted in the low dose level rats receiving a dosage that was 100 times higher than the 0.001 mg/kg/day which FDA later calculated as allowable for protracted ingestion based on human data (FDA, 1973).

For the chronic toxicity study in rats[6], weanling animals of the Charles River CD strain[7] were divided into a control group and 9 treatment groups, each consisting of 50 males and 50 females, with 3 treatment groups assigned to each of the 3 Aroclor products studied (1242, 1254, and 1260). Not all of these animals started at the same time. After about 2 months on test, additional groups of males and females were assigned to each test diet and the controls. These animals were added to allow a sufficient number of animals for sacrifices at 3, 6 and 12 months to provide some information prior to the completion of the 2-year study period. The numbering sequence

and the designation of some animals as "Extra" suggests that additional animals were placed on test.

Groups of 5 males and 5 females were scheduled to be sacrificed after 3, 6, and 12 months of feeding, and survivors were to be sacrificed at the end of the test period.[8] Animals were to be given a gross autopsy and tissues were to be preserved for possible histologic examination. Tumors or lesions suggestive of tumors were to be examined.

RESULTS

Data from the Gordon and Richter reports (1975a,b,c) on liver slides are shown in Tables 1, 2, and 3 for Aroclor 1242, 1254, and 1260, respectively.[9] While the text of the reports contained comments specific to the particular Aroclor, they also contained similar comments such as "There is evidence of a chemical effect on the liver.....This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals to hepatoma or cholangiohepatoma" and "In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia; these are benign tumors rather than malignant carcinomas. There was no evidence of metastasis or invasiveness of these tumors in this study". The reports also stated that "The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material" and "In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report.....No hepatocellular carcinomas were observed".

With respect to Aroclor 1254, it was noted that "One liver tumor (a hepatoma) previously reported in a T-II animal (No. 445) was re-classified as nodular hyperplasia" (Gordon and Richter, 1975a)[10].

DISCUSSION

The initial reports of these studies concluded that the target organ was the liver for each Aroclor product. This was confirmed by the second evaluation of liver slides (Gordon and Richter, 1975a,b,c). These alterations were slow to develop, their incidence being related to both dose level and duration of treatment. Since there were increased incidences of vacuolar changes in the cytoplasm of the hepatocytes and focal hypertrophy at all dose levels for all 3 Aroclor products at the 24-month sacrifice, a "no-effect" level was not established for liver effects.

With respect to the slides from Industrial BIO-TEST, Pour (1975) concluded that Aroclor 1242, 1254, and 1260 "showed a dose-dependent hepatotoxic effect, characterized by degenerative and regenerative processes. With one exception, all lesions were considered non-neoplastic. Structures similar to cholangiocarcinomas and hepatomas were found in one rat. However, the possibility of metastases of a carcinoma into the liver has been also considered." In the report, he noted one lesion which seemed to "represent a metastatic tumor (probably a mammary gland carcinoma of the same animal from which ...[the particular liver section]... was submitted), rather than a cholangiocarcinoma". This occurred in an animal fed 100 ppm of Aroclor 1254. The contract laboratory pathologists diagnosed the presence of mammary tumor metastases in the liver of this rat (Gordon and Richter, 1975b).[11]

SUMMARY and CONCLUSIONS

Groups of male and female rats were fed diets containing either 1, 10, or 100 ppm of one of 3 Aroclor products, 1242, 1254, or 1260, for 2 years. Focal hypertrophy of the liver occurred at 3, 3, and 12 months for rats fed Aroclor 1260, 1254, and 1242, respectively. Focal hypertrophy was not seen in livers of control animals. At the 24-month sacrifice, livers of animals from all dose levels of the 3 Aroclor products had an increased incidence of vacuolar changes and focal hypertrophy. Livers of some animals fed 100 ppm of each Aroclor also had benign liver tumors (hepatoma or cholangiohepatoma). No hepatocellular carcinomas were observed.

Footnotes

1. Dates of initial correspondence and contacts.
   October 3, 1969. E.P. Wheeler to A.R. Glasgow, Division of Pesticides. Food and Drug Administration.
   April 8, 1970. R.E. Kelly to H. Blumenthal, Petitions Review Branch, Food and Drug Administration.
   April 22, 1970. E.P. Wheeler to E.J. Burger, Jr., Office of Science and Technology.
   June 1, 1970. E.P. Wheeler to H.E. Stokinger, Bureau of Occupational Safety and Health.

2. R.D. Kimbrough, personal communication.

3. November 13-14, 1975. Council on Environmental Quality.
   Environmental Protection Agency.
   Food and Drug Administration.
   House Subcommittee Manpower, Compensation, Health and Safety.
   National Cancer Institute.
   National Institute for Environmental Health Sciences.
   National Institute for Occupational Safety and Health.

4. Dr. David Ford of Bath University.

5. At National Cancer Institute on January 21, 1975. Present were D.E. Gordon, R.D. Kimbrough, G.J. Levinskas, R.A. Squire, W.R. Richter.

6. Since the events described earlier, the validity of many toxicity studies conducted by Industrial BIO-TEST Laboratories has been challenged. Therefore, the available raw data supplied by Industrial BIO-TEST was reviewed to determine whether this study could be validated. The review showed that the data bases (including the lack of a protocol) were insufficient for a complete validation of the study. It was decided to focus on presenting the primary liver effects reported by Gordon and Richter (1975a,b,c). Therefore, a complete audit was not undertaken. Available records were examined for a determination that the animals were placed on test and of their ultimate fate. Necropsy and microscopic reports were also examined for findings pertaining to livers of those animals. Significant discrepancies which were found between data in Tables 1, 2, and 3 and the data base for the Gordon and Richter reports are noted in this report. On some records, the labels Aroclor 1242 and Aroclor 1260 are interchanged as determined by a check of the animal numbers.

7. Charles River Breeding Laboratories, North Wilmington, Massachusetts.

8. Animals sacrificed at 6 and 12 months were placed on test about 2 months after the first group. Those sacrifice periods are sometimes labeled 8 and 14 months, respectively, which corresponds to the calendar time from the start of the test but overstates the time on test for those groups.

9. As a result of the examination described in footnote 6, a few animals were reassigned to other dose levels on basis of assigned numbers. Three with no recorded liver lesions were deleted from the 24-month listing because of short duration on test: 14 months at 100 ppm Aroclor 1242, 15 months at 10 ppm Aroclor 1254 and 13 months at 100 ppm Aroclor 1254. Therefore, numbers in Tables vary slightly from those in reports of Gordon and Richter (1975a,b,c).

10. That change and comments in the footnotes to the Tables were noted during the examination described in footnote 6. In addition, the following also were noted during the examination.

Aroclor 1254 - 100 ppm animal marked "Extra[3]" with diagnosis of hepatoma in record of examination for original Industrial BIO-TEST report. Animal not listed in Gordon and Richter report.

- 100 ppm animal no. 542 with gross autopsy notation that liver appears tumorous and white foci has no record of examination.

Aroclor 1260 - 100 ppm animal no. 293 with gross autopsy notation of tumor on liver has no record of examination.

In some instances, diagnoses were crossed out on the available records. These were included in the Tables. Crossed out diagnoses for hepatoma or cholangiohepatoma are noted in the footnotes to the Tables.

11. Dr. Pour's report does not include the following liver sections noted by discrepancies between his tabulation and the Gordon and Richter reports.

1 from control at 12 month sacrifice,
5 from 100 ppm Aroclor 1242 at 24 months,
1 from 100 ppm Aroclor 1260 at 3 months.

None of these animals were reported as having hepatomas or cholangiohepatomas in the Gordon and Richter reports.

References

1. ACGIH (1969). Threshold Limit Values of Airborne Contaminants. American Conference of Governmental Industrial Hygienists. Cincinnati.

2. Calandra, J.C. (1976). Summary of toxicological studies on commercial PCB's. In: National Conference on Polychlorinated Biphenyls, November 19-21, 1975. Chicago, Illinois. EPA Report No. 560/6-75-004. March. NTIS PB-253 248. pp.35-42.

3. Clutterback, D. (1981). What causes environmental conflict? New Scientist 90, 176-177.

4. DHEW (1978). Final Report of the Subcommittee on Health Effects of PCBs and PBBs. Environ. Health Perspect., 24, 129-198.

5. EPA (1976). National Conference on Polychlorinated Biphenyls, November 19-21, 1975. Chicago, Illinois. U.S. Environmental Protection Agency. Washington, D.C. EPA-560/6-75-004, March. NTIS PB-253 248.

6. FDA (1973). Polychlorinated biphenyls (PCB's). Contamination of animal feeds, foods and food-packaging materials. Fed. Regis., July 6, 38, 18096-18103.

7. Gordon, D.E. and Richter, W.R. (1975a). Two-year chronic and toxicity study with Aroclor 1242 in albino rats. Histopathological evaluation of additional liver sections. March 24 (unpublished observations).

8. Gordon, D.E. and Richter, W.R. (1975b). Two-year chronic oral toxicity study with Aroclor 1254 in albino rats. Histopathological evaluation of additional liver sections. March 24 (unpublished observations).

9. Gordon, D.E. and Richter, W.R. (1975c). Two-year chronic oral toxicity study with Aroclor 1260 in albino rats. Histopathological evaluation of additional liver sections. March 24 (unpublished observations).

10. IARC (1978). Polychlorinated biphenyls. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. 18, 43-103. International Agency for Research on Cancer. Lyon, France. October.

11. Jenkins, D.H., Keplinger, M.L., Fancher, O.E., Wheeler, E.P. and Calandra, J.C. (1972). Reproductive effects of polychlorinated biphenyls in white leghorn chickens. Toxicol. Appl. Pharmacol. 22, 316.

12. Keplinger, M.L., Fancher, O.E., Calandra, J.C. (1971). Toxicologic studies with polychlorinated biphenyls. Toxicol. Appl. Pharmacol. 19, 402-403.

13. Keplinger, M.L., Fancher, O.E., Calandra, J.C., et al. (1972). Toxicological studies with polychlorinated biphenyls. Read at PCB Conference, Quail Roost Conference Center, Rougemont, North Carolina, 20-21 December 1971. Cited in Polychlorinated Biphenyls - Environmental Impact. A Review by the Panel on Hazardous Trace Substances. March 1972. Environ. Res. 5, 249-362.

14. Kimbrough, R.D., Squire, R.A., Linder, R.E., Strandberg, J.D., Montali, R.J., and Burse, V.W. (1975). Induction of liver tumors in Sherman Strain female rats by polychlorinated biphenyl Aroclor 1260. J. Natl. Cancer Inst. 55, 1453-1459.

15. Monsanto Company (1980). Polychlorinated biphenyls. PCB's. A report on Uses, Environmental and Health Effects and Disposal.

16. NAS (1979). Polychlorinated biphenyls. National Academy of Sciences. Washington, D.C.

17. Nelson, N. (1972a). Comments on research needs. Environ. Health Perspect., 1, 181-185.

18. Nelson, N. (1972b). Chairman, Panel on Hazardous Trace Substances. Polychlorinated biphenyls - environmental impact. Environ. Res. 5, 249-362.

19. Pour, P. (1975). Histopathological reevaluation of livers for rats treated with Aroclor. August 1 (unpublished observations).

20. Roberts, J.R., Rodgers, D.W., Bailey, J.A., Rorke, M.A. (1978). Polychlorinated Biphenyls: Biological criteria for an assessment of their effects on environmental quality. National Research Council of Canada. Ottawa. Publication No. NRCC 16077.

Table 1

Aroclor 1242: Primary Liver Lesions Among Albino Rats

Sacrifice Interval	3 Months				6 Months				12 Months				Terminal[a]			
Diet Level (ppm)	0	1	10	100	0	1	10	100	0	1	10	100	0	1	10	100
No. Animals Examined	10	8	10	9	10	10	8	9	10	10	10	9	23	32	29	19
Findings																
Vacuolar change	2	0	2	1	1	0	0	0	1	2	4	0	1	7	8	9
Focal necrosis	0	1	0	0	1	1	0	0	0	0	0	0	1	1	1	0
Focal lymphoid infiltration	0	0	0	0	0	3	0	0	0	0	1	0	1	0	0	0
Focal hypertrophy hepatocytes	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	1	1	8
Ductular hyperplasia	0	0	0	1	0	0	0	0	1	0	1	0	5	3	3	3
Hepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3[b]
Cholangiohepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1[c]

[a] Control group has animal dead at 19 months and 2 marked "Extra".
1 ppm group has animals dead at 19, 22, 22, 23, 23 months.
10 ppm group has animals dead at 23, 23 months.
100 ppm group has animals dead at 22, 22, 22 months and 2 marked "Extra".

[b] Includes 1 animal without record of examination in original IBT report. Not listed as hepatoma in worksheets for Gordon and Richter report but appears and was crossed out on typed tabulation for animal marked "Extra". Diagnoses for other 2 animals do not appear in records of examinations for original IBT report.

[c] Diagnosis does not appear in records of examinations for original IBT report.

Table 2

Aroclor 1254: Primary Liver Lesions Among Albino Rats

Sacrifice Interval	3 Months				6 Months				12 Months				Terminal[a]			
Diet Level (ppm)	0	1	10	100	0	1	10	100	0	1	10	100	0	1	10	100
No. Animals Examined	10	10	10	10	10	10	10	10	10	10	10	10	23	30	26	26
Findings																
Vacuolar change	2	3	3	1	1	0	0	0	1	1	4	1	1	7	9	13
Focal necrosis	0	1	1	0	1	2	0	2	0	0	0	1	1	3	1	1
Focal lymphoid infiltration	0	0	0	1	0	0	0	2	0	0	2	1	1	2	0	1
Focal hypertrophy hepatocytes	0	0	0	1	0	0	0	4	0	0	4	2	0	3	4	14
Nodular hyperplasia	0	0	0	0	0	0	0	0	0	0	0	0	1	0	3	14
Ductular hyperplasia	0	0	0	0	0	0	0	0	1	1	1	0	5	6	3	4
Hepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4[b]
Cholangiohepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2[c]

[a] Control group has animal dead at 19 months and 2 marked "Extra".
1 ppm group has animals dead at 22, 22 months, 1 marked "Extra" and 1 other for which date of death is not recorded.
10 ppm group has animals dead at 22, 22, 22 months.
100 ppm group has animals dead at 23, 23 months and 9 marked "Extra".

[b] Includes 2 animals marked "Extra". Diagnoses do not appear in records of examination for original IBT reports.

[c] Both animals marked "Extra" with same designation. 1 without apparent record of examination for original IBT report. Diagnosis for other animal does not appear in records of examinations for original IBT report.

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Table 3

Aroclor 1260: Primary Liver Lesions Among Albino Rats

Sacrifice Interval	3 Months				6 Months				12 Months				Terminal[a]			
Diet Level (ppm)	0	1	10	100	0	1	10	100	0	1	10	100	0	1	10	100
No. Animals Examined	10	10	10[b]	10	10	6	5	9	10	9	10	9	23	26	25	25
Findings																
Vacuolar change	2	0	2	3	1	1	2	6	1	2	5	3	1	5	7	9
Focal necrosis	0	0	4[c]	0	1	0	1[d]	0	0	0	0	0	1	4	3	6
Focal lymphoid infiltration	0	0	0	0	0	2	2	0	0	0	0	0	1	0	1	0
Focal hypertrophy hepatocytes	0	0	0	2	0	0	0	3	0	0	0	4	0	3	13	9
Nodular hyperplasia	0	0	0	0	0	0	0	0	0	0	0	1	1	0	7	6
Ductular hyperplasia	0	0	1	0	0	0	0	0	1	1	0	2	5	6	7	12
Hepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1[e]	7[f,g]
Cholangiohepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4[g,h]

[a] Control group has animal dead at 19 months and 2 marked "Extra".

1 ppm group has animals dead at 20, 22, 22 months.

10 ppm group has animals dead at 19, 22, 22 months and 1 marked "Extra".

100 ppm group has animals dead at 22, 22 months.

[b] Includes 1 marked "Extra".

[c] Worksheets show listings under this diagnosis with arrow pointing to Vacuolar change column.

[d] Date of death of this animal not recorded.

[e] No record of examination for original IBT report. Listed on worksheets for Gordon and Richter report with diagnosis crossed out.

[f] Includes 2 animals without record of examination for original IBT report. Diagnoses for other 5 animals do not appear in records of examinations for original IBT report. 2 of these diagnoses crossed out on worksheets for Gordon and Richter reports.

[g] Includes one animal with both diagnoses. Hepatoma is 1 of 2 crossed out (superscript f).

[h] Includes 3 animals without record of examination for original IBT report. Diagnosis for other animal does not appear in records of examinations for original IBT report. 2 of these diagnoses crossed out on worksheets for Gordon and Richter reports.

EXHIBIT #1

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
BEAUMONT DIVISION

CECIL SCOTT, ET AL.	§	
	§	
VS.	§	CIVIL ACTION NO.
	§	B-84-1103-CA
MONSANTO COMPANY	§	

PLAINTIFFS' NOTICE OF INTENTION TO TAKE ORAL DEPOSITION AND SUBPOENA DUCES TECUM

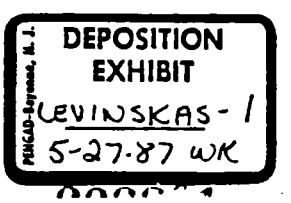
TO: Defendant, MONSANTO COMPANY, by and through its attorneys of record Mr. Robert A. Hall, Mr. Jonathan B. Shoebotham, Woodard, Hall & Primm, 4700 Texas Commerce Tower, Houston, Texas 77002;

Mr. Walter J. Crawford, Jr., Wells, Peyton, Beard, Greenberg, Hunt & Crawford, P. O. Box 3709, Beaumont, Texas 77704;

Mr. John M. Johnson, Mr. Warren B. Lightfoot, Bradley, Arant, Rose & White, 1400 Park Place Tower, Birmingham, Alabama 35203; and

Mr. Michael R. Fruehwald, Mr. Michael Rosiello, and Ms. Anne C. McGown, Barnes & Thornburg, 1313 Merchants Bank Building, 11 South Meridian Street, Indianapolis, Indiana 46204.

Pursuant to the provisions of Rule 30(b)(6) of the Federal Rules of Civil Procedure, the Plaintiffs in this cause hereby give NOTICE to the Defendant that the oral deposition of MONSANTO COMPANY, Defendant, will be taken on the date and time and at the place hereinafter stated. Specifically, the Plaintiffs intend to take the oral deposition of the representative(s) designated by the



Defendant pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure. Plaintiffs request that Defendant designate that current employee of Defendant having held the highest position of any held by a current employee in Monsanto Company's toxicology department during the period 1965 through 1975. Plaintiffs also request that Defendant designate that representative knowledgeable of the documents and subject matter herein below enumerated.

1) Any document(s) which would state or disclose the following:

   a) when Monsanto first began using the services of IBT;

   b) when Monsanto first began using the services of IBT in connection with Monsanto's PCB products;

   c) the dollars spent by Monsanto with IBT (i) each year that Monsanto used IBT's services, (ii) on all PCB related studies, and (iii) totally, from the date Monsanto first began using the services of IBT.

2) All correspondence from IBT to Dr. Paul L. Wright while Dr. Wright was an employee of Monsanto;

3) All correspondence by Monsanto to Paul L. Wright or from Paul Wright to Monsanto;

4) Any document stating, reflecting or referring to the policies and procedures of Monsanto's Toxicology Department for the years 1965 through 1980;

5) Any document stating, reflecting or referring to the current standards, procedures and policies of Monsanto's Toxicology Department;

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6) The results of any IBT PCB test redone by or for Monsanto Company;

7) Any investigation or background file on Dr. Renata Kimbrough;

8) Any correspondence to or from Dr. William Ribelin;

9) Any report, analysis or investigation of IBT misconduct (actual or alleged) in connection with tests performed on Monsanto products (this request includes copies of government reports; independent investigations; internal IBT investigations; Monsanto authored or sponsored investigations; and, investigations by industry groups, bodies or authorities or other private or public body) (IBT includes all of its employees and consultants).

10) Any document which would in any way reflect, relate or pertain to a change by or on behalf of Monsanto to the results (interim or final) of any test of a Monsanto product by IBT;

11) Any document which would in any way reflect, relate or pertain to a change by or on behalf of Monsanto to the results (interim or final) of any test of a Monsanto PCB product by IBT;

12) Any document which would in any way reflect, relate or pertain to a suggestion by Monsanto regarding the outcome of a test to be conducted by IBT for Monsanto on any Monsanto product;

13) Any document which would in any way reflect, relate or pertain to a suggestion by Monsanto regarding the outcome of a test to be conducted by IBT for Monsanto on any Monsanto PCB product.

This deposition will be taken at the offices of Gilpin, Pohl & Bennett, 1300 Post Oak Boulevard, Allied Bank Tower,

000003

23rd Floor, Houston, Texas 77056 beginning at 9:00 a.m. on Saturday, May 23, 1987 and shall continue until completed.

This oral deposition will be taken before a certified court reporter. The testimony given during this oral deposition will be used as evidence in this matter, together with the documents produced at this deposition. You are invited to attend and cross-examine.

As used in this notice, the term "documents" means any printed, typewritten or handwritten matter, or reproduction thereof, of whatever character, in the possession, custody or control of a witness or his agents, representatives or employees, including without limitation, correspondence, contracts, memoranda, agreements, letters, brochures, reports, handwritten or typewritten notes, sound recordings or transcriptions thereof, computer print-outs, inter-company and intra-company communications, work papers, diaries, calendar pads, appointment books, ledgers, financial statements, checks, bank drafts and writings of whatever kind and character, whether originals or reproductions, and whether in draft or final form, including copies bearing different markings or notations.

"PCB" means polychlorinated biphenyl and its contaminants and derivatives.

000004

Respectfully submitted,

By: _____
Michael A. Pohl

OF COUNSEL:

David M. Lacey
GILPIN, POHL & BENNETT
1300 Post Oak Boulevard
Allied Bank Tower, 23rd Floor
Houston, Texas 77056
(713) 623-8800

READ, MORGAN & QUINN
909 Laurel Avenue
Beaumont, Texas 77701
(409) 838-9941

Thomas Henderson
HENDERSON & GOLDBERG
1030 Fifth Avenue
Pittsburgh, Pennsylvania 15219
(412) 471-3980

Benton Musslewhite
LAW OFFICES OF BENTON MUSSLEWHITE
609 Fannin, Suite 517
Houston, Texas 77002
(713) 222-2288

David S. McCrea
McCREA & McCREA
119 S. Walnut Street
Bloomington, Indiana 47402
(812) 336-4840

ATTORNEYS FOR PLAINTIFFS,
CECIL SCOTT, ET AL.

CERTIFICATE OF SERVICE

I hereby certify that on the ____ day of _____, 1987, a true and correct copy of the above Notice of Intent to Take Oral Deposition and Subpoena Duces Tecum was served upon counsel of record either by messenger or by placing same in the United States mail, certified mail, return receipt requested, postage prepaid and addressed as follows:

Mr. Robert A. Hall
Mr. Jonathan B. Shoebotham
Woodard, Hall & Primm
4700 Texas Commerce Tower
Houston, Texas 77002

Mr. Walter J. Crawford, Jr.
Wells, Peyton, Beard, Greenberg,
Hunt & Crawford,
P. O. Box 3708
Beaumont, Texas 77704

Mr. John M. Johnson
Mr. Warren B. Lightfoot
Bradley, Arant, Rose & White
1400 Park Place Tower
Birmingham, Alabama 35203

Mr. Michael R. Fruehwald
Mr. Michael Rosiello
Ms. Anne C. McGown
Barnes & Thornburg
1313 Merchants Bank Building
11 South Meridian Street
Indianapolis, Indiana 46204

_____
Michael A. Pohl

depntc02/txt86551

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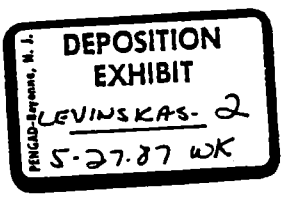
EXHIBIT # 2

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
BEAUMONT DIVISION



CECIL SCOTT, et al Plaintiffs	
V.	C. A. NO. B-84-1103-CA
MONSANTO COMPANY Defendant	

PLAINTIFFS' NOTICE OF INTENTION
TO TAKE ORAL DEPOSITION
AND SUBPOENA DUCES TECUM

TO: Defendant, MONSANTO COMPANY, by and through its counsel of record, Mr. Jonathan B. Shoebotham and Mr. Robert A. Hall, Woodard, Hall & Primm, 4700 Texas Commerce Tower, Houston, Texas 77002

Mr. Walter J. Crawford, Jr., Wells, Peyton, Beard, Greenberg, Hunt & Crawford, 624 Petroleum Bldg., P. O. Box 3708, Beaumont, Texas 77704

Mr. John M. Johnson, Mr. Warren B. Lightfoot, Bradley, Arant, Rose & White, 1400 Park Place Tower, Birmingham, Alabama 35203

Mr. Michael R. Fruewald, Mr. Michael Rosiello, Ms. Anne C. McGown, Barnes & Thornburg, 1313 Merchants Bank Bldg. 11 South Meridian Street, Indianapolis, Indiana 46204

Pursuant to the provisions of Rule 30(b)(6) of the Federal Rules of Civil Procedure, the Plaintiffs in this cause hereby give notice to the Defendant that the oral deposition of Monsanto Company, Defendant, will be taken on the date and time and at the place hereinafter stated. Specifically, the Plaintiffs intend to take the oral deposition of the representative(s) designated by the

Defendant pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure and charged with the responsibility for maintaining custody of the documents listed below and such designated representative(s) shall testify as to matters known or reasonably available to the Defendant as well as the custody of the herein designated records and their maintenance by Defendant:

1. The complete personnel file of Paul L. Wright;

2. Any bonuses, payment dividends or other consideration other than normal salary paid by Monsanto or anyone on its behalf to Paul L. Wright or his designee/assignee;

3. Paul L. Wright's job evaluation and/or reviews;

4. Any payment to or for the account of attorneys hired by or for Paul L. Wright in connection with matters pertaining to his employment at Industrial Bio-Test Laboratories, Inc. ("IBT"). See United States v. Keplinger, 776 F.2d 678 (7th Cir. 1985);

5. Any correspondence to or from Paul L. Wright;

6. Paul L. Wright's job duties and responsibilities as an employee of Monsanto both before and after he was employed by IBT; and,

7. The matters identified in the below listed subpoena duces tecum.

The deposition will be taken at the offices of Gilpin, Pohl & Bennett, 1300 Post Oak Boulevard, Allied Bank Tower, 23rd Floor, Houston, Texas 77056 beginning at 1:30 p.m. on Friday, May 8, 1987, and shall continue until completed.

This oral deposition will be taken before a certified court reporter. The testimony given during this oral deposition will be used as evidence in this matter, together

with the documents produced at this deposition. You are invited to attend and cross-examine.

Pursuant to Rules 30(b)(5) and 34 of the Federal Rules of Civil Procedure, certain documents shall be produced by the designated representative(s) or custodian(s) of Monsanto Company (referred to herein as "Monsanto") at the commencement of the oral deposition or prior thereto by agreement of counsel. The originals and all drafts of the following requested documents shall be produced:

1. The complete personnel file of Paul L. Wright;

2. Any payment by Monsanto or anyone on its behalf to or for the benefit of Wright Paul L. Wright;

3. Any payment by or for Monsanto to attorneys for Paul L. Wright in connection with any criminal prosecution arising out of or in any way related to his employment at IBT;

4. All correspondence to or from Paul L. Wright;

5. All evaluations of Paul L. Wright's performance as an employee of Monsanto;

6. All documents pertaining to the termination of Paul L. Wright's Monsanto employment (both before being first employed by IBT and as a result of or in connection with the criminal proceedings relating to IBT). See United States v. Keplinger, 776 F.2d 678 (7th Cir. 1985);

7. All documents pertaining to Monsanto's efforts to monitor, supervise, keep abreast of or in any way observe the IBT criminal trial. See United States v. Keplinger, 776 F.2d 678 (7th Cir. 1985);

8. Any report, analysis or investigation of IBT misconduct (actual or alleged) in connection with tests performed on Monsanto products (this request includes copies of government reports; independent investigations; internal IBT investigations; Monsanto authored or sponsored investigations;

and, investigation(s) by industry groups, bodies or authorities or other private or public body) (IBT includes all of its employees and consultants).

Unless otherwise specified herein, the documents to be produced include all documents in the possession of Monsanto from the date of the first production or manufacture of PCBs in any form by Monsanto to the present time.

As used in this notice, the term "documents" means any printed, typewritten or handwritten matter, or reproduction thereof, of whatever character, in the possession, custody or control of a witness or his agents, representatives or employees, including without limitation, correspondence, contracts, memoranda, agreements, letters, brochures, reports, handwritten or typewritten notes, sound recordings or transcriptions thereof, computer print-outs, inter-company and intra-company communications, work papers, diaries, calendar pads, appointment books, ledgers, financial statements, checks, bank drafts and writings of whatever kind and character, whether originals or reproductions, and whether in draft or final form, including copies bearing different markings or notations.

By:_____
JOSEPH C. BLANKS

OF COUNSEL:

REAUD, MORGAN & QUINN
909 Laurel Avenue
Beaumont, Texas 77701
(409) 838-9941

Michael A. Pohl
David M. Lacey
GILPIN, POHL & BENNETT
1300 Post Oak Blvd.
Allied Bank Tower, 23rd Floor
Houston, Texas 77056
(713) 623-8800

Thomas Henderson
HENDERSON & GOLDBERG
1030 Fifth Avenue
Pittsburgh, Pennsylvania 15219

Benton Musslewhite
LAW OFFICES OF BENTON MUSSLEWHITE
609 Fannin, Suite 517
Houston, Texas 77002
(713) 222-2288

David S. McCrea
McCREA & McCREA
119 S. Walnut Street
Bloomington, Indiana 47402
(812) 336-4840

ATTORNEYS FOR PLAINTIFFS,
CECIL SCOTT, ET AL.

CERTIFICATE OF SERVICE

I hereby certify that on the ____ day of _____, 1987, a duplicate original of the foregoing Plaintiffs' Notice of Intention to Take Oral Deposition was filed with the Clerk of the Court for the Eastern District of Texas, Beaumont Division. I also certify that a true and correct copy of this Notice was served upon counsel of record on the ____ day of _____, 1987, by messenger delivery and/or by placing same in the United States mail, certified mail, return receipt requested, postage prepaid and addressed as follows:

Mr. Robert A. Hall
Mr. Jonathan B. Shoebotham
Woodard, Hall & Primm
4700 Texas Commerce Tower
Houston, Texas 77002

Mr. Walter J. Crawford, Jr.
Wells, Peyton, Beard, Greenberg,
Hunt & Crawford
P. O. Box 3708
Beaumont, Texas 77704

Mr. John M. Johnson
Mr. Warren B. Lightfoot
Bradley, Arant, Rose & White
1400 Park Place Tower
Birmingham, Alabama 35203

Mr. Michael R. Fruewald
Mr. Michael Rosiello
Ms. Anne C. McGown
Barnes & Thornburg
1313 Merchants Bank Bldg.
11 South Meridian Street
Indianapolis, Indiana 46204

_____
JOSEPH C. BLANKS

MAP:jar/scottmon/054

EXHIBIT # 3

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
BEAUMONT DIVISION

CECIL SCOTT, ET AL.	§	
	§	
VS.	§	CIVIL ACTION NO.
	§	B-84-1103-CA
MONSANTO COMPANY	§	

PLAINTIFFS' NOTICE OF INTENTION TO TAKE ORAL DEPOSITION AND SUBPOENA DUCES TECUM

TO: Defendant, MONSANTO COMPANY, by and through its attorneys of record Mr. Robert A. Hall, Mr. Jonathan B. Shoebotham, Woodard, Hall & Primm, 4700 Texas Commerce Tower, Houston, Texas 77002;

Mr. Walter J. Crawford, Jr., Wells, Peyton, Beard, Greenberg, Hunt & Crawford, P. O. Box 3709, Beaumont, Texas 77704;

Mr. John M. Johnson, Mr. Warren B. Lightfoot, Bradley, Arant, Rose & White, 1400 Park Place Tower, Birmingham, Alabama 35203; and

Mr. Michael R. Fruehwald, Mr. Michael Rosiello, and Ms. Anne C. McGown, Barnes & Thornburg, 1313 Merchants Bank Building, 11 South Meridian Street, Indianapolis, Indiana 46204.

Pursuant to the provisions of Rule 30(b)(6) of the Federal Rules of Civil Procedure, the Plaintiffs in this cause hereby give NOTICE to the Defendant that the oral deposition of the Manager of Toxicology of MONSANTO COMPANY, Defendant, will be taken on the date and time and at the place hereinafter stated. Specifically, the Plaintiffs intend to take the oral deposition of the

representative(s) designated by the Defendant pursuant to Rule 30(b)(6) of the Federal Rules of Civil Procedure and charged with the responsibility for maintaining custody of the documents listed below.

The designated representative(s) shall testify as to:

a) Matters known or reasonably available to the Defendants concerning the policies and procedures of Monsanto's Toxicology Department for the years 1965 through 1980;

b) The current standards, procedures and policies of Monsanto's Toxicology Department;

c) The duties and responsibilities of the Manager of Monsanto's Toxicology Department (i) 1965 through 1980 and (ii) currently;

d) The organization of Monsanto's Toxicology Department (i) 1965 through 1980 and (ii) currently;

e) The interrelationship between Monsanto's Toxicology Department and Monsanto's other departments and/or sections;

f) The relationship between Monsanto's Toxicology Department and any outside testing facilities (i) 1965 through 1980 and (ii) currently;

g) Any industry or government guidelines or regulations relating or pertaining to tests concerning the toxicological effects of Monsanto products on animals;

h) Any participation by Monsanto's Toxicology Department in any effort by Monsanto to avoid or defer the ban of its PCB products;

i) The day-to-day activities of the current Manager of Monsanto's Toxicology Department; and

j) The documents designated in the accompanying Subpoena Duces Tecum.

This deposition will be taken at the offices of Gilpin, Pohl & Bennett, 1300 Post Oak Boulevard, Allied Bank Tower, 23rd Floor, Houston, Texas 77056 beginning at 9:00 a.m. on Saturday, May 23, 1987 and shall continue until completed.

This oral deposition will be taken before a certified court reporter. The testimony given during this oral deposition will be used as evidence in this matter, together with the documents produced at this deposition. You are invited to attend and cross-examine.

Pursuant to Rules 30(b)(5) and 34 of the Federal Rules of Civil Procedure, certain documents shall be produced by the designated representative(s) MONSANTO COMPANY (referred to herein as "Monsanto") at the commencement of the oral deposition. The originals and all drafts of the following requested documents shall be produced:

1) Any manual, compilation or other writing setting forth or reciting the policy or procedures for the Monsanto Toxicology Department from 1965 to date;

2) Any document pertaining to Monsanto's standards for the feeding or care of animals used in connection with the testing of Monsanto products;

3) Any document pertaining to the care, skill or precision to be used (a) by Monsanto and (b) by any outside/independent testing laboratory in gathering, recording, maintaining and/or

reporting of data generated by or from animal studies;

4) Any document comparing or contrasting the results of IBT Aroclor tests with tests conducted by (a) Monsanto, (b) others on Monsanto's behalf and/or (c) independent or government researchers;

5) Any document regarding any investigation or analysis of those Aroclor tests conducted by IBT for Monsanto;

6) Any document regarding or otherwise pertaining to trips (a) by Monsanto employees or representatives (i) to the offices of IBT (ii) to other locations where IBT representatives were met or (b) by IBT employees or representatives (i) to the offices of Monsanto or (ii) to locations where IBT and Monsanto employees or representatives met;

7) All literature regarding PCBs which was supplied or made available to Monsanto's experts, or consultants;

8) All Electrical Power Research Institute reports, articles, papers, etc., pertaining or relating to PCBs;

9) Any list or summary identifying (a) which IBT studies were redone by or for Monsanto and (b) the variances or similarities between the Monsanto tests conducted by IBT and those redone by or for Monsanto;

10) Any industry (and/or government) guidelines, standards or suggested guidelines/standards applicable to toxicological studies from 1960 to date (e.g. Aroclor studies on rats, beagle dogs, leghorn hens and/or fish) including any variations thereof from their inception to date;

11) Any document setting forth or otherwise stating Monsanto's standard of care regarding the following data in connection with toxicological tests (gathering, recording, maintaining):

a) blood data;

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b) urine analysis;
c) body weight;
d) feeding data;
e) autopsy (procedures and results);
f) viscera;
g) microscopic analysis;
h) organ analysis;
i) death of test animals;
j) substitution of animals;
k) loss of animals due to escape or confusion of identity.

12) All correspondence between IBT and Dr. Paul Wright while Dr. Wright was employed by Monsanto;

13) Any document evidencing or suggesting that Monsanto corrected, changed, altered or otherwise amended (a) any report of a test performed by IBT for Monsanto and (b) any paper published or to be published regarding IBT's study of any Aroclor product;

14) Any document (a) evidencing or otherwise pertaining to suggestion by Monsanto as to the "results" to be achieved by IBT in connection with the tests by IBT of Monsanto products, and (b) Monsanto's policy in regarding thereto (i) 1965 to 1980 and (ii) currently; and

15) Those documents relating to items a through j first above listed.

As used in this notice, the term "documents" means any printed, typewritten or handwritten matter, or reproduction thereof, of whatever character, in the possession, custody or control of a witness or his agents, representatives or employees, including without limitation, correspondence, contracts, memoranda, agreements, letters, brochures, reports, handwritten or typewritten notes, sound recordings or transcriptions thereof, computer print-outs,

inter-company and intra-company communications, work papers, diaries, calendar pads, appointment books, ledgers, financial statements, checks, bank drafts and writings of whatever kind and character, whether originals or reproductions, and whether in draft or final form, including copies bearing different markings or notations.

"Aroclor" shall mean any Monsanto product containing PCBs or their contaminants.

"Animal" shall mean any animal, mammal, reptile, bird, or fish used in connection with any study.

"PCB" means polychlorinated biphenyl and its contaminants and derivatives.

"Toxicology Department" means any department or section responsible for investigating or determining the possible toxicological effects of exposure to products manufactured by Monsanto Company.

Respectfully submitted,

By: _____
Michael A. Pohl

OF COUNSEL:

David M. Lacey
GILPIN, POHL & BENNETT
1300 Post Oak Boulevard
Allied Bank Tower, 23rd Floor
Houston, Texas 77056
(713) 623-8800

000013

READUD, MORGAN & QUINN
909 Laurel Avenue
Beaumont, Texas 77701
(409) 838-9941

Thomas Henderson
HENDERSON & GOLDBERG
1030 Fifth Avenue
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(713) 222-2288

David S. McCrea
McCREA & McCREA
119 S. Walnut Street
Bloomington, Indiana 47402
(812) 336-4840

ATTORNEYS FOR PLAINTIFFS,
CECIL SCOTT, ET AL.

CERTIFICATE OF SERVICE

I hereby certify that on the ____ day of _____, 1987, a true and correct copy of the above Notice of Intent to Take Oral Deposition and Subpoena Duces Tecum was served upon counsel of record either by messenger or by placing same in the United States mail, certified mail, return receipt requested, postage prepaid and addressed as follows:

Mr. Robert A. Hall
Mr. Jonathan B. Shoebotham
Woodard, Hall & Primm
4700 Texas Commerce Tower
Houston, Texas 77002

Mr. Walter J. Crawford, Jr.
Wells, Peyton, Beard, Greenberg,
Hunt & Crawford,
P. O. Box 3708

000019

Beaumont, Texas 77704

Mr. John M. Johnson
Mr. Warren B. Lightfoot
Bradley, Arant, Rose & White
1400 Park Place Tower
Birmingham, Alabama 35203

Mr. Michael R. Fruehwald
Mr. Michael Rosiello
Ms. Anne C. McGown
Barnes & Thornburg
1313 Merchants Bank Building
11 South Meridian Street
Indianapolis, Indiana 46204

Michael A. Pohl

depntc02/txt86551

EXHIBIT # 4

BEARD, MORGAN & QUINN
LAWYERS
909 Laurel
Beaumont, Texas 77701

Telex via WUI:
650 263 0717
(409) 838-9941

Answerback:
MCI JBLANKS
MCI ID: 263 0717

May 13, 1987

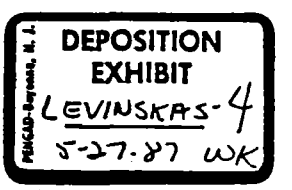
Walter Crawford
WELLS, PEYTON, BEARD, ICEBERG, HUNT & CRAWFORD
624 Petroleum Building
BEAUMONT, TEXAS 77704-3708

Re: *Cecil Scott v. Monsanto Company*, B-84-1103-CA

Dear Walter:

In order to minimize the burden on you of complying with Plaintiffs' requests for item 8 on IBT related documents --- which requests first came December 31, 1986, were renewed via 30(b)(6) notices April 3, 1987, and most recently, April 29, 1987 --- I repeat my verbal agreement with you of this morning that item 8 will at this time be satisfied if you provide each summary report regarding the analyses of, investigations of, and other detailed reports on IBT misconduct (actual or alleged) in connection with tests performed on Monsanto products.

I understand that IBT may have done as many as 650 separate studies for Monsanto on some 55 products. I also understand that third parties may have done some 350 study validations on IBT studies of about 50 Monsanto products. It is not clear whether the study validations were done before or after the IBT misconduct came to light. At this time, we do not insist on having the 350 study validations. We do, however, want to know the results of such validations, that is, whether or not the IBT studies were or were not found to be valid, and if not, why not.



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As concerns this particular request --- reports about IBT misconduct --- I suspect that Monsanto has some summary reports about the tests, the validations, independent investigations, internal IBT investigations, and even governmental investigations or reports. I suggest that you start with the reports presented to the highest level of Monsanto management and work your way downward until you reach the detailed study validations, stopping just short of them. Surely this will simplify your quest, and with the use of the wonderful Monsanto PCB index and document retrieval system and data base, you can gather this handful of documents together in a matter of days --- having already had months since the initial requests to identify the dangerous documents.

Thank you for your ongoing help in this matter.

Sincerely,

Joseph C. Blanks

000022

EXHIBIT #5

Monsanto

FROM (NAME & LOCATION): George Roush, Jr., M. D.

DATE: September 17, 1975

SUBJECT: MONTHLY COMMENTS - MEDICAL DEPARTMENT

REFERENCE:

CONFIDENTIAL

TO: Corporate Administrative Committee

State and federal agency activities related to PCB's continue to require Medical Department attention to support business group efforts. Recent public hearings in Wisconsin served as a forum for Mr. Schweitzer, of EPA's Toxic Substances Office, to make his pitch again in support of the Toxic Substances Control Act now being considered in Congress. Between now and the end of November, FDA, EPA, and NIOSH will conduct hearings on various aspects of the PCB's in foods and the environment.

Questions from outside Monsanto about the long-term health effects of chemicals used in two Monsanto plants on the workers in the plants have required organization of epidemiological studies. These require acquisition of data on individual work assignments within the plant over long periods of time, collection of death certificates of deceased employees, and comparison of causes of death with frequency of cause to some segment of the general population. We will have to do much more epidemiology in the future although clear cut conclusions are almost impossible.

George Roush, Jr., M. D.

GR/ln

EXHIBIT # 6

Monsanto

FROM (NAME & LOCATION): Medical Department A2SA

DATE: October 13, 1971

SUBJECT: AROCLOR® 1260

REFERENCE:

cc R. E. Kelly
M. N. Johnson
E. P. Wheeler

TO : FILE

I spoke with: Renate D. Kimbrough, M.D.
Pathologist
EPA Atlanta Tox. Branch
4770 Buford Highway
Chamblee, Georgia 30341
Tel: (404) 633-3311, ext. 5218

today regarding her observation of bladder tumors in rats fed AROCLOR 1260.

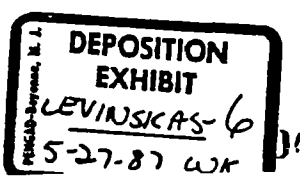
The observations of Vos and Koeman (Toxicol. and Applied Pharmacol. 17, 656-668, 1970) on polychlorinated biphenyls led them to undertake rat reproduction studies with AROCLOR 1254 (Lot AK38) and 1260 (Lot AK3). The materials were obtained from Glasgow at FDA. Their primary findings have been lesions in the liver, and Dr. Kimbrough plans to present a paper on the liver lesions at the 1972 spring meeting of the Society of Toxicology. In addition, she has seen 2 lesions in the bladders of rats fed AROCLOR 1260. The first occurred in a female which died after 6 months on test. This was diagnoaed as a malignant anaplastic carcinoma of the bladder. The second was in a male killed after 8 months on test. The first diagnosis was of epithelial hyperplasia. Sections of both bladders were sent to NCI for diagnosis to Drs. Strauss (?) and Katherine Snell. The diagnosis of carcinoma in the female was confirmed. The lesion in the male was not resolved. Some pathologists believe it is a carcinoma, others believe it is hyperplasia.

Dr. Kimbrough stated that they were trying to analyze the AROCLOR 1260 sample for impurities, but were having some difficulty with their equipment. I indicated that we would try to track down material from the sample that they had received. In the event that we cannot locate this lot, we probably can get some material back through Thomas B. Gaines, Supervisory Research Pharmacologist, at the same location as Dr. Kimbrough. If we have an analysis of this lot, we should make the results known to Dr. Kimbrough.

Dr. Kimbrough said that they had observed porphyria in some rats with both compounds. She also indicated that they were contemplating doing a 2 year feeding study with larger numbers of rats to investigate the problem of bladder tumors. She is perplexed by the bladder tumors, and she is not emphasizing them in her discussions. However, she has mentioned her findings when PCB's have been discussed at various interagency meetings. This is apparrently how Weissburg learned about them.

(cont'd.)

IM-10 REV 11-65



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As a final note, Dr. Kimbrough expressed concern over whether PCB's presented an additional hazard to the employees who manufacture it. I told here that because of the chloracne and liver hazards, there had been medical supervision of the employees. However, I would raise this point with Drs. Kelly and Johnson for their review.

George J. Levinskas

/bks

EXHIBIT # 17

PCB- Biotest

E.P.W.

October 28, 1971

Dr. Moreno L. Keplinger
Industrial Bio-Test Laboratories, Inc.
1810 Frontage Road
Northbrook, Illinois 60062

re AROCLOR® 1260

Dear Kep:

I spoke with Dr. Renate Kimbrough of the EPA in Chamblee, Georgia regarding our proposed visit to her to discuss bladder pathology in rats fed this product. I indicated to her that we expected to have all of the available bladders examined by the latter part of November, and that we would confirm a specific date beforehand. The express purpose of the visit is to exchange information, i.e., view the slides she has, and let her see any slides that Don turns up which may be of interest. This was agreeable to her. She suggested that we might bring extra slides for referral to NCI, if we so desired.

After Don has finished his evaluation of the bladder sections, and after you and he have had a change to review his schedule, I would appreciate a couple of dates that would be convenient for a trip to Chamblee so that I may schedule a visit there.

Kindest personal regards,

George J. Levinskas, Ph. D.
Mgr., Product Evaluation

GJL/bks

cc: Dr. Don Gordon
Mr. W. B. Papageorge
Mr. E. P. Wheeler

DEPOSITION EXHIBIT
LEVINSKAS-7
5-27-87 WC

SCM 023586

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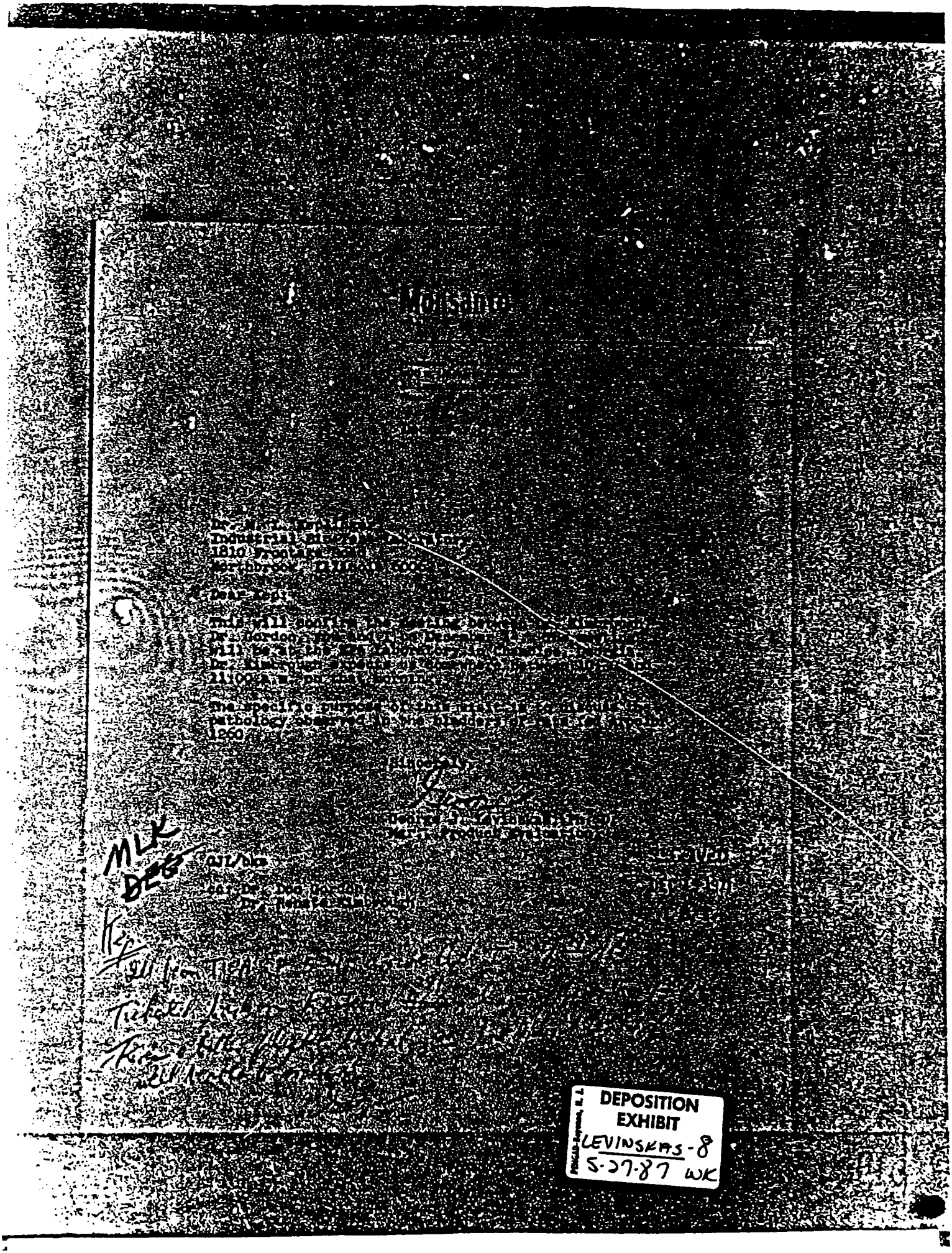
HARTOLDMON0023253

EXHIBIT #8



DEPOSITION EXHIBIT
LEVINSKAS-8
5-27-87 WK

EXHIBIT #9

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

054

November 12, 1974

Renate D. Kimbrough, M.D.
Toxicology Section
Department of Health, Education & Welfare
Center for Disease Control
Atlanta, Georgia 30333

Dear Renate:

Enclosed is a tabulation of the rat tumors in the Aroclor studies. The final figures for the publication may vary slightly, depending upon further deliberations, special stains, etc., but these are quite accurate.

I have avoided the term hepatoma, since it has become too variable in its meaning and have instead provided descriptive terms for those lesions not having the classic appearance of liver carcinoma. However, considering the significance of the results, I define "discrete nodules" and "trabecular (basophilic) hyperplasia" as precancerous lesions and thus indicative of carcinogenic response. The few tumors you called mixed are hepatocellular with pseudoglandular formation.

You knew of the Rat Liver Workshop I am having on this type of lesion on December 11-11th, and wish to thank you for the use of your material. No lesions will be identified with any specific compound, now or in the future. In fact, I selected the slides blindly to represent the spectrum of lesions and could not identify them with an agent myself.

I am inviting a limited number of guests, and would be pleased to have you attend, if you like. It is being held in the Sheraton Motor Hotel in Silver Spring, from 8:30 a.m., December 11 - 12:00 noon December 13th. I cannot pay any of your expenses, since you will not be an official participant.

Call me if you want to discuss anything further. I am sorry for the time on this Aroclor study, but my schedule and obligations have become quite overwhelming. As soon as the special stains are completed, I should be able to write the pathology descriptions and tabulations and send them to you for your consideration. We may also want to get together at that point.

Best regards.

Sincerely,

Robert A. Squire, D.V.M., M.S.D.
Head, Tumor Pathology Section
Carcinogenesis, DCT
National Cancer Institute

RAS:mg

DEPOSITION EXHIBIT
LEVINSKAS-9
5-27-87 WK

AROCLOR STUDY — FINAL SUMMARY	CONTROL	EXPERIMENTAL
Liver:		
Hepatocellular carcinoma	1/173	115/180
Diffuse hyperplasia	0/173	139/180
Discrete nodules	3/173	175/180
Vacuolar foci	20/173	50/180
Trabecular (basophilic) hyperplasia	1/173	44/180
Fibrosis	0/173	24/182
Adenofibrosis	0/173	5/180
Thyroid:		
Parafollicular hyperplasia	17/161	7/153
Parafollicular cell tumors	17/161	10/153
Adrenal:		
Nodular cortical hyperplasia	18/175	38/167
Hemorrhagic cortical cysts (ectasia)	39/175	17/167
Pituitary:		
Chromophobe adenoma	142/153	39/146
Uterus:		
Endometrial polyp	17/154	24/160
Sarcoma	3/154	7/160
Urinary bladder:		
Transitional cell papilloma	1/167	0/169
Mammary gland:		
Fibroadenoma	18/175	12/180
Adenocarcinoma	3/175	2/180

EXHIBIT # 10

DEC 11 1974

F.R.Johannsen - A2SC

December 6, 1974

E. P. Wheeler - A2SA
W. B. Papageorge - D2SK

AROCLOR 1254

G. Roush
A2SA

In a recent lphone conversation between Dr. R. Kimbrough (CDO) and G. J. Levinskas, Dr. Kimbrough expressed the belief that NCI had recently contracted out a carcinogenicity study involving AROCLOR 1254. Consequently, I made a call to Dr. Sidney Siegel at NCI. Dr. Siegel indicated that he had no knowledge of an outside contract with AROCLOR 1254 and further stated he doubted there was one. He did tell me that AROCLOR 1254 has been under test at NCI in their bioassay operation program since September 1972. He reported that the experimental part of the study had been completed as of October, 1974. His expectations are that the necessary histopathology will be completed within the next 6 months, at which time a meeting could be set up for discussion of the test results.

A quick check of the April 3, 1974 list of chemicals being tested under the NCI carcinogenesis program did not reveal that AROCLOR 1254 was on test. However, the NCI list does show

C02664 BIPHENYL, CHLORO

as part of the program. If this is the study he is referring to, it could explain why we had not picked it up sooner.

cc (2) Ruppe
(3) Gossop/C Patton

TO Ralph Ward / R Thompson / D Conn

Frederick R. Johannsen

/bkp

Our fate may be decided one way or another in 6 months. I hope your feeling that it is not carcinogenic are borne out! Should prepare for Arodor 1016 at MCI 1043 coming!

WR

Arodor - Carcinogenic!

SCH 051698

000030

EXHIBIT # 11

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
ATLANTA, GEORGIA 30333
TELEPHONE [illegible]

December 6, 1974

DEC 11 1974

Dr. George Levinskas
Monsanto Industrial Chemicals Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63166

Dear George:

I am enclosing a brief outline of the experiment Aroclor 12-72-A for your information. A copy of Bob Squires letter is also enclosed.

Sincerely yours,

Renata

Renata D. Kimbrough, M.D.
Toxicology Branch

Enclosure

SCM 022812

DEPOSITION EXHIBIT
LEVINSKAS - 11
5-27-87 WK

EXHIBIT # 12

Monsanto 046

Monsanto Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63166
Phone (314) 694-1000

December 17, 1974

Dr. Donovan Gordon
Industrial BIO-TEST Laboratories
1810 Frontage Road
Northbrook, Illinois 60062

Dear Don:

As a follow-up to our phone conversation yesterday, I am sending you copies of the information on Aroclor 1260 study which was sent to me by Dr. Kimbrough. You may find this informative in preparing for your subsequent discussion with them.

When you have had a chance to review your schedule, would you kindly let me know what days may be convenient for a meeting. This probably will be in the Washington area and I anticipate that you, Renate Kimbrough, Bob Squires and I will attend.

Sincerely,

George J. Levinskas, PhD
Mgr., Environmental Assessment
and Toxicology

/bkp
att.
cc: Dr. J. C. Calandra

DES
MLK

RECEIVED
DEC 24
IRDO-TEST

DEPOSITION EXHIBIT
LEVINSKAS-12
5-27-87 WK

000032

NOT FOR PUBLICATION OR CIRCULATION

Aroclor 12-72-A

Animals

Random bred female Sherman strain rats reared under specific pathogen-free conditions were obtained from the NCDC animal farm at Lawrenceville, Ga.

Aroclor 1260

Aroclor 1260 (Lot number AK-3) was supplied by Monsanto Industrial Chemicals Co., St. Louis, Mo.

Statistics

The students t-test was used for comparing body weights and weight gain.

Methods

Four hundred 21-26 day-old weanling female rats, weighing 48-97 g, were distributed into 2 groups of 200 animals each according to a table of random numbers. Each animal was weighed and given an individual ear tag number. The animals were housed 10 rats per cage. Food and water were provided ad libitum. Two hundred animals were fed the control diet of ground Purina laboratory chow; the test animals were fed the same diet fortified with 100 ppm Aroclor 1260.

Aroclor 1260 was incorporated into the diet by dissolving 5.2 g in ethyl ether then adding this to 100 g corn starch and allowing the ether to evaporate. The PCB-cornstarch mixture was blended with 345 g ground chow, then pulverized in a mortar and diluted with additional ground chow in a bakers mixer to give a 1000 ppm concentrate. The concentrate was further diluted to obtain 50 kg of 100 ppm diet. The diet was prepared every 10-14 days. Random samples from the final mixes along with samples of control chow were taken at regular intervals to determine PCB levels in the control chow and to verify the 100 ppm fortification level. Ground laboratory chow was also checked at intervals for aflotoxin at the district office of the Food and Drug Administration in New Orleans.

The combined body weight of rats in each cage was recorded weekly until the rats were 6 months old, bi-weekly until 12 months old, and monthly thereafter. Individual weights were recorded only at the onset of the experiment and at death or sacrifice. The animals were observed

briefly each day and animals exhibiting debilitating signs or large tumors were removed from the group cage and housed individually. At each weighing the animals were examined individually and abnormalities noted. Food consumption was measured on all rats during the first two weeks of the experiment, then during weeks 5, 8, 11 and 20 and every 12 weeks thereafter. Autopsies were performed on all rats that died. Rats that were sacrificed were killed under ether anesthesia by severing the vena cava. Tissues were fixed in buffered formalin and stained with hematoxylin and eosin. Additional special stains will be conducted.

Results

During the course of the study 4 animals in the test group and 8 controls were sacrificed prior to the final kill. These animals had either large tumors which had ulcerated or hindered movement, or the animal appeared moribund. In all, 14 animals in the test group died; 17 animals in the control group died. One animal was accidently killed in each group early in the study.

No definite dose related signs of toxicity were observed in the test animals throughout the study. Comparative curves of body weight gain and food consumption on the basis of body weight, as well as PCB intake of the test group are given in Figure 1. A slight decline in the rate of weight gain of the test group compared to the control group began about 3 months after onset of the experiment. Mean final body weights were 420 g (S.D. 72, S.E. 5.4) for the control group and 392 g (S.D. 62, S.E. 4.6) in the test group; the difference was statistically significant ($p<0.001$). Food consumption (gm/rat/day) was comparable in both groups throughout the study. Mean weight gain was 350 g (S.D. 70, S.E. 5.3) and 323 g (S.D. 60, S.E. 4.5) for the control and test groups, respectively; the difference in weight gain was also statistically significant ($p<0.001$). PCB intake declined from 11.6 mg/kg/day during the first week of exposure to 6.1 mg/kg/day at 3 months of exposure and to 4.3 mg/kg/day at 20 months. A 6 g mean weight loss occurred in both control and test groups during the 6 weeks prior to the final kill.

Preliminary List of Microscopic Findings (Kimbrough)
Please Note: Sections of All Tissues Listed
Were Not Available for All Animals

Tumor Type	Controls	(Tissue of one rat autolyzed) Experimental Rats
Mammary Gland:		
Fibroadenoma	19	14
Adenocarcinoma	7	0
Pituitary:		
Chromophobe Adenoma	38	30
Carcinoma Pituitary	0	1
Uterus:		
Endometrial Polyp	20	23
Endometrial Sarcoma	2	3 and 1 adenocarcinoma
Thyroid:		
Medullary Cell Tumors (parafollicular)	26	18
Liver:		
Nodular Hyperplasia	3 (8188,8192,8232)	7
Nodular Hyperplasia and Hepatomas	1 (8231)	154
Nodular Hyperplasia, Hepatomas, and Hepatocellular carcinomas	0	14
Adenofibrosis	0	4
Bladder:		
Papilloma	1 (8317)	0

In addition, a number of other occasional tumors were found.

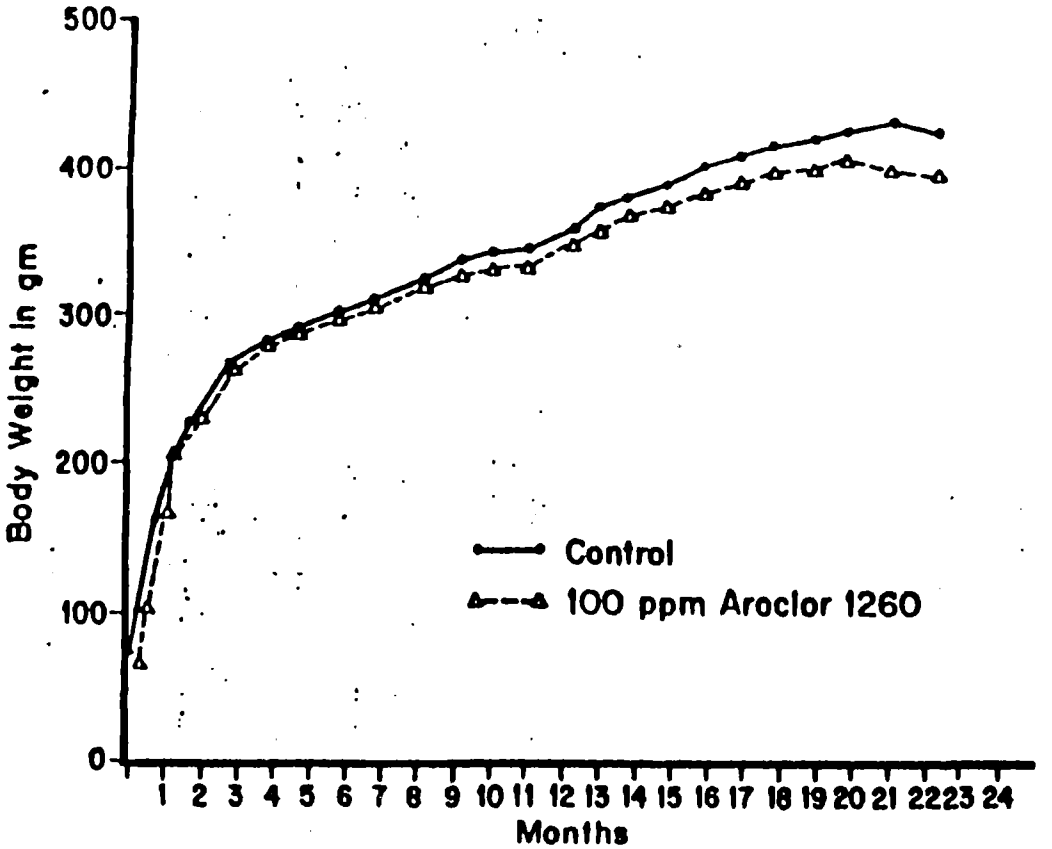
SCM 02281

000035

Out of this group, 4 control rats and 4 rats in the experimental group were sacrificed early because they were sick. All tumors of these animals, outside of the liver lesions, are included in the preceding list. The liver lesions need to be added. The animals are as follows:

Controls	Experimental
8194	8331
8151	8347
8121	8413
8254	8517

Figure 1 BODY WEIGHT



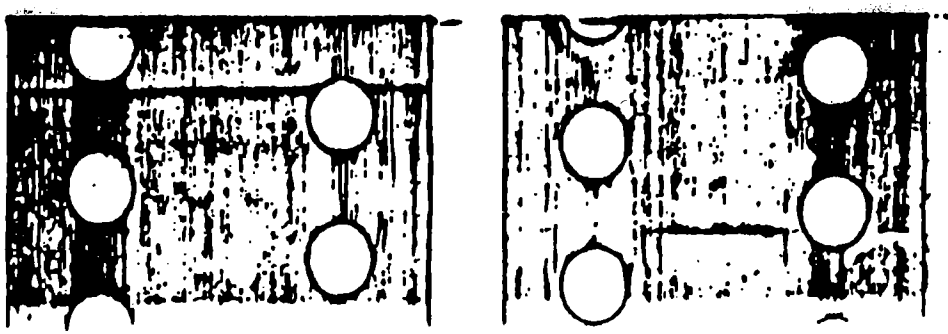
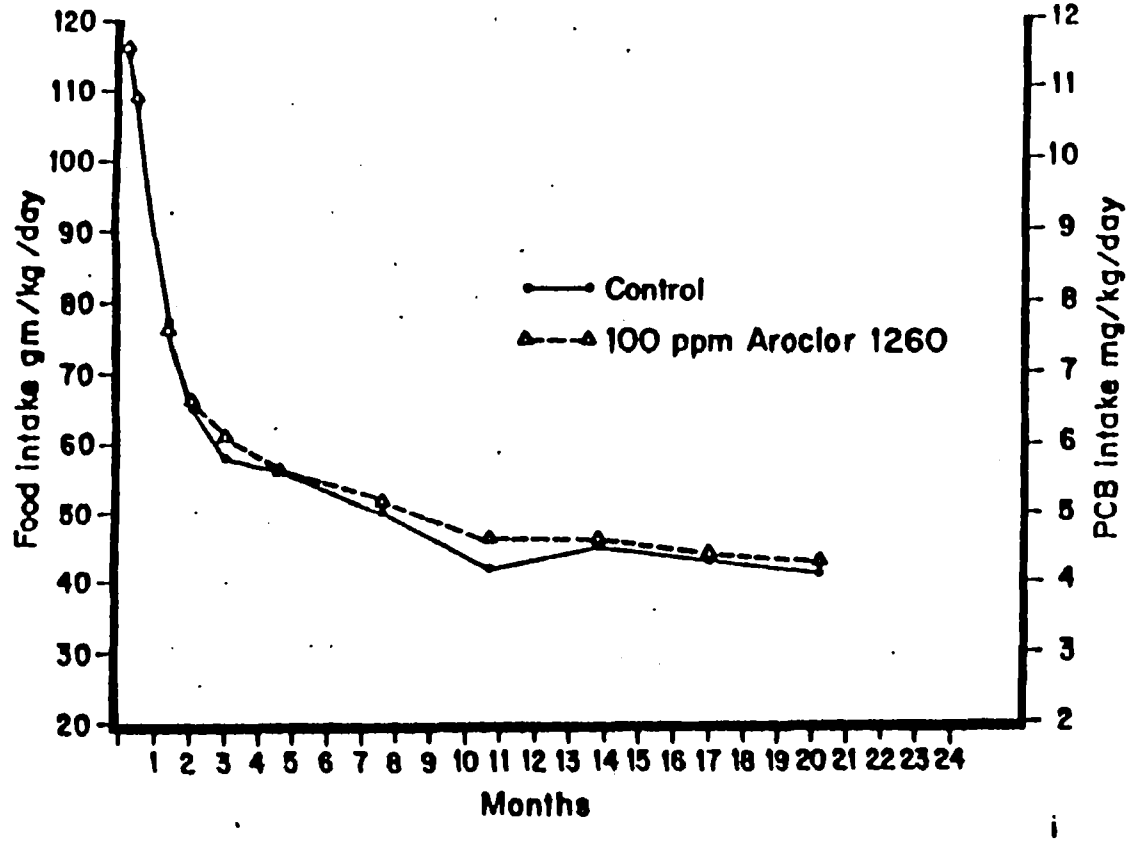


Figure 2 FOOD INTAKE AND PCB CONSUMPTION



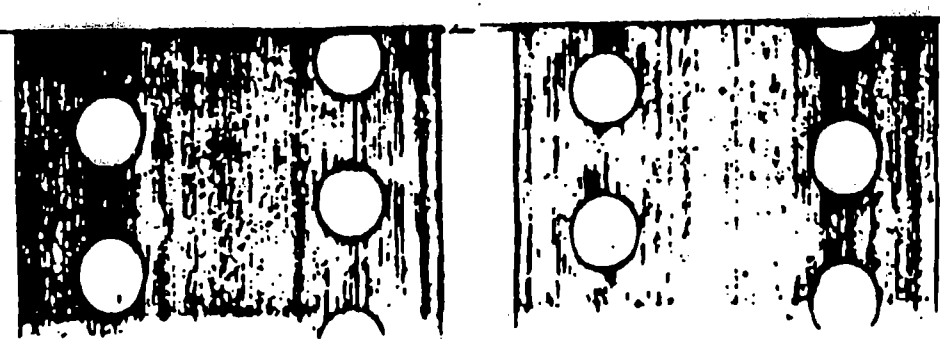


EXHIBIT # 13

AROCLOR 1260: Meeting at MCI, January 31, 1975

The purpose of this meeting was to review sections of liver tissue from Dr. Kimbrough's 2-year study in which female rats were fed 100 ppm of AROCLOR 1260.

Drs. Kimbrough and Squire had studied and classified the findings. Dr. Levitt, either a visiting fellow or a post-doctoral trainee did not participate to any great extent. He was mentioned as having a good knowledge of liver.

Dr. Richter had viewed the slides from our 2-year study in which rats of both sexes had been fed 100 ppm, 10 ppm or 1 ppm of AROCLOR 1260. Subsequently, he and Dr. Gordon reviewed sections of liver from all animals in this study.

Three conclusions can be drawn.

1. In our earlier study, the severity of liver lesions was greater in females than in males.

2. To a large extent, substantially the same type of lesions were observed in both studies except that the lesions seemed to be more advanced in Kimbrough's study. Although there was some variation in terminology, the findings were reasonably close.

3. There were definite liver adenocarcinomas in Kimbrough's study. Dr. Richter expressed the view later that 2 animals in our study approached the type of lesion Kimbrough had observed, but there was agreement by Drs. Gordon and Richter that Dr. Kimbrough's rats had developed a lesion which they had not observed in our earlier study with AROCLOR 1260.

If Drs. Gordon or Richter feel that I have not summarized this meeting correctly, or if they desire to amend or expand my remarks, I invite them to let me know.

GJL

George J. Levinskas

/bkp
2/3/75

EXHIBIT # 14

AROCLOR 1260: Meeting at NCI, January 31, 1975

The purpose of this meeting was to review sections of liver tissue from Dr. Kimbrough's 2-year study in which female rats were fed 100 ppm of AROCLOR 1260.

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If Drs. Gordon or Richter feel that I have not summarized this meeting correctly, or if they desire to amend or expand my remarks, I invite them to let me know.

GJL

George J. Levinskas

/bkp
2/3/75

DEPOSITION EXHIBIT
LEVINSKAS 14
5-27-87 - WK

EXHIBIT # 15

Industrial BIO-TEST *Laboratories, Inc.*
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

TOXICOLOGY
ENVIRONMENTAL SCIENCES
CHEMISTRY
PLANT SCIENCES
MEDICAL SCIENCES

March 24, 1975

AREA CODE 312
TELEPHONE 272-3030

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

I am enclosing the trip reports prepared by Dr. Richter and myself regarding our meeting at N.C.I. on January 31, 1975 with Drs. Kimbrough and Squire on Aroclor 1260 (IBT No. 622-07298).

The micro-slides of the liver sections from all these animals and those from Aroclor 1242 and 1254 will be forwarded today, under separate cover. We are also mailing the reports relevant to these studies today.

The charges for this additional work will be billed under a new Number (IBT No. 641-06672) instead of the previous number.

Sincerely,

D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology Dept.

DEG:hb
Enclosure

February 2, 1975

Trip Report

On January 31, 1975; Drs. Richter, Levinskas and myself met with Drs. Squire and Kimbrough at the National Cancer Institute in Bethesda, Maryland. The purpose of this meeting was to review the slides and data from a 23 month oral feeding study with Aroclor 1260 in rats that was conducted by Dr. Kimbrough while at the E.P.A. In her study, 200 female rats (Sherman strain) were fed 100 ppm of Aroclor 1260 in the diet for 21 months, while 200 female rats of the same strain served as controls and were fed Purina Rat Chow. The Sherman Rat is a random-bred animal derived from the Osborn Mendel Strain. The animals were 21-26 days of age when the study began, and were sacrificed after 23 months on the study. Therefore, there was a 2 month recovery period at the end of the study in which the test material was removed from the diet. The details of the experimental design, procedures and results that were forwarded to Dr. Levinskas are attached. In summary, Dr. Kimbrough found a rather high incidence of hyperplastic (nodular hyperplasia) and neoplastic (hepatomas, carcinomas) lesions in the liver of the test animals. The slides were subsequently reviewed by Dr. Robert Squire, Head of the Tumor Pathology Branch of The National Cancer Institute, who concurred with her findings, although, the terminology he used in classification of the lesions varied slightly from Dr. Kimbrough's. In this regard, it was his impression that all hyperplastic nodules should be regarded as "pre-cancerous lesions" and the term "hepatomas"

be deleted and re-classified as carcinomas or neoplastic nodules. This classification system was based on a Liver Tumor Workshop that was held on Dec. 11-13, 1974 in Silver Springs, Maryland which was attended by a small group of pathologists from the regulatory agencies, research laboratories and industry.

In view of Dr. Kimbrough's findings, additional sections of liver from a 2-Year Oral Feeding Study With Aroclor 1260, in rats, conducted at Industrial Bio-Test were processed and evaluated. In this study, there was a 3, 8 and 14 month interim sacrifice which enabled one to determine the approximate time of onset of the liver changes. No interim sacrifices were conducted in Dr. Kimbrough's study. The additional slides prepared at Bio-Test were examined by Dr. Richter and a tabulation of the liver findings are attached. These slides were reviewed by Drs. Kimbrough and Squire at our meeting. Although there was some disagreement on the terminology used in classification of the lesions, it was apparent that the incidence and severity of liver lesions (hyperplasia, nodular hyperplasia and neoplastic changes - carcinomas) was greater in Dr. Kimbrough's study when compared with the results of the Bio-Test Study, even though the same level of test material was administered in the diet. There are two possible explanations for this difference:

1.) The strain of rat. When questioned, Dr. Kimbrough had no information on the spontaneous incidence of hyperplastic or neoplastic liver lesions in the Sherman strain. However, the incidence of spontaneous liver cell hyperplasia would appear to be extremely low since this finding was reported in only 4 controls. The incidence of liver hyperplasia among control rats of the Bio-Test study was also very low. The incidence of spontaneous hyperplastic liver nodules reached 20% in the Fischer Rat

and in some of the other strains.

2.) Sex difference. On the basis of our studies and those of other investigators in rats and mice, it was found that the incidence of hyperplastic and neoplastic liver lesions are much higher in females.

The results of the liver tumor workshop are to be published in the near future and will include the participants. The views of this group, regarding classification of hyperplastic and neoplastic liver lesions is based on the pathogenesis of such lesions in rats that have been induced by known carcinogens such as the nitrosoamines and 2 - acetylaminoflorine (2-AAF). The adoption of this terminology and classification system by the scientific community will have widespread implications regarding assessment of safety of chemicals and drugs currently on test and those previously studied.

Attached are Dr. Richter's comments in regard to Dr. Kimbrough's findings.

D. E. Gordon

Donovan E. Gordon, D.V.M., Ph.D.
Dipl., Am. College Vet. Path.

February 3, 1975

Dr. Donovan Gordon
Industrial Bio-Test Laboratories

I wish to summarize my observations of the lesions seen in Dr. Kimbrough's study of Aroclor 1260 and the comparison of diagnoses with Dr. Kimbrough and Dr. Squire.

1.) The criteria that I used for diagnosis of the lesions are similar to what they used.

2.) My evaluation tends to be a little more conservative than theirs. For example: they would call some of my hepatomas carcinoma but with some question.

3.) Therefore, if we both read the same slides there might be a little variation in numbers of lesions in the different categories but no major difference.

4.) Dr. Squire and Dr. Kimbrough are using a new and revised terminology for the categories and list them as follows:

My Terminology (Classical Use)	Dr. Squire's (Revised Terminology)
Focal Hypertrophy	Cellular Alteration
Nodular Hyperplasia Hepatoma	Nodular Neoplasia or Neoplastic Nodule
Carcinoma	Carcinoma

5.) However, the lesions in Dr. Kimbrough's study were more severe than those in the Bio-Test study. The lesions that she and Dr. Squire are calling carcinoma are also carcinomas by my criteria. I would

conclude from an examination of their material that Dr. Kimbrough's study demonstrated carcinogenicity.

Ward R. Richter

Ward R. Richter, D.V.M.
Dipl. Am. College Vet. Path.

EXHIBIT # 16

May 25, 1970

Otis E. Fancher, Ph.D.
Director
Industrial Bio-Test Laboratories, Inc.
1810 Frontage Road
Northbrook, Illinois 60062

Dear Otis:

This letter will authorize you to proceed with a study with the leghorn chickens with the Aroclor 1242, lot number AL-55. This should duplicate the study you did previously with Aroclor 1242, lot number AK-255, except in this instance you have suggested using dietary levels of 2, 4, and 8 ppm.

This sample of Aroclor represents our current regular production which involves some clean-up instituted since the previous sample was made available to you. We would hope that we might find a higher "no effect" level with this sample as compared to the previous work.

As soon as suitable reference standards are available, the research laboratory in St. Louis will more carefully characterize the two samples in terms of possible minute amounts of contaminants.

Best personal regards.

Sincerely,

Elmer P. Wheeler
Manager, Environmental Health

EPW:ju

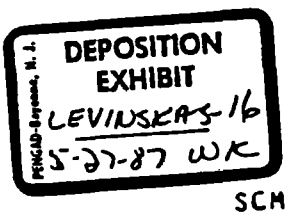

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EXHIBIT # 17

PCB - Ind. Biotest

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

TOXICOLOGY
ENVIRONMENTAL SCIENCES
CHEMISTRY
PLANT SCIENCES
MEDICAL SCIENCES

AREA CODE 312
TELEPHONE 272-3030

September 30, 1971

Dr. George J. Levinskas
Manager, Product Evaluation
Monsanto Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63166

Dear George:

Enclosed are the correction pages for the three teratology studies with Aroclor 1242, Aroclor 1254 and Aroclor 1260.

I discussed the interpretation of the renal caudal ectopia, found with Aroclor 1254, with Dr. Keplinger. He is in agreement with the interpretation that this is probably not a specific teratogenic effect but a general indication of the toxicity of the material. In reviewing the results from the three generation study there appears to be a reduction in both 5 day and 21 day pup survival in the group fed the highest level (100 ppm) of Aroclor 1254. This was not observed in the other Arocler groups or in groups fed 1 or 10 ppm, again suggesting that the level of Aroclor had a general toxic effect.

As I pointed out in our phone conversation, the small differences observed in sex ratios are not significant. A statement to that effect has been inserted.

If you have further questions, contact me at any time.

Sincerely yours,

Paul

Paul L. Wright
Section Head, Toxicology

PLW:lam
Enclosures

EXHIBIT # 18

PCB

April 28, 1972

Dr. Otis Fancher
624 N. Abrego Drive
Green Valley, Arizona 85614

Dear Otis:

I am ashamed that I have been so slow in reviewing the manuscripts and sending you our comments. I guess Kop's sending me the chronic rat and dominant lethal and chicken study on the 18th of April finally stirred me to move.

First of all, I agree we should hold up the publication of the chicken work until the current study is completed.

The only other comment I have of substance is that I wish we could work in several paragraphs reviewing the Treon work on vapors published in 1956 (see enclosed xerox copy of reprint). A logical place for a review of those data would be at the top of the 3rd page of your review paper, before your paragraph at the top which begins with "During succeeding years little information was reported concerning the toxicology of the PCB until McLaughlin et al, 1963, etc."

Most of the review articles on the PCB's have failed to indicate awareness of the Treon work. I believe this is because the Risebroughs, Peakalls, etc., etc. — the environmentalists -- have not encountered the American Industrial Hygiene Association Quarterly in the review of the literature nor is it likely that they ever heard of the AIHA.

In any case, I think the work is worthy of review even though it was inhalation data particularly since Drinker's earlier work in '37 is frequently mentioned and this again concerned inhalation.

In the last paragraph of this same review paper you

refer to the "permissable ambient concentrations of PCB's" as suggested by Drinker in 1939. Actually the ACGIH established the Threshold Limit Values based on Treon's work rather than the earlier Drinker work. I believe we may have arrived at our high dietary level of 100 ppm in the studies done at Bio-Test based on the Treon work rather than Drinker's.

George Levinskas is reviewing each of the papers to see if you, Kep and I have missed typo's and he may well suggest some grammatical changes which we will enter on our copy and send xerox's to you and Kep.

I hope to get copies of all of the studies in the hands of Bill Papageorge, Scott Tucker and the lawyers next week. I do not anticipate a lot of changes from them and hope that the attorneys agree that we can go ahead with publication.

Best personal regards,

Sincerely,

Elmer P. Wheeler
Mgr., Environmental Health
Medical Department

EPW/bks

cc: M. L. Keplinger

EXHIBIT # 19

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

TOXICOLOGY
ENVIRONMENTAL SCIENCES
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MEDICAL SCIENCES

AREA CODE 312
TELEPHONE 272-3030

April 18, 1975

APR 21 1975

Dr. George Roush, Jr.
Monsanto Company
800 North Lindbergh Boulevard
St. Louis, Missouri 63166

Dear George:

I fully appreciate that the meeting on PCB's today was not completely satisfactory and that many nagging questions remain. The enclosed is a brief summary of my personal views and I would appreciate any open and frank comments that you all may have.

Please let me know of any action that you contemplate in the way of seeking additional assistance in pathology or in contacting federal agencies. We will be pleased to be of help in any way that you may wish.

It is my feeling that we need to get together again within the next few weeks to continue our discussions.

Very truly yours,

J. C. Calandra
President

JCC:AR

cc - Dr. George Levinskas
Mr. Elmer Wheeler
Mr. William Papageorge

SCM 022745

EXHIBIT #20

Industrial BIO-TEST Laboratories, Inc.
NEW FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062
TOXICOLOGY
ENVIRONMENTAL SCIENCES
CHEMISTRY
PLANT SCIENCES
MEDICAL SCIENCES

028

April 28, 1972

Dr. George Levinskas
Monsanto Company
800 No. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

Dr. Richter and I have recently re-examined an additional section of liver from Rat No. 543, Female, Group III (10ppm level) of IBT No. 622-07198. The section was cut from the original block of embedded tissue. The hepatic lesion was originally classified by Dr. Richter as a hepatoma. Upon review, Dr. Richter has classified this lesion as nodular hyperplasia and I concur. However, you will also note that when additional sections of liver from this animal were processed (IBT Study Number 641-06672), no liver alterations were observed which attests to the focal nature of these lesions.

This change in re-classification will appear in our revised report of IBT No. 641-06672. I am enclosing a slide of the above lesion.

Sincerely,

D. E. Cordua, D.V.M., Ph.D.
Section Head, Pathology Department

DEC/jl
cc: M. L. Keplinger
J. C. Calandra
enclosure

DEPOSITION EXHIBIT
LEVINSKAS-20
5-27-87 WIC

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AROCLOR - 1260
Tabulation of Individual Liver Lesions in Rats 154 14

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	[illegible]
24 Month	C-III	740M											
	100ppm	722"											
		724"	+++				P						
		744"											
		746"				+							
		748"	++				P						
		768F				+	P						
		771"	+			++	P			P			
		775"				+++							
		Ext"	+++										
		733"											
		765"	+					+					
		766"	++			+	P	+					
		767"							P				
		776"				+	P	+					
		773"				+	P						
		786"	+++										
		789"							P				
		793"	+++										
		Ext"	++			+	P						
	Control	8M						+					
		11"											
		12"											
		21"											
		23"											
		33"						+					
		34"											
		35"											
		Ext"											
		46F			+								
		47"											
		49"						+					
		51"						++					
		52"											
		56"											
		59"											
		62"											

EXHIBIT # 21

Monsanto

Monsanto Company
800 N. Lindbergh Boulevard
St. Louis, Missouri 63166
Phone: (314) 694-1000

July 18, 1975

Dr. J.C. Calandra
Industrial BIO-TEST Laboratories
1810 Frontage Rd.
Northbrook, Ill. 60062

re: AROCLOR 2-year Rat Feeding Studies

Dear Joe:

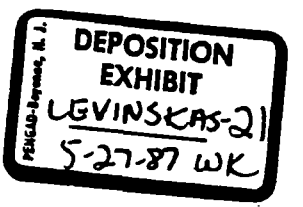
The attached table summarizes a comparison of the 3 revised AROCLOR reports (1242, 1254, 1260).

In 2 instances, the previous conclusion of "slightly tumorigenic" was changed to "does not appear to be carcinogenic". The latter phrase is preferable. May we request that the AROCLOR 1254 report be amended to say "does not appear to be carcinogenic".

The number of hepatomas reported for AROCLORS 1260 and 1242 have been interchanged. This appears to have arisen from confusion regarding the numbering of the animals. The original reports show tumors in animals with numbers in the 100-300 range for AROCLOR 1260 and in the 500 to 800 range for AROCLOR 1242. This leads me to conclude that the numbering scheme shown in the second set of reports is correct. With AROCLOR 1254 confusion is compounded. The original report showed tumors in animals with numbers in the units to teens, but the revised report shows animal numbers ranging from 40 to 1000. Can this be straightened out?

I was unable to reconcile the differences in the animal numbers between the first supplemental report and the original reports, I had inquired as to the changes in the numbers. As I recall, I was told that the sections had been renumbered when the new slides were made and that a key relating to the sets of numbers

cc MLK DEG IBP



RECEIVED
JUL 21 1975
BIO-TEST

would be supplied. This has not been done. It may not be necessary for AROCLORS 1260 and 1242, but AROCLOR 1254 remains unresolved.

Insofar as I can see, the remainder of the reports appear acceptable.

Kindest personal regards,

Sincerely,

George J. Levinskas, PhD
Mgr., Environmental Assessment
and Toxicology

/bkp

att.

cc: Dr. George Roush, Jr., M.D.

Product	Supplemental Report #1 (mailed)	Supplemental Report #2 (JCC delivered)
AROCLOR 1260		
conclusion	slightly tumorigenic	does not appear carcinogenic
hepatomas	3	7
range of test animal nos:		
p. 9	600 to 800	100 to 300
p. 10	1000 series	800 to 900
p. 11	70 to 100	10tto 40
p. 12	500 to 600	80 to 200
p. 13	600 to 700	200 to 300
p. 14	700 series	200 to 300
AROCLOR 1254		
conclusion	slightly tumorigenic	slightly tumorigenic
hepatomas	6	6
AROCLOR 1242		
conclusion	slightly tumorigenic	does not appear carcinogenic
hepatomas	7	3
range of test animal nos.	as in report #2 for AROCLOR 1260	as in report #1 AROCLOR 1260

SCM 022804

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EXHIBIT # 22

AROCLOR 1

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

TOXICOLOGY
ENVIRONMENTAL SCIENCES
CHEMISTRY
PLANT SCIENCES
MEDICAL SCIENCES

AREA CODE 312
TELEPHONE 272-3030

August 4, 1975

Dr. George J. Levinskas, Manager
Environmental Assessment and Toxicology
Monsanto Company
800 North Lindbergh Boulevard
St. Louis, Missouri 63166

Dear George:

Re: Aroclor - 2 Year Rat Studies

In regard to the comments and questions covered in your letter dated July 18, 1975, pertaining to the above, please note the following:

1. We will amend our statement in the last paragraph on page 2 of the Aroclor 1254 report to read, "does not appear to be carcinogenic" in place of "slightly tumorigenic" as requested.

2. In regard to the animal numbers in the Aroclor 1242 and 1260 reports, they are correct in our final revised report. In the original reports, the Aroclor titles for these two materials were reversed.

3. The animal identification numbers appearing in the reports on evaluation of additional liver sections are the same as those in our original report. The animals were not renumbered.

4. We cannot find any discrepancy in animal identification numbers in the reports (original, re-evaluation, final revision) on Aroclor 1254. However, in the report on re-evaluation of additional liver sections dated March 24, 1975, there was a typographical error on page 1 which referred to Aroclor 1260 instead of 1254. Perhaps this is the basis of your confusion.

I hope that this will serve to further clarify the situation. Thank you for your assistance and cooperation.

Sincerely yours,

Joe

J. C. Calandra
President

DEPOSITION EXHIBIT
LEVINSKAS-22
5-27-87 WK

JCC:AR

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000658

EXHIBIT # 23

II. Summary

In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. There were six hepatomas detected among six of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice. No hepatocellular carcinomas were observed. One liver tumor (a hepatoma) previously reported in a T-II animal (No. 445) was re-classified as nodular hyperplasia. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver ascribed to biotransformation of the test material. The latter lesions were confined primarily to test animals of the 12 and 24 month sacrifices and they were dose-related in incidence and severity.

In conclusion, Aroclor 1254 does not appear to be carcinogenic in rats fed for two years at levels up to and including 100 ppm.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

Report Approved by:

M. L. Kaplinger, J., D.
Manager, Toxicology

aew

DEPOSITION EXHIBIT
LEVINSKAS-23
5-27-87 WK

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EXHIBIT # 24

172

Industrial **BIO-TEST** *Laboratories, Inc.*
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

August 5, 1975

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Mr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections from Rats of a Two - Year Chronic Oral Toxicity Study of Aroclor 1254

Enclosed please find 3 copies of page 2 from our revised laboratory report dated March 24, 1975, prepared in connection with the above study.

Very truly yours,

J. C. Calandra

J. C. Calandra
President

JCC/fd

EXHIBIT # 25

File Arochlor 12E

August 14, 1975

Dr. J.C. Calandra
Industrial BIO-TEST Laboratories
1810 Frontage Road
Northbrook, Ill. 60062

re: AROCLOR 2-year Rat Feeding Studies

Dear Joe:

With respect to your letter of August 4, 1975, we appear to be reading from different scripts.

The attached copies of pages from the revised AROCLOR 1254 report (IBT No. 641-06672), dated March 24, 1975 shows that virtually all animal numbers have 3-digits. The exceptions include a 4-digit number on page 10, a series of 2-digit numbers ranging from 71-70 on page 11, and slides marked Ext or Ex appearing on pages 12 and 14.

Copies of pages 83-88 from the original report, IBT No. B7298 dated November 12, 1971 also are attached. These contain the tables listing tumors, and they are the only ones in which individual animal numbers appear. As summarized below, there is a repetition of low digit numbers in each group.

		AROCLOR 1254		
	Control	1 ppm	10 ppm	100 ppm
Male rat nos.	1,2	1,2	1,2	4,5,7
Female rat nos.	46-48,50, 52,59,64, 69	3-13	3-11	1-3,6, 8-15

The only pages which contain similar numbers are page 11 of the revised report and page 83 of the original report. How-

DEPOSITION EXHIBIT
LEVINSKAS 25
5-27-87 WK

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ever, even in those instances where the same numbers appear, there are inconsistancies as shown below:

animal no.	group and sex page 11	page 83
46	1 ppm Female	all shown as control females
47	1 ppm Female	
48	1 ppm Female	
50	1 ppm Female	
52	10 ppm Male	
59	10 ppm Female	
64	100 ppm Male	
66	100 ppm Female	

Although it is of minimal significance, pages 84 and 85 of the original report are misnumbered in that page 84 is a continuation of the table which begins on page 85.

The page for the AROCLOR 1254 containing the phrase "does not appear to be carcinogenic" has been received.

We note the interchange of the numbers 1242 and 1260 on those 2 AROCLOR reports, and will destroy the mislabeled copies.

Sincerely,

George J. Levinskas, PhD
Mgr., Environmental Assessment
and Toxicology

/bkp

att.

SCM 022808

000062

EXHIBIT # 26

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

TOXICOLOGY
ENVIRONMENTAL SCIENCES
CHEMISTRY
PLANT SCIENCES
MEDICAL SCIENCES

AREA CODE 312
TELEPHONE 272-3030

~~DF~~
~~CDS~~
~~EHA~~
~~FLB~~
~~FAF~~
File

October 17, 1975

George J. Levinskas, Ph.D.
Mgr., Environmental Assessment & Toxicology
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

I am returning the black and white photomicrographs of Aroclor lesions in the rat liver that were taken by Dr. Pour at the Eppley Institute in Omaha, Nebraska and delivered to me by Jim Hill. I found his report interesting, although I do not concur with his classification and interpretation of some of the liver lesions.

Per your request, I am also enclosing a copy of Dr. Kimbrough's findings and report on Aroclor 1260 in the rat which you sent to me earlier in the year.

Sincerely,

D. E. Gordon

Donovan E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

DEG/ji

enclosures

SCM 022821

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EXHIBIT # 27

003

INTER-OFFICE CORRESPONDENCE

~~Industrial~~ BIO-TEST ~~Laboratories, Inc.~~

FROM: GLK

TO: DEC

DATE: December 24, 1975

SUBJECT: PCB Papers

George Levinskas has some questions regarding the pathology section of the PCB papers. He wants to visit Northbrook after Jan. 1 at a time convenient to you. Please make the necessary arrangements.

Gary

G. L. Kennedy

GLK/lam

(312) 564-1000
2184

9½ JAN. MON

DEPOSITION EXHIBIT
LEVINSKAS-27
5-27-87 WK

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EXHIBIT # 28

INTER-OFFICE CORRESPONDENCE 002

Industrial BIO-TEST Laboratories, Inc.

FROM D. E. Gordon DATE December 31, 1975

TO MLK, FKK, SUBJECT

cc: JCG

C

Dr. Levinskas will be here on Friday, January 9, 1976 to discuss the pathology section of the PCB papers.

January 12, 1976

Dr. Levinskas has rescheduled his trip for Thursday, January 15.

DEPOSITION EXHIBIT LEVINSKAS-28 5-27-87 WK

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EXHIBIT # 29

Toxicity and Environmental Effects of Commercial PCBs

Introduction

Polychlorinated biphenyls (PCBs) are not a single chemical entity. They are produced by chlorinating biphenyl to acheive a final product with specified properties. These products, sold under the trade name AROCLOR by Monsanto, are mixtures of chlorine-containing biphenyls with different numbers and positions of the chlorine substituents.

Over the years, a series of investigations have been conducted to assess potential health and environmental hazards of PCBs. The 3 predominant commercial mixtures (AROCLORS 1242, 1254 and 1260) have been studied most intensively. Toxicity tests performed on these 3 commercial mixtures were typical in scope of those designed for the evaluation and establishment of the safety of direct and indirect food additives.

It may be noted that AROCLOR 1260 no longer is produced in this country since it does not meet the physical specifications for its restricted uses.

Conclusions Based on Monsanto Studies

1) As a class, the AROCLORS are relatively harmless materials for routine industrial handling under ambient conditions.

2) Threshold Limit Values of 1 mg/m^3 and 0.5 mg/m^3 have been established for materials containing average chlorine values of 42% and 54%, respectively, of the available sites.

3) The no-effect level for these materials in chronic

rat and dog feeding studies is about 10 ppm in the diet. No hepatocellular carcinomas were present.

4) The no-effect level on rat reproduction is between 1 and 10 ppm in the diet since higher levels result in low mating indices.

5) No teratogenic or mutagenic effects were observed in studies with rats and mice.

6) In chicken reproduction and teratology studies, AROCLOR 1242, which produced the most severe effects, had a no-effect level of 2-4 ppm in the diet.

7) Acute toxicity to fish varies from less than 1 ppm to greater than 100 ppm depending on the specific AROCLOR and species of fish tested.

8) PCBs containing 3 or less chlorine substituents per molecule are reasonably biodegradable.

Summary of Monsanto's Long-term Toxicity Studies on Commercial PCBs.

These tests consisted of 2-year (lifetime) feeding to rats, 2-year feeding to dogs, 3-generation rat reproduction studies with 2 litters cast per generation, rat teratology studies and dominant lethal mutagenic studies in mice. Toxicity and reproduction studies in chickens were performed to evaluate possible untoward effects in birds such as decreases in eggshell thickness. In addition, biodegradation and tissue accumulation studies have been conducted.

The highest dietary level (100 ppm) in the lifetime rat feeding studies produced a weight depression at 24 months in females fed AROCLOR 1254 and liver weight increases in all

groups except males fed AROCLOR 1242. As with other halogenated hydrocarbons, the important histopathologic changes were present in the livers of animals sacrificed at the end of the study. These consisted of hepatocellular alterations such as focal hypertrophy, cytoplasmic lipid changes and in some animals from the 100 ppm groups, hepatomas or cholangiohepatomas. No evidence of hepatocellular carcinogenicity of the AROCLORS was found.

In the dog 2-year studies, some slight decreases in body weight gain were noted. At the highest feeding level (100 ppm), AROCLOR 1260 produced an increase in serum alkaline phosphatase activity and liver weights without concomitant histopathologic changes. However, there was evidence of gastrointestinal inflammatory lesions and ulcerations which appear to be similar to those found by Allen in rhesus monkeys fed AROCLOR 1248. (AROCLOR 1248 was an experimental product which never was commercialized.)

In the rat reproduction studies, none of the AROCLORS produced adverse effects in the 2 litters of the first generation. In the second and third generations, there was a reduction in the mating index at the 2 highest feeding levels (10 ppm and 100 ppm). The ability of females to conceive, carry the delivery process to parturition, and to successfully nourish the young was not affected by the 3 AROCLORS. No changes were produced in the reproductive tracts of either male or female rats by any of the 3 AROCLORS.

There was no evidence of teratogenic or mutagenic changes with any of the PCBs at maximally tolerated dose levels in

rats and mice.

In the chicken toxicity/reproduction study, AROCLOR 1260 was without effect at all test levels. AROCLORS 1242 and 1254 at 100 ppm in the diet decreased egg hatchability. In fact, poor hatchability of eggs was found from hens fed 8 ppm of AROCLOR 1242. In addition, AROCLOR 1242 at 10 and 100 ppm and AROCLOR 1254 at 100 ppm were associated with reduced eggshell thickness. Chick viability was affected by both substances at a dietary level of 10 ppm.

Biodegradation studies were conducted using semi-continuous activated sludge systems and tissues of rats fed PCBs were analyzed to measure accumulation and retention of these materials. These factors are influenced by the number and position of the chlorine substituents. Higher chlorine-containing members are more resistant to biodegradation and they accumulate more readily and are less readily metabolized and/or excreted from lipoid tissue in animals. PCBs containing 3 or less chlorine substituents per molecule are reasonably biodegradable.

Comments

The conclusion that "No evidence of hepatocellular carcinogenicity of the AROCLORS was found" in the 2-year rat feeding study was reached only after extensive re-evaluation of the original liver slides as well as additional liver sections from all of the animals after the Kimbrough results on AROCLOR 1260 became known to us. The slides were read

independently by Dr. D. Gordon of Industrial BIO-TEST Laboratories, Professor W. Richter of the University of Chicago, and by Professor P. Pour of the Eppley Institute for Research in Cancer. In addition, Dr. Pour evaluated the Kimbrough slides and does not agree with the reported findings.

Barsotti and Allen have reported that 2.5 ppm of AROCLOR 1248 in the diet of rhesus monkeys adversely affected reproduction. This approximates a dosage of 100 μg/kg/day. It is higher than the safe human intake (1 μg/kg/day) estimated by FDA from human data when it promulgated its tolerances for PCBs in food.

GT

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Human data

(F.R. July 6, 1973. p. 18097, Section (2))

Lowest level of PCBs producing effect in man = 500 mg total.
500 mg consumed by 50 kg individual over 50 days.
500 mg ÷ 50 kg ÷ 50 days = 200 µg/kg/day (effect level)
Using 10-fold safety factor leads to estimate that 20 µg/kg/day may be safe over a 50-day interval.
Since PCBs have long half-life; calculating same intake over a 22-month span arrives at an estimated safe intake for a protracted period of 1 µg/kg/day.

Primate data

(Fed. Proc. 34:338 (1975). Abstract 675. Barsotti & Allen)

At 2.5 ppm in diet, primates ingested 182 mg over 52 weeks.
182 mg ÷ 365 days = 0.5 mg/day which produced effects.
Assuming 5 kg primate, 500 µg ÷ 5 kg = 100 µg/kg/day
Conclusions: Primate study done at dosages (100 µg/kg/day) greater than the safe dosage (1 µg/kg/day) esimated from human data.
Primate study does show effects at lower dosages over longer time span (100 µg/kg/365 days) than had been observed in man (200 µg/kg/50 days).
The total amount of PCBs producing effects in primates (182 mg) was lower than that producing effects in man (500 mg).

(N.B. Abrahamson & Allen, Env. Health Perspectives. June, 1973, 81-86. Report that infant monkeys are able to tolerate doses of PCBs that produce extreme morbidity in adult monkeys.)

Dog and Rodent Data

(F.R. July 6, 1973. p. 18097, Section (1))

"No-effect" level for man using a 100-fold safety factor and accepting 10 ppm as a "no-effect" level in animals would be 2.5 µg/kg/day based on dog data and 3 µg/kg/day based on rat data.
If rat data "no-effect" level drops to 1 ppm, then corresponding estimate of human "no-effect" level drops to 0.3 µg/kg/day.
Question: In a "collision" between rat data using a 100-fold safety factor and human data using a 10-fold safety factor, which data base would you like to be riding on?
Comment: Since human data is available, it could be argued that the traditional 100-fold safety factor is not necessary. Application of a 30-fold safety factor to rat data, supported by dog and human data, makes present estimate of safe human intake appear reasonable.

PCB Primate and Human Residue Data

	Primates		Human
Conc. in diet, ppm	25	2.5	-
Intake, µg/kg/day	800	100	-
Estimated safe dose, µg/kg/day		-	-/
Liver conc., µg/g	56.3(0.01)*		-
Fat conc., µg/g	50.0(27.7)*		0 (314 samples)**
			<1 (125 samples)
			1-2 (165 samples)
			>2 (33 samples)

*Value in ( ) from infant primate.
Allen et al., TAP 30: 440-451 (1974)

**Yobs, Env. Health Persp.,79-81, April 1972

SCM 019645

000672

EXHIBIT #30

BIO-TEST Laboratories, Inc.
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TOXICOLOGY
ENVIRONMENTAL SCIENCES
CHEMISTRY
PLANT SCIENCES
MEDICAL SCIENCES

001

February 18, 1976

George J. Levinskas, Ph. D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

I am enclosing the revised tumor tables for the Aroclor paper that we discussed during your visit on January 15, 1976. You will notice there are two tables with the same data. One table is a listing of tumors by organ system, as you suggested, to replace the original table. I think I also prefer the former although it will require more space when printed.

Should you have any further questions, please contact me.

Sincerely yours,

Donovan E. Gordon, D.V.M., Ph.D.
Section Head Pathology

DEG/ji
cc: M. L. Keplinger

EXHIBIT # 31

Monsanto

Dept. of Medicine & Environmental Health - G. J. Levinskas, A2SA

DATE November 17, 1978

SUBJECT AROCLOR 1260

REFERENCE

TO FILE

cc G. Roush, Jr. - A2SA
J.C. Weber - B2SK
G.F. Barton - A3NC
W.J. McCarville - A3NC
C.F. Callis - B2SA
J.T. Garrett - A2SA

DEPOSITION EXHIBIT
LEVINSKAS-31
5-27-87 WK

On Wednesday, November 15, 1978, I had a call from Joan Ranson, an industrial hygienist with OSHA in Philadelphia.

About two weeks ago, a Philadelphia trucking firm picked up two used transformers Westinghouse was having shipped. The truck carried other cargo of a consumer nature, namely shoes, toys and candy. The transformers were not accepted at the receiving end because their contents had spilled. Consequently, the driver took them to the truck terminal. The transformers contained AROCLOR 1260. An estimated 168 gallons of transformer fluid was spilled.

CPSC has been tracking down the consumer products. Most are believed to have been recovered.

EPA is on the scene. Details as to exactly what they are doing were not discussed at length. They apparently are offering advice on cleanup of the spill.

Two local TV stations have camera crews at hand, and the emotional level is rising.

The two leaking transformers have been removed to an enclosed area in the truck terminal. Ms. Ransom wanted to know about monitoring air levels in the enclosed area for PCBs. She also inquired about clinical or other tests which could be done on exposed workers to gauge their exposure and the nature of protective equipment which clean-up crew members should wear.

Without reiterating all aspects of this somewhat lengthy discussion, I made several statements to Ms. Ranson. She was told that there were no tests we know of to measure the after effects of exposure, and none should be necessary since there was no reason to expect that persons exposed under the conditions she had described would become ill from PCBs. With respect to air monitoring, the analysts should be careful to identify PCBs as such since AROCLOR 1260 was mixed with another chlorinated hydrocarbon. The latter was more volatile and, if detected, and expressed as PCBs, could create unnecessary concern in addition to being misleading. I saw no reason for concern about the health of employees' families from possible contact with PCB-contaminated workclothes. With respect to the emotional tensions, I suggested that they tell people there was no health hazard involved, but that efforts were being made to limit the potential environmental effects of PCBs. The use of disposable or protective clothing was justified to keep workers from taking soiled garments home and having PCBs flushed down the drain. THere was no need for respiratory protection for cleanup crews. Finally, if the truck had a wooden floor-bed, it

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might be advisable to replace it. The loading dock apparently is concrete. All wastes, including spillage initially swept up with sawdust, should be disposed of in an acceptable manner according to prevailing regulations. Ms. Ranson appeared to be aware of those requirements.

I don't know how many places have been contacted. Ms. Ranson stated that they had called Dow in the mistaken belief that they manufactured PCBs. They received a suggestion that adipose tissue assays might provide a useful measure of exposure. My comments on that suggestion ended with the observation that obtaining fat samples by biopsy would be the most traumatic part of the entire episode for the individuals involved. Ms. Ranson expressed appreciation for my remarks and indicated that her supervisor, Mark Durham, Sr. Industrial Hygiene Supervisor probably would call me tomorrow - Thursday, November 16, 1978.

Let's see what happens.

George J. Levinskas

/bks

EXHIBIT # 32

Monsanto

FROM (NAME & LOCATION): G. J. Levinskas - A2SC

DATE: September 25, 1975

SUBJECT: PCBs

REFERENCE:

cc H. S. Bergen - B2SL
D. R. Bishop - B1ND
W. B. Papageorge - B2SK
R. G. Potter - B3SA
W.W. Withers - B2SA

TO:

G. Roush, Jr.
A2SA

The attached represents a final (?) version of the toxicity statement on PCBs. This takes note of all the comments which have been received since the version mailed to you on August 29, 1975.

This was discussed on the phone with Wayne Withers, and he agreed that it was acceptable. Since Wayne was the only one who had comments regarding the August 29 version, this should be satisfactory to all concerned.

George J. Levinskas

/bkp

att.

PCBs

Recently, we were informed that liver carcinomas were observed in female Sherman strain rats fed AROCLOR 1260 for 20½ months. This prompted us to re-examine livers from male and female rats of the Charles River strain which had been fed AROCLOR 1242, AROCLOR 1254 or AROCLOR 1260 for 2 years in earlier studies conducted for Monsanto Company.

There are 4 elements which are closely interwoven in this matter: (1) differences in test procedures, (2) differences in results obtained by various investigators, (3) definition of what is a cancer, and (4) evaluation of potential risks, if any, to man. These will be summarized briefly.

(1) Several animal studies have been conducted with various brands of PCBs. In some studies, the test material has been identified by trade name (AROCLOR, KANECLOR). In others, there was just a general reference to PCB. Consequently, the quality of test material with respect to the amounts and nature of contaminating impurities or by-products cannot be determined in ~~all~~ case. In addition, several strains of test animals were used, the duration of the experimental periods varied, and there was a wide range in the depth of detail with which the observations were reported. Consequently, it is difficult to make comparisons between these studies.

(2) In general, studies have shown mice to be more susceptible than rats and females to be more sensitive than males to the liver effects of PCBs. Beyond these generalizations, the results have not been consistent. Some investigators have

reported liver carcinomas. Others have observed only benign tumors. Several have noted changes in liver tissue without detecting tumor formation. For the reasons just cited, it is difficult to determine the bases for these different results. The most direct comparison can be made between the 2 studies on AROCLOR 1260 since the same high dosage level of the same lot of AROCLOR 1260 was employed in both experiments. In the studies reported to us, liver carcinomas occurred in approximately 8% of female rats of the Sherman strain (the only sex used), In Monsanto's study, none of the liver lesions had progressed beyond the stage of benign tumors (hepatomas) despite a slightly longer duration of feeding of AROCLOR 1260 to rats of Sprague Dawley, Charles River strain. The Monsanto study employed rats of both sex and it did confirm the previously noted greater sensitivity of female rats to liver effects of PCBs.

(3) A review of the liver alterations seen in all 3 AROCLORS in Monsanto's studies shows that the lesions were benign in character in the traditional pathologic sense. An evaluation of all information available to us, including the contradiction between the recent data showing AROCLOR 1260 to be a carcinogen and our earlier negative results on the same product, leads to a conclusion that AROCLOR 1260 is not carcinogenic to all commonly used strains of laboratory test animals.

(4) In 1972, the manufacture of AROCLOR 1260 was discontinued in the United States and the sale of AROCLORs was restricted to a single use, i.e., as dielectric fluids. As such they are used in closed systems which will at least minimize additional environmental contamination. Considering the

high degree of fire risk associated with this use, and recognizing that AROCLOR 1260 may have a weak carcinogenic potency which has not been fully proven and that AROCLORS 1242 and 1254 have not been shown to be carcinogens, it is concluded that the continued use of AROCLORS 1242 + 1254 as dielectric fluids will not present an unreasonable human health hazard.

bcc W. B. Papageorge - B2SK

January 14, 1975

Dr. Donovan E. Gordon
Industrial BIO-TEST Laboratories, Inc.
1810 Frontage Road
Northbrook, Illinois 60062

Re: Polychlorinated Biphenyl (PCB)

Dear Don:

Enclosed are copies of three reprints dealing with liver tumorigenisis of PCB's. These are from:

(1) Gann, (1972).63: 805.

(2) Gann, (1973).64: 105-108.

(3) J. Nat'l Canc. Inst., (1973).51:1637-1646.

The studies were performed with Japanese materials (Kanechlors), but the comments are of direct interest to our meeting on AROCLOR 1260. You and Dr. Richter should be familiar with the contents of those papers as you review the AROCLOR slides.

Our meeting is scheduled for January 31, 1975 in Room 201, Building 37, at NCI in Bethesda. We will be meeting with Drs. Kimbrough and Squires. No specific time has been set, but we can plan on starting in the morning. I will confirm a specific time and will check with you or Kep on a place to stay the night before.

Sincerely,

George J. Levinskas, Ph. D.
Manager, Environmental Assessment and Toxicology

mlw
cc Dr. M. L. Keplinger

DEPOSITION EXHIBIT
LEVINSKAS-13
5-27-87 WK

SCM 022820

000010

HARTOLDMON0023331

EXHIBIT # 33

Monsanto

FROM - NAME & LOCATION: D. R. Bishop - B1ND 2891

DATE: Nov. 17, 1975

SUBJECT:

REFERENCE:

TO:

~~Mr. T. H. Bottini - B2CA~~ 2772
~~Dr. P. O. DeGarmo - B3NA~~
~~Dr. W. C. Hammann - B3SA~~ 4101
~~Mr. E. H. Harbison - D1K~~ 3:09
~~Dr. G. J. Levinskas - A2SC~~
~~Mr. W. B. Papageorge - B2SK~~
~~Mr. W. R. Corey - B2SA~~ 2517
~~Mr. F. J. Fitzgerald - B2SA~~ 2091
Dr. J. P. Mieure - T2F 4737
~~Mr. D. Wood - B2SD~~ 2623
~~Dr. C. Paton - B2SC~~ 2509
~~Mr. R. G. Potter - B2SB~~ 2102
~~Dr. G. Roush - A2SA~~
~~Mr. J. C. Weber - B1ND~~ 2127
~~Mr. W. W. Withers - B2SA~~ 2151
~~Dr. P. E. Wright - A2SC~~

→ FJL

These people should be informed, this material is not to be released. Plw

Attached is the second draft of a news release summarizing Dr. Pour's re-evaluation of Dr. Kimbrough's study. It incorporates comments from Dr. Levinskas, Messrs. Papageorge and Wood.

Please let me have your comments and/or approvals as soon as possible tomorrow morning.

We need to clear the final version with Dr. Pour and have copies printed for distribution in Chicago on Wednesday, following Dr. Kimbrough's presentation.

I'll have to print the news release late tomorrow morning. Your cooperation is appreciated.

D. R. Bishop/mks

D. R. Bishop

/mks
attachment

Dr. Khubika of Eppley Institute does not want Dr. Pour's name or his Institute mentioned in the press. This is not to be released.

SCM 058058

IN - 10 REV. 1

000030

EXHIBIT # 34

Monsanto

FROM (NAME & LOCATION) D. R. Bishop - B1ND

DATE: Nov. 17, 1975

SUBJECT:

REFERENCE:

TO:

Mr. T. H. Bottini - B2CA
Dr. P. O. DeGarmo - B3NA
Dr. W. C. Hammann - B3SA
Mr. E. H. Harbison - D1K
Dr. G. J. Levinskas - A2SC
Mr. W. B. Papageorge - B2SK
Mr. W. R. Corey - B2SA
Mr. F. J. Fitzgerald - B2SA
Dr. J. P. Mieure - T2F
Mr. D. Wood - B2SD
Dr. C. Paton - B2SC
Mr. R. G. Potter - B2SB
Dr. G. Roush - A2SA
Mr. J. C. Weber - B1ND
Mr. W. W. Withers - B2SA
Dr. P. L. Wright - A2SC

Attached is the second draft of a news release summarizing Dr. Pour's re-evaluation of Dr. Kimbrough's study. It incorporates comments from Dr. Levinskas, Messrs. Papageorge and Wood.

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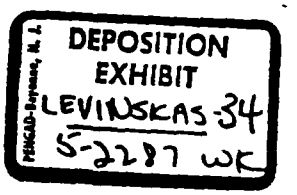
D. R. Bishop/mks

D. R. Bishop

/mks
attachment



SCM 058337

IN-10 REV. 1-

000081

MONSANTO INDUSTRIAL CHEMICALS CO.
D. R. Bishop
(314) 694-2891
PUBLIC RELATIONS DEPARTMENT
800 N. Lindbergh Boulevard
St. Louis, Missouri 63166

IMMEDIATELY 1975

CHICAGO, Nov. 19 -- Monsanto Company today announced that a newly completed scientific report, commissioned by the St. Louis-based company, does not confirm the presence of malignant liver tumors in experimental rats fed a commercial polychlorinated biphenyl (PCB) mixture...a conclusion that had been previously reached and widely reported by Dr. Renate D. Kimbrough of the Center for Disease Control of the U.S. Public Health Service in Atlanta.

The Monsanto-sponsored report, a re-evaluation of Dr. Kimbrough's work, is titled, "Histopathological Re-evaluation of Tissues from Sherman Rats Fed Aroclor 1260," and is authored by Dr. Peter Pour, a pathologist with the renowned Eppley Institute for Research in Cancer of the University of Nebraska Medical Center at Omaha. Aroclor is a Monsanto trademark for a class of chlorinated hydrocarbon industrial chemicals it manufactures.

In her study, Dr. Kimbrough reported that when Sherman strain female rats were fed 100 parts per million of PCB (Aroclor 1260) for about 21 months, 170 of the 184 experimental animals developed neoplastic lesions (precursors of malignant tumors). She further identified 26 of these lesions as hepatocellular carcinomas (malignant liver tumors).

During his re-evaluation, Dr. Pour saw the same alteration but identified them as being hyperplastic or non-tumorous lesions, further pointing out that it was his strong impression that many of the detectable alterations were a degenerative and reparative rather than a neoplastic process. Dr. Pour's re-evaluation is consistent with conclusions drawn from Monsanto's own PCB feeding studies which have never produced a carcinogenic response in experimental animals.

In his discussion, Dr. Pour reported that he observed 20 cases of abnormal lesions which presented such structural criteria as to be considered possible precursors to tumors, although a most significant criteria for malignancy -- namely invasiveness -- was missing, and the sign of ongoing toxic, degenerative and regenerative processes in the rest of the tissue was evident. "At present, the statement that these lesions may have metastasized (infiltrated adjacent tissue) if the treatment had been continued is as much as unreliable as the possibility that they might have been regressed if the animal would have been kept longer or for life," he stated.

"In summary," the Eppley Institute pathologist reported, "it is difficult at present to conclude whether or not some of the examined lesions represent a malignant lesion, because of the lack of invasion and metastases. In the case of such organs, as the liver, with its marked tendency toward regeneration, it is, in my

opinion, difficult and sometimes impossible to distinguish between regeneration, hyperplasia and neoplasia, particularly when the tissue is continuously exposed to a toxic substance."

Quoting further from Dr. Pour's report, he wrote, "In this context, Dr. Kimbrough's study seems of particular interest, in that polychlorinated compounds may be retained in the body, even in higher concentrations for several months after feeding has been stopped. This finding may explain the continuing degenerative and regenerative processes in the livers of most experimental rats, even two months after Aroclor was removed from the diet.

"One should also bear in mind that some animal strains may react more specifically to a compound because of common endogenous diseases, as in the case of the Sherman rats used in this experiment which tend toward spontaneous liver lesions.

"In my opinion," he concluded, "many of the lesions induced were of a degenerative nature, and without further studies, the induced liver lesions could not be definitely designated as neoplasia (tumorous).

-oOo-

NOTE TO EDITORS: Copies of Dr. Pour's report are available on request, in writing, from Public Relations Department, Monsanto Industrial Chemicals Co., 800 N. Lindbergh Blvd., St. Louis, Mo. 631

EXHIBIT #35

Industrial BIO-TEST *Laboratories, Inc.*
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

TOXICOLOGY
CHEMISTRY
MEDICAL SCIENCES
MICROBIOLOGY
INDUSTRIAL SAFETY & HEALTH

AREA CODE 312
TELEPHONE 272-3030
TELEX 72-4427

July 31, 1981

Dr. George Levinskas
Monsanto Company
800 North Lindbergh Boulevard
St. Louis, Missouri 63166

Dear Dr. Levinskas:

As per your request of July 30, 1981, Dr. D. E. Gordon is attempting to locate the raw data for the pathology reports on histologic examination of additional liver sections from rats fed Aroclors 1242, 1254 and 1260 (IBT study no. 641-06672).

These data will be microfilmed and a diazo copy sent to Mr. A. Uelner, Manager, Quality Assurance. Xerox copies of these data will be mailed to your attention.

If I can be of further help, please contact me.

Sincerely,

Marilyn A. Biederer
Validation Assistance Specialist

MAB:AR

cc - Mr. A. Uelner
Monsanto Company

EXHIBIT # 36

Monsanto

De, of Medicine & Environmental Health .J. Levinskas, G2WF (4-8809)

DATE July 9, 1981

SUBJECT AROCLOR Products 1242, 1254 and 1260:
Two Year Rat Feeding Studies

REFERENCE

TO J.H. Craddock

cc J.R.G. Ortiz, E2ND
A.F. Uelner, G2WC

A complete audit of these three past IBT studies will require considerable time. So much time, in fact, that the results of the audit would not be available until long after completion of the monograph which is being prepared. As a result, it has been decided to limit the audit to a determination of how long animals were on test and as to whether or not liver reactions were taken for microscopy. These are the crucial elements for assessing potential carcinogenicity of these materials.

G.J. Levinskas

GJL/mcl

DEPOSITION EXHIBIT
LEVINSKAS-36
5-27-87 WK

SCM 058929

IN-10M (REV. 2/78)

000036

EXHIBIT # 37

Monsanto

Name of Nominee			Location
Paul L. Wright			Creve Coeur
Company Unit or Staff Dept.	Division	Business Group	Department
Corporate Staff	Medical		Medical
Position Title	Salary Grade	Annual Salary	Date of Last Increase
Toxicology Manager	19	$28,980.00	2/75
Performance		Growth	Date Last Employe Review
Excellent		Excellent	2/75

Type of Award (Select the award category from the opposite side of this sheet which most appropriately describes the award and enter the category and code below.)
Staff

Award Category	Category Code Number
Solution to product toxicity problem which permitted Monsanto to continue product manufacturing and sale.	28

Describe the achievement and its significance to Monsanto below

Dr. Paul L. Wright has performed his regular duties exceedingly well and has, in addition, completed a specific "ad hoc" assignment with dispatch and distinction.

Dow informed us that they had encountered lung tumors in rats fed maleic anhydride and that they felt they had to report these findings to the Food and Drug Administration (FDA) at once under their "product stewardship" program. Dr. Wright was asked to contact Dow's toxicologists for details of their findings. This he did, and by his personal and professional efforts he convinced Dow personnel that while they had an obligation to report their findings to FDA, it would be foolhardy to act precipitously. Instead, Dr. Wright advised Dow to defer contacting FDA until they had thoroughly evaluated their findings and a subsequent course of action had been developed to allow resolution of questions which undoubtedly would be raised by their report of tumors. Dow agreed to this.

Dr. Wright then contacted the Process Chemicals business group and informed them of Dow's findings. He proposed a dual course of action. The first step was a commitment to support a repeat of the feeding study to determine whether Dow's findings were reproducible. The results of such a study would not necessarily resolve FDA's concern over the potential carcinogencity of maleic anhydride, but the intent to conduct the study promptly would serve to forestall precipitous action against the product by FDA. The subsequent step was to provide assurance to FDA that a thorough investigation of the toxicity of maleic anhydride would be undertaken, either by Monsanto alone or in cooperation with others. This proposal was acceptable to the business group, and Dr. Wright so informed Dow.

Subsequently, Dr. Wright accompanied Dow personnel to FDA when they presented their findings on maleic anhydride. FDA's toxicologists reviewed the data and the proposed plans of actions. They concluded that while the questions of carcinogenicity would need to be resolved, there was no apparent need for immediate prohibition of maleic anhydride or polymers containing maleic anhydride in food contact applications. Thus, we believe that Dr. Wright played a singular, outstanding role in preventing FDA from publicly proclaiming that maleic anhydride was a suspect

Recommended By:	Date	Award Amount Recommended:	Approved By:	Date	Award amount approved for payment:
[signature]	16 Sep 75		[signature]	10 Sept 1975	$2,500.00

G-2532

DEPOSITION EXHIBIT
LEVINSKAS-37
5-27-87 WK

SCM 058799
000103

carcinogen. Because of the many uses of maleic anhydride in food contact polymers, this was a significant accomplishment.

Subsequently, when maleic anhydride was included in the priority list for study by CIIT, Dr. Wright undertook writing of a literature review on the toxicity of this material. Notwithstanding the fact that he had assistance in locating pertinent articles in the literature, Dr. Wright had to read, digest, and write a substantive review in a relatively short time. This meant considerable extra work on nights and weekends. He completed his assignment on time, and it was a credit to him personally and to Monsanto. At present, Dr. Wright has been given the added assignment of preparing protocols for further toxicity testing of maleic anhydride by CIIT. We are confident that he will complete this assignment with equal professional competence. Therefore, it is a pleasure to nominate Dr. Paul L. Wright for a merit award on the basis of his demonstrated performance.

G. J. Levinskas

EXHIBIT # 38

Monsanto

...HIEVEMENT AWARD ...

Name of Nominee			Location
Paul L. Wright			Creve Coeur
Company Unit or Staff Dept.	**Division**	**Business Group**	**Department**
Med. & Env. Hlth.			
Position Title	**Salary Grade**	**Annual Salary**	**Date of Last Increase**
Toxicology Manager	19	$31,800	2/1/76
Performance		**Growth**	**Date Last Employe Review**

Type of Award (Select the award category from the opposite side of this sheet which most appropriatety describes the award and enter the category and code below.)

Award Category	Category Code Num
Technical - Accomplishment of significant results	106

Describe the achievement and its significance to Monsanto below:

At a recent meeting in Creve Coeur, Glenn Schweitzer, head of the Office of Toxic Substances of EPA, offered some interesting comments. He observed that Monsanto's toxicologists were held in high regard at EPA. However, since it lacked an in-house toxicology facility, Monsanto as a company was not as highly regarded overall as duPont, Carbide, or Dow.

Dr. Wright's professional and personal characteristics have contributed significantly to Monsanto's image at EPA. He has shown unusual perseverance and dedication, frequently involving his own time, to review and interpret large volumes of data which he subsequently organized for presentation to EPA officials. Particularly noteworthy were his efforts on polychlorinated biphenyls (Aroclors) and chlorinated isocyanurates (ACL products). In the former instance, his excellent analysis and synthesis of widely scattered observations played a prominent role in forestalling EPA's promulgation of unrealistic regulations to limit discharges of polychlorinated biphenyls. EPA's proposed regulations would have precluded the use of these materials by Monsanto's customers. With respect to chlorinated isocyanurates, Dr. Wright has had several contacts with individual scientists at EPA to answer specific questions that they had raised or to inform them of the status of additional studies which had been undertaken.

Overall, by virtue of the qualities of leadership which Dr. Wright has displayed, he has made an important contribution to Monsanto's image at EPA. That favorable image will become increasingly important to Monsanto as the areas of interaction with EPA multiply.

DEPOSITION EXHIBIT
LEVINSKAS-38
5-27-87-WK

Recommended By:	Date	Award Amount Recommended:	Approved By:	Date	Award amount approved for payment:
[signature]	16 July '76		[signature]	7/4/76	$1,000

G-2532 (Rev. 10/74)

SCM 058795

000005

EXHIBIT # 39

PROB 11G
(Rev. 9/82)

AUTHORIZATION TO RELEASE INFORMATION
(PRIVATE PERSON OR ORGANIZATION)
TO PROBATION OFFICER

TO WHOM IT MAY CONCERN:

I, Paul L. Wright, the undersigned, hereby authorize the United States Probation Office for the Eastern District of Missouri or its authorized representative(s) or employee(s), bearing this release or copy thereof, to obtain any information in your files pertaining to my:

- [x] Employment
- [ ] Education Records (including but not limited to academic achievement, attendance, athletic, personal history, and disciplinary records)
- [ ] Medical Records
- [ ] Psychological and Psychiatric Records

I hereby direct you to release such information upon request of the bearer. This release is executed with full knowledge and understanding that the information is for the United States Probation Office's official use.

I hereby release you, as custodian of such records, any school, college, or university, or other educational institution; hospital or other repository of medical records; social service agency; any employer, or retail business establishment including its officers, employees, or related personnel both individually and collectively, from any and all liability for damages of whatever kind which may at any time result to me, my heirs, family, or associates because of compliance with this authorization and request for information or any other attempt to comply with it.

The information hereby obtained by the aforementioned probation office is to be used only for the purpose of presentence investigation and report and, if applicable, for supervision.

Paul L. Wright — *(Authorizing Signature—Full Name)* — Paul Lee Wright — *(Full Name—Printed or Typed)* — 3/2/84 — *(Date)*

WITNESS — *(Probation Officer)* — 3/2/84 — *(Date)*

DEPOSITION EXHIBIT
LEVIUSKAS-39
5-2287 WK

SCM 058741

000106

PROB 14D
(3/64)

UNITED STATES DISTRICT COURT
FEDERAL PROBATION SYSTEM

REQUEST FOR EMPLOYMENT DATA

DATE 3/7/84

ADDRESS OF PROBATION OFFICE
111 U.S. Court & Custom House
1114 Market Street
St. Louis, MO 63101-2071

Dear Sir:

The person identified below is under investigation by this office. The information requested is needed to complete this investigation. Your cooperation will be greatly appreciated.

Please return this form within three days in the enclosed envelope. No postage is necessary.

Patricia M. Pickert

SIGNATURE OF PROBATION OFFICER

Personnel Department
Monsanto Company
800 North Lindbergh Blvd.
St. Louis, MO 63141

NAME OF PERSON BEING INVESTIGATED (Last - First - Middle)
WRIGHT, Paul Lee

ADDRESS OF PERSON BEING INVESTIGATED
2001 North Geyer Rd.
St. Louis, MO 63131

DATE OF BIRTH	PLACE OF BIRTH	SEX	RACE
1/24/35	South Bend, Indiana	M	White

ALSO KNOWN AS

SOCIAL SECURITY NUMBER
308-34-3416

States employed from Nov., 1972, to Feb. 29, 1984, as manager of special projects in Dept. of Medical & Environmental Health earning $55,000 per year. Please INFORMATION DESIRED verify.

WAS THIS PERSON EVER IN YOUR EMPLOY?	IF "YES" GIVE DATE STARTED	DATE LEFT	SALARY OR WAGE
☒ YES ☐ NO	11/1/72	2/29/84	$55,000

POSITIONS HELD
Mgr. Special Studies
Environmental Policy Staff

REASON FOR TERMINATING EMPLOYMENT
Engaging in activities detrimental to Monsanto's interest.

WAS THIS PERSON'S SALARY ATTACHED?
☐ YES ☐ NO

WOULD YOU CONSIDER REEMPLOYING THIS PERSON?
☐ YES ☒ NO

REMARKS (Concerning this person's attendance, ability, industry, reliability, and different times employed by your organization.)

AUTHORIZATION TO RELEASE CONFIDENTIAL INFORMATION form attached.

SIGNATURE OF EMPLOYER	TITLE	DATE
M E Shirley	Mgr., Personnel	3/19/84

FPI-MAR—9-23-78-75M-8621 PAP:rcl

IF ADDITIONAL SPACE IS REQUIRED, USE REVERSE SIDE

SCM 058742

030:07

HARTOLDMON0023350

EXHIBIT #10

Monsanto TECHNOLOGY

DMEH
Toxicology Section/St. Louis
(CO./DIV./DEPT./LOCATION)

SPECIAL REPORT
(TYPE OF REPORT)

REPORT NO.: MSL-2002

JOB/PROJECT NO.:

DATE: October 14, 1981

TITLE: TOXICITY OF AROCLOR PRODUCTS 1242, 1254 AND 1260 TO THE LIVER OF ALBINO RATS

AUTHORS: George J. Levinskas, Ph.D.

ABSTRACT: This report is a tabulation of the results of microscopic evaluation of liver sections from rats fed AROCLOR 1242, AROCLOR 1254 or AROCLOR 1260 for two years.

AUTHORS: George J. Levinskas, Ph.D.
TITLE: TOXICITY OF AROCLOR PRODUCTS 1242, 1254 AND 1260 TO THE LIVER OF ALBINO RATS

REPT. NO.: MSL-2002
COPY NO.: 4

R-1068(B)

SCM 058930

000103

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8 - G.J. Levinskas, G2WF
9 - J.G. Nassif, E2ND
10 - J.M. Norris, Dow Chemical
11 - R.A. Stohr, B3NJ

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R-1088(C) (REV. 1/80)

000103

SCM 058931

INTRODUCTION

The polychlorinated biphenyls (PCBs) comprise a family of compounds of variable chlorine content. PCBs manufactured by Monsanto (tradenamed "Aroclor") bear a four digit number, the '12' indicating biphenyl and the last two digits indicating the chlorine content by weight percent. Since the chlorine atoms are randomly distributed among the 10 ring positions available for substitution, each material is a mixture of isomers.

In 1969, Monsanto sponsored a series of animal studies at Industrial BIO-TEST Laboratories in Northbrook, Illinois, on Aroclor 1242, 1254, and 1260 for the assessment of the health and environmental hazards of these materials. This series consisted of 2-year chronic feeding studies to rats and dogs, a 3-generation rat reproduction study, a rat teratology study, a dominant lethal mutagenic study in mice and a toxicity/reproduction study in chickens on each of the 3 Aroclor products. Even though no such action was contemplated, such a broad battery of tests would have been adequate to support Food Additive Petitions for each of these materials. These studies were initiated by reports that PCBs had been detected in the environment. A report (Nelson, 1972b) by a Panel on Hazardous Trace Substances of an Ad Hoc Committee on Environmental Health Research covers the development of information on the environmental and biological effects of PCBs. There have been subsequent literature reviews which need not be recapitulated here [DHEW, 1978; EPA, 1976; IARC, 1978; NAS, 1979; Roberts, et al. (1978)].

Starting in 1969, while these studies still were in progress, information regarding them was made available to various government groups.[1] Subsequently, data from these studies were presented at a conference

sponsored by the National Institute of Environmental Health Sciences at Rougemont, N.C. on December 20-21, 1971, but the account of these studies was omitted from the published proceedings (Keplinger, et al., 1972; Nelson, 1972a).

Subsequently, it was reported that female Sherman strain rats developed hepatocellular carcinomas when fed Aroclor 1260[2] from Lot No. AK-3; the same lot used for the earlier Monsanto study with this material. As a result, Monsanto requested the contract laboratory's pathologists to review livers from all available rats from the 3 Aroclor studies. That review (which could have included new sections of liver from animals examined previously in addition to sections from animals not examined previously) was presented in the reports of Gordon and Richter (1975a,b,c).

In November 1975, reports containing evaluations of liver sections from the 2-year rat feeding studies (Gordon and Richter, 1975a,b,c) and the results of an independent evaluation of the same liver sections (Pour, 1975) were presented to and discussed with several federal regulatory agencies[3]. Later that month, a summary of data from all of the studies was presented at the National Conference on Polychlorinated Biphenyls sponsored by the Environmental Protection Agency and held in Chicago on November 19-21, 1975 (Calandra, 1976). Only summaries of data from these and other toxicity studies conducted over the years have been published (Jenkins, et al., 1972; Keplinger, et al., 1971; Monsanto, 1980). Knowledge of these efforts may have prompted the statement in a recent article that "...Monsanto, whose reaction to the possibility that polychlorinated biphenyls (PCBs) might be an ecological disaster was a classic of how such issues should be handled, says Ford[4]. Monsanto began to investigate the dangers as soon as they were

seriously voiced. It insisted on keeping an open mind about them. As soon as evidence appeared that there was a strong chance PCBs were a hazard, it published the results of its investigations, admitting the danger. It thus established a reputation of honesty even among the environmentalists." (Clutterbuck 1981).

At a later meeting in Bethesda, MD.[5], pathologists selected and reviewed some liver slides from the Monsanto-sponsored and Kimbrough studies. The pathologists differed in the terminology used to classify the lesions. They did conclude that the general incidence and severity of liver lesions (hyperplasia, nodular hyperplasia and neoplastic changes - carcinomas) were greater in the rats from the study subsequently published by Kimbrough, et al. (1975). No carcinomas were seen in the Monsanto-sponsored studies. It was noted that either the strain of rat or sex could have accounted for the differences. The spontaneous incidence of hyperplastic or neoplastic liver lesions in the Sherman strain rat was unknown, and the occurrence of such lesions appears to be higher in female rats and mice.

The different diagnoses were discussed with Dr. Philippe Shubik of the Eppley Institute for Research in Cancer at the University of Nebraska. Dr. Shubik suggested that the liver sections from these studies could be reviewed by Dr. Parvis Pour. This was done.

This publication is an effort to make readily available information in the Gordon and Richter reports (1975a,b,c) which are only summarized in the literature (Calandra, 1976).

METHODS

It appears that the Threshold Limit Value of 0.5 mg/m^3 for chlorobiphenyl with 54% chlorine (ACGIH, 1969) was used to estimate suitable dose levels for the rat feeding studies. For that purpose the following assumptions were made: if the ambient air concentration of PCBs is 0.5 mg/m^3, and if all of the inhaled PCBs are absorbed, and if 15 m^3 of air are inhaled during the working day, a person would receive a PCB dose of 7.5 mg/day. The corresponding dosage would be approximately 0.1 mg/kg/day for a 70-kilogram person. Consequently, dosages of 0.1, 1, and 10 mg/kg/day were decided upon, and the dietary concentrations were set at 1, 10, and 100 ppm. As it turned out, the assumptions used to set dosages for the feeding study resulted in the low dose level rats receiving a dosage that was 100 times higher than the 0.001 mg/kg/day which FDA later calculated as allowable for protracted ingestion based on human data (FDA, 1973).

For the chronic toxicity study in rats[6], weanling animals of the Charles River CD strain[7] were divided into a control group and 9 treatment groups, each consisting of 50 males and 50 females, with 3 treatment groups assigned to each of the 3 Aroclor products studied (1242, 1254, and 1260). Not all of these animals started at the same time. After about 2 months on test, additional groups of males and females were assigned to each test diet and the controls. These animals were added to allow a sufficient number of animals for sacrifices at 3, 6 and 12 months to provide some information prior to the completion of the 2-year study period. ~~The numbering~~ sequence

and the designation of some animals as "Extra" suggests that additional animals were placed on test.

Groups of 5 males and 5 females were scheduled to be sacrificed after 3, 6, and 12 months of feeding, and survivors were to be sacrificed at the end of the test period.[8] Animals were to be given a gross autopsy and tissues were to be preserved for possible histologic examination. Tumors or lesions suggestive of tumors were to be examined.

RESULTS

Data from the Gordon and Richter reports (1975a,b,c) on liver slides are shown in Tables 1, 2, and 3 for Aroclor 1242, 1254, and 1260, respectively.[9] While the text of the reports contained comments specific to the particular Aroclor, they also contained similar comments such as "There is evidence of a chemical effect on the liver.....This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals to hepatoma or cholangiohepatoma" and "In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia; these are benign tumors rather than malignant carcinomas. There was no evidence of metastasis or invasiveness of these tumors in this study". The reports also stated that "The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material" and "In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report.....No hepatocellular carcinomas were observed".

With respect to Aroclor 1254, it was noted that "One liver tumor (a hepatoma) previously reported in a T-II animal (No. 445) was re-classified as nodular hyperplasia" (Gordon and Richter, 1975a)[10].

DISCUSSION

The initial reports of these studies concluded that the target organ was the liver for each Aroclor product. This was confirmed by the second evaluation of liver slides (Gordon and Richter, 1975a,b,c). These alterations were slow to develop, their incidence being related to both dose level and duration of treatment. Since there were increased incidences of vacuolar changes in the cytoplasm of the hepatocytes and focal hypertrophy at all dose levels for all 3 Aroclor products at the 24-month sacrifice, a "no-effect" level was not established for liver effects.

With respect to the slides from Industrial BIO-TEST, Pour (1975) concluded that Aroclor 1242, 1254, and 1260 "showed a dose-dependent hepatotoxic effect, characterized by degenerative and regenerative processes. With one exception, all lesions were considered non-neoplastic. Structures similar to cholangiocarcinomas and hepatomas were found in one rat. However, the possibility of metastases of a carcinoma into the liver has been also considered." In the report, he noted one lesion which seemed to "represent a metastatic tumor (probably a mammary gland carcinoma of the same animal from which ...[the particular liver section]... was submitted), rather than a cholangiocarcinoma". This occurred in an animal fed 100 ppm of Aroclor 1254. The contract laboratory pathologists diagnosed the presence of mammary tumor metastases in the liver of this rat (Gordon and Richter, 1975b).[11]

SUMMARY and CONCLUSIONS

Groups of male and female rats were fed diets containing either 1, 10, or 100 ppm of one of 3 Aroclor products, 1242, 1254, or 1260, for 2 years. Focal hypertrophy of the liver occurred at 3, 3, and 12 months for rats fed Aroclor 1260, 1254, and 1242, respectively. Focal hypertrophy was not seen in livers of control animals. At the 24-month sacrifice, livers of animals from all dose levels of the 3 Aroclor products had an increased incidence of vacuolar changes and focal hypertrophy. Livers of some animals fed 100 ppm of each Aroclor also had benign liver tumors (hepatoma or cholangiohepatoma). No hepatocellular carcinomas were observed.

Footnotes

1. Dates of initial correspondence and contacts.
   October 3, 1969. E.P. Wheeler to A.R. Glasgow, Division of Pesticides. Food and Drug Administration.
   April 8, 1970. R.E. Kelly to H. Blumenthal, Petitions Review Branch, Food and Drug Administration.
   April 22, 1970. E.P. Wheeler to E.J. Burger, Jr., Office of Science and Technology.
   June 1, 1970. E.P. Wheeler to H.E. Stokinger, Bureau of Occupational Safety and Health.

2. R.D. Kimbrough, personal communication.

3. November 13-14, 1975. Council on Environmental Quality.
   Environmental Protection Agency.
   Food and Drug Administration.
   House Subcommittee Manpower, Compensation, Health and Safety.
   National Cancer Institute.
   National Institute for Environmental Health Sciences.
   National Institute for Occupational Safety and Health.

4. Dr. David Ford of Bath University.

5. At National Cancer Institute on January 21, 1975. Present were D.E. Gordon, R.D. Kimbrough, G.J. Levinskas, R.A. Squire, W.R. Richter.

6. Since the events described earlier, the validity of many toxicity studies conducted by Industrial BIO-TEST Laboratories has been challenged. Therefore, the available raw data supplied by Industrial BIO-TEST was reviewed to determine whether this study could be validated. The review showed that the data bases (including the lack of a protocol) were insufficient for a complete validation of the study. It was decided to focus on presenting the primary liver effects reported by Gordon and Richter (1975a,b,c). Therefore, a complete audit was not undertaken. Available records were examined for a determination that the animals were placed on test and of their ultimate fate. Necropsy and microscopic reports were also examined for findings pertaining to livers of those animals. Significant discrepancies which were found between data in Tables 1, 2, and 3 and the data base for the Gordon and Richter reports are noted in this report. On some records, the labels Aroclor 1242 and Aroclor 1260 are interchanged as determined by a check of the animal numbers.

7. Charles River Breeding Laboratories, North Wilmington, Massachusetts.

8. Animals sacrificed at 6 and 12 months were placed on test about 2 months after the first group. Those sacrifice periods are sometimes labeled 8 and 14 months, respectively, which corresponds to the calendar time from the start of the test but overstates the time on test for those groups.

9. As a result of the examination described in footnote 6, a few animals were reassigned to other dose levels on basis of assigned numbers. Three with no recorded liver lesions were deleted from the 24-month listing because of short duration on test: 14 months at 100 ppm Aroclor 1242, 15 months at 10 ppm Aroclor 1254 and 13 months at 100 ppm Aroclor 1254. Therefore, numbers in Tables vary slightly from those in reports of Gordon and Richter (1975a,b,c).

10. That change and comments in the footnotes to the Tables were noted during the examination described in footnote 6. In addition, the following also were noted during the examination.

Aroclor 1254 - 100 ppm animal marked "Extra[3]" with diagnosis of hepatoma in record of examination for original Industrial BIO-TEST report. Animal not listed in Gordon and Richter report.

- 100 ppm animal no. 542 with gross autopsy notation that liver appears tumorous and white foci has no record of examination.

Aroclor 1260 - 100 ppm animal no. 293 with gross autopsy notation of tumor on liver has no record of examination.

In some instances, diagnoses were crossed out on the available records. These were included in the Tables. Crossed out diagnoses for hepatoma or cholangiohepatoma are noted in the footnotes to the Tables.

11. Dr. Pour's report does not include the following liver sections noted by discrepancies between his tabulation and the Gordon and Richter reports.

1 from control at 12 month sacrifice,
5 from 100 ppm Aroclor 1242 at 24 months,
1 from 100 ppm Aroclor 1260 at 3 months.

None of these animals were reported as having hepatomas or cholangiohepatomas in the Gordon and Richter reports.

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1. ACGIH (1969). Threshold Limit Values of Airborne Contaminants. American Conference of Governmental Industrial Hygienists. Cincinnati.

2. Calandra, J.C. (1976). Summary of toxicological studies on commercial PCB's. In: National Conference on Polychlorinated Biphenyls, November 19-21, 1975. Chicago, Illinois. EPA Report No. 560/6-75-004. March. NTIS PB-253 248. pp.35-42.

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5. EPA (1976). National Conference on Polychlorinated Biphenyls, November 19-21, 1975. Chicago, Illinois. U.S. Environmental Protection Agency. Washington, D.C. EPA-560/6-75-004, March. NTIS PB-253 248.

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Table 1

Aroclor 1242: Primary Liver Lesions Among Albino Rats

Sacrifice Interval	3 Months				6 Months				12 Months				Terminal[a]			
Diet Level (ppm)	0	1	10	100	0	1	10	100	0	1	10	100	0	1	10	100
No. Animals Examined	10	8	10	9	10	10	8	9	10	10	10	9	23	32	29	19
Findings																
Vacuolar change	2	0	2	1	1	0	0	0	1	2	4	0	1	7	8	9
Focal necrosis	0	1	0	0	1	1	0	0	0	0	0	0	1	1	1	0
Focal lymphoid infiltration	0	0	0	0	0	3	0	0	0	0	1	0	1	0	0	0
Focal hypertrophy hepatocytes	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	1	1	8
Ductular hyperplasia	0	0	0	1	0	0	0	0	1	0	1	0	5	3	3	3
Hepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3[b]
Cholangiohepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1[c]

[a] Control group has animal dead at 19 months and 2 marked "Extra".
1 ppm group has animals dead at 19, 22, 22, 23, 23 months.
10 ppm group has animals dead at 23, 23 months.
100 ppm group has animals dead at 22, 22, 22 months and 2 marked "Extra".

[b] Includes 1 animal without record of examination in original IBT report. Not listed as hepatoma in worksheets for Gordon and Richter report but appears and was crossed out on typed tabulation for animal marked "Extra". Diagnoses for other 2 animals do not appear in records of examinations for original IBT report.

[c] Diagnosis does not appear in records of examinations for original IBT report.

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Table 2

Aroclor 1254: Primary Liver Lesions Among Albino Rats

Sacrifice Interval	3 Months				6 Months				12 Months				Terminal[a]			
Diet Level (ppm)	0	1	10	100	0	1	10	100	0	1	10	100	0	1	10	100
No. Animals Examined	10	10	10	10	10	10	10	10	10	10	10	10	23	30	26	26
Findings																
Vacuolar change	2	3	3	1	1	0	0	0	1	1	4	1	1	7	9	13
Focal necrosis	0	1	1	0	1	2	0	2	0	0	0	1	1	3	1	1
Focal lymphoid infiltration	0	0	0	1	0	0	0	2	0	0	2	1	1	2	0	1
Focal hypertrophy hepatocytes	0	0	0	1	0	0	0	4	0	0	4	2	0	3	4	14
Nodular hyperplasia	0	0	0	0	0	0	0	0	0	0	0	0	1	0	3	14
Ductular hyperplasia	0	0	0	0	0	0	0	0	1	1	1	0	5	6	3	4
Hepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4[b]
Cholangiohepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2[c]

[a] Control group has animal dead at 19 months and 2 marked "Extra".
1 ppm group has animals dead at 22, 22 months, 1 marked "Extra" and 1 other for which date of death is not recorded.
10 ppm group has animals dead at 22, 22, 22 months.
100 ppm group has animals dead at 23, 23 months and 9 marked "Extra".

[b] Includes 2 animals marked "Extra". Diagnoses do not appear in records of examination for original IBT reports.

[c] Both animals marked "Extra" with same designation. 1 without apparent record of examination for original IBT report. Diagnosis for other animal does not appear in records of examinations for original IBT report.

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Table 3

Aroclor 1260: Primary Liver Lesions Among Albino Rats

Sacrifice Interval	3 Months				6 Months				12 Months				Terminal[a]			
Diet Level (ppm)	0	1	10	100	0	1	10	100	0	1	10	100	0	1	10	100
No. Animals Examined	10	10	10[b]	10	10	6	5	9	10	9	10	9	23	26	25	25
Findings																
Vacuolar change	2	0	2	3	1	1	2	6	1	2	5	3	1	5	7	9
Focal necrosis	0	0	4[c]	0	1	0	1[d]	0	0	0	0	0	1	4	3	6
Focal lymphoid infiltration	0	0	0	0	0	2	2	0	0	0	0	0	1	0	1	0
Focal hypertrophy hepatocytes	0	0	0	2	0	0	0	3	0	0	0	4	0	3	13	9
Nodular hyperplasia	0	0	0	0	0	0	0	0	0	0	0	1	1	0	7	6
Ductular hyperplasia	0	0	1	0	0	0	0	0	1	1	0	2	5	6	7	12
Hepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1[e]	7[f,g]
Cholangiohepatoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4[g,h]

[a] Control group has animal dead at 19 months and 2 marked "Extra".

1 ppm group has animals dead at 20, 22, 22 months.

10 ppm group has animals dead at 19, 22, 22 months and 1 marked "Extra".

100 ppm group has animals dead at 22, 22 months.

[b] Includes 1 marked "Extra".

[c] Worksheets show listings under this diagnosis with arrow pointing to Vacuolar change column.

[d] Date of death of this animal not recorded.

[e] No record of examination for original IBT report. Listed on worksheets for Gordon and Richter report with diagnosis crossed out.

[f] Includes 2 animals without record of examination for original IBT report. Diagnoses for other 5 animals do not appear in records of examinations for original IBT report. 2 of these diagnoses crossed out on worksheets for Gordon and Richter reports.

[g] Includes one animal with both diagnoses. Hepatoma is 1 of 2 crossed out (superscript f).

[h] Includes 3 animals without record of examination for original IBT report. Diagnosis for other animal does not appear in records of examinations for original IBT report. 2 of these diagnoses crossed out on worksheets for Gordon and Richter reports.

EXHIBIT # 41

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1254 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1254 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

II. Summary

In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. There were six hepatomas detected among six of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice. No hepatocellular carcinomas were observed. One liver tumor (a hepatoma) previously reported in a T-II animal (No. 445) was re-classified as nodular hyperplasia. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver ascribed to biotransformation of the test material. The latter lesions were confined primarily to test animals of the 12 and 24 month sacrifices and they were dose-related in incidence and severity.

In conclusion, Aroclor 1254 does not appear to be carcinogenic in rats fed for two years at levels up to and including 100 ppm.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D. V. M., Ph. D.
Section Head, Pathology

Report Approved by:

M. L. Keplinger, Ph. D.
Manager, Toxicology

aew

SCM 058167

030125

IBT No. 622-07298
Monsanto

I have examined additional sections of liver from rats of IBT No. 622-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Aroclor 1254 on the following pages:

There is evidence of a chemical effect on the liver which is most pronounced at time of the 12-Month and 24-Month sacrifice. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals to hepatoma or cholangiohepatoma. The hypertrophic cells contain large amounts of light staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some cases ring shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. They also contained the same hypertrophic cells.

Those lesions classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia; these are benign tumors rather than malignant carcinomas. There was no evidence of metastasis or invasiveness of these tumors in this study.

With exception of the vacuolar changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 24-Month Sacrifice.

Ward R. Richter

Ward R. Richter, D.V.M., M.S.
Dipl., Am. College Vet. Path.

Primary Liver Lesions - Aroclor 1254

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	3/10	3/10	1/10	2/10
Focal Hypertrophy	0/10	0/10	1/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	0/10	0/10	0/10	0/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	1/10	1/10	0/10	0/10

Primary Liver Lesions - Aroclor 1254

6 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/10	0/10	1/10	1/10
Focal Hypertrophy	0/10	0/10	4/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	0/10	0/10	0/10	0/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	2/10	0/10	1/10	1/10

Primary Liver Lesions - Aroclor 1254

12 Month Sacrifice - Rats

Lesion	Group			
	II	III	IIII	Control
Vacuolar Change	1/10	4/10	1/10	1/10
Focal Hypertrophy	0/10	4/10	2/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	1/10	1/10	0/10	1/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	0/10	0/10	1/10	0/10

Primary Liver Lesions - Aroclor 1254

Terminal Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	8/31	10/26	13/27	1/23
Focal Hypertrophy	3/31	5/26	13/27	0/23
Nodular Hyperplasia	0/31	3/26	13/27	1/23
Hepatoma	0/31	0/26	4/27	0/23
Ductular Hyperplasia	6/31	3/26	4/27	5/23
Cholangio-Hepatoma	0/31	0/26	2/27	0/23
Hepatocellular Necrosis	3/31	1/26	2/27	1/23

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholanglo-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
3 Month	B-I	356M	++										
	1ppm	357"	+										
		358"											
		359"		+									
		360"	+										
		396F											
		397"											
		398"											
		399"											
		400"											
	B-II	436M	+										
	10ppm	437"											
		438"	+										
		439"											
		440"	+										
		476F		+									
		477"											
		478"											
		479"											
		430"											
	B-III	516M											
	100ppm	517"											
		518"	+	+	+								
		519"											
		520"											
		555F											
		557"											
		558"											
		559"											
		560"											

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Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholanglo-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic
6 Month	B-I 1ppm	921M		+								
		922"										
		923"		+								
		924"										
		925"										
		936F										
		937"										
		938"										
		939"										
		940"										
	B-II 10ppm	950M										
		951"										
		952"										
		953"										
		954"										
		966F										
		967"										
		968"										
		969"										
		970"										
	B-III 100ppm	981M		+	+							
		982"			+							
		983"										
		984"										
		985"										
		996F				+						
		997"				+						
		998"										
		999"		+		+						
		1000"				+						

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic
2 Month	B-I 1ppm	41M	+									
		42"										
		43"										
		44"										
		45"										
		46F										
		47"										
		48"						+				
		49"										
		50"										
	B-II 10ppm	51M										
		52"	++									
		53"	++									
		54"			+							
		55"	+									
		56F			+							
		57"	+			+						
		58"				+						
		59"				+						
		60"				+		+				
	B-III 100ppm	61M				+						
		62"										
		63"										
		64"										
		65"	++			+						
		66F										
		67"			+							
		68"										
		69"										
		70"		+								

SCM 058176

Tabulation of Individual Liver Lesions in Rats

acrifice erval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic
2 Month	B-I 1ppm	326M										
		330"										
		335"										
		338"										
		351"	++	+								
		323"		+								
		325"										
		343"	+									
		346"			+	+						
		342F										
		362"										
		368"	-					+				
		374"										
		375"						+				
		376"				+						
		475"	+++									
		366"						+				
		367"										
		372"						+				
		377"	++	++		+		+				
		378"	+									
		379"	+									
		380"										
		381"										
		384"										
		387"										
		388"										
		389"										
		391"	+					+				
		394"	+++									
		Ext"			++							

SCM 058177

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholanglo-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic
24 Month	B-II 10ppm	415M										
		417"				++		+				
		418"										
		419"										
		423"										
		426"	++									
		427"	+									
		491"									p	
		402"	+									
		403"	++									
		405"										
		410"										
		434"	+									
		450F										
		451"	+				p					
		452"	+	+			p					
		456"				+						
		459"				++		++				
		463"	++									
		469"				+						
		470"										
		471"										
		478"						+				
		443"										
		445"					p					
		448"										

SCM 058178

000136

HARTOLDMON0023381

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	
2 Month	B-III 100ppm	484M	++										+
		491"				+	P		P				
		497"				++	P						
		499"				+	P						
		507"					P						
		509"											
		510"	+										
		512"											
		483"	++					+					
		489"	+			+							
		522F	++			++							
		524"	++			+	P						
		527"	+++			+	P					P	
		541"				+			P				
		547"	++				P						
		Ext1"	++			++++	P						
		Ext2"					P	+		P			
		Ext3"	++			+++							
		Ext4"					P		P				
		Ext5"		+			P						
		536"	++			+++	P						
		537"											
		539"	++			++		+					
		441"											
		Ex1"							P				
		Ex2"	++							P			
		Ex3"				+	P	+					

Grading System

+ = minimal in severity
++ = mild in severity
+++ = moderate in severity
++++ = marked in severity
P = Present, no grade
- = Absent

SCM 058179

EXHIBIT #42

Industrial BIO-TEST *Laboratories, Inc.*
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1260 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1260 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1260 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

II. Summary

In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. There were seven hepatomas detected among seven of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice. No hepatocellular carcinomas were observed. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material. In general, the latter findings were confined primarily to test animals of the 6-, 12- and 24-Month Sacrifices, and they were dose-related in incidence and severity.

In conclusion, Aroclor 1260 does not appear to be carcinogenic in rats fed for two years at levels up to and including 100 ppm.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D. V. M., Ph. D.
Section Head, Pathology

Report Approved by:

M. L. Keplinger, Ph. D.
Manager, Toxicology

IBT No. 622-07298
Monsanto

I have examined additional sections of liver from rats of IBT No. 622-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Aroclor 1260 on the following pages:

There is evidence of a chemical effect on the liver which was most evident at time of the 12-Month and terminal (24-Month) sacrifices. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals, to hepatoma or cholangiohepatoma. The hypertrophic cells contain large amounts of light staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some cases, ring-shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. They also contained the same hypertrophic cells.

Those lesions classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses or other evidence of anaplasia, these are benign tumors rather than malignant carcinomas. There was no evidence of metastasis or invasiveness of these tumors in this study.

With exception of the vacuolar changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 12- and 24-Month Sacrifice periods.

Ward R. Richter

Ward R. Richter. D.V.M., M.S.
Diplomate. American College of
Veterinary Pathologists

Primary Liver Lesions - Aroclor 1260

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/11	4/10	3/10	2/10
Focal Hypertrophy	0/11	0/10	2/10	0/10
Nodular Hyperplasia	0/11	0/10	0/10	0/10
Hepatoma	0/11	0/10	0/10	0/10
Ductular Hyperplasia	0/11	1/10	0/10	0/10
Cholangio-Hepatoma	0/11	0/10	0/10	0/10
Hepatocellular Necrosis	0/11	0/10	0/10	0/10

Primary Liver Lesions - Aroclor 1260

6 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	THI	Control
Vacuolar Change	1/6	2/5	5/9	1/10
Focal Hypertrophy	0/6	0/5	3/9	0/10
Nodular Hyperplasia	0/6	0/5	0/9	0/10
Hepatoma	0/6	0/5	0/9	0/10
Ductular Hyperplasia	0/6	0/5	0/9	0/10
Cholangio-Hepatoma	0/6	0/5	0/9	0/10
Hepatocellular Necrosis	0/6	1/5	0/9	1/10

Primary Liver Lesions - Aroclor 1260

12 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	2/9	5/10	3/9	1/10
Focal Hypertrophy	0/9	0/10	4/9	0/10
Nodular Hyperplasia	0/9	0/10	1/9	0/10
Hepatoma	0/9	0/10	0/9	0/10
Ductular Hyperplasia	1/9	0/10	2/9	1/10
Cholangio-Hepatoma	0/9	0/10	0/9	0/10
Hepatocellular Necrosis	0/9	0/10	0/9	0/10

Primary Liver Lesions - Aroclor 1260

Terminal Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	5/25	6/23	10/27	1/23
Focal Hypertrophy	3/25	10/23	11/27	0/23
Nodular Hyperplasia	0/25	9/23	7/27	1/23
Hepatoma	0/25	0/23	5/27	0/23
Ductular Hyperplasia	6/25	5/23	14/27	5/23
Cholangio-Hepatoma	0/25	0/23	2/27	0/23
Hepatocellular Necrosis	4/25	2/23	6/27	1/23

Sacrifice Interval	Dose Level	Anima No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Nucrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
3 Month	AI	116M								
		117"								
		118"								
		119"	-							
		120"								
		147F								
		156"								
		157"								
		158"								
		159"								
		160"				-				
	AII	195M	++							
		196"	++							
		198"	+							
		200"	++							
		Extra"								
		236F								
		237"								
		238"								
		239"								
		240"								
	AIII	276M								
		277"	++							
		278"	++			+				
		279"				++				
		280"	++							
		315F								
		317"								
		318"								
		319"								
		320"								

SCM 058189

AROCLOR 1260
Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Anima No. and Sex	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma	
6 Month	AI	832M									
		834"			+						
		835"									
		846F									
		848"	+								
		849"			+						
	AII	864M	+		+						
		865"	+		+						
		873"		+							
		878F									
		879"									
	AIII	891M	+			++					
		893"	++			+					
		894"	+			+					
		895"	+								
		906F	+								
		907"									
		908"									
		909"									
		910"									

SCM 056190

Sacrifice Interval	Dose Level	Anima No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
12 Month	AI	11M								
		12"	+					+		
		13"	+							
		14"								
		15"								
		16F								
		17"								
		18"								
		19"								
	AII	21M	+							
		22"								
		23"	+							
		24"	+							
		25"	++							
		26F								
		27"	+							
		28"								
		29"								
		30"								
	AIII	31M	++							
		32"								
		33"	++							
		34"	+							
		36F				+				
		37"				+				
		38"				+		+		
		39"					P			
		40"				+		+		

SCM 058191

ARCCLOR 1260

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma	
Final	AI	85M		+							
		86"	++	+		+					
		87"		++							
		101"									
		106"						+			
		112"									
		114"									
		105"	+								
		107"									
		109"		+		+		+			
		122F									
		125"						+			
		127"						+			
		129"						+			
		130"									
		138"	+++								
		141"									
		147"									
		151"									
		155"	+								
		144"									
		131"	+								
		132"									
		135"				+		+			
		139"									
	AII	167M			+						
		168"	+			+					
		179"				+		+			
		182"					P				
		184"	++								
		187"									
		Extra'				+		+			
		205F					P	+			
		208"									
		210"									

SCM 058192

Sacrifice Interval	Dose Level	Anima No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
Final (continued)	AII	212F					P	+		
		213"	+			+				
		220"				+				
		221"								
		224"					P			
		233"								
		234"				++		+		
		219"	++	+		+				
		230"		++						
		203"				++				
		204"								
		206"	+							
		207"	+			++				
	AIII	241M		+			P	+		
		253"								
		261"				+		+		
		264"	+	+		++				
		270"				+		+		
		271"	++			+				
		272"	+++							
		275"	++				P			
		243"	+					++		P
		244"		+						
		312"				+		+		
		231F				++	P	+		
		274"	+			+++				
		275"	+++	++		+++		++		
		294"							P	
		297"	++	+					P	
		302"					P			
		306"				+		+		
		308"					P	+		
		311"	++						P	
		314"							P	
		240"	++			+		+		

SCM 058193

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal lymphoid Infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma	
Final (continued)	AIII	245F				++		+			
		281"					P	+			
		287"					P	+			
		291"						++	P		
		309"		+						P	

Grading System

+ = minimal in severity
++ = mild in severity
+++ = moderate in severity
++++ = marked in severity
P = Present, no grade

SCM 058194

000352

THE EPPLEY INSTITUTE
for
RESEARCH IN CANCER

October 31, 1975

Paul L. Wright, Ph.D.
Monsanto Company
800 North Lindbergh Boulevard
St. Louis, Missouri 63166

Dear Dr. Wright:

Enclosed please find the report on Histopathological Re-evaluation of Tissues from Female Sherman Rats Fed Aroclor 1260. As mentioned in this report, there were about 20 animals with lesions, which on a morphological basis alone, could be interpreted as neoplastic. However, the definite malignant nature of these lesions cannot be proved in the presented material because of the factors mentioned in the section entitled "discussion" in the enclosed report.

I am sorry that I was not able to contact you by telephone. I was very much tied up with several visitors last week.

If you have any questions concerning the report, please contact me.

Sincerely,

P. Pour, M.D.
Professor

rmj

SCM 058195

030253

EXHIBIT # 43

Industrial BIO-TEST *Laboratories, Inc.*
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1242 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1242 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1242 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

II. Summary

In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. There were three hepatomas detected among three of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice. No hepatocellular carcinomas were observed. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material. In general, the latter findings were confined primarily to test animals of the final sacrifice and they were dose-related in incidence and severity.

In conclusion, Aroclor 1242 does not appear to be carcinogenic in rats fed for two years at levels up to and including 100 ppm.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES,

Report Prepared and Reviewed by: D. E. Gordon

D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

Report Approved by: M. L. Keplinger

M. L. Keplinger, Ph.D.
Manager, Toxicology

fd

IBT No. 622-07298
Monsanto

I have examined additional sections of liver from rats of IBT No. 622-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Aroclor 1242 on the following pages:

There is evidence of a chemical effect on the liver which is most pronounced at time of the terminal (24-Month) sacrifice. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals to hepatoma or cholangiohepatoma. The hypertrophic cells contain large volumes of light staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some sections, ring-shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. These nodules also contained the same hypertrophic cells.

Those lesions classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia, these are benign tumors rather than malignant tumors (carcinomas). There was no evidence of metastasis or invasiveness of these tumors in this study.

With exception of the vacular changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 24-Month Sacrifice.

Ward R. Richter

Ward R. Richter, D.V.M., M.S.
Dipl., Am. College Vet. Path.

Primary Liver Lesions - Aroclor 1242

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/8	2/10	1/9	2/10
Focal Hypertrophy	0/8	0/10	0/9	0/10
Nodular Hyperplasia	0/8	0/10	0/9	0/10
Hepatoma	0/8	0/10	0/9	0/10
Ductular Hyperplasia	0/8	0/10	1/9	0/10
Cholangio- Hepatoma	0/8	0/10	0/9	0/10
Hepatocellular Necrosis	1/8	0/10	0/9	0/10

Primary Liver Lesions - Aroclor 1242

6 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/10	0/8	0/9	1/10
Focal Hypertrophy	0/10	0/8	0/9	0/10
Nodular Hyperplasia	0/10	0/8	0/9	0/10
Hepatoma	0/10	0/8	0/9	0/10
Ductular Hyperplasia	0/10	0/8	0/9	0/10
Cholangio-Hepatoma	0/10	0/8	0/9	0/10
Hepatocellular Necrosis	1/10	0/8	0/9	1/10

Primary Liver Lesions - Aroclor 1242

12 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	T III	Control
Vacuolar Change	2/10	4/10	0/9	1/10
Focal Hypertrophy	0/10	0/10	1/9	0/10
Nodular Hyperplasia	0/10	0/10	0/9	0/10
Hepatoma -	0/10	0/10	0/9	0/10
Ductular Hyperplasia	0/10	1/10	0/9	1/10
Cholangio-Hepatoma	0/10	0/10	0/9	0/10
Hepatocellular Necrosis	0/10	0/10	0/10	0/10

Primary Liver Lesions - Aroclor 1242

Terminal Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	7/31	8/30	9/20	1/23
Focal Hypertrophy	2/31	3/30	8/20	0/23
Nodular Hyperplasia	0/31	2/30	8/20	1/23
Hepatoma	0/31	0/30	2/20	0/23
Ductular Hyperplasia	3/31	3/30	3/20	5/23
Cholangio-Hepatoma	0/31	0/30	1/20	0/23
Hepatocellular Necrosis	1/31	1/30	0/20	1/23

SCM 058157

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Telangiectasia, focal
3 Month	C-I 1ppm	596M											
		598"											
		599"											
		636F											
		637"											
		638"											
		639"		+									
		640"											
	C-II 10ppm	676M											
		677"	+										
		678"	+										
		679"											
		680"											
		716F											
		717"											
		718"											
		719"											
		720"											
	C-III 100ppm	756M											
		757"											
		758"	++										
		759"											
		760"						+					
		796F											
		797"											
		798"											
		800"											
	Con-trol	36M	+										
		37"											
		38"											
		39"	+										
		40"											
		76F											
		77"											
		78"											
		79"											
		80"											

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions											
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Telangiectasia, focal
6 Month	C-I 1ppm	1011M		+	+								
		1012"											
		1013"			+								
		1014"											
		1015"											
		1026F											
		1027"											
		1028"											
		1029"											
		1030"			+								
	C-II 10ppm	1041M											
		1042"											
		1043"											
		1045"											
		1056F											
		1057"											
		1058"											
		1059"											
	C-III 100ppm	1071M											
		1072"											
		1073"											
		1075"											
		1086F											
		1087"											
		1088"											
		1089"											
		1090"											
	Control	801M	+	+									
		802"											
		803"											
		804"											
		805"											
		816F											
		817"											
		818"											
		819"											
		820"											

Sacrifice terval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholanglo-hepatoma	teticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Telangectasia, focal
2 Month	C-I 1ppm	71M											
		72"	+										
		73"											
		74"											
		75"											
		76F	+										
		77"											
		78"											
		79"											
		80"											
	C-II 10ppm	81M	+										
		82"											
		83"											
		84"	+					+					
		85"											
		86F											
		87"			+								
		88"											
		89"											
		90"	+										
	C-III	91M											
		92"											
		93"											
		94"											
		95"											
		96F											
		97"				+							
		98"											
		99"											
	Control	1M											
		2"	+										
		3"											
		4"											
		5"											
		6F											
		7"											
		8"											
		9"						+					

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Anima No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic
24 Month	C-I 1ppm	564M										
		566"										
		591"										
		567"				+						
		569"									P	
		572"						+				
		576"										
		580"										
		588"										
		589"									P	
		595"	+									
		601F						+				
		604"										
		605"										
		582"	+									
		583"										
		607"				+		+				
		608"	+									
		609"										
		613"	+									
		621"										
		627"	+									
		628"	+									
		631"										
		634"										
		635"		+								
		606"										
		610"	+									
		620"										
		626"										
		633"										

SCM 058161

000166

acrifice Interval	Dose Level	Anima No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholanglo-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Pulmonary focal
24 Month	C-II 10ppm	655M											
		657"	+										
		662"	++										
		667"											
		640"					P						
		641"											
		643"											
		644"						+++					
		645"											
		646"											
		649"											
		651"	+										
		673"	+			+							
		686F											
		687"						+					
		689"											
		685"											
		690"											
		695"										P	
		697"											
		700"				+							
		703"	++										
		707"					P						
		708"	++	+				+++					
		711"											
		712"	+										
		682"	+										
		683"											
		691"											
		702"				+							

Sacrifice Interval	Dose Level	Anima No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholanglo-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic
½ Month	C-III	740M										
	100ppm	722"										
		724"	+++				P					
		744"										
		746"				+						
		748"	++				P					
		768F				+	P					
		771"	+			++	P			P		
		775"				+++						
		Ext"	+++									
		733"										
		765"	+					+				
		766"	++			+	P	+				
		767"							P			
		776"				+	P	+				
		773"				+	P					
		786"	+++									
		789"							P			
		793"	++++									
		Ext"	++			+	P					
	Control	8M						+				
		11"										
		12"										
		21"										
		23"										
		33"						+				
		34"										
		35"										
		Ext"										
		46F			+							
		47"										
		49"						+				
		51"						++				
		52"										
		56"										
		59"										
		62"										

SCM 058163

000163

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Telangiectasis, focal
½ Month	Control	63F											
		64"		+			P						
		66"											
		70"											
		71"											
		Ext"	+					+					

Grading System

+ = Minimal in severity
++ = Mild in severity
+++ = Moderate in severity
++++ = Marked in severity
P = Present, no grade

SCM 058164

Industrial BIO-TEST *Laboratories, Inc.*
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1254 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

EXHIBIT #44

[redacted]

Dr. Gaylor

Industrial BIO-TEST Laboratories Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

221

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1254 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

[redacted]

[redacted]

Industrial BIO-TEST Laboratories, Inc.
1816 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

March 24, 1975

222

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections From Rats of a Two - Year Chronic Oral Toxicity Study of Aroclor 1254

We are submitting herewith our laboratory report dated March 24, 1975; prepared in connection with the above study.

Very truly yours,

J. C. Calandra
President

[redacted]

000672

[redacted]

Industrial BIO-TEST Laboratories, Inc.

223

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY
STUDY WITH AROCLOR 1254
IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1254 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

[redacted]

000173

224

II. Summary

The spectrum of (in most instances) treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. However, there were six benign liver tumors detected among six of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice which were not previously reported. One liver tumor (a hepatoma) previously reported as a TE animal (No. 6) was reclassified as reported. The other treatment-related lesions reported are regarded as regenerative hyperplasia. degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver ascribed to associated with biotransformation of the test material. The latter lesions were confined primarily to test animals of the 12 and 24 month sacrifices and they were dose-related in incidence and severity.

In conclusion, Aroclor 1254 appears to be slightly tumorigenic at levels of 100 ppm when fed continously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D. V. M., Ph. D.
Section Head, Pathology

Report Approved by:

M. L. Koplinger, Ph. D.
Manager, Toxicology

IBT No. 622-07298
Monsanto

I have examined additional sections of liver from rats of Study Number 622-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Aroclor 1254 on the following pages.

There is evidence of a chemical effect on the liver which is most pronounced at time of the 12-Month and 24-Month sacrifice. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals to hepatoma or cholangiohepatoma. The hypertrophic cells contain large amounts of light staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some cases ring shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. They also contained the same hypertrophic cells.

These lesions which I classified as hepatomas or cholangio-hepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia; I chose to call these benign tumors rather than malignant (carcinomas). There was no evidence of metastasis or invasiveness of these tumors in this study.

~~It should be pointed out that other pathologists might call these tumors carcinomas on the basis of other criteria but, this diagnosis could be debated.~~ With exception of the vacuolar changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 24-Month Sacrifice.

Ward R. Richter

Ward R. Richter, D.V.M., M.S.
Dipl., Am. College Vet. Path.

Primary Liver Lesions - Aroclor 1254

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	THI	Control
Vacuolar Change	3/10	3/10	1/10	2/10
Focal Hypertrophy	0/10	0/10	1/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	0/10	0/10	0/10	0/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	1/10	1/10	0/10	0/10

Primary Liver Lesions - Aroclor 1254

6 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/10	0/10	1/10	1/10
Focal Hypertrophy	0/10	0/10	4/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	0/10	0/10	0/10	0/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	2/10	0/10	1/10	1/10

239

Primary Liver Lesions - Arocler 1254

14 Month Sacrifice - Rats

Lesion	Group I	II	III		Control
Vacuolar Change	1/10	4/10	1/10	c/c	1/10
Focal Hypertrophy	0/10	4/10	2/10	c/c	0/10
Nodular Hyperplasia	0/10	0/10	0/10		0/10
Hepatoma	0/10	0/10	0/10		0/10
Ductular Hyperplasia	1/10	1/10	0/10		1/10
Cholangio-Hepatoma	0/10	0/10	0/10		0/10
Hepatocellular Necrosis	0/10	0/10	1/10	c/c	0/10

Primary Liver Lesions - Aroclor 1254

Terminal Sacrifice - Rats

Lesion	TI	TII	TIII	Control
	3 1 2	3 1 2	3 1 2	1 2
Vacuolar Change	8/31	10/26	[illegible]/27	1/23
Focal Hypertrophy	3/31	5/26	13/27	[illegible]/23
Nodular Hyperplasia	0/31	3/26	13/27	1/23
Hepatoma	0/31	0/26	4/27	0/23
Ductular Hyperplasia	6/31	3/26	4/27	5/23
Cholangio-Hepatoma	0/31	0/26	2/27	0/23
Hepatocellular Necrosis	3/31	1/26	2/27	1/23

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats 231

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
3 Month	B-I 1ppm	356M	++										
		357"	+										
		358"											
		359"		+									
		360"	+										
		396F											
		397"											
		398"											
		399"											
		400"											
	B-II 10ppm	436M	+										
		437"											
		438"	+										
		439"											
		440"	+										
		476F		+									
		477"											
		478"											
		479"											
		480"											
	B-III 100ppm	516M											
		517"											
		518"	++	+-	+								
		519"											
		520"											
		555F											
		557"											
		558"											
		559"											
		560"											

000131

AROCLOR - 1254
Tabulation of Individual Liver Lesions in Rats

232

10

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
6 Month	B-I 1ppm	921M		+									
		922"											
		923"		+									
		924"											
		925"											
		936F											
		937"											
		938"											
		939"											
		940"											
	B-II 10ppm	950M											
		951"											
		952"											
		953"											
		954"											
		966F											
		967"											
		968"											
		969"											
		970"											
	B-III 100ppm	981M		+ (-)		+ (-)							
		982"				+ (-)							
		983"											
		984"											
		985"											
		996F				+ (-)							
		997"				+ (-)							
		998"											
		999"		+ (-)		+ (-)							
		1000"				+ (-)							

000182

AROCLOR - 1254
Tabulation of Individual Liver Lesions in Rats 233

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
14 Month	B-I 1ppm	41M	+										
		42"											
		43"											
		44"											
		45"											
		46F											
		47"											
		48"						+					
		49"											
		50"											
	B-II 10ppm	51M											
		52"	++										
		53"	++										
		54"			+								
		55"	+										
		56F			+								
		57"	+			+							
		58"				+							
		59"				+							
		60"				+		+					
	B-III 100ppm	61M				++							
		62"											
		63"											
		64"											
		65"	++			++							
		66F											
		67"			++								
		68"											
		69"											
		70"		+(-)									

AROCLOR - 1254 234 12

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nuclear hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma/Hepatocellular	Mammary tumor, metastatic	Hepatitis/Cirrhosis
24 Month	B-1 1ppm	326M						S	(+)				
		330"											
		335"											
10/9		338"											
		351"	(+)	(+)	(+)								
		323"		(+)									
		325"											
		343"	(+)										
		346"			+	+							
		342F											
		362"			(+)								
		368"						(+)	+	(+)			
		374"											
		375"				(P)		(+)	+				
		376"				(+)							
		475"	(+)	+++									
22/22		366"						(+)	+	(+)			
		367"											
		372"						(+)	+	(+)			
		377"	(+)	++	(+)	(+)		(+)	+				
		378"	(+)	(+)									
		379"	(+)	(+)	(+)								
		380"											
		381"											
		384"		(+)									
		387"											
		388"											
		389"											
		391"	(+)	(+)		(P)		(+)	+	(+)			
		394"	(+)	(+)									
		Ent"		(+)	(P)	(+)	++			(+)			

S = no liver section on slide
- = animal missing

000184

AROCLOR - 1254 13

Tabulation of Individual Liver Lesions in Rats 235

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
24 Month	B-II	415M											
	10ppm	417"											
		418"											
B/13		419"											
		423"											
		426"											
		427"											
		491"											
		402"											
		403"											
		405"											
		410"											
		434"											
		450F											
		451"											
		452"											
		456"											
		459"											
/13		463"											
		469"											
		470"											
		471"											
		478"											
		443"											
		445"											
		448"											

000135

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats

236

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
24 Month	B-III	484M	+										
	100ppm	491"											
		497"											
		499"											
		507"											
		509"											
		510"											
		512"											
		483"											
		489"											
		522F											
		524"											
		527"											
		541"											
		547"											
		Ext1"											
		Ext2"											
		Ext3"											
		Ext4"											
		Ext5"											
		536"											
		537"											
		539"											
		441"											
		Ex1"											
		Ex2"											
		Ex3"											

Grading System

- \- = minimal in severity
- +- = mild in severity
- ++ = moderate in severity
- +++ = marked in severity
- P = Present, no grade
- \- = Absent

II. Summary

In most instances, treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. However, there were six benign liver tumors detected among six of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice which were not previously reported. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material. The latter lesions were confined primarily to test animals of the 14 and 24 month sacrifices and they were dose-related in incidence and severity.

In conclusion, Aroclor 1254 appears to be slightly tumorigenic at levels of 100 ppm when fed continously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D. V. M., Ph. D.
Section Head, Pathology

Report Approved by:

M. L. Keplinger, Ph. D.
Manager, Toxicology

[redacted]

188

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1254 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 64[illegible] - 06672

[redacted]

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

189

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections From Rats of a Two - Year Chronic Oral Toxicity Study of Aroclor 1254.

We are submitting herewith our revised laboratory report dated March 24, 1975; prepared in connection with the above study.

Very truly yours,

J. C. Calandra
President

000183

[redacted]

Industrial BIO-TEST Laboratories, Inc.

190

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY
STUDY WITH AROCLOR 1254
IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1254 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

[redacted]

000190

II. Summary

In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. However, there were six benign liver tumors detected among six of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice which were not previously reported. One liver tumor (a hepatoma) previously reported in a T-II animal (No. 445) was re-classified as nodular hyperplasia The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver ascribed to biotransformation of the test material. The latter lesions were confined primarily to test animals of the 12 and 24 month sacrifices and they were dose-related in incidence and severity.

In conclusion, Aroclor 1254 appears to be slightly tumorigenic at levels of 100 ppm when fed continuously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by: D. E. Gordon

D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

Report Approved by: M. L. Kaplinger

M. L. Kaplinger, Ph.D.
Manager, Toxicology

fd

[redacted]

IBT No. 622-07298
Monsanto

I have examined additional sections of liver from rats of Study Number 622-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Arocler 1254 on the following pages.

There is evidence of a chemical effect on the liver which is most pronounced at time of the 12-Month and 24-Month sacrifice. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals to hepatoma or cholangiohepatoma. The hypertrophic cells contain large amounts of light staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some cases ring shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. They also contained the same hypertrophic cells.

Those lesions which I classified as hepatomas or cholangio-hepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia; I chose to call these benign tumors rather than malignant (carcinomas). There was no evidence of metastasis or invasiveness of these tumors in this study.

[redacted]

[redacted]

[redacted] BIO-TEST [redacted]

193

With exception of the vacuolar changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 24-Month Sacrifice.

Ward R. Richter

Ward R. Richter, D.V.M., M.S.
Dipl., Am. College Vet. Path.

[redacted]

000193

5

Primary Liver Lesions [illegible]

[illegible]

Lesion	Group			
	II	[illegible]	[illegible]	Control
Vacuolar Change	3/10	3/10	[illegible]/10	2/10
Focal Hypertrophy	0/10	0/10	1/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	0/10	0/10	0/10	0/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	1/10	1/10	0/10	0/10

Primary Liver Lesions - Aroclor 1254

6 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/10	0/10	1/10	1/10
Focal Hypertrophy	0/10	0/10	4/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	0/10	0/10	0/10	0/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	2/10	0/10	1/10	1/10

Primary Liver Lesions - Aroclor 1254

12 Month Sacrifice - Rats

Lesion	Group			
	II	III	IIII	Control
Vacuolar Change	1/10	4/10	1/10	1/10
Focal Hypertrophy	0/10	4/10	2/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	1/10	1/10	0/10	1/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	0/10	0/10	1/10	0/10

Primary Liver Lesions - Aroclor 1254

Terminal Sacrifice - Rats

Lesion	Group			
	TI	TII	THI	Co.
Vacuolar Change	8/31	10/26	13/27	1/23
Focal Hypertrophy	3/31	5/26	13/27	0/23
Nodular Hyperplasia	0/31	3/26	13/27	1/23
Hepatoma	0/31	0/26	4/27	0/23
Ductular Hyperplasia	6/31	3/26	4/27	5/23
Cholangio-Hepatoma	0/31	0/26	2/27	0/23
Hepatocellular Necrosis	3/31	1/26	2/27	1/23

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats 198

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic Hepatitis/Cirrhosis
3 Month	B-I	356M	++									
	1ppm	357"	+									
		358"										
		359"		+								
		360"	+									
		396F										
		397"										
		398"										
		399"										
		400"										
	B-II	436M	+									
	10ppm	437"										
		438"	+									
		439"										
		440"	+									
		476F		+								
		477"										
		478"										
		479"										
		480"										
	B-III	516M										
	100ppm	517"										
		518"	+	+	-							
		519"										
		520"										
		555F										
		557"										
		558"										
		559"										
		560"										

000138

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats

199

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
6 Month	B-I 1ppm	921M		+									
		922"											
		923"		+									
		924"											
		925"											
		936F											
		937"											
		938"											
		939"											
		940"											
	B-II 10ppm	950M											
		951"											
		952"											
		953"											
		954"											
		966F											
		967"											
		968"											
		969"											
		970"											
	B-III 100ppm	981M		+		+							
		982"				+							
		983"											
		984"											
		985"											
		996F				+	+						
		997"											
		998"											
		999"		+		+							
		1000"				+							

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats

200

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
12 Month	B-I 1ppm	41M	+										
		42"											
		43"											
		44"											
		45"											
		46F											
		47"											
		48"						+					
		49"											
		50"											
	B-II 10ppm	51M											
		52"	++										
		53"	++										
		54"			+								
		55"	+										
		56F			+								
		57"	+			+							
		58"				+							
		59"				+							
		60"				+		+					
	B-III 100ppm	61M				+							
		62"											
		63"											
		64"											
		65"	++			+							
		66F											
		67"			+								
		68"											
		69"											
		70"		+									

000200

AROCLOR - 1254
Tabulation of Individual Liver Lesions in Rats 201 12

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
24 Month	B-1 1ppm	326M											
		330"											
		335"											
		338"											
		351"	++	+									
		323"		+									
		325"											
		343"	+										
		346"			+	+							
		342F											
		362"											
		368"						+					
		374"											
		375"						+					
		376"				+							
		475"	+++										
		366"						+					
		367"											
		372"						+					
		377"	++	++		+		+					
		378"	+										
		379"	+										
		380"											
		381"											
		384"											
		387"											
		388"											
		389"											
		391"	+					+					
		394"	+++										
		Ext"			++								

000201

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats

202

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic
24 Month	B-II	415M										
	10ppm	417"				++		+				
		418"										
		419"										
		423"										
		426"	++									
		427"	+									
		491"									P	
		402"	+									
		403"	++									
		405"										
		410"										
		434"	+									
		450F										
		451"	+				P					
		452"	+	+			P					
		456"				+						
		459"				++		++				
		463"	++									
		469"				+						
		470"										
		471"										
		479"						+				
		443"										
		445"					P					
		448"										

000202

AROCLOR - 1254 14

Tabulation of Individual Liver Lesions in Rats 203

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, malignant	Hepatitis/Cirrhosis
24 Month	B-III	484M	++										
	100ppm	491"				+	P		P				
		497"				++	P						
		499"				+	P						
		507"					P						
		509"											
		510"	+										
		512"											
		483"	++					+					
		489"	+			+							
		522F	++			+							
		524"	++			+	P						
		527"	+++			+	P					P	
		541"				+			P				
		547"	++				P						
		Ext1"	++			++++	P						
		Ext2"					P	+		P			
		Ext3"	++			+++							
		Ext4"					P		P				
		Ext5"		+			P						
		536"	++			-++	P						
		537"											
		539"	++			++		-					
		441"											
		Ex1"							P				
		Ex2"	++							P			
		Ex3"				+	P	-					

Grading System

- - minimal in severity
- -- - mild in severity
- --+ - moderate in severity
- ---+ - marked in severity
- P - Present, no grade
- . - Absent

Industrial BIO-TEST Laboratories, Inc. 056
1616 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY
STUDY WITH
AROCLOR 1254
IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1972

IBT NO. 641 - 06672

Final Report

000204

[redacted]

Industrial BIO-TEST Laboratories, Inc.
[redacted]
NORTHBROOK, ILLINOIS 60062

057

July 1, 1975

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections From Rats of a Two - Year Chronic Oral Toxicity Study of Aroclor 1254.

We are submitting herewith our revised laboratory report dated March 24, 1975, prepared in connection with the above study.

Very truly yours,

J. C. Calandra

J. C. Calandra
President

JCC/kk

[redacted]

000205

[redacted]

[redacted] BIO-TEST [redacted]

058

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY
STUDY WITH AROCLOR 1254
IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1254 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

[redacted]

000206

[redacted]

Submitted BIO-TEST Laboratories, Inc. 2

059

II. Summary

In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. There were six hepatomas detected among six of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice. No hepatocellular carcinomas were observed. One liver tumor (a hepatoma) previously reported in a T-H animal (No. 445) was re-classified as nodular hyperplasia. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver ascribed to biotransformation of the test material. The latter lesions were confined primarily to test animals of the 12 and 24 month sacrifices and they were dose-related in incidence and severity.

In conclusion, Aroclor 1254 appears to be slightly tumorigenic at levels of 100 ppm when fed continously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D. V. M., Ph. D.
Section Head, Pathology

Report Approved by:

M. L. Kopfinger, M. D.
Manager, Toxicology

sew

[redacted]

000007

HARTOLDMON0023455

IRT No. 922-07216
Mammals

060

I have examined additional sections of liver from [illegible] IRT No. 922-07216 and have re-evaluated them for evidence of carcinogenesis. I have modified my findings for Animal 1264 on the following pages:

There is evidence of a chemical effect on the liver which is most pronounced at time of the 12-Month and 24-Month sacrifice. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals to hepatoma or cholangiohepatoma. The hypertrophic cells contain large amounts of light staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some cases ring shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. They also contained the same hypertrophic cells.

Those lesions classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia; these are benign tumors rather than malignant carcinomas. There was no evidence of metastasis or invasiveness of these tumors in this study.

Submitted BIO-TEST Laboratories, Inc. 001

With exception of the vacuolar changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 24-Month Sacrifice.

Ward R. Richter

Ward R. Richter, D.V.M., M.S.
Dipl., Am. College Vet. Path.

062

Primary Liver Lesions - Aroclor 1254

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	3/10	3/10	1/10	2/10
Focal Hypertrophy	0/10	0/10	1/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	0/10	0/10	0/10	0/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	1/10	1/10	1/10	0/10

Primary Liver Lesions - Arocior 1254

6 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/10	0/10	1/10	1/10
Focal Hypertrophy	0/10	0/10	4/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	0/10	0/10	0/10	0/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	2/10	0/10	3/10	1/10

Primary Liver Lesions - Aroclor 1254

12 Month Sacrifice - Rats

Lesion	Group			
	II	III	IIII	Control
Vacuolar Change	1/10	4/10	1/10	1/10
Focal Hypertrophy	0/10	4/10	2/10	0/10
Nodular Hyperplasia	0/10	0/10	0/10	0/10
Hepatoma	0/10	0/10	0/10	0/10
Ductular Hyperplasia	1/10	1/10	0/10	1/10
Cholangio-Hepatoma	0/10	0/10	0/10	0/10
Hepatocellular Necrosis	0/10	0/10	1/10	0/10

065

Primary Liver Lesions - Aroclor 1254

Terminal Sacrifice - Rats

Focal Hypertrophy	3/31	1/26	13/27	0/23
Nodular Hyperplasia	0/31	3/26	13/27	1/23
Hepatoma	0/31	0/26	4/27	0/23
Ductular Hyperplasia	6/31	3/26	4/27	5/23
Cholangio-Hepatoma	0/31	0/26	2/27	0/23
Hepatocellular Necrosis	3/31	1/26	3/27	1/23

000213

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats 066

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangiohepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
3 Month	B-I 1ppm	356M	++										
		357"	+										
		358"											
		359"		+									
		360"	+										
		396F											
		397"											
		398"											
		399"											
		400"											
	B-II 10ppm	436M	+										
		437"											
		438"	+										
		439"											
		440"	+										
		476F		+									
		477"											
		478"											
		479"											
		480"											
	B-III 100ppm	516M											
		517"											
		518"	+	+	+								
		519"											
		559"											
		560"											

000214

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats

067

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic / Hepatitis/Cirrhosis
6 Month	B-I 1ppm	921M		+								
		922"										
		923"		+								
		924"										
		925"										
		936F										
		937"										
		938"										
		939"										
		940"										
	B-II 10ppm	950M										
		951"										
		952"										
		953"										
		954"										
		966F										
		967"										
		968"										
		969"										
		970"										
	B-III 100ppm	981M		+	+							
		982"			+							
		983"										
		984"										
		985"										
		996F				+						
		997"				+						
		998"										
		999"		+		+						
		1000"				+						

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats 068

Sacrifice Interval	Dose Level	Animal No. Sex	Liver Lesions: Cytoplasmic Accumulation of Lymphocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, Metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
12 Month	B-I 1ppm	41M	+										
		42F											
		43F											
		44F											
		45F											
		46F											
		47F											
		48F						+					
		49F											
		50F											
	B-II 10ppm	51M											
		52F	++										
		53F	++										
		54F			+								
		55F	+										
		56F			+								
		57F	+			+							
		58F				+							
		59F				+							
		60F				+		+					
	B-III 100ppm	61M				+							
		62F											
		63F											
		64F											
		65F	++			+							
		66F											
		67F			+								
		68F											
		69F											
		70F		+									

Tabulation of Individual Liver Lesions in Rats 069

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
24 Month	B-1 1ppm	326M											
		330"											
		335"											
		338"											
		351"	++	+									
		323"		+									
		325"											
		343"	+										
		346"			+	+							
		342F											
		362"											
		368"						+					
		374"											
		375"						+					
		376"				+							
		475"	+++										
		366"						+					
		367"											
		372"						+					
		377"	++	+		+		+					
		378"	+										
		379"	+										
		380"											
		381"											
		384"											
		387"											
		388"											
		389"											
		391"	+					+					
		394"	+++										
		Ext"			++								

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats

070 13

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
24 Month	B-II	415M											
	10ppm	417"				++		+					
		418"											
		419"											
		423"											
		426"	++										
		427"	+										
		491"									P		
		402"	+										
		403"	++										
		405"											
		410"											
		434"	+										
		450F											
		451"	+				P						
		452"	+	+			P						
		456"				+							
		459"				++		++					
		463"	++										
		469"				+							
		470"											
		471"											
		478"						+					
		443"											
		445"					P						
		448"											

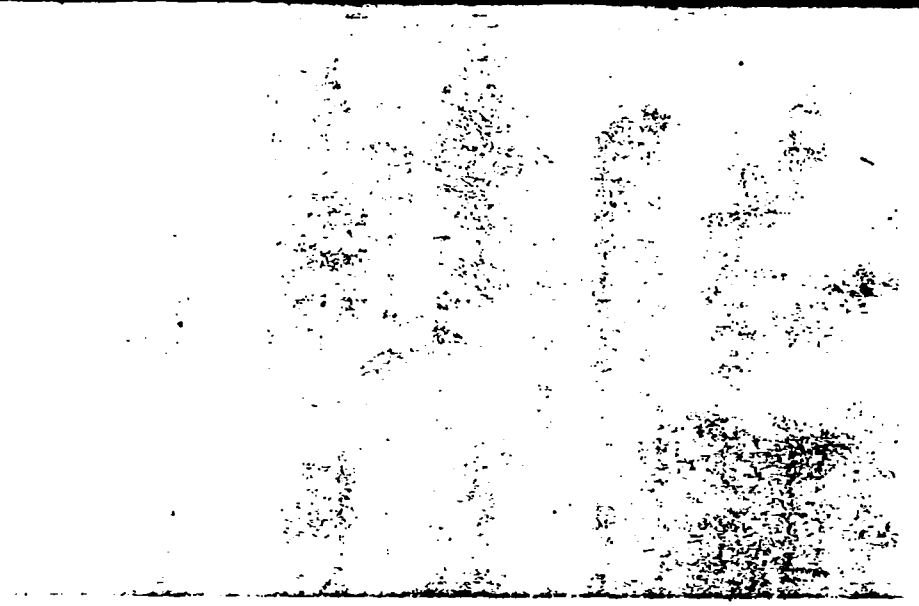
AROCLOR - 1254
Tabulation of Individual Liver Lesions in Rats

071

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
24 Month	B-III	484M	++										
	100ppm	491"				+	P		P				
		497"				++	P						
		499"				+	P						
		507"					P						
		509"											
		510"	+										
		512"											
		483"	++					+					
		489"	+			+							
		522F	++			++							
		524"	++			+	P						
		527"	+++			+	P					P	
		541"				+			P				
		547"	++				P						
		Ext1"	++			++++	P						
		Ext2"					P	+		P			
		Ext3"	++			+++							
		Ext4"					P		P				
		Ext5"		+			P						
		536"	++			+++	P						
		537"											
		539"	++			++		+					
		441"											
		Ex1"							P				
		Ex2"	++							P			
		Ex3"				+	P	+					

Grading System

- \- = minimal in severity
- — = mild in severity
- --- = moderate in severity
- ---- = marked in severity
- P = Present, no grade
- . = Absent



Primary Liver Lesions - Aroclor 1254

Terminal Sacrifice - Rats

Lesion	Group TI 1	TI 2	TI 3	TII 1	TII 2	TII 3	TIII 1	TIII 2	TIII 3	Control 1	Control 2
Vacuolar Change	3/31	5/28	8/31	4/26	4/25	10/26	13/27	3/25	13/27	1/23	0/24
Focal Hypertrophy	1/31	2/28	3/31	1/26	1/25	5/26	6/27	3/25	13/27	0/23	0/24
Nodular Hyperplasia		0/28	0/31	1/26	3/25	3/26	3/27	9/25	13/27	1/23	0/24
Hepatoma		0/28	0/31	½	0/25	0/26	1/27	2/25	4/27	0/23	0/24
Ductular Hyperplasia	3/31	6/28	6/31	3/26	4/25	3/26	5/27	2/25	4/27	5/23	6/24
Cholangio-Hepatoma		9/28	0/31		0/25	0/26	0/27	1/25	2/27	0/23	0/24
Hepatocellular Necrosis	2/31	2/28	3/31	1/26	2/25	1/26	1/27	1/25	2/27	1/23	0/24

1 = First evaluation of original slides
2 - Re-evaluation of original slides
3 - Evaluation of additional tissue sections

There were 5 animals in which this lesion was not seen at time of the second evaluation but was present on the first.
Similar to above involving 4 animals.

Submitted BIO-TEST Laboratories, Inc.

073

Primary Liver Lesions - AROCLOR 1254

Terminal Sacrifice - Rats

Re-evaluation of Original Slides

	E-1	E-2	E-3	Control
Vacuolar Change	5/28	4/25	3/25	0/24
Focal Hypertrophy	2/28	1/25	3/25	0/24
Nodular Hyperplasia	0/28	3/25	9/25	0/24
Ductular Hyperplasia	6/28	4/25	2/25	6/24
Cholangio-hepatoma	2/28	0/25	1/25	0/24
Hepatoma	0/28	0/25	2/25	0/24

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats

Exposure Material	Dose Level	Rat No.	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltration	Basal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio hepatoma	Hepatocellular Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
24 Months													
								•					
			1	1									
			M	Liver	necrosis	M	chole						
						P		•					
								•					
			1	•				•					
			•										
			1	P		P		•					
								•					

Industrial BIO-TEST Laboratories, Inc.

075

ARACLOR - 1254

Tabulation of Individual Liver Lesions in Rats

Exposure Interval	Dose Level	Rat No.	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltration	Focal hyperplasia of hepatocytes	Nuclear hypertrophy of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Hemangio-sarcoma, metastatic	Hepatocellular carcinoma
24 Month	5-ppm	1	1										
		2											
		3		1									
		4											
		5											
		6											
		7											
		8											
		9											
		10											
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		52											

000223

AROCLOR - 1254

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No.	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltration	Focal hypertrophy of hepatocytes	Nuclear hypertrophy of hepatocytes	Focal bile duct hyperplasia	Hepatosis	Cholangio-hepatitis	Squamous Cell Carcinoma, Metastatic	Mammary tumor, malignant	Hyperplastic/nodular
24 Months	5-ppm	484 M					P	—					
	100 ppm	491											
		497											
		498											
		509											
		510											
		511											
		512											
		513	moderate										
		514	+			P	P						
		515					P						
		516					P						
		517					P						
		518					P						
		519	++			P	P			P			
		520					P						
		521											
		522				P							
		523											
		524							P				
		525	+										
		526					P						
		527					P						
		528											
		529							P				

Grading System

- + = minimal in severity
- ++ = mild in severity
- +++ = moderate in severity
- ++++ = marked in severity
- P = Present, no grade

EXHIBIT #15

[redacted]

Dr Ecdar

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

204

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY
STUDY WITH
AROCLOR 1248 and 1254
IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

E-292

[redacted]

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

March 24, 1975

205

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St Louis, Missouri 63166

Dear Dr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections From Rats of a Two Year Chronic Oral Toxicity Study of Arocior 1242, 1260

We are submitting herewith our laboratory report dated March 24, 1975, prepared in connection with the above study.

Very truly yours,

J. C. Calandra
President

[redacted] BIO-TEST [redacted]

206

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY
STUDY WITH AROCLOR [redacted] 1260
IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor [redacted] 1260 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

~~Submitted~~ BIO-TEST ~~Laboratories, Inc.~~

207

II. ~~Summary~~ Discussion

In most instances, ~~no~~ treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. However, there were seven benign liver tumors detected among seven of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice which were not previously reported. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material. In general, the latter findings were confined primarily to test animals of the 6-, 12- and 24-Month Sacrifices, and they were dose-related in incidence and severity.

In conclusion, Aroclor ~~1242~~ 1254 appears to be slightly tumorigenic at levels of 100 ppm when fed continuously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by: _____
D. E. Gerdes, D.V.M., Ph.D.
Section Head, Pathology

Report Approved by: _____
M. L. Kaplumpur, Ph.D.
Manager, Toxicology

BIO-TEST

IBT No. 622-07298 208
Monsanto

I have examined additional sections of liver from rats of IBT No. 622-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Aroclor - 1260 on the following pages:

There is evidence of a chemical effect on the liver which was most evident at time of the 12-Month and terminal (24-Month) sacrifices. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals, to hepatomas or cholangiohepatomas. The hypertrophic cells contain large amounts of light-staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some cases, ring-shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. They also contained the same hypertrophic cells.

Those lesions which I classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses or other evidence of anaplasia, I chose to call these benign tumors rather than malignant carcinomas. There was no evidence of metastasis or invasiveness of these tumors in this study.

[redacted] BIO-TEST [redacted]

~~It should be pointed out that other pathologists might call these tumors carcinomas on the basis of other criteria, but this diagnosis could be debated.~~ With exception of the vacuolar changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 18- and 24-Month Sacrifice periods.

Ward R. Richter

Ward R. Richter, D. V. M., M. S.
Diplomate, American College of
Veterinary Pathologists

Primary Liver Lesions - Aroclor 1260

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/11	4/10	3/10	2/10
Focal Hypertrophy	0/11	0/10	2/10	0/10
Nodular Hyperplasia	0/11	0/10	0/10	0/10
Hepatoma	0/11	0/10	0/10	0/10
Ductular Hyperplasia	0/11	1/10	0/10	0/10
Cholangio-Hepatoma	0/11	0/10	0/10	0/10
Hepatocellular Necrosis	0/11	0/10	0/10	0/10

211

Primary Liver Lesions - Aroclor 1242

8 Month Sacrifice - Rats

Lesion	Group				
	TI	TII	THI		Control
Vacuolar Change	1/6	2/5	5/9	c/q	1/10
Focal Hypertrophy	0/6	0/5	3/9	c/q	0/10
Nodular Hyperplasia	0/6	0/5	0/9		0/10
Hepatoma	0/6	0/5	0/9		0/10
Ductular Hyperplasia	0/6	0/5	0/9		0/10
Cholangio-Hepatoma	0/6	0/5	0/9		0/10
Hepatocellular Necrosis	0/6	1/5	0/9		1/10

Primary Liver Lesions - Aroclor 1262

14 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	THI	Control
Vacuolar Change	2/9	5/10	3/9	1/10
Focal Hypertrophy	0/9	0/10	4/9	0/10
Nodular Hyperplasia	0/9	0/10	1/9	0/10
Hepatoma	0/9	0/10	0/9	0/10
Ductular Hyperplasia	1/9	0/10	2/9	1/10
Cholangio-Hepatoma	0/9	0/10	0/9	0/10
Hepatocellular Necrosis	0/9	0/10	0/9	0/10

Primary Liver Lesions - Aroclor 1260

Terminal Sacrifice - Rats

Lesion	Group									
	TI		TII		THI		Control			
Vacuolar Change	5/25		6/23		10/27		1/23			
Focal Hypertrophy	3/25		10/23		1/27		0/23			
Nodular Hyperplasia	0/25		9/23		7/27		1/23			
Hepatoma	0/25		0/23		5/27		0/23			
Ductular Hyperplasia	6/25		5/23		14/27		5/23			
Cholangio-Hepatoma	0/25		0/23		2/27		0/23			
Hepatocellular Necrosis	4/25		2/23		6/27		1/23			

AROCLOR 1242

Tabulation of Individual Liver Lesions in Rats 214

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
3 Month	AI	116M								
		117"								
		118"								
		119"								
		120"								
		147F								
		156"								
		157"								
		158"								
		159"								
		160"								
	AII	195M	++							
		196"	++							
		198"	+							
		200"	++							
		Extra"								
		236F								
		237"								
		238"								
		239"								
		240"								
	AIII	276M								
		277"	++							
		278"	++			+				
		279"				++				
		280"	++							
		315F								
		317"								
		318"								
		319"								
		320"								

000235

AROCLOR 1242

Tabulation of Individual Liver Lesions in Rats

10

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma	
1 Month	AI	832M									
		834"			+						
		835"									
		846F									
		848"	+								
		849"			+						
	AII	864M	+		+						
		865"	+		+						
		873"		+							
		878F									
		879"									
	AIII	891M	+ (+)			++					
		893"	+ (+)			+					
5 1/2		894"	+ (+)			+					
		895"	+ (+)								
		906F	+ (-)								
		907"									
5 1/2		908"									
		909"									
		910"									

AROCLOR 1242

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma	
12 Month	AI	11M									
		12"	+					+			
		13"	+								
		14"									
		15"									
		16F									
		17"									
		18"									
		19"									
	AII	21M	+								
		22"									
		23"	+								
		24"	+								
		25"	++								
		26F									
		27"	+								
		28"									
		29"									
		30"									
	AIII	31M	++								
		32"									
4/4		33"	+								
		34"	+ (-)								
		36F				(-) +					
5/5		37"				(-) +					
		38"				(-) +		(-) +			
		39"					(-) P				
		40"				(-) +		(-) +			

AROCLOR 1242

Tabulation of Individual Liver Lesions in Rats 217

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
Final	AI	85M		+						
		86"	++	+		+				
		87"		++						
1/10		101"								
		106"						+		
		112"								
		114"								
		105"	+							
		107"								
		109"		+		+		+		
		122F								
		125"						+		
14/15		127"						+		
		129"						+		
		130"								
		138"	+++							
		141"								
		147"			+					
		151"							+	
		155"	+							
		144"								
		131"	+							
		132"								
		135"				+		+		
		139"								
	AII	167M			+					
		168"	+	+		+				
7, 7		179"				+	P	+		
		182"				P				
		184"	++							
		187"								
		Extra"	-			+		+		
		205F				+	P	+		
		208"								
		210"				P				

000238

AROCLOR 1254 13

Tabulation of Individual Liver Lesions in Rats 218

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions							
			Vascular Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
Final (continued)	AII	212F					P			
		213"								
		220"								
		221"								
		224"					P			
		233"								
		234"								
		219"								
		230"								
		203"								
		204"								
		206"								
		207"								
	AIII	241M					P			
		253"								
		261"								
		264"								
		270"								
		271"								
		272"								
		275"					P			
		243"								P
		244"								
		312"								
		231F					P			
		274"								
		279"								
		296"							P	
		297"							P	
		302"					P			
		306"								
		308"					P			
		311"							P	
		314"							P	
		240"								

000239

AROCLOR 1242

Tabulation of Individual Liver Lesions in Rats 219

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
Final (continued)	AIII	245F				+(-) ++(P)		+(-) +		
		281"				+(-)	--- P (+)	+(-) +	(+)	
		287"				(+) P		+(-) +	"	
		291"	(+)			+(-)	(+)	(P)+(-) ++	(-)P	
		309"		+(---) (+)						P

Grading System

+ = minimal in severity
++ = mild in severity
+++ = moderate in severity
++++ = marked in severity
P = Present, no grade

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

172

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1260 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

Industrial BIO-TEST Laboratories, Inc.
1810 PRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

173

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections From Rats of a Two - Year Chronic Oral Toxicity Study of Arocior 1260.

We are submitting herewith our revised laboratory report dated March 24, 1975: prepared in connection with the above study.

Very truly yours,

J. C. Calandra
President

000242

Industrial BIO-TEST Laboratories, Inc.

174

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1260 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1260 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

II. Summary

In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. However, there were seven benign liver tumors detected among seven of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice which were not previously reported. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material. In general, the latter findings were confined primarily to test animals of the 6-, 12- and 24-Month Sacrifices, and they were dose-related in incidence and severity.

In conclusion, Aroclor 1260 appears to be slightly tumorigenic at levels of 100 ppm when fed continuously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D. V. M., Ph. D.
Section Head, Pathology

Report Approved by:

M. L. Kapleger, M. D.
Manager, Toxicology

Submitted BIO-TEST Laboratories, Inc.

IBT No. 622-07298 176
Monsanto

I have examined additional sections of liver from rats of IBT No. 622-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Aroclor - 1260 on the following pages:

There is evidence of a chemical effect on the liver which was most evident at time of the 12- Month and terminal (24-Month) sacrifices. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals, to hepatomas or cholangiohepatomas. The hypertrophic cells contain large amounts of light-staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some cases, ring-shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. They also contained the same hypertrophic cells.

Those lesions which I classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses or other evidence of anaplasia, I chose to call these benign tumors rather than malignant carcinomas. There was no evidence of metastasis or invasiveness of these tumors in this study.

With exception of the vacuolar changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 12- and 24-Month Sacrifice periods.

Ward R. Richter

Ward R. Richter, D.V.M., M.S.
Diplomate, American College of
Veterinary Pathologists

Primary Liver Lesions - Aroclor 1260

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	THI	Control
Vacuolar Change	0/11	4/10	3/10	2/10
Focal Hypertrophy	0/11	0/10	2/10	0/10
Nodular Hyperplasia	0/11	0/10	0/10	0/10
Hepatoma	0/11	0/10	0/10	0/10
Ductular Hyperplasia	0/11	1/10	0/10	0/10
Cholangio-Hepatoma	0/11	0/10	0/10	0/10
Hepatocellular Necrosis	0/11	0/10	0/10	0/10

Primary Liver Lesions - Aroclor 1260

6 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	THI	Control
Vacuolar Change	1/6	2/5	5/9	1/10
Focal Hypertrophy	0/6	0/5	3/9	0/10
Nodular Hyperplasia	0/6	0/5	0/9	0/10
Hepatoma	0/6	0/5	0/9	0/10
Ductular Hyperplasia	0/6	0/5	0/9	0/10
Cholangio-Hepatoma	0/6	0/5	0/9	0/10
Hepatocellular Necrosis	0/6	1/5	0/9	1/10

150

Primary Liver Lesions - Arocior 1260

12 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	2/9	5/10	3/9	1/10
Focal Hypertrophy	0/9	0/10	4/9	0/10
Nodular Hyperplasia	0/9	0/10	1/9	0/10
Hepatoma	0/9	0/10	0/9	0/10
Ductular Hyperplasia	1/9	0/10	2/9	1/10
Cholangio-Hepatoma	0/9	0/10	0/9	0/10
Hepatocellular Necrosis	0/9	0/10	0/9	0/10

Primary Liver Lesions - Aroclor 1260

Terminal Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	5/25	6/23	10/27	1/23
Focal Hypertrophy	3/25	10/23	19/27	0/23
Nodular Hyperplasia	0/25	9/23	7/27	1/23
Hepatoma	0/25	0/23	5/27	0/23
Ductular Hyperplasia	6/25	5/23	14/27	5/23
Cholangio-Hepatoma	0/25	0/23	2/27	0/23
Hepatocellular Necrosis	4/25	2/23	6/27	1/23

AROCLOR 1260

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
3 Month	AI	116M								
		117"								
		118"								
		119"								
		120"								
		147F								
		156"								
		157"								
		158"								
		159"								
		160"								
	AII	195M	++							
		196"	++							
		198"	+							
		200"	++							
		Extra"								
		236F								
		237"								
		238"								
		239"								
		240"								
	AIII	276M								
		277"	++							
		278"	++			+				
		279"				+				
		280"	++							
		315F								
		317"								
		318"								
		319"								
		320"								

AROCLOR 1260 10

Tabulation of Individual Liver Lesions in Rats 183

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
6 Month	AI	832M								
		834"			+					
		835"								
		846F								
		848"	+							
		849"			+					
	AII	864M	+		+					
		865"	+		+					
		873"		+						
		878F								
		879"								
	AIII	891M	+			++				
		893"	++			+				
		894"	+			+				
		895"	+							
		906F	-							
		907"								
		908"								
		909"								
		910"								

000252

AROCLOR 1260

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma	
12 Month	AI	11M									
		12"	+					+			
		13"	+								
		14"									
		15"									
		16F									
		17"									
		18"									
		19"									
	AII	21M	+								
		22"									
		23"	+								
		24"	+								
		25"	++								
		26F									
		27"	+								
		28"									
		29"									
		30'									
	AIII	31M	++								
		32"									
		33"	++								
		34"	+								
		36F				+					
		37"				+					
		38"				+		+			
		39"					P				
		40"				+		+			

AROCLOR 1260
Tabulation of Individual Liver Lesions in Rats 185 12

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma	
Final	AI	85M		+							
		86"	++	+		+					
		87"		++							
		101"									
		106"						+			
		112"									
		114"									
		105"	+								
		107"									
		109"		+		+		+			
		122F									
		125"						+			
		127"						+			
		129"						+			
		130"									
		138"	+++								
		141"									
		147"									
		151"									
		155"	+								
		144"									
		131"	+								
		132"									
		135"				+		+			
		139"									
	AII	167M			+						
		168"	+			+					
		179"				+		+			
		182"					P				
		184"	++								
		187"									
		Extra"				+		+			
		208F					P	+			
		208"									
		210"									

000254

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
Final (continued)	AII	212F	+			+	P	+		
		213"				+				
		220"					P			
		221"								
		224"								
		233"				++		+		
		234"	++	+		+				
		219"		++						
		230"				++				
		203"								
		204"	+							
		206"	+			++				
		207"					P	+		
	AIII	241M		+						
		253"				+		+		
		261"	+	+		++		+		
		264"				+		+		
		270"	++			+				
		271"	+++				P			P
		272"	++					++		
		275"	+			+		+		
		243"		+			P	+		
		244"				+			P	
		312"				++			P	
		231F	+			+++		++		
		274"	+++	++		+++			P	
		275"	++	+			P		P	
		294"					P	+		
		297"				+		+		
		302"					P	+		
		306"				+			P	
		308"	++					+		
		311"								
		314"	++			+				
		240"								

AROCLOR 1260

Tabulation of Individual Liver Lesions in Rats 187 14

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
Final (continued)	AIII	248F				++		+		
		281"					P	+		
		287"					P	+		
		291"						++	P	
		309"		+						P

Grading System

\+ = minimal in severity
++ = mild in severity
+++ = moderate in severity
++++ = marked in severity
P = Present, no grade

[redacted]

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

077

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1260 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 0072

[redacted]

000257

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

078

July 1, 1975

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections From Rats of a Two - Year Chronic Oral Toxicity Study of Aroclor 1260.

We are submitting herewith our revised laboratory report dated March 24, 1975, prepared in connection with the above study.

Very truly yours,

J. C. Calandra
President

JCC/fd

000258

[redacted]

Industrial BIO-TEST Laboratories, Inc.

079

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY
STUDY WITH AROCLOR 1260
IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1260 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

[redacted]

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080

II. Summary

In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. There were seven hepatomas detected among seven of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice. No hepatocellular carcinomas were observed. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material. In general, the latter findings were confined primarily to test animals of the 6-, 12- and 24-Month Sacrifices, and they were dose-related in incidence and severity.

In conclusion, Aroclor 1260 does not appear to be carcinogenic in rats fed for two years at levels up to and including 100 ppm.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D. V. M., Ph. D.
Section Head, Pathology

Report Approved by:

M. L. Kaplinger, Ph. D.
Manager, Toxicology

001

IBT No. 422-07298
Monsanto

I have examined additional sections of liver from rats of IBT No. 422-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Arochlor 1260 on the following pages:

There is evidence of a chemical effect on the liver which was most evident at time of the 12-Month and terminal (24-Month) sacrifices. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals, to hepatoma or cholangiohepatoma. The hypertrophic cells contain large amounts of light staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some cases, ring-shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. They also contained the same hypertrophic cells.

Those lesions classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses or other evidence of anaplasia, these are benign tumors rather than malignant carcinomas. There was no evidence of metastasis or invasiveness of these tumors in this study.

[redacted]

[redacted] BIO-TEST [redacted]

082

With exception of the vacuolar changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 12- and 24-Month Sacrifice periods.

Ward R. Richter

Ward R. Richter, D.V.M., M.S.
Diplomate, American College of
Veterinary Pathologists

[redacted]

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Primary Liver Lesions - Aroclor 1260

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	THI	Control
Vacuolar Change	0/11	4/10	3/10	2/10
Focal Hypertrophy	0/11	0/10	2/10	0/10
Nodular Hyperplasia	0/11	0/10	0/10	0/10
Hepatoma	0/11	0/10	0/10	0/10
Ductular Hyperplasia	0/11	1/10	0/10	0/10
Cholangio-Hepatoma	0/11	0/10	0/10	0/10
Hepatocellular Necrosis	0/11	0/10	0/10	0/10

Primary Liver Lesions - Aroclor 1260

6 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	THI	Control
Vacuolar Change	1/6	2/5	5/9	1/10
Focal Hypertrophy	0/6	0/5	3/9	0/10
Nodular Hyperplasia	0/6	0/5	0/9	0/10
Hepatoma	0/6	0/5	0/9	0/10
Ductular Hyperplasia	0/6	0/5	0/9	0/10
Cholangio-Hepatoma	0/6	0/5	0/9	0/10
Hepatocellular Necrosis	0/6	1/5	0/9	1/10

Primary Liver Lesions - Aroclor 1260

2 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	2/9	5/10	3/9	1/10
Focal Hypertrophy	0/9	0/10	4/9	0/10
Nodular Hyperplasi_	0/9	0/10	1/9	0/10
Hepatoma	0/9	0/10	0/9	0/10
Ductular Hyperplasia	1/9	0/10	2/9	1/10
Cholangio-Hepatoma	0/9	0/10	0/9	0/10
Hepatocellular Necrosis	0/9	0/10	0/9	0/10

Primary Liver Lesions - Aroclor 1260

Terminal Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	5/25	6/23	10/27	1/23
Focal Hypertrophy	3/25	10/23	1/27	0/23
Nodular Hyperplasia	0/25	0/23	7/27	1/23
Hepatoma	0/25	0/23	5/27	0/23
Ductular Hyperplasia	6/25	5/23	14/27	5/23
Cholangio-Hepatoma	0/25	0/23	2/27	0/23
Hepatocellular Necrosis	4/25	2/23	6/27	1/23

AROCLOR 1260
Tabulation of Individual Liver Lesions in Rats 087

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct Hyperplasia	Hepatoma	Cholangio-hepatoma
3 Month	AI	116M								
		117"								
		118"								
		119"								
		120"								
		147F								
		156"								
		157"								
		158"								
		159"								
		160"								
	AII	195M	++							
		196"	++							
		198"	+							
		200"	++							
		Extra"								
		236F								
		237"								
		238"								
		239"								
		240"								
	AIII	276M								
		277"	++							
		278"	++							
		279"				+				
		280"	++							
		315F								
		317"								
		318"								
		319"								
		320"								

AROCLOR 1260 10
Tabulation of Individual Liver Lesions in Rats 088

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma	
6 Month	AI	832M									
		834"			+						
		835"									
		846F									
		848"	+								
		849"			+						
	AII	864M	+		+						
		865"	+		+						
		873"		+							
		878F									
		879"									
	AIII	891M	+			++					
		893"	++			+					
		894"	+			+					
		895"	+								
		906F	+								
		907"									
		908"									
		909"									
		910"									

AROCLOR 1260

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions								
			Vascular Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Neoplasms	Cholangio-hepatoma	
12 Month	AI	11M	+								
		12"	+					+			
		13"	+								
		14"									
		15"									
		16F									
		17"									
		18"									
		19"									
	AII	21M	+								
		22"									
		23"	+								
		24"	+								
		25"	++								
		26F									
		27"	+								
		28"									
		29"									
		30"									
	AIII	31M	++								
		32"									
		33"	++								
		34"	+								
		36F				+					
		37"				+					
		38"				+		+			
		39"					P				
		40"				+		-			

AROCLOR 1260
Tabulation of Individual Liver Lesions in Rats 090 12

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct Hyperplasia	Hepatoma	Cholangio-hepatoma	
Final	AI	85M		+							
		86"	++	+		+					
		87"		+							
		101"									
		106"						+			
		112"									
		114"									
		105"	+								
		107"									
		109"		+		+		+			
		122F									
		125"						+			
		127"						+			
		129"						+			
		130"									
		138"	+++								
		141"									
		147"									
		151"									
		155"	+								
		144"									
		131"	+								
		132"									
		135"				+		+			
		139"									
	AII	167M			+						
		168"	+			+					
		179"				+		+			
		182"					P				
		184"	++								
		187"									
		Extra*				+		+			
		205F					P	-			
		208"									
		210"									

AROCLOR 1260

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions							
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal Bile Duct Hyperplasia	Hepatoma	Cholangio-hepatoma
Final (continued)	AII	212F					P	+		
		213"	+			+				
		220"				+				
		221"								
		224"					P			
		233"								
		234"				++		-		
		219"	++	-		+				
		230"		-+						
		203"				++				
		204"								
		206"	+							
		207"	+			++				
	AIII	241M		+			P	+		
		253"								
		261"				+		-		
		264"	+	+		++				
		270"				+		+		
		271"	++			+				
		272"	+++							
		275"	++				P			
		243"	+					++		P
		244"		-						
		312"				+		+		
		231F				++	P	+		
		274"	+			+++				
		275"	+++	++		+++		++		
		294"							P	
		297"	++	-					P	
		302"					P			
		306"				+		-		
		308"					P	+		
		311"	++						P	
		314"							P	
		240"	-+			+		-		

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hypertrophy of hepatocytes	Focal bile Duct Hyperplasia	Hepatosis	Cholangio-hepatoma	
Final (continued)	AIII	245F				++		+			
		281"					P	+			
		287"					P	+			
		291"						++	P		
		309"		+						P	

Grading System.

\+ = minimal in severity
++ = mild in severity
+++ = moderate in severity
++++ = marked in severity
P = Present, no grade

Primary Liver Lesions - Aroclor 1260

Terminal Sacrifice - Rats

Lesion	Group II			Group III			Group IIII			Control	
	1	2	3	1	2	3	1	2	3	1	2
Vacuolar Change	1/25	2/25	5/25	3/23	2/20	6/23	8/27	7/24	10/27	1/23	0/24
Focal Hypertrophy	0/25	0/25	3/25	1/23	4/20	10/23	9/27	6/24	11/27	0/23	0/24
Nodular Hyperplasia		0/25	0/25	0/23	4/20	9/23	2/27	3/24	7/26	1/23	0/24
Hepatoma		0/25	0/25		0/20	0/23	0/27	4/24	5/27	0/23	6/24
Dictular Hyperplasia	1/25	1/25	6/25		2/20	5/23	1/27	3/24	14/27	5/23	0/24
Cholangio-Hepatoma		0/25	0/25		0/20	0/23	0/27	0/24	2/27	0/23	0/24
Hepatocellular Necrosis		1/25	4/25	0/23	0/20	2/23	2/27	11/24	6/27	1/23	

1 = First evaluation of original slides
2 - Re-evaluation of original slides
3 - Evaluation of additional tissue sections

[redacted]

Industrial BIO-TEST [redacted]

094

Primary Liver Lesions - AROCLOR - 1260

Terminal Sacrifice - Rats

Re-evaluation of Original Slides

	A-1	A-2	A-3	Control
Vacuolar Change	2/25	2/20	7/24	0/24
Focal Hypertrophy	0/25	4/20	6/24	0/24
Nodular Hyperplasia	0/25	4/20	3/24	0/24
Bile Duct Hyperplasia	1/25	2/20	3/24	6/24
Cholangio-hepatoma	0/25	0/20	0/24	0/24
Hepatoma	0/25	0/20	4/24	0/24

[redacted]

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[redacted]

[redacted] BIO-TEST [redacted]

095

AROCLOR 1260

Tabulation of Individual Liver Lesions in Rats

Duration Interval	Dose Level	Animal [redacted]	Liver Lesions								
			Vacuolar Change	Focal Steatosis	Focal hypertrophy of hepatocytes	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal Bile Duct Hyperplasia	Hepatosis	Cholangiofibrosis	
Final	A1	[redacted]		•	•						Congestion
			—		•			•			Congestion
	A2	[redacted]	•			•	•				
			—								

000275

HARTOLDMON0023524

AROCLOR 1260

Tabulation of Individual Liver Lesions in Rats

Secondary Material	Dose Level	Animal No.	Liver Lesions								
			Vascular Change	Focal Necrosis	Focal Hyperplastic Infiltration	Focal hypertrophy of hepatocytes	Nuclear hyperchromia of hepatocytes	Focal Bile Duct Hyperplasia	Angiosis	Cholangio-fibrosis	
Fluid (continued)	All					•	•				
						•		•			
					•		•				
					•	•		•			
							•				
	All					•		•			Autolysis
			•								
			•					•			
						•			•		

AROCLOR 1260

Tabulations of Individual Liver Lesions in Rats

Duration Interval	Dose Level	Animal No.	Liver Lesions								
			Vacuolar Change	Focal Necrosis	Focal Lymphoid Infiltration	Focal Hypertrophy of Hepatocytes	Nodular Hyperplasia of Hepatocytes	Focal Bile Duct Hyperplasia	Hyperemia	Cholangio-fibrosis	
Final (continued)	All										
			+	—	•	P	P		P		
						P	P		P		
						P					

Grading System
• = minimal, in severity
+ = mild, in severity
++ = moderate, in severity
+++ = marked, in severity
P = Present, no grade

EXHIBIT # 46

In order

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

239

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR ~~1260~~ 1242 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

2:0

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062
March 24, 1975

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections From Rats of a Two - Year Chronic Oral Toxicity Study of Aroclor 1260 (2.42)

We are submitting herewith our laboratory report dated March 24, 1975; prepared in connection with the above study.

Very truly yours,

J. C. Calandra
President

000279

Industrial BIO-TEST Laboratories, Inc.

241

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY
STUDY WITH AROCLOR 1260
IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1260 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

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242

II. Summary

The spectrum of
In most instances, the treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. However, there were three benign liver tumors detected among three of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice which were not previously reported. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material. In general, the latter findings were confined primarily to test animals of the final sacrifice and they were dose-related in incidence and severity.

In conclusion, Aroclor 1260 appears to be slightly tumorigenic at levels of 100 ppm when fed continously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

Report Approved by:

M. L. Keplinger, Ph.D.
Manager, Toxicology

Industrial BIO-TEST Laboratories, Inc.

243

IBT No. 622-07298
Monsanto

I have examined additional sections of liver from rats of Study Number 622-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Aroclor 1242 on the following pages.

There is evidence of a chemical effect on the liver which is most pronounced at time of the terminal (24-Month) sacrifice. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals to hepatoma or cholangiohepatoma. The hypertrophic cells contain large volumes of light staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some sections, rim-shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. These nodules also contained the same hypertrophic cells.

Those lesions which I classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia, I chose to call these benign tumors rather than malignant tumors (carcinomas). There was no evidence of metastasis or invasiveness of these tumors in this study.

It should be pointed out that other pathologists might call these tumors carcinomas on the basis of other criteria but, this diagnosis could be debated. With exception of the vacuolar changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 24-Month Sacrifice.

Ward R. Richter

Ward R. Richter, D.V.M., M.S.
Dipl., Am. College Vet. Path.

Primary Liver Lesions - Aroclor 1260

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/8	2/10	1/9	2/10
Focal Hypertrophy	0/8	0/10	0/9	0/10
Nodular Hyperplasia	0/8	0/10	0/9	0/10
Hepatoma	0/8	0/10	0/9	0/10
Ductular Hyperplasia	0/8	0/10	1/9	0/10
Cholangio - Hepatoma	0/8	0/10	0/9	0/10
Hepatocellular Necrosis	1/8	0/10	0/9	0/10

Primary Liver Lesions - Aroclor 1260

8 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/10	0/8	0/9	1/10
Focal Hypertrophy	0/10	0/8	0/9	0/10
Nodular Hyperplasia	0/10	0/8	0/9	0/10
Hepatoma	0/10	0/8	0/9	0/10
Ductular Hyperplasia	0/10	0/8	0/9	0/10
Cholangio-Hepatoma	0/10	0/8	0/9	0/10
Hepatocellular Necrosis	1/10	0/8	0/9	1/10

Primary Liver Lesions - Arocior 1260

14 Month Sacrifice - Rats

247

Lesion	Group				
	TI	TII	T III		Control
Vacuolar Change	2/10	4/10	0/9	0/7	1/10
Focal Hypertrophy	0/10	0/10	1/9	0/9	0/10
Nodular Hyperplasia	0/10	0/10	0/9		0/10
Hepatoma	0/10	0/10	0/9		0/10
Ductular Hyperplasia	0/10	1/10	0/9		1/10
Cholangio-Hepatoma	0/10	0/10	0/9		0/10
Hepatocellular Necrosis	0/10	0/10	0/10		0/10

Primary Liver Lesions - Arocior 1260

248

Terminal Sacrifice - Rats

Lesion	Group TI	TII	TIII	Control
Vacuolar Change	7/31	8/30	9/20	1/23
Focal Hypertrophy	2/31	3/30	8/20	0/23
Nodular Hyperplasia	0/31	2/30	8/20	1/23
Hepatoma	0/31	0/30	2/20	0/23
Ductular Hyperplasia	3/31	3/30	3/20	5/23
Cholangio-Hepatoma	0/31	0/30	1/20	0/23
Hepatocellular Necrosis	1/31	1/30	0/20	1/23
	(3) (1) (2)	(3) (1) (2)	3	2

4 animals pos. on 1st eval not on 2nd

AROCLOR - 1260

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Telangiectasis, focal
3 Month	C-I 1ppm	596M											
		598"											
		599"											
		636F											
		637"											
		638"											
		639"		+									
		640"											
	C-II 10ppm	676M											
		677"	+										
		678"	+										
		679"											
		680"											
		716F											
		717"											
		718"											
		719"											
		720"											
	C-III 100ppm	756M											
		757"											
		758"	++										
		759"											
		760"											
		796F											
		797"											
		798"											
		800"											
	Control	36M	+										
		37"											
		38"											
		39"	+										
		40"											
		76F											
		77"											
		78"											
		79"											
		80"											

[illegible] except [illegible]

AROCLOR - 1260

Tabulation of Individual Liver Lesions in Rats

10

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma, metastatic	Mammary tumor, metastatic	Telangiectasis, focal
6 Month	C-I 1ppm	1011M		+	+								
		1012"											
		1013"			+								
		1014"											
Not Processed (Shipwreck)		1015"											
		1026F											
		1027"											
		1028"											
		1029"											
		1030"			+								
	C-II 10ppm	1041M											
		1042"											
		1043"											
		1045"											
		1056F											
		1057"											
		1058"											
		1059"											
	C-III 100ppm	1071M											
		1072"											
		1073"											
Processed [illegible] findings		1075"											
		1086F											
		1087"											
		1088"											
		1089"											
		1090"											
	Control	801M	+	+									
		802"											
5/5		803"											
		804"											
		805"											
		816F											
		817"											
5/5		818"											
		819"											
		820"											

AROCLOR - 1268

Tabulation of Individual Liver Lesions in Rats

251

11

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor metastatic	Telangiectasis, focal
18 Month	C-I 1ppm	71M											
		72"	+										
		73"											
		74"											
Not Examined		75"											
		76F	+										
		77"											
		78"											
		79"											
		80"											
	C-II 10ppm	81M	+										
		82"	+										
		83"											
		84"	+					+					
		85"											
"		86F											
		87"			+								
		88"											
		89"											
		90"	+										
	C-III	91M											
		92"											
		93"											
		94"											
		95"											
		96F											
		97"				+							
		98"											
		99"											
	Control	1M											
S/S		2"	+										
		3"											
		4"											
		5"											
		6F											
S/C		7"											
		8"											
		9"						(+)	+				
		10"											

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AROCLOR - 1260

Tabulation of Individual Liver Lesions in Rats

252

12

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Pulmonary tumor, focal
24 Month	C-I 1ppm	564M											
		566"						(+)					
		591"											
		567"				(+) +							
		569"		W	(+)						(+)P		
		572"						(+) +					
		576"											
		580"											
		588"											
		589"											
		595"	(+) +								(-) P(F)		
		601F						(-) +	(-)				
		604"											
		605"											
		582"	+										
		583"											
		607"				(+) +		(+) +	(-)				
		608"	(+) -										
		609"											
		613"	(+) +										
		621"						(+)	(-)				
		627"	(+) +										
		628"	(+) -										
		631"											
		634"											
		635"		+									
		606"											
		610"	+										
		620"											
		626"											
		633"											
		6--											

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AROCLOR - 1254 253 13

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic
24 Month	C-II 10ppm	655M										
		657"	+/+									
		662"	+/++			(+)	(+)					
		667"										
		640"					(+) P					
		641"										
		643"										
		644"						(+) → (+)				
		645"										
		646"										
		649"										
		651"	+/+									
		673"	+/+ (+)			+/+						
		686F										
		687"						+/+				
		689"										
		685"										
13/17		690"										
		695"										P
		697"										
		700"				+/+						
		70_"	++									
		707"					P					
		708"	++	+				++				
		711"										
		712"	+/+									
		682"	+									
		683"										
		691"										
		702"				+/+						

000292

AROCLOR - 1260 1/2

Tabulation of Individual Liver Lesions in Rats 254

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Pulmonary tissue, focal
24 Month	C-III 100ppm	740M											
		722"											
		724"					P						
		744"											
		746"											
		748"					P						
		768F					P						
		771"					P			P			
		775"											
		Ext"											
		733"											
		765"											
		766"					P						
		767"							P				
		776"					P						
		773"					P						
		786"											
		799"							P				
		793"											
		Ext"					P						
	Control	8M											
		11"											
		12"											
		21"											
		23"											
		33"											
		34"											
		35"											
		Ext"											
		46F											
		47"											
		49"											
		51"											
		52"											
		56"											
		59"											
		62"											

000293

AROCLOR - 1262

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic
24 Month	Control	63F	(-)									
		64"		(-) +			(-) P					
		66"										
		70"										
		71"										
		Ent"	(-) +					(-) +				

Grading System

+ = Minimal in severity
++ = Mild in severity
+++ = Moderate in severity
++++ = Marked in severity
P = Present, no grade

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

153

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1242 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections From Rats of a Two - Year Chronic Oral Toxicity Study of Aroclor 1242.

We are submitting herewith our revised laboratory report dated March 24, 1975; prepared in connection with the above study.

Very truly yours,

J. C. Calandra
President

[redacted]

Industrial BIO-TEST Laboratories, Inc.

157

REPORT

MONSANTO CO..

TWO - YEAR CHRONIC ORAL TOXICITY
STUDY WITH AROCLOR 1242
IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1242 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

[redacted]

II. Summary

In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. However, there were three benign liver tumors detected among three of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice which were not previously reported. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material. In general, the latter findings were confined primarily to test animals of the final sacrifice and they were dose-related in incidence and severity.

In conclusion, Aroclor 1242 appears to be slightly tumorigenic at levels of 100 ppm when fed continously in the diet for two years.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report Prepared and Reviewed by:

D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

Report Approved by:

M. L. Keplinger, Ph.D.
Manager, Toxicology

IBT No. 622-07298
Monsanto

I have examined additional sections of liver from rats of Study Number 622-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Aroclor 1242 on the following pages.

There is evidence of a chemical effect on the liver which is most pronounced at time of the terminal (24-Month) sacrifice. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals to hepatoma or cholangiohepatoma. The hypertrophic cells contain large volumes of light staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some sections, ring-shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. These nodules also contained the same hypertrophic cells.

Those lesions which I classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia, I chose to call these benign tumors rather than malignant tumors carcinomas. There was no evidence of metastasis or invasiveness of these tumors in this study.

With exception of the vacular changes in the cytoplas . of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 24-Month Sacrifice.

Ward R. Richter

Ward R. Richter, D. V. M., M. S.
Dipl., Am. College Vet. Path.

Primary Liver Lesions - Arocler 1242 **161**

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	THI	Control
Vacuolar Change	0/8	2/10	1/9	2/10
Focal Hypertrophy	0/8	0/10	0/9	0/10
Nodular Hyperplasia	0/8	0/10	0/9	0/10
Hepatoma	0/8	0/10	0/9	0/10
Ductular Hyperplasia	0/8	0/10	1/9	0/10
Cholangio- Hepatoma	0/8	0/10	0/9	0/10
Hepatocellular Necrosis	1/8	0/10	0/9	0/10

Primary Liver Lesions - Aroclor 1242

6 Month Sacrifice - Rats

162

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/10	0/8	0/9	1/10
Focal Hypertrophy	0/10	0/8	0/9	0/10
Nodular Hyperplasia	0/10	0/8	0/9	0/10
Hepatoma	0/10	0/8	0/9	0/10
Ductular Hyperplasia	0/10	0/8	0/9	0/10
Cholangio-Hepatoma	0/10	0/8	0/9	0/10
Hepatocellular Necrosis	1/10	0/8	0/9	1/10

Primary Liver Lesions - Aroclor 1242

12 Month Sacrifice - Rats

163

Lesion	Group			
	T I	T II	T III	Control
Vacuolar Change	2/10	4/10	0/9	1/10
Focal Hypertrophy	0/10	0/10	1/9	0/10
Nodular Hyperplasia	0/10	0/10	0/9	0/10
Hepatoma	0/10	0/10	0/9	0/10
Ductular Hyperplasia	0/10	1/10	0/9	1/10
Cholangio-Hepatoma	0/10	0/10	0/9	0/10
Hepatocellular Necrosis	0/10	0/10	0/10	0/10

Primary Liver Lesions - Arocior 1242

164

Terminal Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	7/31	8/30	9/20	1/23
Focal Hypertrophy	2/31	3/30	8/20	0/23
Nodular Hyperplasia	0/31	2/30	8/20	1/23
Hepatoma	0/31	0/30	2/20	0/23
Ductular Hyperplasia	3/31	3/30	3/20	5/23
Cholangio-Hepatoma	0/31	0/30	1/20	0/23
Hepatocellular Necrosis	1/31	1/30	0/20	1/23

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Pulmonary tumor, focal
3 Month	C-I 1ppm	596M											
		595 "											
		599 "											
		636F											
		637 "											
		638 "											
		639 "		+									
		640 "											
	C-II 10ppm	676M											
		677 "	+										
		678 "	+										
		679 "											
		680 "											
		716F											
		717 "											
		718 "											
		719 "											
		720 "											
	C-III 100ppm	756M											
		757 "											
		758 "	++										
		759 "											
		760 "											
		796F											
		797 "											
		798 "											
		800 "											
	Control	36M	+										
		37 "											
		38 "											
		39 "	+										
		40 "											
		76F											
		77 "											
		78 "											
		79 "											
		80 "											

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolization of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Telangiectasis, focal
6 Month	C-I 1ppm	1011M		+	+								
		1012"											
		1013"			+								
		1014"											
		1015"											
		1026F											
		1027"											
		1028"											
		1029"											
		1030"			+								
	C-II 10ppm	1041M											
		1042"											
		1043"											
		1045"											
		1056F											
		1057"											
		1058"											
		1059"											
	C-III 100ppm	1071M											
		1072"											
		1073"											
		1075"											
		1086F											
		1087"											
		1088"											
		1089"											
		1090"											
	Control	801M	+	+									
		802"											
		803"											
		804"											
		809"											
		816F											
		817"											
		818"											
		819"											
		820"											

AROCLOR - 1242

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hyperplasia of hepatocytes	Nuclear hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Inflammation, focal
12 Month	C-I 1ppm	71M	+										
		72"											
		73"											
		74"											
		75"											
		76F	-										
		77"											
		78"											
		79"											
		80"											
	C-II 10ppm	81M	+										
		82"	+										
		83"											
		84"	+										
		85"											
		86F						+					
		87"			+								
		88"											
		89"											
		90"	+										
	C-III	91M											
		92"											
		93"											
		94"											
		95"											
		96F											
		97"				+							
		98"											
		99"											
	Control	1M											
		2"	+										
		3"											
		4"											
		5"											
		6F											
		7"											
		8"											
		9"											
		10"											

AROCLOR - 1242
Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic
24 Month	C-I 1ppm	564M										
		566"										
		591"										
		567"				+						
		569"									P	
		572"						+				
		576"										
		580"										
		588"										
		589"									P	
		595"	+									
		601F						+				
		604"										
		605"										
		582"	+									
		583"										
		607"				+		+				
		608"	+									
		609"										
		613"	+									
		621"										
		627"	+									
		628"	+									
		631"										
		634"										
		635"		+								
		606"										
		610"	+									
		620"										
		626"										
		633"										

AROCLOR - 1242
Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic
24 Month	C-II	655M										
	10ppm	657"	+									
		662"	++									
		667"										
		640"					P					
		641"										
		643"										
		644"						+++				
		645"										
		646"										
		649"										
		651"	+									
		673"	+			+						
		686F										
		687"						+				
		689"										
		685"										
		690"										
		695 '										P
		697"										
		700"				+						
		703"	++									
		707"					P					
		708"	++	+				+++				
		711"										
		712"	+									
		682"	+									
		683"										
		691"										
		702"				+						

AROCLOR - 1242

Tabulation of Individual Liver Lesions in Rats 170 14

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions									
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic
24 Month	C-III 100ppm	740M										
		722"										
		724"	+++				P					
		744"										
		746"				+						
		748"	++				P					
		768F				+	P					
		771"	+			++	P			P		
		775"				+++						
		Ext"	+++									
		733"										
		765"	+					+				
		766"	++			+	P	+				
		767"							P			
		776"				+	P	+				
		773"				+	P					
		786"	+++									
		789"							P			
		793"	++++									
		Ext"	++			+	P					
	Control	8M						-				
		11"										
		12"										
		21"										
		23"										
		33"						-				
		34"										
		35"										
		Ext"										
		46F			+							
		47"										
		49"						+				
		51"						--				
		52"										
		56"										
		59"										
		62"										

000310

ARCCLOR - 1262

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Pituitary tumor, focal
24 Month	Control	63F											
		64"		+			P						
		66"											
		70"											
		71"											
		Ext'd	+					+					

Grading System

\+ = Minimal in severity
++ = Mild in severity
+++ = Moderate in severity
++-- = Marked in severity
P = Present, no grade

[redacted]

Industrial BIO-TEST Laboratories Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

098

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY STUDY WITH AROCLOR 1248 IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

[redacted]

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

099

July 1, 1975

George J. Levinskas, Ph.D.
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, Missouri 63166

Dear Dr. Levinskas:

Re: IBT No. 641-06672 - Histopathological Evaluation of Additional Liver Sections From Rats of a Two - Year Chronic Oral Toxicity Study of Aroclor 1242.

We are submitting herewith our revised laboratory report dated March 24, 1975, prepared in connection with the above study.

Very truly yours,

J. C. Calandra

J. C. Calandra
President

JCC/fd

006313

[redacted] BIO-TEST [redacted]

REPORT TO

MONSANTO COMPANY

TWO - YEAR CHRONIC ORAL TOXICITY
STUDY WITH AROCLOR 1242
IN ALBINO RATS

HISTOPATHOLOGICAL EVALUATION
OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

I. Introduction

At the request of Dr. Levinskas of the Monsanto Company, additional sections of liver from a two - year chronic oral toxicity study of Aroclor 1242 in rats (IBT No. 622-07298) were processed into H & E stained sections and evaluated by light microscopy. The following report presents the results of this study.

101

II. Summary

In most instances, the spectrum of treatment-related histopathological findings in the liver from this re-evaluation did not differ significantly from that previously reported in our original report dated November 12, 1971. There were three hepatomas detected among three of the animals at the highest treatment level (100 ppm) of the 24-Month Sacrifice. No hepatocellular carcinomas were observed. The other treatment-related lesions reported are regarded as degenerative or hyperplastic in nature and they are morphologic manifestations of an adaptive response of the liver associated with biotransformation of the test material. In general, the latter findings were confined primarily to test animals of the final sacrifice and they were dose-related in incidence and severity.

In conclusion, Aroclor 1242 does not appear to be carcinogenic in rats fed for two years at levels up to and including 100 ppm.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES,

Report Prepared and Reviewed by: D. E. Gordon

D. E. Gordon, D.V.M., Ph.D.
Section Head, Pathology

Report Approved by: M. L. Keplinger

M. L. Keplinger, Ph.D.
Manager, Toxicology

fd

I have examined additional sections of liver from rats of IBT No. 622-07298 and have re-evaluated them for evidence of carcinogenesis. I have tabulated my findings for Aroclor 1262 on the following pages:

There is evidence of a chemical effect on the liver which is most pronounced at time of the terminal (24-Month) sacrifice. This consists of a hepatocellular alteration beginning as focal hypertrophy which progresses to nodular hyperplasia, and in a few animals to hepatoma or cholangiohepatoma. The hypertrophic cells contain large volumes of light staining cytoplasm which is probably rich in glycogen and endoplasmic reticulum. In some sections, ring-shaped structures, probably representing whorls of proliferative endoplasmic reticulum, were seen in the cytoplasm of these cells.

The hyperplastic nodules occupied larger areas and often compressed surrounding cells of the normal liver parenchyma. These nodules also contained the same hypertrophic cells.

Those lesions classified as hepatomas or cholangiohepatomas were larger nodules which showed evidence of confluence or some variation in cell size, shape, staining or a ductular or adenomatous pattern of growth. In the absence of metastasis, invasiveness, severe basophilia, mitoses, or other evidence of anaplasia, these are benign tumors rather than malignant tumors (carcinomas). There was no evidence of metastasis or invasiveness of these tumors in this study.

[redacted]

[redacted] BIO-TEST [redacted]

With exception of the vacuolar changes in the cytoplasm of hepatocytes, the more severe hepatocellular alterations were confined to animals of the 24-Month Sacrifice.

Ward R. Richter

Ward R. Richter, D.V.M., M.S.
Dipl., Am. College Vet. Path.

[redacted]

Primary Liver Lesions - Aroclor 1242

3 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/8	2/10	1/9	2/10
Focal Hypertrophy	0/8	0/10	0/9	0/10
Nodular Hyperplasia	0/8	0/10	0/9	0/10
Hepatoma	0/8	0/10	0/9	0/10
Ductular Hyperplasia	0/8	0/10	1/9	0/10
Cholangio- Hepatoma	0/8	0/10	0/9	0/10
Hepatocellular Necrosis	1/8	0/10	0/9	0/10

Primary Liver Lesions - Aroclor 1242

6 Month Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	0/10	0/8	0/9	1/10
Focal Hypertrophy	0/10	0/8	0/9	0/10
Nodular Hyperplasia	0/10	0/8	0/9	0/10
Hepatoma	0/10	0/8	0/9	0/10
Ductular Hyperplasia	0/10	0/8	0/9	0/10
Cholangio-Hepatoma	0/10	0/8	0/9	0/10
Hepatocellular Necrosis	1/10	0/8	0/9	1/10

Primary Liver Lesions - Aroclor [redacted]

12 Month Sacrifice - Rats

Lesion	Group			
	II	III	[redacted] III	Control
Vacuolar Change	2/10	4/10	0/9	1/10
Focal Hypertrophy	0/10	0/10	1/9	0/10
Nodular Hyperplasia	0/10	0/10	0/9	0/10
Hepatoma	0/10	0/10	0/9	0/10
Ductular Hyperplasia	0/10	1/10	0/9	1/10
Cholangio-Hepatoma	0/10	0/10	0/9	0/10
Hepatocellular Necrosis	0/10	0/10	0/10	0/10

Primary Liver Lesions - Aroclor 1262

Terminal Sacrifice - Rats

Lesion	Group			
	TI	TII	TIII	Control
Vacuolar Change	7/31	8/30	9/20	1/23
Focal Hypertrophy	2/31	3/30	8/20	0/23
Nodular Hyperplasia	0/31	2/30	8/20	1/23
Hepatoma	0/31	0/30	2/20	0/23
Ductular Hyperplasia	3/31	3/30	3/20	5/23
Cholangio-Hepatoma	0/31	0/30	1/20	0/23
Hepatocellular Necrosis	1/31	1/30	0/20	1/23

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Tubangiectasis, focal
3 Month	C-I 1ppm	596M											
		598 "											
		599 "											
		636F											
		637 "											
		638 "											
		639 "		+									
		640 "											
	C-II 10ppm	676M											
		677 "	+										
		678 "	+										
		679 "											
		680 "											
		716F											
		717 "											
		718 "											
		719 "											
		720 "											
	C-III 100ppm	756M											
		757 "											
		758 "	++										
		759 "											
		760 "							+				
		796F											
		797 "											
		798 "											
		800 "											
	Control	36M	+										
		37 "											
		38 "											
		39 "	+										
		40 "											
		76F											
		77 "											
		78 "											
		79 "											
		80 "											

AROCLOR - 1242

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Cytoplasmic vacuolization of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatosis	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Telangiectasis, focal
6 Month	C-I 1ppm	1011M		+	+								
		1012"											
		1013"			+								
		1014"											
		1015"											
		1026F											
		1027"											
		1028"											
		1029"											
		1030"			+								
	C-II 10ppm	1041M											
		1042"											
		1043"											
		1045"											
		1056F											
		1057"											
		1058"											
		1059"											
	C-III 100ppm	1071M											
		1072"											
		1073"											
		1075"											
		1086F											
		1087"											
		1088"											
		1089"											
		1090"											
	Control	801M	+	+									
		802"											
		803"											
		804"											
		805"											
		816F											
		817"											
		818"											
		819"											
		820"											

AROCLOR - 1242

Tabulation of Individual Liver Lesions in Rats

110

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Telangiectasis, focal
12 Month	C-I 1ppm	71M											
		72"	+										
		73"											
		74"											
		75"											
		76F	+										
		77"											
		78"											
		79"											
		80"											
	C-II 10ppm	81M	+										
		82"	+										
		83"											
		84"	+					+					
		85"											
		86F											
		87"			+								
		88"											
		89"											
		90"	+										
	C-III	91M											
		92"											
		93"											
		94"											
		95"											
		96F											
		97"				+							
		98"											
		99"											
	Control	1M											
		2"	+										
		3"											
		4"											
		5"											
		6F											
		7"											
		8"											
		9"						+					
		10"											

AROCLOR - 1262

Tabulation of Individual Liver Lesions in Rats 111

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangiohepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Pituitary tumor, [illegible]
24 Month	C-I 1ppm	564M											
		566"											
		591"											
		567"				+							
		569"									P		
		572"						+					
		576"											
		580"											
		588"											
		589"									P		
		598"	+										
		601F						+					
		604"											
		605"											
		582"	+										
		583"											
		607"				+		+					
		608"	+										
		609"											
		613"	+										
		621"											
		627"	+										
		628"	+										
		631"											
		634"											
		635"		+									
		606"											
		618"	+										
		620"											
		626"											
		633"											

AROCLOR - 1262

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltration	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Pheochromocytoma, found at
24 Month	C-II	635M											
	10ppm	657"	+										
		662"	++										
		667"											
		640"					P						
		641"											
		643"											
		644"						+++					
		645"											
		646"											
		649"											
		651"	+										
		673"	+			+							
		686F											
		687"						+					
		689"											
		685"											
		690"											
		695"										P	
		699"											
		700"				+							
		703"	++										
		707"					P						
		708"	++	+				+++					
		711"											
		712"	+										
		682"	+										
		683"											
		691"											
		702"				+							

ARCOLOR - 1242

Tabulation of Individual Liver Lesions in Rats 113 14

Sacrifice Interval	Dose Level	Animal No. Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Pulmonary tumor, [illegible]
24 Month	C-III 100ppm	740M											
		722"											
		724"	+++				P						
		744"											
		746"				+							
		748"	++				P						
		768F				+	P						
		771"	+			++	P			P			
		775"				+++							
		Ent"	+++										
		733"											
		765"	+					+					
C		766"	++			+	P	+					
		767"							P				
		776"				+	P	+					
		773"				+	P						
		786"	+++										
		789"							P				
		793"	+++										
		Ent"	++			+	P						
	Control	814						+					
		11"											
		12"											
		21"											
		23"											
		33"						+					
		34"											
		35"											
		Ent"											
		46F			+								
		47"											
		49"						+					
		51"						++					
		52"											
		56"											
		59"											
		62"											

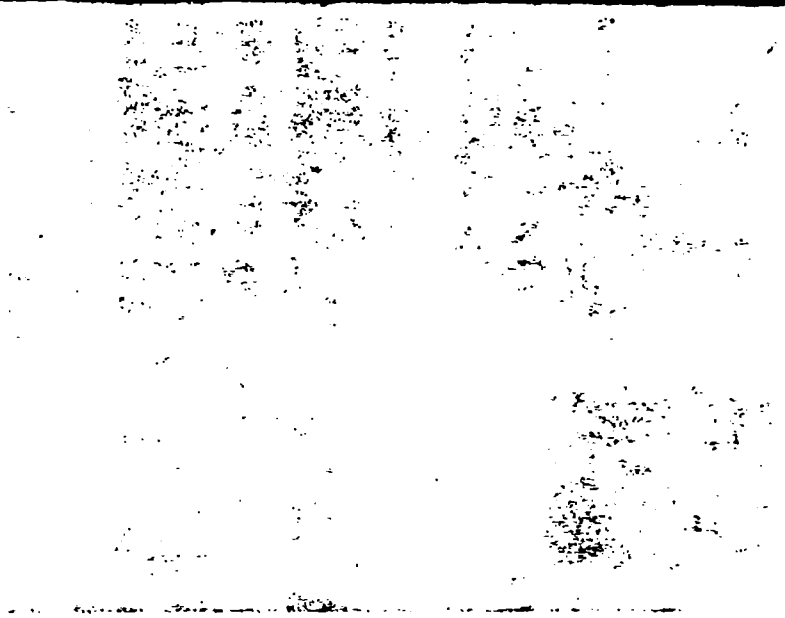
AROCLOR - 1268

Tabulation of Individual Liver Lesions in Rats 114

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions										
			Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangiocarcinoma	Reticulum Cell Sarcoma, metastatic	Mammary tumor, metastatic	Tubulectasis, focal
24 Month	Control	63F											
		64"		+			P						
		66"											
		70"											
		71"											
		Est"	+					+					

Grading System

\+ = Minimal in severity
++ = Mild in severity
+++ = Moderate in severity
++++ = Marked in severity
P = Present, no grade



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Primary Liver Lesions - Aroclor 1242

Terminal Sacrifice - Rats

Lesion	Group TI 1	TI 2	TI 3	TII 1	TII 2	TII 3	TIII 1	TIII 2	TIII 3	Control 1	Control 2
Vacuolar Change	0/31	0/27	7/31	4/30	1/19	8/30	13/20*	5/21	9/20	1/23	0/24
Focal Hypertrophy	0/31	0/27	2/31	1/30	2/19	3/30	8/20	2/21	8/20	0/23	0/24
Nodular Hyperplasia	0/31	0/27	0/31	1/30	0/19	2/30	2/20	5/21	8/20	1/23	0/24
Hepatoma	0/31	0/27	0/31	0/30	1/19	0/30	0'20	0/21	2/20	0/23	0/24
Ductular Hyperplasia	0/31	4/27	3/31	1/30	0/19	3/30	20	2/21	3/20	5/23	6/24
Cholangio-Hepatoma	0/31	0/27	0/31	0/30	0/19	0/30	0/20	0/20	1/20	0/23	0/24
Hepatocellular Necrosis	1/31	0/27	1/31	1/30	0/19	1, 30	0/20	0/21	0/20	1/23	0/24

1 = First evaluation of original slides
2 = Re-evaluation of original slides
3 = Evaluation of additional tissue sections

Four animals positive on first evaluation, not on second.

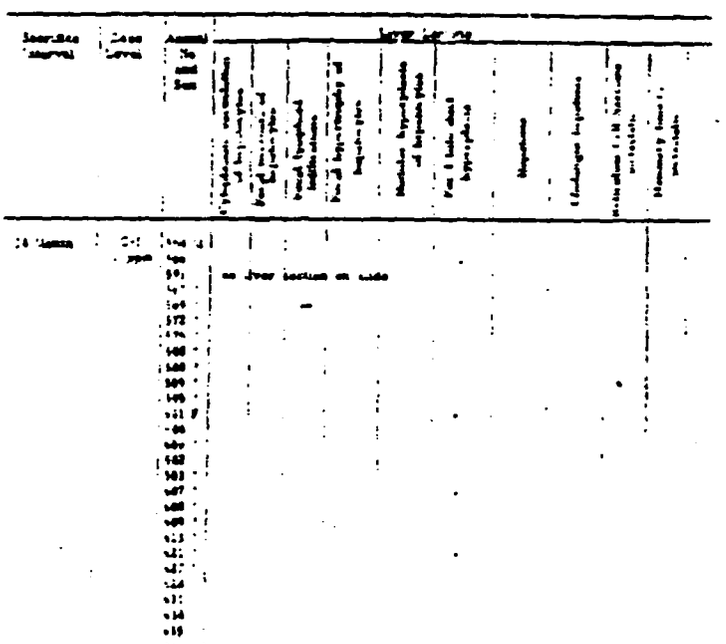
Primary Liver Lesions - AROCLOR 1242

Terminal Sacrifice - Rats

Re-evaluation of Original Slides

	C-1	C-2	C-3	Control
Vacuolar Change	0/27	1/19	5/21	0/24
Focal Hypertrophy	0/27	2/19	2/21	0/24
Nodular Hyperplasia	0/27	0/19	5/21	0/24
Ductular Hyperplasia	4/27	1/19	2/21	6/24
Cholangio-hepatoma	0/27	0/19	0/21	0/24
Hepatoma	0/27	0/19	0/21	0/24

AROCLOR - 1254



BIO-TEST Laboratories, Inc.

AROCLOR - 1242

Tabulation of Individual Liver Lesions in Rats

Sacrifice Interval	Dose Level	Animal No. and Sex	Liver Lesions: Cytoplasmic vacuolation of hepatocytes	Focal necrosis of hepatocytes	Focal lymphoid infiltrations	Focal hypertrophy of hepatocytes	Nodular hyperplasia of hepatocytes	Focal bile duct hyperplasia	Hepatoma	Cholangio-hepatoma	Metastases [illegible]	Malignant lymphoma [illegible]
[illegible] Months	[illegible] ppm	[illegible]										
		[illegible]	no liver sections on slide									
		[illegible]	no liver sections on slide									
		[illegible]	no liver section on slide									

AROCLOR - 1242

Tabulations of Individual Liver Lesions in Rats

Exposure Interval	Dose Level	Animal	Liver Lesions									
24 months	100 ppm											
	Control											

ARACLOR - 1248

Tabulation of Individual Liver Lesions in Rats

Secretion Interval	Dose Level	Animal	Liver Lesions									
24 hours	Control											

Grading System

- = Decrease in severity
- = Slight in severity
- = Moderate in severity
- = Marked in severity
- = Present, no grade

EXHIBIT # 47

Monsanto TECHNOLOGY

DMEH
Toxicology Section/St. Louis
(CO./CIV./DEPT./LOCATION)

SPECIAL REPORT
(TYPE OF REPORT)

REPORT NO.: MSL-2003

JOB/PROJECT NO.:

DATE: October 14, 1981

TITLE: A REVIEW AND EVALUATION OF CARCINOGENICITY STUDIES IN MICE AND RATS AND MUTAGENICITY STUDIES WITH POLYCHLORINATED BIPHENYLS

AUTHORS: George J. Levinskas, PH.D.

ABSTRACT: This is a review and evaluation of studies which deal with the potential carcinogenicity and mutagenicity of polychlorinated biphenyls (PCBs). It is subdivided into 4 sections: Chronic Rodent Studies, Metabolism Studies, Co-Carcinogenesis Studies and Mutagenicity Studies. A brief summary of Epidemiology Studies is added to complete coverage of the issue of carcinogenicity.

AUTHORS: George J. Levinskas, Ph.D.
TITLE: A REVIEW AND EVALUATION OF CARCINOGENICITY STUDIES IN MICE AND RATS AND MUTAGENICITY STUDIES WITH POLYCHLORINATED BIPHENYLS

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INTRODUCTION

This is a review and evaluation of studies which deal with the potential carcinogenicity and mutagenicity of polychlorinated biphenyls (PCBs). It is subdivided into 4 sections: Chronic Rodent Studies, Metabolism Studies, Co-Carcinogenesis Studies and Mutagenicity Studies. A brief summary of Epidemiology Studies is added to complete coverage of the issue of carcinogenicity.

This review does not discuss the effects of impurities or contaminants, particularly polychlorinated dibenzofurans (PCDF), which are reported to be present in some PCB mixtures (Brinkman and deKok, 1980). The presence and amounts of such impurities have not been specified in the materials used in many studies. Thus, attempts to apportion the observed biological effects between impurities and PCBs would only add further conjecture to a subject which currently is rife with speculation.

By contrast, specific chemical and trade names have been used to identify materials that were studied instead of the all encompassing term PCBs. This was deemed necessary because there are too many one-sided generalizations in the literature. Every adverse finding is, by implication at least, extrapolated to the entire class of materials designated as PCBs. Conversely, every report which has failed to find an adverse effect is careful to stipulate that it relates only to the substance studied. Even more difficult to contend with are misleading references to adverse findings which are not substantiated by the actual publications referred to. An example of this occurred in a discussion of <u>in vitro</u> metabolism studies with liver microsomal enzymes which stated that the formation of PCB-macromolecular adducts had been demonstrated. Among the references

cited was a paper entitled "The in vitro binding of 2,2',5,5'-tetrachloro-biphenyl metabolites to rat liver microsomal proteins". The latter paper clearly states "There is no clear evidence in the data obtained from the work reported here to substantiate covalent binding; however, it is also not possible to exclude the nondialyzable radioactivity as being covalently bound". (Hargraves and Allen, 1979).

To emphasize the point that dose is important in evaluating safety, test exposure conditions have been described so that the reader can compare them to ambient exposure levels encountered in the literature and elsewhere. Hoopingarner, et al. (1972) in their studies with Aroclor 1254 on cultured human lymphocytes are among the few authors who acknowledged that "The toxic dose of the chemical was several times greater than is usually found biologically". They used concentrations of 100 ppm of Aroclor 1254 in their studies discussed under Mutagenicity.

Chronic Rodent Studies

Difficulties in comparing and assessing different studies are compounded not only by problems of histopathologic diagnosis but also by variations in experimental design and animal strain differences. Animal feeding studies cited in the literature as evidence for the carcinogenicity of PCBs and related studies of similar duration have been tabulated for mice in Table 1 and for rats in Table 2. Studies have been grouped by the approximate weight percent of chlorine in the materials tested to facilitate comparisons between products from different manufacturers with the same chlorine content.

Mouse studies in Table 1 were conducted with high dietary levels of PCBs. Kimbrough and Linder (1974) reported a 52% mortality for mice fed 300 ppm of Aroclor 1254 for 6 months and then held an additional 5 months. During that interval, control mice had a 32% mortality. This appears to be quite high for control mice about 1 year of age. In a report discussed under Co-carcinogenesis, Koller (1977) studied mice injected with Aroclor products and Moloney leukemia virus. Some data from his study, although not shown in Table 1, are quite similar to those of Kimbrough and Linder (1974). Koller (1977) fed diets containing Aroclor 1221, 1242, or 1254 to groups of 25 Balb/c male mice for 6 months. After that time, some mice were sacrificed for examination and others were returned to a control diet for another 3 months and then sacrificed. Dietary levels of each Aroclor were 375, 37.5, or 3.75 ppm. The only feeding regimen that was toxic was 375 ppm of Aroclor 1254. Only 8 mice of that group survived for 6 months, giving a mortality of 68%. Other authors cited in Table 1 (Ito, et al., 1973a,b and Nagasaki, et al., 1972, 1974, 1975) did not indicate how many of the mice in their studies died when fed 500 ppm of Kanechlor 500, which has a chlorine content similar to Aroclor 1254. Koller (1977) reported that "PCBs did not produce hepatic neoplasia". There was marked liver injury in mice fed 375 ppm of Aroclor 1254, mild liver injury which persisted through the 3-month recovery period at 37.5 ppm, and no hepatic lesions at 3.75 ppm. Moderate liver injury was produced by 375 ppm of Aroclor 1242, but this regressed and no hepatic lesions were seen 3 months after mice were returned to a control diet. Other dietary levels of Aroclor 1242 and all levels of 1221 did not produce liver changes. Highly significant mean liver weight increases after 6 months of feeding occurred in all Aroclor 1254 groups and in the group fed 375 ppm of Aroclor 1242. Three months after mice were placed on a

control diet, mean liver weights of each group had decreased. The decreases were highly significant for the 37.5 ppm Aroclor 1254 and the 375 ppm Aroclor 1242 groups. These observations are generally consistent with those of other investigators which show regression of lesions when PCB dosing is ended, the degree of regression depending upon the duration of the recovery period.

Data for mice reported earlier by Nagasaki, et al. (1972) appear to have been included in the later publications of Ito, et al. (1973a,b). It is interesting to note that the tumors were called hepatomas in the former publication and were labeled well-differentiated hepatocellular carcinomas in the latter. Kimbrough and Linder (1974) apparently also felt that these same data on mice were reported in these 2 papers as they reference the production of hepatomas in male dd mice to the later publication by Ito, et al. (1973b). Similar terminology troubles beset the 1974 and 1975 Nagasaki publications. Data from the later publication list 9/17 males and 4/17 females fed Kanechlor 500 as having liver tumors. Table 1 shows data from the earlier publication; among males, 9/17 had nodular hyperplasia and 7/17 had hepatocellular carcinoma while the female incidence of 4/17 was described as nodular hyperplasia. The hepatomas described by Kimbrough and Linder (1974) were later referred to as "neoplastic nodules (hematomas [sic], hyperplastic nodules)" by Kimbrough, et al. (1978). The use of the term hepatoma has created confusion. With respect to terminology of tumors in the mouse liver, "Hepatoma is a collective term used to describe the progressive stages of tumour development from the lesion called "hyperplastic nodule" or "simple hyperplastic growth" to the morphologically and biologically malignant neoplasms" (Turusov and Takayama, 1979). Nevertheless, whatever

terminology is used to describe them, tumors were attributed only to PCBs containing 52-54 percent chlorine. Lower doses of the 52-54 percent chlorine materials, as well as lower chlorinated materials, were not described as tumorigenic.

Table 2 summarizes results of rat studies with PCBs. As in the mouse studies, only some studies with materials having a chlorine content of 52-54 percent, or higher, were reported to produce carcinomas in the livers of rats, and even for those materials this was not a consistent, reproducible observation.

Odashima (1976) reported the results from a series of different tests used to evaluate potential carcinogenicity of several compounds, including PCBs. Two tests are of sufficient interest to mention here. One is the transplacental method in which rats were treated for 3 days during pregnancy. These were days 15, 17, and 19 or 14, 16, and 18, depending on the strain used. The total dose was approximately the maximum one that did not cause abortion or early death of the weanlings. In the other, the newborn method, pups were dosed subcutaneously on days 1, 8, 15, and 22 after birth. The maximum dose was one that did not cause early death of over 20% of the animals. The subsequent observation period in each test was limited to one year after birth. For both Kanechlor 300 and Kanechlor 500, the transplacental test was scored negative and the newborn one as equivocal. Both of these tests gave positive results with some known carcinogens such as 4-aminobiphenyl, benzo[α]pyrene, butyl-nitrosourea and N-methyl-N-nitrosourea.

Objective appraisal of chronic rodent feeding studies is difficult. Some of the rodent studies in Table 1 and Table 2 are of the type used to detect potent carcinogens. They use relatively few animals, high doses of the test material, and have a relatively short duration. Studies of that nature have been included in Tables 1 and 2 to illustrate the various diagnoses of the rodent hepatic lesions observed after dosing with PCBs and to aid in the stepwise analysis of the results of all the reported carcinogenicity studies.

In any short-term test with a few animals, the chance occurrence of some tumors is a possibility which must be considered. The probability that an event is a chance occurrence is decreased if it is repeatable. Many of the studies in Table 1 did not produce tumors. Those which were reported to produce hepatocellular carcinoma apparently were also reported in other publications as producing nodular hyperplasia, or tumors, or hepatomas. Since terminology of tumors and the use of those terms have subjective, i.e., judgemental, elements it may not be valid to make direct comparisons between different studies on the basis of terminology alone.

The rodent studies which were of less than lifetime duration raise a question as to whether or not cancers would have occurred had the feeding periods been extended. That question is speculative, and it cannot be answered from the present data. Nevertheless, negative studies even if they are of relatively short duration are part of the overall evidence which has to be considered. As a first step in the analysis of the data, the evidence shows that at a minimum, PCBs are not potent carcinogens to rodents because they do not produce cancers when tested in studies designed to detect potent carcinogens.

With respect to further analysis of the mouse studies, greater significance can be attached to the data of Kimbrough and Linder (1974) because their study had a larger number of animals, a longer duration, and a relatively high dietary level of PCB. In those respects, it more closely resembles conventional cancer studies. They did not observe any hepatocellular carcinomas. Thus, it can reasonably be concluded that PCBs are not carcinogenic to mice.

Review of the rat data in Table 2 shows that there are 2 studies on PCBs with an average chlorine content of 40% (Levinskas, 1981 and Weltman and Norback, 1979) and 3 on PCBs with an average chlorine content of 52-54% (Levinskas, 1981; NCI, 1978; Wasserman, et al., 1978). Results of those studies are consistent with respect to the absence of hepatocellular carcinomas. This consistency reasonably suggests a conclusion that PCBs with those chlorine contents are not carcinogenic.

Of the 3 studies with PCBs having an average chlorine content of 60%, one reported hepatocellular carcinomas (Kimbrough, et al. 1975) and 2 did not (Levinskas, 1981 and Weltman and Norback, 1978). Since Kimbrough, et al. (1975) and Levinskas (1981) both used Lot No. AK-3 of Aroclor 1260, the different conclusions they reached are not related to differences in the test material. In addition to the use of a different strain of rat, Kimbrough, et al. (1975) used a different histologic diagnostic criteria. Kimbrough, et al. (1975) used the criteria for classification of specific hepatocellular lesions in rats developed at a National Cancer Institute Workshop (Squire and Levitt, 1975). That workshop recommended that the term "neoplastic nodules" replace so-called "hyperplastic nodules" because "Such nodules are proliferative lesions and

are known to be induced by carcinogens and, at the least, they indicate an increased probability for the development of hepatocellular carcinoma" (Squire and Levitt, 1975). However, Pitot, et al. (1978) in a discussion of stages in the progression of hepatocarcinogenesis in rat liver have noted that "The demonstration of carcinoma cells that appeared to arise within the nodules was also reported (13)[1], suggesting the nodule was a precursor to the malignant neoplasm. On the other hand, as was shown by Farber and others, the vast majority of the regenerating or hyperplastic nodules disappeared on removing the animals from the carcinogenic diet. Thus, despite the more recent suggestion that these nodules be termed "neoplastic nodules" (14)[2], it is difficult to understand a precursor relationship of the nodule to carcinomas if the existence of the putative precursor is so transient." Further, the use of those criteria for classifying experimental hepatic lesions was considered and rejected by Kimura, et al. (1976) in their studies on the co-carcinogenesis of Kanechlor 400 and 3'-methyl-4-dimethylaminoazobenzene.

There is concern that a presently benign lesion might at some future date or under other circumstances be transformed into a malignant lesion. Kimbrough (1979) apparently had that concern when she stated "Although it has been shown many times that the neoplastic nodules are part of the carcinogenic response they are not always included in the statistical evaluation of bioassays, which may lead to erroneously interpreted results, particularly when they are classified as hyperplastic nodules or "nodular hyperplasia" and when the number of animals studied was small (Carcinogenesis Testing Program, 1977)".[3] A similar concern appears to have been behind the statement in a recent review (Anon., 1981) that "hexachlorobiphenyl administered to groups of 50 male and 50 female

Sprague Dawley rats at dietary levels of 0 and 100 ppm for 105 weeks was carcinogenic in female rats, producing an increased incidence of liver hepatocellular carcinomas among the dosed animals (Norback and Weltman, 1980. Personal communication)". Contact with Dr. Norback (Ribelin, 1981) revealed that her data were available only as an abstract (Weltman and Norback, 1979), and that the abstract and her oral presentation of the data referred to the lesions as neoplastic nodules, i.e., not distinctly tumorous. These 2 examples illustrate the difficulty in establishing that cancer is not present, and they strongly suggest that the different findings reported by various researchers are a reflection of their orientation, training, and philosophical perspective. The latter is defined as the difficulty in separating what is actually being observed under the microscope, from a concern over what it might have become if the animals had lived longer.

Since only an abstract has been published, details on the studies by Weltman and Norback (1979) are limited . Their studies are of particular interest because they observed the sequential development of liver changes over a 2-year period. They noted that hexachlorobiphenyl was more toxic than tetrachlorobiphenyl, and that the more toxic, more highly chlorinated hexachlorobiphenyl produced neoplastic nodules only. Again, the weight of the evidence leads to a reasonable conclusion that the carcinogenicity of biphenyls with an average chlorine content of 60% has not been established.

Overall, one can surmise that the inability to resolve the crucial issue of whether or not a lesion is neoplastic in character was one of the factors which led to the following statement from a recent Surgeon General's report: "Science and society have not yet arrived at a final consensus on the definition of a carcinogen either in the human population or in experimental animals" (DHHS, 1980).

Metabolism Studies

Several reviews (Goldstein, 1980; IARC, 1978; Matthews and Kato, 1979; Roberts, et al., 1978; and Safe, 1980) discuss the metabolism of specific isomers as well as mixtures of PCBs. While there are some exceptions, the following general conclusions can be drawn. Both the degree of chlorination and the positions of the chlorine substituents determine the ease with which PCBs are metabolized. In general, the lower chlorinated ones are metabolized and excreted more readily while the more highly chlorinated materials are stored in fat. The process of metabolism converts the fat soluble PCB into a water soluble hydroxylated derivative which can be excreted in the urine. This metabolism and excretion appears to occur via arene oxide intermediates, and the carcinogenicity of some compounds has been attributed to formation of arene oxide intermediates and their binding to subcellular macromolecules. Chlorination at the 4,4' position blocks the metabolism and excretion of PCBs as illustrated below.

Studies in rats (Hansell, et al., 1977) and in mice (Morales and Matthews, 1978, 1979) are of interest because they report the metabolism of isomers which were fed to rats for 2 years by Weltman and Norback (1979). Hansell, et al. (1977) gave groups of male rats single intraperitoneal injections of 0.2 nmoles/kg of 2,2',5,5'-tetra- or 2,2',4,4',5,5'-hexachlorobiphenyl (TCB and HCB, respectively). They measured changes in hepatic mixed function oxidases and the persistence of the PCB in the livers of animals killed at selected intervals for 35 days after dosing. TCB produced a transient, but significant increase in O-demethylase activity only at day 3 while HCB produced significant increases in O-demethylase and aniline hydroxylase activities within 24-48 hours. Induced enzyme activities by HCB peaked at 4-6 times control activity during days 7-14 and were about 3 times control activity at the end of 35 days. Even though equimolar amounts of each isomer were given, liver residues of HCB one day after dosing were about 7 times higher than those of TCB. HCB residues decreased relatively slowly with time while TCB residues were more rapidly eliminated and had almost returned to control values by 35 days. Livers from HCB treated rats had centrolobular necrosis at day 35. They also were significantly increased in size, showed increased amounts of smooth endoplasmic reticulum (SER), and appeared to contain increased numbers of microbodies and reduced amounts of rough endoplasmic reticulum throughout the 35 day interval. By contrast, TCB treated livers were similar to control ones except for occasionally increased aggregates of SER on days 3 and 4. Hansell, et al. (1977) stated "It would be interesting to speculate that...2,4,5,2',4',5'-hexachlorobiphenyl undergoes direct hydroxylation whereas 2,5,2',5'-tetrachlorobiphenyl undergoes biotransformation via the arene oxide intermediate, thereby accounting for the different slope for the

elimination curve of the latter compound." Thus, the metabolism (Hansell, et al. 1977) and feeding (Weltman and Norback, 1979) study results lead to somewhat different conclusions. The more potent enzyme inducing, less readily excreted HCB which appears to resist hydroxylation produces neoplastic nodules in rat livers. By contrast, the more readily excreted TCB, which apparently is excreted via an arene oxide intermediate, does not produce tumors when fed to rats for 2 years.

Covalent binding to cellular macromolecules also appears to be greater for the more readily metabolized PCB isomers. Morales and Matthews (1978, 1979) compared the covalent binding of 2 hexachlorobiphenyls; the more readily metabolized 2,2',3,3',6,6'-hexachlorobiphenyl (2,3,6-isomer) and the more slowly metabolized 2,2',4,4',5,5'-hexachlorobiphenyl (2,4,5-isomer). Each PCB, with a radiocarbon label, was given orally to groups of mice at a dosage of 7.28 mg/kg on each of five successive days. Animals were killed 1, 5, and 8 days later. The concentration of each PCB was determined in liver, muscle, and kidney. All tissues had consistently higher concentrations of the less readily metabolized 2,4,5-isomer. The more readily metabolized 2,3,6-isomer showed a consistently greater binding to purified macromolecules. The binding was at least one order of magnitude greater than that seen with the 2,4,5-isomer. Results of animal feeding studies with the 2,3,6-isomer would be of particular interest to determine the degree of correlation, if any, between the carcinogenicity of this isomer and its covalent binding to cellular macromolecules.

Taken as a whole, metabolism studies suggest that if PCBs are carcinogenic, it should be those PCBs which are more readily metabolized and excreted, i.e., the lower chlorinated materials. This is in sharp

contrast to results on animal studies in which questions of carcinogenicity arise regarding higher chlorinated materials only. On balance, metabolism studies on the formation of arene oxide intermediates would lead one to expect lower chlorinated materials to show a more pronounced carcinogenic response in animals. Conclusions drawn from metabolism studies are not supported by animal feeding studies.

Co-Carcinogenesis Studies

The position and degree of chlorination of PCBs also are important in inducing microsomal mixed function monooxygenases (Goldstein, 1980 and Yoshimura, et al., 1979). Such induction of microsomal monooxygenases could alter the metabolism of exogenous and endogenous substances in the body, as reported in a variety of studies which have been conducted to determine whether PCBs might be cocarcinogens. These are summarized in Table 3 and discussed in greater detail below.

Uchiyama and Chiba (1974) inserted 20-methylcholanthrene impregnated threads into the uteri of virgin mice and fed them diets containing up to 100 ppm of Kanechlor 400 or DDT. Animals were killed at various times and the cervical epithelium was examined for cancerous changes. Kanechlor 400 dosed mice showed no significant changes as compared to the controls, but those receiving 100 ppm of DDT "showed a remarkable tendency towards the induction of cancer."

Diets containing benzene hexachloride (BHC) isomers and Kanechlor 500 separately and in various combinations were fed to male mice by Ito, et al. (1973a,b). Concentrations of the BHC isomers ranged from 250 ppm to

50 ppm. The amount of Kanechlor 500 was 250 ppm or 100 ppm. Test groups consisted of 20 to 30 animals. When fed alone, only α-BHC at 250 ppm produced a high incidence of nodular hyperplasia and a moderate incidence of hepatocellular carcinoma. A diet containing 250 ppm each of α-BHC and Kanechlor 500 increased the number of hepatocellular carcinomas. In comparison, combinations of 100 or 50 ppm of α-BHC and 250 ppm of Kanechlor 500 yielded a moderate incidence of nodular hyperplasia and produced only a few hepatocellular carcinomas. There were a few nodular hyperplasias in mice fed 100 ppm each of α-BHC and Kanechlor 500. A mixture of 50 ppm α-BHC and 100 ppm of Kanechlor 500 was without effect. Diets containing 250 ppm or 100 ppm of β-BHC and 250 ppm of Kanechlor 500 produced both nodular hyperplasia and hepatocellular carcinomas at a lower incidence than that seen with comparable diets of α-BHC. No liver nodules were seen with 50 ppm of β-BHC and 250 ppm of Kanechlor 500 or with 100 ppm of each. γ-BHC and Kanechlor 500 did not produce liver nodules either singly or in combination. Nagasaki, et al. (1974, 1975) reported a similar series of experiments except that Kanechlor 400 was included. The same concentrations of the PCBs, 250 and 100 ppm, were used. Their test groups consisted of 20 to 38 male mice. For α-BHC and Kanechlor 500, they presented essentially the same data as Ito, et al. (1973a,b). While Kanechlor 400 did not produce liver nodules when fed alone at 250 ppm, there was an increase in the incidence of hepatocellular carcinomas when it was fed in combination with 250 ppm of α-BHC. The increase was similar to that reported by Ito, et al. (1973a,b) for α-BHC and Kanechlor 500. A combination of 100 ppm of α-BHC and 250 ppm of Kanechlor 400 produced only a few nodular hyperplasias and 100 ppm of each in the diet did not induce any liver nodules.

The effects of PCBs on tumor induction by diethylnitrosamine (DEN) have been studied extensively. Male rats were given 25 ppm of DEN in their drinking water and 500 ppm of Kanechlor 500 in their diet concurrently for 20 weeks, returned to a control diet for 4 weeks, and then killed (Makiura, et al. 1974). Neither liver tumors nor nodular hyperplasia were seen, even though rats receiving the same DEN treatment alone had a 92% incidence of liver cancer. The livers of rats treated with Kanechlor 500 only also had no tumors. When administered after DEN, Kanechlor 500 markedly enhanced liver tumor production as reported in a series of papers by Nishizumi (1976, 1979a, 1979b). He described studies in which male rats were given 50 ppm DEN in drinking water for 2 to 10 weeks, after which they were intubated twice weekly with a corn oil solution of Kanechlor 500 for 6 to 12 weeks. Kanechlor 500 doses were either 0.2 ml of a 5% or 0.1 ml of a 10% solution. Since experiments were terminated at 20 or 52 weeks after dosing, some animals received untreated diets prior to sacrifice. Only one paper (Nishizumi, 1976) contained results for animals dosed only with Kanechlor 500 alone. That treatment produced enlargement of the livers of rats but no neoplastic lesions. After pre-treatment with DEN, however, hepatocarcinogenesis was enhanced as evidenced by the earlier appearance and a significant increase in the number of tumors. A similar dosing pattern was used by Preston, et al. (1981). Male rats were given drinking water containing 66 µg DEN/ml (66 ppm) for 5 weeks after which they were fed for 18 weeks on a control diet or one containing 100 ppm of either of 2 Aroclor 1254 diets. One was Aroclor 1254 as received. The other was an Aroclor 1254 which the authors claimed to have purified by removing polychlorinated dibenzofuran (PCDF) impurities by adsorption onto and subsequent elution from activated Florisil. No analysis was made of Aroclor 1254 as received for

PCDF. The authors reported recovery of PCDF at a level comparable to 30 μg of tetrachlorodibenzofuran (TCDF) per 10 g of Aroclor 1254. TCDF was used as a positive control and a standard for quantification for the purification process. Other animals received one of the 2 Aroclor 1254 diets only during the latter 18-week interval. No evidence of hepatic tumor formation was seen in control animals or those receiving 100 ppm of either Aroclor 1254 diet. However, using the diagnostic criteria of Squire and Levitt (1975), they reported that both Aroclor 1254 diets resulted in significantly greater incidences of hepatocellular carcinomas in rats pretreated with DEN as compared to those dosed with DEN alone. Thus, they concluded that the hepatic tumor-promoting ability appears to reside in Aroclor 1254 itself. As the authors of this paper pointed out, it cannot be concluded that PCDFs are not promoters of hepatocarcinogenesis since appropriate studies have not been done on PCDFs alone. Similarly, their findings do not invalidate the hypothesis that some of the other effects reported for some PCBs may have been due to PCDF impurities.

The dependence of the inhibition or promotion effect of PCBs on DEN-induced tumors on the dosing sequence was illustrated in a different manner by Nishizumi (1980). Pregnant female rats were given oral doses of 200 mg/kg or 50 mg/kg Kanechlor 500 on days 5, 10, and 15 of gestation and were allowed to deliver their pups. At 28 days of age, pups were given 50 ppm of DEN in their drinking water for 5 weeks. Groups of these pups were sacrificed at 16, 20, and 24 weeks after the start of DEN dosing and their livers were examined. The number of liver tumors in the offspring from Kanechlor 500 treated dams was significantly decreased as compared to the controls. The decreases were more pronounced in males. This decrease in DEN-induced tumors apparently resulted from induction of

microsomal enzymes in the livers of the pups. Those livers contained Kanechlor 500 residues and electron microscopy showed an increase in the smooth endoplasmic reticulum of hepatic cells.

Rainbow trout were fed 6 ppb of aflatoxin B_1 (AFB_1), or 100 ppm of Aroclor 1254, or a combination of both for a year (Hendricks, et al., 1977). At intervals during the year, some fish were killed. The remainder were killed at the end of that time. All livers were examined grossly and microscopically. There were no tumors in those fed a control diet or Aroclor 1254 alone, and growth was not affected by 100 ppm of Aroclor 1254. The number of tumor-bearing fish in the group fed AFB_1, plus Aroclor 1254 was significantly reduced (to less than one-half) when compared to those fed AFB_1, alone. There also were fewer tumors per liver and the tumors were smaller in those fed the mixture.

In the studies cited earlier, Makiura, et al. (1974) also fed combinations of 500 ppm Kanechlor 500 with 300 ppm of 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) or 150 ppm of N-2-fluorenylacetamide (2-FAA). Results similar to those when PCBs were fed concurrently with DEN were obtained. Kanechlor 500 reduced the incidence of liver tumors to zero from 65% for those treated with 3'-Me-DAB and from 54% for those treated with 2-FAA. However, the effect of PCBs on the tumorigenicity of 3'-Me-DAB appears to depend on the dosing sequence as shown for DEN. Kimura, et al. (1976) used different sequences to feed groups of rats diets containing 400 ppm of Kanechlor 400 for six months and 600 ppm of 3'-Me-DAB for 2 months. Some received Kanechlor 400 alone and some only 3'-Me-DAB. Others received one diet, then the other, after a 2-month interval on control diet. A final group received Kanechlor 400 for

4 months and both materials for another 2 months. No hepatocarcinomas were produced by Kanechlor 400 alone or when it was given before or during the overlap with 3'-Me-DAB. No hepatocarcinomas occurred in control animals. The incidence of liver cancer rose from 13% in those receiving 3'-Me-DAB alone to 64% in the group which received Kanechlor 400 after 3'-Me-DAB.

The inhibitory effect of Kanechlor 500 on rat liver tumors was evident when rats were dosed with two carcinogens (Makiura, et al., 1974). Combinations of 3'-Me-DAB and DEN or 2-FAA and DEN were administered with and without Kanechlor 500 at the concentrations stated earlier. The liver cancer incidence fell from 92% to 8% when Kanechlor 500 was given to rats dosed with 3'-Me-DAB and DEN. It went to zero from 82% for those receiving 2-FAA and DEN.

Nishizumi (1979a,b) studied the effects of various combinations of DDT and sodium phenobarbital (SPB), in the absence and in the presence of Kanechlor 500, on the induction of rat liver hepatocellular carcinoma by DEN. Pretreatment of rats with DEN followed by DDT, by SPB, or by a combination of both produced low incidences of liver cancer while DEN pretreatment alone did not induce cancer. When Kanechlor 500 was included with each of the preceding dosing regimens, there was a marked increase in liver cancers. Increases resulting from joint administration of compounds after pretreatment with DEN were lower than those observed for DEN followed by Kanechlor 500 alone discussed earlier.

Ito, et al. (1978) fed diets containing 200 ppm of 2-FAA to male rats for two weeks and then a diet containing 1000 ppm of an unspecified Kanechlor

mixture for 8 weeks. Partial hepatectomies (PH) were performed on some rats during the third week of the study. Feeding of 2-FAA was without effect, but that diet plus PH produced a few hyperplastic nodules in the liver. Treatment with both diets caused an even greater incidence of hyperplastic nodules and both diets combined with PH produced a marked rise in the number of liver nodules.

DiGiovanni, et al. (1977) and Berry, et al. (1978, 1979) studied Aroclor 1254 in a two-stage mouse skin carcinogenesis assay to see if it was a tumor initiator or promoter. The shaved skin of female mice was dosed with Aroclor 1254 at a level of 100 µg or 625 µg per mouse. This was applied alone as an initiator or from 5 minutes to 72 hours before initiation with 7,12-dimethylbenz[α]anthracene (DMBA). One week later, mice received twice weekly applications of 5 µg of the phorbol diester promoter 12-0-tetradecanoylphorbol-13-acetate (TPA) for 32 weeks. Animals were observed for both papillomas and carcinomas. Aroclor 1254 alone produced a few papillomas. The authors of these reports apparently faced a dilemma common to scientists, i.e., how much significance should be attached to the observation of a low incidence finding which may or may not have a causal relationship to treatment. On the basis of these few papillomas, Aroclor 1254 was called a "weak tumor initiator" (DiGiovanni, 1977). Later, it was described as possessing "little or no tumor-initiating properties" (Berry, et al., 1979). While Aroclor 1254 had a negligible effect on tumor induction when given 5 minutes before an initiating dose of DMBA, it markedly inhibited tumor induction when given 18 to 72 hours before DMBA. In other studies, an initiating dose of 200 nmole of DMBA was applied to the shaved backs of mice. After one week, 100 µg of Aroclor 1254 was applied twice weekly for 30 weeks. Aroclor 1254 failed to

promote tumors while 0.2 μg doses of TPA applied in a similar manner induced an average of 8 papillomas per mouse. The authors concluded that Aroclor 1254 possessed little or no tumor-initiating or tumor-promoting properties.

The transplantability and growth of Walker 256 carcinosarcoma in rats was inhibited by Aroclor 1254 (Kerkvliet and Kimeldorf, 1977a,b). Diets containing up to 800 ppm of Aroclor 1254 were fed to rats of both sexes for 30 days, after which they were given intramuscular injections of Walker tumor cells. Nine days later, during which time they continued to receive Aroclor 1254 in their diets, animals were killed and the tumors were dissected out and weighed. Mean tumor weights of all Aroclor 1254 fed groups were significantly reduced as compared to their sex-matched controls, and the reductions were dose-related to the dietary level of Aroclor 1254. Body weight gain was depressed in males receiving 400 ppm or more of Aroclor 1254. Females showed reduced body weight at 100 ppm, the lowest level fed to that sex. Intraperitoneal injections of 50 to 200 mg/kg every other day for 14 days after injection of a small inoculum of Walker 256 cells (10^3) inhibited both the development and growth of the Walker tumor. The number of tumor takes and the size of the tumors were reduced and the tumor latency period was increased. Body weight gain was reduced only at the 200 mg/kg dosage. Alternate day intraperitoneal injections of 100 mg/kg and 200 mg/kg of Aroclor 1254 after a large inoculum of Walker 256 cells (10^7) were continued for 60 days. Control animals receiving tumor cells only had 100% mortality by day 20 with a mean survival time of 13.5 days. Mean survival times were significantly increased to 17.7 days and 18.9 days for animals dosed with 100 mg/kg and 200 mg/kg of Aroclor 1254. A few animals survived to 60

days, and four receiving the higher dosage of Aroclor 1254 showed total regression of their bilateral tumors. Tumor growth rates in Aroclor-treated animals were significantly reduced. Again, body weight gain was depressed only at the 200 mg/kg dosage. An experiment was undertaken to determine if there was an optimum time period for the antitumor effect of Aroclor 1254. Intraperitoneal injections of 100 mg/kg of Aroclor 1254 were given on 5 consecutive days before tumor inoculation, on 5 days after inoculation, and daily from 5 days before until 10 days after inoculation. This study was ended 14 days after the initiating tumor inoculum was given. While all dosing schedules reduced tumor growth, there were variations in the responses. The greatest inhibition of tumor growth resulted from dosing animals for 15 days. Almost equally effective were pretreatment and treatment starting with inoculation of the Walker cells. The delayed treatment starting after 5 days was least effective as the tumor had become established. While early treatment reduced tumor growth, it was less effective in preventing metastases and death of the animals.

Kerkvliet and Koller (1980) offered groups of male mice diets containing 10, 100, or 500 ppm of Aroclor 1254 for 15 weeks prior to injecting them with MSB, an established tissue culture cell line derived from Moloney sarcoma virus. They measured tumor growth and cell-mediated toxicity over the next 19 days. A dietary level of 500 ppm of Aroclor 1254 resulted in marked weight loss and deaths. This was reduced to 250 ppm at 11 weeks, and a few weeks later surviving animals were placed on a control diet. They reported that Aroclor 1254 pretreatment enhanced the growth rate of the MSB tumor and inhibited or delayed the development of cellular immunity against the tumor.

Koller (1977) fed groups of mice diets containing 3.75, 37.5, or 375 ppm of Aroclor 1221, Aroclor 1242, or Aroclor 1254 for 6 months. About 2 weeks after being placed on test diets, some mice in each group were inoculated intraperitoneally with Moloney leukemia virus. None of the dietary levels of any Aroclor affected, i.e., did not promote or induce, the oncogenesis of Moloney leukemia virus.

Since PCBs are enzyme inducers, their biological effects resemble those of other enzyme inducers. Peraino, et al. (1978) noted that phenobarbital had a specific tumorigenic enhancing effect that was restricted to the liver. With the exception of the mouse skin painting studies and those in which tumor cells or a virus were injected, all of the studies in Table 3 were concerned with liver tumors. Peraino, et al. (1978) also pointed out resemblances between phenobarbital and PCBs. Both substances "enhanced hepatic tumorigenesis" when given after DEN, and both "exerted a protective effect against hepatic tumorigenesis" when administered concurrently with AAF or DEN. The comparison between PCBs and phenobarbital is extended by the observation of Berry, et al. (1978, 1979) that PCBs did not promote skin tumors in mice pretreated with DMBA. Peraino, et al. (1978) refer to a study[4] in which skin tumorigenesis was not enhanced in mice fed phenobarbital after skin painting with DMBA.

Lichti, et al. (1978) described the induction of ornithine decarboxylase (ODC) in mouse epidermal cell cultures by TPA. Aroclor 1254, apparently at much higher concentrations than TPA, induced a low but reproducible stimulation of ODC in the same system. They also noted a report[5] that a high intraperitoneal dose of Aroclor 1254 induced ODC in the liver of rats. After commenting that PCBs "warrant further investigation into their

possible action as tumor promoters," they added that "These compounds are being tested on carcinogen-initiated mouse skin (T.J. Slaga, personal communication)". The series of publications by Berry, et al. (1978, 1979) and DiGiovanni, et al. (1977) show that PCBs are not promoters on mouse skin.

Authors of some of the mutagenicity studies to be discussed (Danz and Urban, 1980; Norback, et al., 1981; and Stadnicki, et al., 1979) have suggested that PCBs may act as promoters of carcinogenicity. In general, those comments appear to have been offered as hypotheses to aid in understanding the observations which had been made. This also appears to be the case for the NCI study on Aroclor 1254 which was reviewed by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens. That group, charged with the responsibility of providing a peer review of NCI bioassay reports on chemicals studied for carcinogenicity, made and accepted a motion to add the following to the report summary: "Based on the liver proliferative lesions in the treated rats and published reports, it is suggested that Aroclor 1254 may be a tumor promoter" (NCI, 1978).

With respect to tumor promotion, Weisburger and Williams (1980) state that "certain inducers of liver metabolic enzyme systems, such as phenobarbital, DDT and BHT, when administered after minimal doses of primary hepatocarcinogens exerted a powerful promoting effect". As mentioned earlier, PCBs also induce liver metabolic enzyme systems. However, since the carcinogen alone produced tumors in animals in the co-carcinogenesis studies summarized in Table 3, it appears that the doses were greater than minimal. In addition, even though the co-carcinogenesis studies were of

shorter duration, several used much higher dietary levels of PCBs than those fed to rats for 2 years. The latter studies are the ones which gave rise to questions of carcinogenicity. Thus, while the evidence indicates that PCBs are not carcinogenic, their reported effects in rodent livers following prolonged exposure in conjunction with an initiator may be promotion or inhibition.

When administered to animals together with a biological agent, PCBs show a promoting or inhibitory effect similar to that seen with chemical agents. Pretreatment with PCBs inhibited the growth of Walker 256 carcinosarcomas in rats and increased their survival time (Kerkvliet and Kimmeldorf, 1977a,b), enhanced the growth of MSB tumor in mice (Kerkvliet and Koller, 1978) and neither promoted nor induced the oncogenesis of Moloney leukemia virus in mice (Koller, 1977).

Mutagenicity Studies

Mutagenicity testing of PCBs has ranged from bacterial systems to intact animal studies. A series of studies with eleven bacterial test strains (Heddle and Bruce, 1977; Hsia, et al. 1978; McMahon, et al. 1979; Odashima, 1976; Probst, et al., 1981; Sugimura, et al., 1976; and Wyndham, et al., 1976) are summarized in Table 4. Hsia, et al. (1978) used both phenobarbital and Aroclor 1254 to induce liver enzymes in rats for preparation of S-9 activation systems. They also tested 4-hydroxy-2,2',5,5'-tetrachlorobiphenyl and 2,2',5,5'-tetrachlorobiphenyl-3,4-oxide, a known and a presumed metabolite of 2,2',5,5'-tetrachlorobiphenyl, respectively. All three materials gave negative responses with each activation system. Odashima (1976) presented data in tabular form from a series of screening tests. In addition to the results shown in Table 9,

bacterial strains WP2, TA100, TA98, H-17, M-45, W3110, and TA1978 are shown in groups in their Table 5 with a text notation that not all chemicals were tested with each strain. For Kanechlor 300 and 500, such of the preceding strains as were tested showed a negative response. The group consisting of H-17 & M-45, WP_2 try^- (hcr^+ & hcr^-) shows a plus sign for Kanechlor 300. Presumably, one or more of those bacterial strains gave a positive response. Kanechlor 500 was listed as giving a negative response with the latter group.

With the exception of Wyndham, et al., (1976), all of the studies were negative with and without the addition of a microsomal enzyme activation system. It is somewhat difficult to reconcile the text and the graphs in the publication by the latter authors. They stated that their "results clearly showed that as the degree of chlorination decreased the mutagenicity increased, a concentration of 100 µg of 4-chlorobiphenyl in the test medium gave over 2000 revertant colonies per plate. The higher chlorinated biphenyls show very little activity as mutagens". While Figure 3 in their article shows their marked increase in revertants for 4-chlorobiphenyl, the same figure also shows results for Aroclor 1221, which averages 1.15 chlorine units per molecule. The mutagenicity of Aroclor 1221 is not discussed in the text, but Figure 3 shows that at a concentration of 100 µg per plate, it produced about one-tenth of the revertant colonies that 4-chlorobiphenyl did. Thus, a 15% increase in chlorine content produced a 10-fold decrease in the reported mutagenic activity. In light of that sharp reduction of mutagenic activity with a slight chlorine increase, it is difficult to understand the statement in their text that Aroclor 1254 "was only weakly mutagenic." Results from Aroclor 1254 (average of 4.96 chlorine per molecule) are not shown in their

Table 3, but 2,2',5,5'-tetrachlorobiphenyl (average of 4 chlorine per molecule) was presented. At 100 µg per plate, 2,2',5,5'-tetrachlorobiphenyl was virtually devoid of mutagenic activity. Overall, primarily because McMahon, et al. (1979) reported that 4-chlorobiphenyl was not mutagenic, it can only be concluded that the findings of Wyndham, et al. (1976) are aberrant. A similar conclusion that the findings reported by Wyndham, et al. (1976) are unfounded because attempts to repeat them have been unsuccessful was reached by the State of California (Anon. 1981).

In a variant of this test, Stott and Sinnhuber (1978) used Aroclor 1221, 1242, 1254, and 1260 to induce the mixed function oxidase system of the liver in trout. The submitochondrial fraction of those livers was used to activate the metabolism of AFB_1 which was assayed for mutagenicity using strain TA 1538 of S. typhimurium. The mutagenic response was decreased compared to the concurrent control using untreated trout liver. A general pattern of decreasing response with increasing degree of chlorination was observed, except for Aroclor 1260. Induction of mutagen detoxifying enzyme systems was suggested as a possible explanation for the apparent conflict between the reported induction of trout mixed function oxidases and the decrease in mutagenic activity. These results are consistent with those of Hendricks, et al. (1977) discussed earlier who reported that Aroclor 1254 reduced hepatic tumors in trout fed AFB_1.

On the basis of slower sedimentation rates in alkaline sucrose gradients, Stadnicki, et al. (1979) reported that 2,2',5,5'-tetrachlorobiphenyl (TCB), a mixture of the 3-hydroxy and 4-hydroxy derivatives of TCB and the 3,4-epoxide of TCB induced single strand breaks in DNA of L-929 cells.

At 100 µg/ml, each of the three materials caused all of the DNA to come out in fractions at the top of the gradient. The epoxide caused some breakage down to 1 µg/ml. The mixture of hydroxy derivatives caused significant breakage at 20 µg/ml and only slight breakage at 1 and 10 µg/ml. TCB, the least potent, caused lesser breakage at 20 µg/ml and was without effect at 1 and 10 µg/ml.

Nilsson and Ramel (1974) conducted genetic tests on adults and larvae of Drosophila melanogaster fed Clophen 30 and Clophen 50. These PCB mixtures were without effect on the loss of sex chromosomes used to measure chromosome breaking action and nondisjunction of the sex chromosomes. Tazima (1980) has described a specific locus test using the silkworm (Bombyx mori). Neither Kanechlor 300 nor Kanechlor 500 showed mutagenic activity in that system.

Hoopingarner, et al. (1972) induced mitosis in cultured human lymphocytes with phytohemagglutinin and treated them with 100 ppm of Aroclor 1254. There was no effect on the mitotic index, satellite association, chromatid gaps or chromatid breaks in comparison to control human lymphocytes.

Odashima (1976) also studied the incidence of chromosomal aberrations. Their in vitro test used Yoshida ascites sarcoma cells cultured for 6 to 72 hours in the presence of PCBs at concentrations producing a minimal or 50% growth inhibition. Kanechlor 300 gave a positive response and Kanechlor 500 a negative one. For an in vivo system, they examined bone marrow cells 6 to 48 hours after adult or newborn animals were given an approximately lethal dose of PCBs. This test gave the opposite result; Kanechlor 500 was positive and Kanechlor 300 was negative. They noted

that chromosomal aberrations frequently occurred in controls and that chemicals were called positive when they induced more than twice the aberrations in controls.

In a Syrian hamster cell transformation system (Pienta, 1980), Aroclor 1254 was one of several chemicals tested double-blind. It gave a negative result. Mouse embryo fibroblasts also have been exposed to different PCBs. Nesnow, et al. (1981) studied the cocarcinogenic action of agents which increase microsomal mixed-function oxidase activity in the C3H10T½CL8 transformation assay. After a 48-hour pretreatment with Aroclor 1254, cells were then treated with benzo(a)pyrene [B(a)P] and the agent for an additional 24 hours. Aroclor 1254 did not increase B(a)P-mediated transformation and no Type II or Type III foci were observed. Norback, et al. (1979, 1980, 1981) exposed C3H10T½ cells continuously for 6 weeks to 10 µg Aroclor 1254 per ml of medium. Treated cells developed Type III foci. Cells exposed to the same concentration of Aroclor 1254 for 24 hours or to 1 µg of Aroclor 1254 per ml of medium did not develop Type III foci. Continuous exposure of cells to Aroclor 1260 and 2,4,5,2',4',5'-hexachlorobiphenyl also caused formation of Type III foci. A clone from a focus transformed by Aroclor 1254 induced sarcoma formation when inoculated in irradiated mice. Foci from Aroclor 1260 and 2,4,5,2',4',5'-hexachlorobiphenyl had not been characterized further. Since transformation occurred only after continuous exposure, Norback, et al. (1981) suggested that the effects of PCBs in culture include promotion. When fed to rats, however, 2,4,5,2',4',5'-hexachlorobiphenyl produced neoplastic liver nodules, not hepatocarcinomas (Weltman and Norback, 1979).

Wong, et al. (1979) claimed that 4-chlorobiphenyl induced an increase in unscheduled DNA synthesis in Chinese hamster ovary cell cultures in the presence of hydroxyurea, a chemical agent which suppresses normal replicative DNA synthesis. Few details were presented regarding the validation and reliability of their test system. By contrast, Aroclor 1254 gave a negative response in an unscheduled DNA synthesis in primary cultures of adult rat hepatocytes (Probst, et al., 1981). The latter authors presented results of an extended series of compounds tested in their system.

Danz and Urban (1980) have proposed using the mitogenic response of the rat adrenal cortex after dosing the animals with a test substance as a short-term test for evaluating the promoting action of chemical compounds. Clophen A60, Delor 103[6], Delor 106[6], and Phenoclor DP6 all gave positive responses in their test system.

At 3-6 days of incubation, embryos from ring doves (Streptopelia risoria) fed a control diet or one containing 10 ppm of Aroclor 1254 were examined for cytogenetic changes (Peakall, et al., 1972). The relative frequencies of chromosome aberrations in the 8 largest chromosome pairs in metaphase cells of allantoic sac and limb bud origin were scored. The 6 control embryos had a mean aberration rate of 0.8% (0-2.0). The aberration rate in 17 embryos from Aroclor 1254 treated birds was 1.8% (0-9.4). In the latter group, there was one chromosome rearrangement, 13 embryos with aberration rates exceeding the mean control rate, and 4 embryos which exeeded the highest control rate. Aroclor 1242 was injected into fertile White Leghorn eggs to give estimated final concentrations of 10 or 20 ppm (Blazak and Marcun, 1975). After 4 or 5 days of incubation, eggs were

injected with colcemide, incubated an additional 45-60 minutes, and embryos were harvested for examination. There was a high degree of early embryonic death, and a few live embryos showed drastically retarded development without malformation. The first five pairs of chromosomes, constituting over 50% of the chromatin material per cell, were examined for detection of clastogenesis. There were no chromosomal aberrations.

Heddle and Bruce (1977) injected mice with Aroclor 1254 for five consecutive days and then examined bone marrow preparations for chromosomal breakage and sperm cell preparations for sperm with abnormally shaped heads. While nonspecific factors can induce sperm abnormalities, the authors believe the latter also can result from point mutations or small deletions. Aroclor 1254 was judged to be neither carcinogenic or mutagenic.

Dikshith, et al. (1975) gave male rats oral dosages of 50 mg/kg of Aroclor 1254 on each of 7 consecutive days. Animals were killed at intervals over the next 3 days. Those scheduled for cytogenetic analysis were injected with colchicine 2 hours before killing, after which time the seminiferous tubules were prepared for such study. At autopsy of the other animals, testis, epididymis, and liver weight were recorded and sections were prepared for microscopic study and histochemical determinations. Livers were markedly enlarged and showed a significant increase in weight compared to controls. There were no differences in body weight or weight and appearance of testis, epididymis, or vas deferens between control and treated rats. Aroclor 1254 treated rats showed a few metaphase figures with abnormal chromosomes whch appeared to be sporadic and not specific to any one type. Histological examination showed testis

and epididymis from Aroclor 1254 treated rats were comparable to controls although interstitial cells were increased in Aroclor 1254 dosed rats. These cells showed an increase in acid phosphatase activity. The authors concluded that they "found no evidence to suggest that Aroclor 1254 causes significant chromosome damage or histopathological changes in the rat testis."

Similar studies were conducted by Green, et al. (1973, 1975a) who gave male rats single oral dosages of 5000 mg/kg, 2500 mg/kg or 1250 mg/kg or four successive daily dosages of 500 mg/kg of Aroclor 1242. Other rats received five consecutive daily dosages of 300 mg/kg, 150 mg/kg or 75 mg/kg of Aroclor 1254. Animals were injected with colcemide 3 or 4 hours before sacrifice which occurred about 24 hours after the single dose or the series of doses. There were some body weight losses and some deaths occurred. Bone marrow from rats dosed with both PCB mixtures and spermatogonial preparations from Aroclor 1242 treated rats were prepared for cytogenetic study. Repeated dosages of 150 mg/kg and 300 mg/kg of Aroclor 1254 produced decreases in the number of mitoses in bone marrow cells. Repeated dosages of 75 mg/kg of Aroclor 1254 and all dosages of Aroclor 1242 were without effect. Neither PCB mixture at any dosage produced a significant number of chromosomal abnormalities in bone marrow cells. At the lower dosages, Aroclor 1242 did not affect mitoses of spermatogonial cells, but 5000 mg/kg or 4 dosages of 500 mg/kg significantly reduced the rate of cell division. No dosage of Aroclor 1242 produced cytogenetic abnormalities in spermatogonial cells. The authors concluded from their studies that Aroclor 1242 and Aroclor 1254 did not possess mutagenic potential. Garthoff, et al. (1977) fed male rats diets containing 5, 50, or 500 ppm of Aroclor 1254 for 5 weeks, after which they

examined bone marrow and testis samples. There was no significant difference between test and control animals with respect to the incidence of chromosomal abnormalities and the number of cells in mitosis from bone marrow and spermatogonial cells.

In a dominant lethal study (Keplinger, et al., 1972 and Calandra, 1976), albino mice were given single intraperitoneal dosages of 500 or 1000 mg/kg of Aroclor 1242, Aroclor 1254, or Aroclor 1260 and mated on successive weeks to virgin females. There was no evidence of mutagenic effects. Although details on their studies are limited, their results are in general agreement with those from another dominant lethal study in rats conducted by Green, et al. (1975b) with Aroclor 1242 and Aroclor 1254. The former was administered orally at a single dosage of 625, 1250, or 2500 mg/kg or in five daily dosages of 125 or 250 mg/kg. Aroclor 1254 was given orally in five daily dosages of 75, 150, or 300 mg/kg. After dosing, they were mated with untreated females for 10-11 weeks. Another group of rats was given 150 mg/kg of Aroclor 1254 for five successive days and starved overnight before admittance to females. Other male rats were offered diets containing 25 or 100 ppm of Aroclor 1254 for 70 days, then mated with untreated females for one week. TEM (triethylenemelamine) was used as a positive control. There was a body weight loss and some deaths occurred in a few groups. Neither the oral dosing nor the dietary feeding of Aroclor 1242 or Aroclor 1254 had any effect on the number of implantations or the number of dead implantations per pregnant female while TEM produced significant postimplantation losses in weeks 2, 3, and 4. These authors noted that the reduction in the number of dividing spermatogonial cells reported earlier for Aroclor 1242 (Green, et al., 1973, 1975a) did not impair the reproductive performance of male animals.

Review of the various mutagenicity tests and their results prompts three comments. Chlorinated hydrocarbons do not generally give positive results in Salmonella strains. Therefore, the mutagenic responses with TA1538 (Wyndham, et al. 1976) are either aberrant or else the response is, indeed, limited to essentially monochlorobiphenyl. The degree of correlation between in vitro mutagenicity tests and carcinogenicity depends upon the initial classification of the test materials. Pienta (1980) classifies Aroclor 1254 as a non-carcinogen. Rinkus and Legator (1980) regard Aroclor 1254 and Kanechlor 500 as having known or suspected carcinogenic activity. Odashima (1976) and Sugimura, et al. (1976, 1977) consider Kanechlor 500 to be carcinogenic and Kanechlor 300 to be non-carcinogenic. Apart from the difficulties they present for correlation, these different opinions about the carcinogenicity of PCBs are a reflection of what data these individuals considered and how they evaluated those data. Finally, in light of the large number of tests conducted to evaluate various mutagenic parameters, it is not surprising that an occasional suspicious or positive finding resulted, simply on a statistical basis. Those occurred in in vitro systems. In vivo tests gave negative results and provide a basis for concluding that ambient levels of PCBs do not present a mutagenic risk.

Epidemiology Studies

With respect to epidemiologic studies, it should be noted that there are frequent references in the literature to an epidemiologic study of workers exposed to Aroclor 1254 (Bahn, et al., 1976, 1977). Those articles are cited in two recent reviews. One states "The epidemiological data provide suggestive evidence of a relationship between exposure to polychlorinated biphenyls and the development of malignant melanoma. ...for practical

purposes, polychlorinated biphenyls should be regarded if they were carcinogenic to humans" (IARC, 1978). The other states "No conclusive evidence has thus far been reported which demonstrates that occupational exposure to PCBs has caused an increased incidence of cancer" (Kimbrough, 1980). The latter author then proceeds to discuss the study by Bahn, et al. (1976). Among the references for these 2 reviews are NIOSH (1978) which has the following comment on the Bahn study, "PCB exposure histories were based on recollections of two company employees. Exposures to other chemicals could not be ascertained.----To correct these deficiencies in the preliminary study, a more intensive investigation is being conducted (B.N. Kightlinger, written communication, November 1976). A substantial change has occurred in the cohort since release of the preliminary report by Bahn and her coworkers, and it seems likely that the findings on this new cohort will differ significantly from those of the preliminary study. The final report is not yet available."

Recently, Gaffey (1981) reviewed and evaluated existing reports concerning health effects and exposure to PCBs. The reports he discussed dealt with diverse potential health effects. With respect to liver effects, he concluded that "Alterations of liver function and fat metabolism associated with PCB exposure have been observed in several studies, but are characterized by investigators as mild and of no clinical significance."

He also concluded that "Mortality studies concerned primarily with cancer present problems of interpretation due to the small sample size of some of the studies, and to the confounding effect of other exposures. However, they do exhibit a pattern, which is that none of the studies agree on the cancer sites at which an excess mortality was found, and the excesses that

were found are in general not statistically significant. One must conclude that the findings of the mortality studies reflect a sporadic pattern of excess mortality at different sites which is not consistent with a carcinogenic effect of PCBs. In addition, where an examination of duration and latency of exposure was possible, no association with these variables was found [32][7].

"Taken as a whole, the epidemiologic studies find that high occupational exposures to PCBs may cause dermatitis of various kinds, but that there are no other clinically observable effects, including the occurrence of cancer."

Summary

Some remarks by Cole and Merletti (1980), although written in a more general vein, appear to be particularly suited for ending a discussion on the potential carcinogenicity of PCBs. "In view of the difficulty of deciding whether a "suspect" carcinogen is in fact a weak carcinogen or in fact harmless, we point out one aspect of this scientific judgement which, though well known, is often lost sight of; namely, that in principle, it is more likely that a non-carcinogen will appear to be a weak carcinogen than the reverse. This asymmetry should be fully appreciated by legislators and regulators. It is summed-up succinctly, if not very accurately, in the oft-heard phrase "you can prove a positive but not a negative". This is clearly illustrated in the case of PCBs.

Review of the results of a large number and wide range of chronic feeding and metabolism studies in animals and of mutagenicity studies in various systems has failed to establish that PCBs are carcinogenic. However,

presently available rodent data raise some suspicions and lead to disputes about the carcinogenicity of PCBs. Attempts to compare and evaluate results of rodent studies reported in the literature are complicated by different uses of similar terminology and variations in the criteria employed for diagnosing hepatic tumors in rodents. Co-carcinogenesis studies have reported both promotion and inhibition of tumors in rodent livers following prolonged administration of PCBs in conjunction with an initiator. Thus, it is not likely that animal studies and other laboratory procedures will lead to a universal consensus on the carcinogenicity or non-carcinogenicity of PCBs.

While epidemiology studies of humans exposed to PCBs present problems of interpretation due to their small sample size and the confounding effect of other exposures, they present the best available evidence for assessing the carcinogenic potential of PCBs to humans. Epidemiology studies, including recent studies involving large cohorts with lengthy exposures to PCBs, demonstrate a pattern that is not consistent with a carcinogenic effect of PCBs.

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TABLE 1

PCBs: Tabulation of Liver Nodules Reported in Mice[1]

Approx. wt. % Cl[2]	Product	Strain	Dosing Duration	PCB in diet (ppm)	No. Animals	Nodular Hyperplasia	Hepatoma	Hepato-cellular Carcinoma	Reference
52-54	Aroclor 1254	BALB/cJ	6 mos[3]	0	34	-	0	-	Kimbrough + Linder (1974)
				300	24	-	1	-	
			11 mos	0	24	-	0	-	
				300	22	-	9[4]	-	
	Kanechlor 500	dd	32 weeks	0	6	0	-	0	Nagasaki, et al. (1972) Ito, et al. (1973a,b)
				100	12	0	-	0	
				250	12	0	-	0	
				500	12	7	(-)[5]	5[5]	
	Kanechlor 500	dd	32 weeks	0	20	-	-	0	Nagasaki, et al. (1974, 1975)
				100	18	-	-	0	
				250	20	-	-	0	
				500	17	9	-	7[6]	
	Kanechlor 500	dd[7]	32 weeks	0	12	-	-	0	Nagasaki, et al. (1974, 1975)
				100	19	-	-	0	
				250	20	-	-	0	
				500	17	4	-	0[6]	
48	Kanechlor 400	dd	32 weeks	0	6	0	-	0	Nagasaki, et al. (1972) Ito, et al. (1973a,b)
				100	12	0	-	0	
				250	12	0	-	0	
				500	12	0	-	0	
	Kanechlor 400	dd	32 weeks	0	0	-	-	0	Nagasaki, et al. (1974, 1975)
				100	17	-	-	0	
				250	19	-	-	0	
				500	20	-	-	0	
	Kanechlor 400	dd[7]	32 weeks	0	12	-	-	0	Nagasaki, et al. (1974, 1975)
				100	20	-	-	0	
				250	20	-	-	0	
				500	17	-	-	0	

TABLE 1-continued

PCBs: Tabulation of Liver Nodules Reported in Mice[1]

Approx. wt. % Cl[2]	Product	Strain	Dosing Duration	PCB in diet (ppm)	No. Animals	Nodular Hyperplasia	Hepatoma	Hepato-cellular Carcinoma	Reference
40-42	Kanechlor 300	dd	32 weeks	0	6	0	-	0	Nagasaki, et al.
				100	12	0	-	0	(1972)
				250	12	0	-	0	Ito, et al. (1973a,b)
				500	12	0	-	0	
	Kanechlor 300	dd	32 weeks	0	20	-	-	0	Nagasaki, et al.
				100	19	-	-	0	(1974, 1975)
				250	19	-	-	0	
				500	20	-	-	0	
	Kanechlor 300	dd[7]	32 weeks	0	12	-	-	0	Nagasaki, et al.
				100	19	-	-	0	(1974, 1975)
				250	20	-	-	0	
				500	20	-	-	0	

[1] Males, except as noted.
[2] From Brinkman and deKok (1980).
[3] Held an additional 5 months before sacrifice.
[4] No. of animals. One had 2 hepatomas for a tumor total of 10.
[5] Apparently same data reported as hepatoma and hepatocellular carcinoma. See references and text.
[6] Apparently same data reported as nodular hyperplasia and hepacellular carcinoma or tumor. See references and text.
[7] Females.

TABLE 2

PCBs: Tabulation of Liver Nodules Reported in Rats

Approx. wt. % Cl[1]	Product	Strain	Sex	Dosing Duration	PCB in diet (ppm)	No. Animals	Adenomatous Nodules	Nodular Hyperplasia	Neoplastic Nodules	Adenoma	Hepatoma	Hepatocellular Carcinoma	Cholangiohepatoma	Reference
60	Aroclor 1260	Sherman	F	21 mos.[2]	0	171	-	-	0	-	-	1	-	Kimbrough, et al. (1975)
					100	184	-	-	144	-	-	26	-	
	Aroclor 1260	Charles River	M, F	24 mos.	0	27	-	1	-	-	0	-	0	Levinskas et (1981)
					1	26	-	0	-	-	0	-	0	
					10	25	-	7	-	-	1	-	0	
					100	25	-	6	-	-	7	-	4	
	2,2',4,4',5,5'-Hexachlorobiphenyl[3]	-	-	24 mos.	100	-	-	-	+[4]	-	-	-	-	Weltman & Norback (1979)
52-54	Aroclor 1254	Charles River	M, F	24 mos.	0	23	-	1	-	-	0	-	0	Levinskas (1981)
					1	30	-	0	-	-	0	-	0	
					10	26	-	3	-	-	0	-	0	
					100	26	-	14	-	-	4	-	2	
	Aroclor 1254	Fischer 344	M	105 weeks	0	24	-	-	-	0	-	0	-	NCI (1978)
					25	24	-	-	-	0	-	0	-	
					50	24	-	-	-	0	-	1	-	
					100	24	-	-	-	1	-	2	-	
	Aroclor 1254	Fischer 344	F	105 weeks	0	21	-	-	-	0	-	-	-	NCI (1978)
					25	24	-	-	-	0	-	-	-	
					50	22	-	-	-	1	-	-	-	
					100	24	-	-	-	2	-	-	-	
	Aroclor 1254	Local	F	28 mos.[5]	0	4	-	-	-	0	-	-	-	Wasserman, et al. (1978)
					200	6	-	-	-	+[4]	-	-	-	
	Kanechlor 500	Wistar	M	28-52 wks	0	18	-	0	-	-	-	-	-	Ito, et al (1974)
					100	25	-	1	-	-	-	-	-	
					500	16	-	5	-	-	-	-	-	
					1000	11	-	5	-	-	-	-	-	

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TABLE 2-continued

PCBs: Tabulation of Liver Nodules Reported in Rats

Approx. wt. % Cl[1]	Product	Strain	Sex	Dosing Duration	PCB in diet (ppm)	No. Animals	Adenomatous Nodules	Nodular Hyperplasia	Neoplastic Nodules	Adenoma	Hepatoma	Hepatocellular Carcinoma	Cholangiohepatoma	Reference
48	Kanechlor 400	Donryu	M	21-62 wks	38.5-616	5	0	-	-	-	-	-	-	Kimura & Baba (1971)
						10	0	-	-	-	-	-	-	
			F			5	0	-	-	-	-	-	-	
						10	6	-	-	-	-	-	-	
	Kanechlor	Wistar	M	28-52 wks	0	18	-	0	-	-	-	-	-	Ito, et al. (1974)
					100	16	-	2	-	-	-	-	-	
					500	8	-	0	-	-	-	-	-	
					1000	10	-	3	-	-	-	-	-	
40-42	Aroclor 1242	Charles River	M, F	24 mos.	0	21	-	1	-	-	0	-	0	Levinskas (1981)
					1	32	-	1	-	-	0	-	0	
					10	29	-	1	-	-	0	-	0	
					100	19	-	8	-	-	3	-	1	
	Kanechlor	Wistar	M	28-52 wks	0	18	-	0	-	-	-	-	-	Ito, et al. (1974)
					100	22	-	1	-	-	-	-	-	
					500	19	-	0	-	-	-	-	-	
					1000	15	-	0	-	-	-	-	-	
	2,2',5,5'-tetrachlorobiphenyl[3]	-	-	24 mos.	100	-	-	-	-	-	-	-	-	Weltman & Norback (1979)

[1] From Brinkman and deKok (1980).
[2] Held an additional 2 months before sacrifice.
[3] Abstract. Details limited.
[4] Presence reported.
[5] Ethanol solution in drinking water.

TABLE 3

SUMMARY OF CO-CARCINOGENESIS STUDIES WITH PCBs

Product	Mode	Time	Other Treatment[1]	Mode	Species	Observations	Ref.
Kanechlor 400	Diet	With	2O-MeCh	Uterine implant	dd mouse	Hepatocellular carcinoma with 2O-MeCh. None with combination.	Ichiyama, and Chiba, 1974
Kanechlor 500	Diet	With	α-BHC	Diet	dd mouse	Combination increased hepatocellular carcinoma over α-BHC alone.	Ito, et al. 1973a,b Nagasaki, et al. 1974, 1975
Kanechlor 500	Diet	With	β-BHC	Diet	dd mouse	Combination produced hepatocellular carcinoma. Each alone negative.	Ito, et al. 1973a,b Nagasaki, et al. 1974, 1975
Kanechlor 400	Diet	With	α-BHC	Diet	dd mouse	Combination increased hepatocellular carcinoma over α-BHC alone.	Nagasaki, et al. 1974, 1975
Kanechlor 500	Diet	With	DEN	Water	Sprague-Dawley rat	Hepatocellular carcinoma with DEN. None with combination.	Makiura, et al. 1974
Kanechlor 500	Gavage	After	DEN	Water	Wistar rat	Combination increased hepatocellular carcinoma over DEN alone.	Nishizumi, 1976, 1979a, b
Aroclor 1254	Diet	After	DEN	Water	Sprague-Dawley rat	Combination increased hepatocellular carcinoma over DEN alone.	Preston, et al. 1981
Kanechlor 500[2]	Gavage	Before	DEN[2]	Water	Wistar rat	Combination decreased hepatocellular carcinoma in offspring.	Nishizumi, 1980
Aroclor 1254	Diet	With	AFB_1	Diet	Rainbow trout	Hepatocellular carcinoma with AFB_1. None with combination.	Hendricks, et al. 1977
Kanechlor 500	Diet	With	2-FAA	Diet	Sprague-Dawley rat	Hepatocellular carcinoma with 2-FAA. None with combination.	Makiura, et al. 1974
Kanechlor 500	Diet	With	3'-Me-DAB	Diet	Sprague-Dawley rat	Hepatocellular carcinoma with 3'-Me-DAB. None with combination.	Makiura, et al. 1974 Kimura, et al. 1976
Kanechlor 500	Diet	Before	3'-Me-DAB	Diet	Sprague-Dawley rat	Hepatocellular carcinoma with 3'-Me-DAB. None with combination.	Kimura, et al. 1976
Kanechlor 500	Diet	After	3'-Me-DAB	Diet	Sprague-Dawley rat	Combination increased hepatocellular carcinoma over 3'-Me-DAB alone.	Kimura, et al. 1976

SCM 019702

TABLE 3-continued

SUMMARY OF CO-CARCINOGENESIS STUDIES WITH PCBs

Product	Mode	Time	Other Treatment[1]	Mode	Species	Observations	Ref.
Kanechlor 500	Diet	With	3'-Me-DAB + DEN	Diet	Sprague-Dawley rat	Combination decreased hepatocellular carcinoma over 3'-Me-DAB + DEN.	Makiura, et al. 1974
Kanechlor 500	Diet	With	2-FAA + DEN	Diet	Sprague-Dawley rat	Combination decreased hepatocellular carcinoma over 2-FAA + DEN.	Makiura, et al. 1974
Kanechlor 500	Gavage	After & With	DEN DDT	Water Gavage	Wistar rat	Combination increased hepatocellular carcinoma over DEN + DDT.	Nishizumi, 1979a,b
Kanechlor 500	Gavage	After & With	DEN SPB	Water Water	Wistar rat	Combination increased hepatocellular carcinoma over DEN + SPB.	Nishizumi, 1979a,b
Kanechlor 500	Gavage	After & With	DEN SPB, DDT	Water Water, Gavage	Wistar rat	Combination increased hepatocellular carcinoma over DEN, SPB, + DDT.	Nishizumi, 1979a,b
Unspecified Kanechlor	Diet	After & With	2-FAA Partial hepatectomy	Diet	Fischer rat	Marked increase in hyperplastic liver nodules.	Ito, et al. 1978
Aroclor 1254	Skin	After	7,12-DMBA	Skin	CDI mouse	Not a promoter of skin tumors.	Berry, et al. 1978, 1979
Aroclor 1254	Skin	Before	TPA	Skin	CDI mouse	Little or no skin tumor initiation.	Berry, et al. 1979 DiGiovanni, et al. 1977
Aroclor 1254	Skin	Before	7,12-DMBA + TPA	Skin	CDI mouse	No difference or decrease in skin tumor induction over 7,12-DMBA & TPA, depending on pretreatment interval.	Berry, et al. 1979 DiGiovanni, et al. 1977
Aroclor 1254	Diet	Before	Walker 256 tumor cells	Intra-muscular	Sprague-Dawley rat	Tumor growth inhibited. Survival time increased.	Kerkvliet and Kimmeldorf, 1977a, b
Aroclor 1254	Diet	Before	MSH cells[1]	Intra-muscular	C57BL/6 mouse	Enhanced growth of MSH tumor.	Kerkvliet and Keller, 1978
Aroclor 1254	Diet	Before	Moloney leukemia virus	Intra-peritoneal	balb/c mouse	Did not affect oncogenesis of Moloney leukemia virus.	Keller, 1977

SCM 019703

TABLE 3-continued

SUMMARY OF CO-CARCINOGENESIS STUDIES WITH PCBs

Product	Mode	Time	Other Treatment[1]	Mode	Species	Observations	Ref.
Aroclor 1242	Diet	Before	Moloney leukemia virus	Intra-peritoneal	Balb/c mouse	Did not affect oncogenesis of Moloney leukemia virus.	Keller, 1977
Aroclor 1221	Diet	Before	Moloney leukemia virus	Intra-peritoneal	Balb/c mouse	Did not affect oncogenesis of Moloney leukemia virus.	Keller, 1977

[1]Chemicals used:
20-MeCh = 20-methylcholanthrene
α-BHC = α-benzene hexachloride
β-BHC = β-benzene hexachloride
DEN = diethylnitrosamine
AFB_1 = aflatoxin B_1
2-FAA = N-2-fluorenylacetamide
3'-Me-DAB = 3'-methyl-4-dimethylaminoazobenzene
DDT = dichlorodiphenyltrichloroethane
SPB = sodium phenobarbital
7,12-DBA = 7,2-dimethylbenz[a]anthracene
TPA = 12-O-tetradecanoylphorbol-13-acetate

[2]Pregnant dams dosed with Kanechlor 400.
Offspring dosed with DEN.

[3]Established tissue culture cell line derived from Moloney sarcoma virus-induced tumors in N6 mice.

TABLE 4

PCBs: Tabulation of Microbial Mutagenicity Tests

Tester Strain	S. typhimurium C3076	D3052	G46	TA98	TA100	TA1000	TA1535	TA1536	TA1537	TA1538	E. coli WP2	WP2 uvrA⁻	Ref.
Product													
AROCLOR 1268	•	•	•	•	•	•	•	•	•	Neg.	•	•	Wyndham, et al. 1976
AROCLOR 1254	Neg.	Neg.	Neg.	Neg.	•	Neg.	Neg.	•	Neg.	Neg.	Neg.	Neg.	Probst, et al. 1981
AROCLOR 1254	• •		•	Neg.	Neg.	•	Neg.	•	Neg.	•	•	•	Heddle and Bruce 1977
AROCLOR 1254	• •		•	•	•	•	•	•	•	Pos[?]	•	•	Wyndham, et al. 1976
Kanechlor 500[2]	• •		•	•	•	•	Neg.	Neg.	Neg.	Neg.	•	•	Odashima, 1976
Kanechlor 500	• •		•	Neg.	Neg.	•	•	•	•	•	Neg.[o]	•	Sugimura, et al. 1976
2,2',5,5-tetra-chlorobiphenyl	• •		•	•	•	•	•	•	•	Neg.	•	•	Wyndham, et al. 1976
2,2'5,5'-tetra-chlorobiphenyl	• •		•	Neg[1]	Neg[1]	•	Neg[1]	•	Neg[1]	•	•	•	Ueno, et al. 1978
Kanechlor 300[2]	• •		•	•	•	•	Neg.	Neg.	Neg.	Neg.	•	•	Odashima, 1976
Kanechlor 300	• •		•	Neg.	Neg.	•	•	•	•	•	Neg.[o]	•	Sugimura, et al. 1976
AROCLOR 1221	• •		•	•	•	•	•	•	•	Pos[1]	•	•	Wyndham, et al. 1976
4-chlorobiphenyl	• •		•	•	•	•	•	•	•	Pos[1]	•	•	Wyndham, et al. 1976
4-chlorobiphenyl	Neg.	Neg.	Neg.	Neg.	Neg.	•	Neg.	•	Neg.	Neg.	Neg.	Neg.	McMahon, et al. 1979.

1. All tests done with and without microsomal activation except as noted.

2. Other strains tested, see text and reference.

• = Not tested.

Neg. = Negative.

Neg[o] = Only tested without activation.

Neg[1] = Only tested with activation.

Pos[1] = Positive only with activation.

Pos[?] = Uncertain. See text.

EXHIBIT #48

Decision Analysis. Phil-
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HUMAN HEALTH EFFECTS OF POLYCHLORINATED BIPHENYLS (PCBs) AND POLYBROMINATED BIPHENYLS (PBBs)[1]

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INTRODUCTION

Polychlorinated biphenyls (PCBs) are chemical compounds with the empirical formula $C_{12}H_{10-n}Cl_n$, with n = 1–10. They are a mixture of chlorinated biphenyl congeners. Theoretically, 209 such congeners are possible, but at least 20 congeners have never been identified in commercial products. In addition, PCBs may contain polychlorinated dibenzofurans and chlorinated quaterphenyls as impurities. PCBs were discovered before the turn of the century, and the useful industrial properties of mixtures obtained by chlorination of biphenyl were recognized early. In 1966 the discovery of PCBs in environmental samples (1) spurred renewed interest in the analysis and toxicity of these compounds.

In recent years many industrial nations have taken steps to control the flow of PCBs into the environment. PCBs and PCB-containing formulations are restricted (an exception is sometimes made for mono- and dichloro-PCB) for most uses, except for categories such as closed-system electrical equipment and hydraulic fluids in mining equipment.

Commercial production of PCBs began in the United States in the late 1920s. In 1971, Monsanto Chemical Company voluntarily stopped open-ended uses of PCBs, and subsequently only the lower chlorinated biphenyls

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were produced (Aroclor 1242 and 1016). In 1977 the company ceased production entirely (2). Many PCBs manufactured in the past (3) are still in use in old transformers, but even this use is decreasing. The estimated cumulative production and consumption of PCBs in the United States in the period 1930–1975 (in millions of pounds) was as follows: total production, 1400; imports, 3; domestic sales, 1253; exports, 150.

PCBs are inert chemicals that are fairly resistant to degradation. Because of their stability and lipophilicity, they have accumulated in the environment and in organisms. They have been identified in indoor air (4) at concentrations of 0.1 $\mu g/m^3$ (5), in fish (6, 7) and other food products, and in sediments from lakes and rivers (8, 9). PCBs have also been identified at varying concentrations in soil (0.01 mg/kg–100 mg/kg) (10). They do not occur naturally. Thus, their presence in the environment is linked with human activities, and concentrations are higher in urban and heavily industrialized areas than in rural and remote areas. However, trace amounts are also found in remote areas, since the air may transport such chemicals over large distances.

Although PCBs are no longer used commercially in the United States because of their persistence, they are still present in our environment. A number of transformers and capacitors that contain PCBs, however, are still in use. Results of laboratory experiments showed that pyrolysis of PCBs at temperatures of 200–600°C could result in the formation of significant amounts of the more toxic polychlorinated dibenzofurans (PCDFs) (11).

In February 1981, an electrical fire occurred in a New York State office building in Binghamton, N.Y. The fire, which originated in a switch gear in the basement, caused the bushings to crack on a nearby transformer. About 180 gallons of PCB dielectric fluid Pyralon (65% Aroclor 1254, 35% chlorinated benzenes and trace additives) were lost. A fine layer of oily soot covered many of the internal surfaces of the 18 floors of the building. Analysis of a soot sample showed that it contained various isomers of chlorinated dibenzofurans, 2,3,7,8-tetrachlorodibenzodioxin, other chlorinated dibenzodioxins, and chlorinated biphenylenes. Some of these chemicals are much more toxic than the PCBs. Because of these findings the Binghamton state office building was closed, and workers wearing respirators and protective clothing began an extensive cleanup of the building. The cleanup operations lasted four years, and the cost has been enormous (12). Since then several other transformer fires have occurred. These fires have not resulted in as much contamination as the one in Binghamton, partly because the transformers in the other fires were usually located in a separate vault (13).

The problems with polybrominated biphenyls (PBBs), which are also a mixture of chemicals, have been quite different. In 1970 a chemical company in Michigan manufactured polybrominated biphenyls as flame retardants. The same company also produced magnesium oxide, a chemical commonly mixed

into feed for livestock. The flame retardant was called Firemaster and the magnesium oxide, Nutrimaster. In 1973 some bags of Firemaster were accidentally sold as Nutrimaster and mixed into animal feed. This resulted in widespread contamination in the state of Michigan (14). Since 1974 PBBs have not been produced in the United States. At the time of the exposure little was known about the toxic effects of PBBs. Ten years after the Michigan residents were exposed, no clinical illness has been causally linked to PBB exposure in this group, although chloracne was apparently noted in some workers who manufactured PBB.

HUMAN EXPOSURE

Because PCBs are ubiquitous and very persistent in the environment, humans have been and will continue to be exposed to them, particularly in industrialized countries. PCBs may be inhaled in small amounts through the air or ingested through food. In the United States today, people are primarily exposed to PCBs by consuming fish from contaminated waters (9). In the past, some farm families were exposed to PCBs from dairy products; these PCBs originated from coating material used in the inside of silos (15). In addition, workers who repair transformers and workers who handle toxic wastes may also be exposed (16).

The PCB products that were manufactured by Monsanto in the United States had the trade name "Aroclor." The particular kind of Aroclor is identified by a four-digit number. The first two digits refer to the 12 carbon atoms, and the second two refer to the percent, by weight, of chlorine in the mixture. Thus, Aroclor 1254 contains about 54% chlorine, and Aroclor 1260, about 60% chlorine.

The composition of this mixture of chemicals, with different properties, changes once it gets into the environment and into organisms. Some components of the mixture are more easily degraded in the environment than others. As a result the PCBs identified in the environment resemble Aroclor 1254 but are not identical to it. Similarly, the PCB mixtures found in humans usually resemble Aroclor 1254 if exposure occurred primarily through the environment. A different composition of the PCBs may be found in serum or adipose tissue samples from occupationally exposed workers. For instance, if the workers are primarily exposed to Aroclor 1016 or Aroclor 1242, which contain much less of the more highly chlorinated homologs, then their gas-chromatographic patterns resemble a combination of Aroclor 1016 or 1242 and Aroclor 1254. For this reason Smith et al (17), in evaluating occupational exposure, divided PCBs into high and low chlorinated biphenyls. The gas-chromatographic pattern of the PCB mixture present in humans can be used to determine whether the exposure occurred primarily

through occupation or through the environment, or, in the case of occupational situations, whether most of the exposure was recent or occurred many years ago.

Although 93% of the US population eats fish, the average annual per capita consumption is small: 15 lbs. per year (6, 7). If PCBs are to be quantitated in fish, the edible portion rather than the whole fish must be examined. Because of their lipophilicity, PCBs are preferentially stored in the hepatopancreas of the fish, giving erroneously high levels if the whole fish is analyzed. Similarly, levels in cooked fish are lower (6).

Generally, PBBs are not found in the environment because they have had less commercial use than PCBs. PBB contamination is essentially restricted to Michigan's lower peninsula. Most persons who lived in Michigan during the 1973–1974 period have low-level PBB body burdens (18). The greatest degree of contamination occurred mainly in areas with contaminated farms; this segment of the population still has appreciable body burdens (19).

Since PBBs and PCBs are lipophilic, they are preferentially stored in adipose tissue. They are also present, to a smaller extent, in serum and other organs and in human milk. The concentration of these materials in different organs depends upon the lipid content of such organs, with the exception of the brain where the concentration is lower than the lipid content would indicate. PCBs and PBBs pass the placenta and are primarily excreted through bile and milk. In addition to lipid content, the ratios between adipose tissue, blood, and vital organs are influenced by exposure level, sex, age, length of exposure, and also by whether exposure is current. At very low concentrations an analytical imprecision influences the ratios much more than at higher concentrations (19). Since human milk is relatively easy to obtain, it has been used to monitor human exposure. Jensen (20) recently summarized results of such monitoring studies. Average levels of PCBs below 2 ppm (mg/kg) in milk fat have normally been found, although women living in heavily industrialized urban areas may have higher levels. The fat concentration in human milk averages 2.6–4.5% (21). At 2% fat, 1 liter (l) of milk would contain 0.04 mg or 40 μg if the PCBs were present in milk fat at a concentration of 1 ppm. If an infant weighed 5 kg and imbibed 750 ml of milk per day, it would take in about 6 μg/kg, a dose that exceeds the 1.5 μg/kg dose calculated as acceptable by Cordle et al (6). At 1% milk fat this dose would be reduced to 3 μg/kg. As the infant gains weight, the dose on a kilogram body weight basis will be reduced to some extent, however; milk is the sole food source for only about six months. After the first week, the daily milk intake is estimated to be 150 ml/kg body weight per day. This consumption gradually falls after two months and declines to 120 ml/kg body weight at four-to-six months. Finally, the amount of PCBs and other halogenated organic chemicals declines with time. However, at low concentrations this

may not be obvious because of continued exposure of the mother and the variability of the analytical results. In addition to PCBs, human milk contains trace amounts of many other persistent chemicals. Whether the infant's consumption of such chemicals has any adverse health effects is not known.

Most persons, particularly in industrialized countries, have had some exposure to polychlorinated biphenyls even if they do not eat fish. The concentrations at which such exposure presents a risk are not clear. Recently, Cordle et al (6, 7) calculated the dose of PCBs to people consuming fish from Lake Michigan. They concluded that persons eating Lake Michigan fish ingested an average of 46.5 mg of PCBs per year; this amount ranged from 14.17 to 114.31 mg/year/person. The calculated mean daily dose received by the exposed group was 1.7 μg/kg/day and ranged from 0.09 to 3.94 μg/kg/day. Thus, the average sports fisherman consuming contaminated fish would receive a total PCB dose equal to 200 mg in about 4.3 years. No adverse health effects or groups of symptoms clearly related to PCB exposure could be identified in this exposed group. The presence of PCBs in the exposed persons has not caused any observable adverse health effects similar to those observed in the Yusho population (see below). However, this finding does not exclude the possibility that the effects are too subtle for detection or that they require long-term observation.

Similarly, in Michigan an analysis of 1,075 human milk samples showed that all contained PCB residues and that the residues ranged from trace amounts to 5 ppm (mg/kg) based on fat level. The public health significance of PCB residues in human breast milk and their effects on breast-fed infants are unclear. Since there are no human data on which to base public health policy, risk predictions for PCBs have been based on results from animal studies, particularly the positive bioassay studies. Reviewing these data, Cordle et al (6, 7) concluded that a 2-ppm (mg/kg) tolerance for PCB in fish be established, since a 1-ppm (mg/kg) tolerance does not greatly reduce the estimated risk.

As previously mentioned, some of the isomers of the PCBs and PBBs are much more easily degraded or metabolized. Because they can be metabolized, they are more easily excreted. Others may be retained in the body for long periods; in general, the PBBs appear to be more persistent in human tissues than the PCBs (19, 22).

POLYCHLORINATED BIPHENYLS

Background

When PCBs were first used industrially some workers developed chloracne. Results of early animal studies seemed to suggest that PCBs might have some toxic effects on the liver. Beyond that observation no information was avail-

able. Because PCBs were so inert chemically, they were not considered to cause a great deal of toxicity. In 1968 a poisoning outbreak occurred in Japan (23) that affected over 1,000 persons. These individuals had purchased rice oil, in large drums, from a single source and had used this rice oil for cooking. Chloracne was one of the leading signs in those who became ill. It was soon discovered that PCBs had been used as a heat-exchange fluid in the factory where the rice oil originated. PCBs had leaked out of the columns in which they were contained into the rice oil when the rice oil was heated. Since the disease was caused by ingesting contaminated rice oil, it was called Yusho (rice-oil disease). When the outbreak first occurred, its association with exposure to PCBs was not clear. At that time the capabilities for measuring these types of chemicals in tissues and body fluids were limited, particularly in Japan. Therefore, early in the investigation total chlorine, rather than PCBs, was measured. Retrospectively determining the precise dose these patients received is difficult. Whether the consumed oil was uniformly contaminated is also not clear. However, a relationship between the amount of rice oil ingested and some symptoms could be established (24). Because of this poisoning outbreak and other environmental problems, animal studies were started in Japan, in the United States, and in other countries to elucidate the toxic effects of PCBs. These data are summarized in several detailed reviews (16, 25, 26).

Animal Studies

This article addresses primarily the human health effects of PCBs and PBBs. Therefore we highlight only recent results from animal studies that might give a better understanding of implemented public health policies and potential human health effects. One of the difficulties in using animal data to predict human health effects for PCBs and related compounds is that animal species vary greatly in their responses. Further, many of the animal studies use relatively high doses. Therefore, determining how such animal studies relate to the human situation is difficult. Some animal species, such as the subhuman primates, the guinea pig, and the mink, are much more sensitive to the toxic effects of PCBs than the rat or the mouse; also the types of toxic effects and morphological changes in the organs of different species vary.

Most animal studies conducted during the 1970s used mixtures of PCBs. In general, PCBs were found to affect reproduction and the immune response, and to cause liver tumors in rodents (16). When different mixtures of PCBs were studied, however, the results were inconsistent. For instance, the mixture Aroclor 1254 affects reproduction in rats at much lower doses than does Aroclor 1260 (27).

More recently some of the isomers of the PCB mixture were found to be much more toxic than others (28–32). The more toxic isomers constitute only

a very small portion of the mixture, particularly those with less chlorine by weight, such as Aroclor 1242 or Aroclor 1016. Recently, Schaeffer et al (33) found that a German PCB mixture—Clophen A-30, with an average composition of 1% monochlorobiphenyl, 20.7% dichlorobiphenyl, 57.4% trichlorobiphenyl, 17.3% tetrachlorobiphenyl, 1.8% pentachlorobiphenyl, 1.0% hexachlorobiphenyl, 0.6% heptachlorobiphenyl, and 0.1% octachlorobiphenyl—produced a 3% incidence of hepatocellular carcinoma, whereas Clophen A-60 produced a 61% incidence of hepatocellular carcinoma in Wistar rats. The incidence of the disease in the controls was 2%. The Clophen A-60 had an average composition of 0.2% monochlorobiphenyl, 1.1% dichlorobiphenyl, 2.2% trichlorobiphenyl, 3.1% tetrachlorobiphenyl, 19.8% pentachlorobiphenyl, 43.2% hexachlorobiphenyl, 25.3% heptachlorobiphenyl, 4.7% octachlorobiphenyl, and 0.3% nonachlorobiphenyl. Similarly, Norback & Weltman (34) and Kimbrough et al (35) were able to produce hepatocellular carcinomas in rats with Aroclor 1260, the more highly chlorinated Monsanto product.

When Aroclor 1254 was fed to rats, fewer liver tumors developed in exposed rats (36); however, the incidence of gastric intestinal metaplasia and adenocarcinoma of the stomach increased (37, 38). Whether PCB fractions without hexachlorobiphenyls, heptachlorobiphenyls, and octachlorobiphenyls produce hepatocellular carcinomas in rodents should be explored.

Particularly in the United States, mixtures such as Aroclor 1242, 1254, and 1016 were used more than Aroclor 1260. Because of these differences in potency, the PCBs in heavily contaminated areas of our environment should be characterized according to their isomeric composition. For instance, whether the PCBs in Lake Michigan are of the same composition as those found in New Bedford Harbor, Massachusetts, is not clear.

Aside from tumor formation, PCBs cause a variety of other biological effects, such as the induction of enzymes (39). In some species they may cause atrophy of the thymus, intrahepatic bile duct hyperplasia, hyperplasia of the epithelial lining of the urinary bladder, atrophy of the sebaceous glands, and hyperkeratosis of the ducts (40). Some isomers are fetotoxic, and some produce metaplasia of the sebaceous glands, nailbeds, ameloblasts, thymus corpuscles, and gastric mucosa (28, 41). Subhuman primates, mink, and guinea pigs are particularly sensitive to the toxic effects of PCBs; other species, such as the rat, the mouse, and the dog, can tolerate much higher doses. From empirical observations, humans also appear to be less sensitive to the toxic effects of PCBs. The ability to store these chemicals in adipose tissue may be protective. Generally, the subhuman primates and mink have less adipose tissue than humans. Animals with greater ability to store vitamin A on a quantitative basis, such as the hamster and the rat, are somewhat less susceptible to the toxic effects of these types of compounds (42). The

mechanism by which these types of chemicals affect hepatic retinoids is not clear. Apparently, the duration of the reduction of hepatic retinoids does not correlate with the induced aryl hydrocarbon hydroxylase (AHH) activity (43).

Body Burdens

Many investigators have reported PCBs in human tissues (44, 45). In the United States, according to data from the Centers for Disease Control (CDC), mean PCB serum levels are about 5–7 ng/ml (pbb), although some patients may have higher serum levels without any documented unusual exposure. These data were also summarized by Kreiss (46). Levels in adipose tissue and in human milk fat are 100–200 times as high, since PCBs are highly lipid soluble (20). Mes et al (47) reported that PCB levels in adipose tissue of accident victims ranged from 0.9–9.4 mg/kg.

Sahl et al (48) surveyed PCB blood levels in 738 pre-employed and 1,058 currently employed workers of a utility company. The median blood level before employment was 4 mg/l and the range, 1–37 mg/l. These levels were quite similar to those in the currently employed group.

Patients who died of cancer in Denmark had somewhat higher levels of PCBs in their adipose tissue (49). Since terminal cancer patients have usually lost a great deal of weight, bioconcentration may have occurred. Similarly, in patients with highly impaired liver function, tissue concentrations of xenobiotics may be slightly higher than those in healthy persons. However, levels remained higher if parameters such as weight, height, occupation, and residence were considered (50), whereas levels of PCBs in breast fat tissue from patients with breast cancer were similar to those of controls (51).

Furthermore, Lawton et al (52) demonstrated that random errors and interlaboratory variations in procedure and methods of data reporting can influence serum and adipose PCB levels. Unless an interlaboratory quality-control system is set up, measured levels between laboratories are not necessarily comparable. For instance, Lawton et al (52) found that the results of repeated analyses on serum samples of known composition showed the 95% prediction interval for an individual measurement to be about ± 42%. This interval depends on the method of extraction, the procedure used, and the means of quantitation.

Summary of Human Epidemiology Studies

Recently, investigators studied the predominantly black population of Triana, a small rural town in the southern United States (53). This population was excessively exposed to DDT residues by consuming contaminated fish. The residents also had PCB body burdens. Fish consumption correlated positively with PCB blood levels; no other source of PCB exposure could be established. These researchers noted that PCB serum levels increased with age and that

levels were lower in females of each age group. Similar findings were made for DDT residues. The serum cholesterol level was positively associated with the log PCB level, independent of age, sex, fish consumption, body-mass index, and alcohol consumption. Rates of borderline and definite hypertension for study participants were 30% higher than those expected on the basis of national rates (54). Log PCB serum values contributed significantly to explaining the variability of log systolic and diastolic blood pressure in multiple regression analysis (55). Median total cholesterol levels of individuals in the United States increase with age from about 150 to 160 mg/dl at age 20 to over 200 mg/dl at age 50. PCBs in blood are influenced by serum lipid content, and populations with inherently lower total serum cholesterol levels appear to have a different PCB serum to adipose tissue ratio. The age-associated increase in blood PCB levels could be related to the long half-life of some PCB isomers that are preferentially retained in mammals (29); as long as exposure continues, a true steady state between intake and excretion is never reached. Other variables affecting body burdens may be differences in metabolism with age. In the Triana studies, the blood levels of total DDT residues also increased with age, and others have made similar observations (56, 57). Lawton et al (58) studied workers who had been exposed to electrical-grade Aroclor 1016, 1242, and/or 1254; the study covered the period from before the workers were exposed to two years after PCB exposure ceased. Serum levels for the lower chlorinated PCBs in 1977 ranged from 57–2270 ppb and in 1979, from 12–392 ppb; for the higher chlorinated PCBs serum levels ranged from 6–142 ppb in 1977 and from 4–108 ppb in 1979. These findings again illustrate the preferential excretion of lower chlorinated PCB. Lawton et al (58) also found that cholesterol levels correlated with log serum PCBs. Similar associations with log serum PCBs were found for log gamma glutamyl transpeptidase (GGTP) and, in some cases, for log alanine aminotransferase. When the PCB concentrations were expressed as levels in serum lipids, all the associations between serum lipids or enzymes and log serum PCBs disappeared except for those between log GGTP and log PCBs. Similarly, Chase et al (59) found no significant correlation between either serum triglycerides or aminotransferases and the PCB levels in adipose tissue. How age and length of exposure affect these parameters is not adequately explained in the article. Finally, Akagi & Okumura (60) were not able to confirm a positive association between PCB blood levels and elevated blood pressure in Yusho patients.

Thus, as Brown (61) has suggested, the positive association between PCB serum levels and elevated triglycerides and serum cholesterol can be explained by the increased solubility of PCB in serum with higher lipid content.

In several cross-sectional studies of exposed workers, only minor abnormalities not necessarily related to PCB exposure have been detected

(62–66). In cross-sectional studies, however, the ability to evaluate chronic health effects is limited. In several studies, a positive association between results of one liver function test—the test for γ-glutamyltranspeptidase—and PCB blood levels has been found. Kimbrough (67) has summarized earlier studies on the health effects of PCBs observed in workers.

In 1930 and 1940, chloracne, a disfiguring skin disease, was reported among workers exposed to PCBs. One of the clinical features of chloracne is the chloracne cyst, which is skin colored and measures from 1–10 mm in diameter, with a central opening. The other dominant lesion is the comedo. The skin lesions may only involve the face, but many also extend to other parts of the body. Microscopic examination of human skin biopsies from chloracne cases shows markedly dilated hair follicles filled with keratin. The sebaceous glands involute partially or completely. The epithelial cells lining the hair follicles and the adjacent surface epithelium proliferate, and acanthosis is present. In old lesions, the epithelial lining of the greatly dilated hair follicles becomes atrophic.

Jones & Alden (68) examined 17 of 23 workers engaged in the production of PCBs. The workers had chloracne involving the face, genitalia, trunk, and extremities. Before the outbreak of chloracne in the plant, the electrical property of the PCBs had fallen below specifications, and the color had deepened. In the report, symptoms of illness were extensively described for the first worker who was diagnosed as having chloracne. This worker complained of lassitude, loss of appetite, and loss of libido. Over the years, other cases of chloracne following exposure to PCBs have been reported. Most of these involved exposure to vapors that developed when PCBs were heated (69).

At times, the skin rashes that developed in workers were accompanied by pruritus. Some workers also complained of burning of the eyes, nose, and throat; dry throat; nausea; and dizziness. Meigs et al (70) reported chloracne in workers who had been exposed to PCB vapors for 5–14 months. The concentration of PCBs in the workers' breathing zone was 0.1 mg/m^3. Evidence of slight liver injury was also present. Ouw et al (71) found air levels in a capacitor plant that ranged from 0.32–1.44 mg/m^3 Aroclor 1242 (PCB). Here workers complained of burning eyes, face, and skin in general, and persistent body odor. One worker suffered from chloracne, five complained of eczematous rashes, and a few had abnormal liver function tests. These workers had a mean PCB blood level of about 400 ppb (μg/kg). In most studies of workers with chloracne, evidence of liver injury was also found; in one study, workers who did not have chloracne were found to have abnormal liver function (69).

PCBs also affect the liver by inducing mixed-function oxidases. Alvares et al (72) determined that in five workers occupationally exposed to Aroclor 1016—a PCB mixture primarily composed of dichlorobiphenyls, trichlorobiphenyls, tetrachlorobiphenyls, and pentachlorobiphenyls—plasma antipyrine half-life was significantly lower than that in matched controls, suggesting the induction of mixed-function oxidases in the liver. These workers had been exposed to Aroclor 1016 for at least two years and had no obvious symptoms of PCB poisoning.

Other health effects are eye and upper respiratory irritation. Warshaw et al (65) studied a group of 326 workers in a capacitor plant with a mean employment of more than 15 years and mean employee ages of 41.1 years for males and 47.3 years for females. Work-related eye or upper respiratory irritation was reported by 48% of the workers, and 10% had experienced tightness in the chest. Spirometric studies were conducted on 309 workers; 66 of them were dropped from the study because they had been exposed to talc, textile dust, or asbestos. Thus, 243 men were available for analysis. In males, there were about twice as many smokers and exsmokers as nonsmokers. In females, the proportion of nonsmokers was higher. Thirty-four of the workers (14%) had a reduced vital capacity, and 27 of these demonstrated a restrictive pattern of impairment. Because of additional variables such as smoking and asbestos exposure, these findings are difficult to interpret.

Taylor et al (73), in an attempt to determine whether the fetus would be affected in capacitor workers, examined pregnancy outcome and birth weight, and found that the gestation period was reduced by one week. The infants weighed slightly less than the controls; this finding could be explained by the reduced gestation period. Smoking and alcohol consumption were not controlled, however; furthermore, whether the socioeconomic status of this group of women was similar to that of the control group is not clear. Thus, until other studies confirm these findings, they should be viewed with caution.

In several papers Jacobson and his associates reported behavioral changes and a reduced gestation period in association with higher fish intake or higher intake of PCBs (9, 74–76). Furthermore, Jacobson et al (74) reported that intrauterine PCB exposure may have a delayed effect on central nervous system functioning. Since genetic makeup, the mother's lifestyle, and acute illness also affect these parameters, these findings are difficult to interpret. Furthermore, many other chemicals are also excreted in human milk (20). Rogan & Gladen (77), for instance, found that mothers with high levels of DDE [1,1'-(2,2-dichloroethenylidene)-bis-4-chlorobenzene] in their milk tended to wean their infants earlier, as they did not thrive. Apparently, PCB levels in milk were higher in older women, women who drank alcohol regularly, and primiparas (78).

Whether high levels of DDE affect lactation is not clear. In animals, DDT

homologs, but not specifically DDE, have been shown to have estrogenic effects (79). Before these findings can be clarified, additional studies must be done.

No conclusive evidence thus far reported shows that occupational exposure to PCBs causes an increased incidence of cancer. Bahn et al (80) reported results of a preliminary study of a group of 51 research and development employees and 41 refinery plant employees at a New Jersey petrochemical facility. Between 1949 and 1957 these workers had been exposed to Aroclor 1254. Three melanomas and two carcinomas of the pancreas were found. This incidence was significantly higher than expected. Exposure to other chemicals also occurred, however, and the cohort was small.

Brown & Jones (81) conducted a retrospective mortality study of 2,567 workers in two capacitor plants. The relatively few deaths (163) severely limited the statistical power of the study, and the average follow-up was only 15 years, whereas latency periods of 20–30 years are not uncommon for cancer. Over 50% of the sample had exposure to PCBs for two years or less. Deaths from liver cancer, cirrhosis of the liver, and rectal cancer were slightly higher than expected, but not significantly for both sites combined. The observed increase for cancer of the rectum was statistically significant among females at one of the plants. In a follow up study (82) no additional cancers of the rectum were noted, and the standardized mortality ratio (SMR) dropped from 336 to 211. However, two additional cancers of the liver and biliary tract were observed, bringing the total of these tumors to five as reported on the death certificates. However, a review of the medical records raises questions about at least one of these tumors.

Bertazzi et al (83) reviewed the mortality of 290 males and 1,020 females who had worked for six months or more in capacitor production. Males had a statistically significant increased number of deaths from all neoplasms. When deaths were analyzed by organ system, deaths from neoplasms of the digestive system, the peritoneum, and the lymphatic and hematopoietic tissues were higher. Among females, all causes of deaths were significantly elevated. The actual numbers in this study, however, were small.

Yusho and Yucheng

Two outbreaks of poisoning have been reported that followed the ingestion of rice oil contaminated with polychlorinated dibenzofurans, biphenyls, and quaterphenyls (PCQs). The first outbreak occurred in Japan in the summer of 1968 and the second outbreak, in Taiwan in 1979. Ironically, the outbreak in Taiwan repeated what had occurred 10 years earlier in Japan. Many studies of these two outbreaks have been published in Japanese or Chinese. In 1984 some of the information in these reports was published in English in the

American Journal of Industrial Medicine 5:1–153; the information is also summarized in volumes 59 and 60 of *Environmental Health Perspectives*.

In Japan and Taiwan the disease was first recognized because chloracne developed in the affected patients (84). In Japan, members of all of the affected households had purchased rice oil from a specific company, and the toxic rice oil produced or shipped on February 5 and 6 of 1968 contained large amounts of Kanechlor 400, a brand of PCB with a chlorine content of 48%. At the time of the outbreak, no analytical methods specific for PCBs were available in Japan; the concentration of Kanechlor 400 in the oil was therefore estimated from the organic chlorine content to be 2,000–3,000 ppm. Kanechlor 400 had been used for heating the rice oil in a metal container at over 200°C, at a reduced pressure of 3–44 mm Hg, to remove odorous material from it. Kanechlor (K) must have leaked from the heating pipe into the processed oil, but the actual mechanism of the contamination has apparently not been determined. The reanalysis of the K-rice oil, once the methods were developed, showed that some of the oil samples contained 1,000 ppm (mg/kg) PCB. This concentration was much lower than had originally been estimated. Therefore, other chlorine-containing compounds were assumed to be in the oil, and additional samples were analyzed. The oil was found to contain an average of 5-ppm polychlorinated dibenzofurans (85). According to Buser et al (86), the Yusho oil contained more than 40 polychlorinated dibenzofuran isomers, including the highly toxic 2,3,7,8-tetrachlorodibenzofuran (TCDF) and 2,3,4,7,8-pentachlorodibenzofuran (PCDF). In addition, the oil contained PCQs at a concentration of 866 ppm (87, 88).

According to estimates made by Kuratsune (89), the total amount of PCB, PCDF, and PCQs consumed by the patients was, on the average, 633 mg of PCB, 3.4 mg of PCDF, and 596 mg of PCQ. This calculates to roughly 157 μg/kg body weight/d. PCB, 0.9 μg/kg body weight/d. PCDF, and 148 μg/kg body weight/d. PCQ. At this dose the length of the latent period between exposure and onset of clinical illness was roughly 71 days, with a range from 20 to 190 days. Some of the oil the patients consumed may have contained higher or lower levels because in such situations contamination is usually not uniform. Furthermore, the patients consumed different amounts of contaminated rice oil. The severity of symptoms was positively associated with the amount of contaminated rice oil consumed (24).

Early in the outbreak the patients had chloracne, dark-brown pigmentation of the nails, itching, pigmentation of the skin, swelling of the limbs, pigmented mucous membranes, eye discharge, hyperemic conjunctivae, jaundice, swelling of the upper eyelids, a feeling of weakness, numbness of the limbs, and fever. Over 1,000 people were affected. Thirty-six babies showed fetal PCB syndrome, which consists primarily of a dark-brown pigmentation

of the skin (Cola babies). The cutaneous pigmentation was caused by an increase in melanin pigment in the epidermis (90). The mucous membranes were also pigmented. In all cases, the pigmentation disappeared by the time the babies were between two and five months old. In affected infants, the face was edematous, and spotty calcifications were noticed in the parietal and occipital areas of the skull. In a few of the infants, the teeth had erupted at birth. Subsequently, the adult patients with clinical disease complained of having to expectorate a great deal and, on auscultation, wheezing was noted; however, on examination, there was no evidence of bronchial asthma or pulmonary emphysema. In many of these patients, the respiratory symptoms have persisted, and the patients have chronically infected airways. In the early 1970s, some changes were noted in the patients' serum immunoglobulin levels, but the levels returned to normal. Over time the severity and the extent of the skin lesions improved considerably in the exposed population. Fifteen years after the accident, only a very few patients had extensive chloracne (91).

About five years after the outbreak of Yusho, tissue and body fluids of Yusho patients were analyzed for various congeners of PCB and PCDF. At this time, the PCB levels in adipose tissue were 1.9 ± 1.4 ppm (mg/kg). In the liver they were 0.08 ± 0.06 ppm and in blood, 6.7 ± 5.3 ppb (μg/kg); thus, they were not very different from levels in the general population in Japan. On the other hand, the isomeric distribution for the PCBs in the Yusho patients varied from that in the control population in the same area (92). About 40 PCDF congeners were identified in the rice oil that the Yusho patients ingested. Only some PCDF congeners were retained in the body for a long time; they included 2,3,6,8-TCDF, 2,3,7,8-TCDF, 1,2,4,7,8-PCDF, 2,3,4,7,8-PCDF, and 1,2,3,4,7,8-hexachlorinated dibenzofurans. Since these congeners do not have free adjacent carbon atoms, they are not as easily metabolized and excreted. More of the 2,3,4,7,8-PCDF than the other isomers was retained in the patients' tissues. In the five patients studied, the concentration of this isomer ranged from 6.9 ppb (μg/kg) in a specimen obtained in 1969 to 0.1 ppb (μg/kg) in a specimen collected in 1977. Measurable concentrations of TCDFs were only detected in the earlier years. Although not the most toxic isomer, the 2,3,4,7,8-PCDF caused mixed-function oxidase induction at a dose of 1 μg/kg in rats, and atrophy of the thymus, suggesting toxicity at a very low dosage level. Thus, the clinical manifestations observed in these patients were primarily caused by the PCDFs, specifically by the more toxic isomers.

In the Yucheng episode, it was never determined with certainty how the rice oil was contaminated (93). In 1979 a school for blind persons informed a local health bureau in Taichung County that a strange disease characterized by an acnelike skin eruption had been occurring frequently among students and

staff since the end of March. At the same time, 85 of 150 workers in a nearby plastic shoe factory had the same symptoms. Later that year, this outbreak was also reported to a local health bureau. Victims in both outbreaks had consumed the same brand of cooking rice oil, which had been manufactured by the same company and which had been purchased in the same store. For this reason the rice oil was the prime suspect in the outbreak. In additional reports of outbreaks in other companies and in the general population, all victims had consumed the same type of C-rice oil.

Finally, because the disease resembled the Yusho disease in Japan, samples of C-rice oil and patients' blood were analyzed in Japan and were found to contain either a Kanechlor-400 or a Kanechlor-500 mixture at concentrations as high as 65 and 108 ppm (mg/kg), respectively. Over 2,000 patients were finally identified as having been poisoned by contaminated rice oil. Oil samples collected from other outbreaks contained PCBs at concentrations of 31–300 ppm (mg/kg). Retrospective studies determined that the period of PCB intake ranged from 3 to 9 months. The average total intake for each person varied from 0.77 to 1.8 mg of PCB. Within the first year of the outbreak, the blood levels of PCB in 13 patients ranged from 3 ppb to 1,156 ppb. Most of the patients had blood levels between 11 and 150 ppb (μg/kg). The symptoms observed in these patients were quite similar to those already described for the patients in the 1968 Yusho outbreak in Japan.

The rice oil was not only contaminated with PCBs but also with PCDFs and polychlorinated quaterphenyls. It contained the same major components of PCDFs observed in the rice oil in Japan—namely, 2,3,4,6,7-PCDF and 2,3,4,7,8-PCDF. Relatively high concentrations of 2,3,4,5,3',4'-hexachlorobiphenyl were found in the blood and adipose tissue of the Yucheng patients. This particular PCB isomer is biologically quite active, and the concentration of 2,3,4,3'4'-pentachlorobiphenyl was also elevated in these patients. Furthermore, as in the Yusho patients, the concentration of 2,3,7,8-TCDF was comparatively low (92). Chen et al (94) analyzed additional samples of the oil, blood, and adipose tissue of the Yucheng patients. These investigators identified several TCDF and PCDF isomers. Apparently, 2,3,7,8-TCDF was only a minor component in the oil; the major component was 2,3,4,8-TCDF. One of the major furans in the toxic oil was 2,3,4,7,8-PCDF.

The concentrations of the PCDFs in different oil samples ranged from 0.21 to 1.68 ppm. Polychlorinated quaterphenyls were present in concentrations ranging from 25 to 53 ppm (mg/kg). Overall, the concentrations of PCDFs and PCQs were lower in these oil samples than in the oil samples that had caused the Yusho outbreak. Whether these oil samples were representative is not really known. The 3,4,3'4'-tetrachlorobiphenyl was also identified in the oil that caused Yucheng disease in Taiwan. This isomer is considered to be

the most toxic PCB isomer present in commercial PCB preparations (95); it was present at a concentration of about 1%. Most other commercial PCB preparations, such as the Aroclors, in the United States have not been shown to contain this particular isomer.

In addition to the epidemiological studies, some disease-specific investigations were also conducted. The blood pressure of the Yucheng and Yusho patients was not affected (60). Although some of the patients in the Yusho cohort have died of cancer (90), the number has been small; because the latency period may be long, the population should be followed for a longer period to determine whether the cancer incidence will increase.

Although PCBs and related compounds are known to affect reproduction in animals, and although they affected some fetuses and neonates in the Yusho and Yucheng episodes, the information on reproduction and fetal toxicity in general is very limited. In one such study, Hara (96) examined women working in a capacitor plant who also nursed their infants and who themselves had mild chloracne and erythema of the skin. The human milk of some of these women contained, on a whole milk basis, PCB levels that ranged from below 50 ppb (μg/kg) to about 400 ppb (μg/kg). Forty children of these mothers were followed for a five-year period. Some children were found to have "decayed" nails, gingival pigmentation, mottled enamel, and dental caries. No relationships between these changes or symptoms to PCB blood levels, however, were observed. The general population in the United States and other countries also has body burdens of PCBs, PCDFs, and polychlorinated dibenzodioxins (97, 98). However, these background concentrations—particularly for the biologically active isomers—are far lower than they were in the Yusho and Yucheng patients, even several years after exposure.

Chang et al (99) examined the delayed immune response in 30 Yucheng patients and compared their responses with those of 50 controls. The mean age of patients in both groups was about 14 years. The authors injected a solution of streptokinase and streptodomase subcutaneously into the flexor side of the forearm. The response was read at 24 hours (hr) and again at 48 hr after injection. Eighty percent of the controls had an induration of 5 mm or more in diameter 24 or 48 hr after they were injected; only 43% of the exposed group responded similarly. All of the poisoned patients had dermal lesions, and the percentage of patients with a positive response decreased with increasing severity of the skin lesions (chloracne). Furthermore, the degree of the dermal lesions appeared to be associated with the whole blood PCB concentrations. Patients with minor skin lesions that were classified as grade 1 appeared to have a normal skin response. The same authors found that PCBs caused a decreased concentration of IgA and IgM, but not of IgG, in serum.

Furthermore, the percentages of total T cells, active T cells, and T mu cells decreased, whereas the percentage of B cells and T gamma cells were not

affected (100). These two reports are the first in which the effect on the immune response was actually correlated with body burdens of PCBs and in which only severely poisoned patients showed this effect. This finding is consistent with the findings from animal studies in which relatively high doses of PCBs affected the immune response and also caused some other adverse effects.

In the Japanese and the Taiwanese Yusho and Yucheng poisoning outbreaks, sensory neuropathy was reported in a number of patients for whom nerve conduction velocities were measured (101, 102). The blood levels of the various chemicals (PCBs, PCDFs, PCQs) were negatively correlated with the lowered nerve conduction velocity, suggesting that these types of chemicals affect nerve conduction velocity. (It is not quite clear why most investigators measure nerve conduction velocity to detect sensory neuropathy. Other tests that would measure the detection of vibration, touch, and temperature would be more useful from a clinical perspective.)

Seppalainen et al (103) examined 16 men working in a cardboard plant who were exposed to fumes that resulted from the explosion of 15 capacitors containing Clophen A-30. The first PCB air concentrations, measured 5.5 hr after the explosion, were 8,000 to 16,000 μg/m^3 air. PCDFs were also formed. The soot samples contained tetrachlorodibenzofuran up to 90 μg/g, of which 6.5 μg/g was 2,3,7,8-tetrachlorodibenzofuran. In addition, monochloropyrenes and dichloropyrenes were found. Most of the men had a transient sensory neuropathy in their lower extremities.

Chang et al (104) reported increased urinary δ-aminolevulinic acid uroporphyrin excretion in 69 Yucheng patients over that of 20 controls. No information on the patients' clinical conditions or on how these findings related to degree of exposure was given. No such observations have been reported from Japan.

POLYBROMINATED BIPHENYLS

Since the toxicity of PBBs both in laboratory animals and livestock was recently reviewed (105), we do not review it here in detail. In laboratory animals, PBBs generally cause effects similar to those that the PCBs cause. They produce morphological changes in the liver, affect reproduction, and promote biochemical changes, such as hepatic porphyria and induction of mixed-function oxidases. Teratogenic effects have also been noted. In addition, atrophy of the thymus has been reported, and hepatocellular carcinomas have been produced in both rats and mice. The overall findings reported in animal studies are similar to those that have been reported for PCBs.

Although the PCB contamination of the environment is a more general problem, the PBB contamination primarily affects certain areas within the state of Michigan. Most persons living within the lower peninsula of Michi-

gan have had slight exposure, since the contamination resulted from dairy products and since normal marketing channels for these products involved the mixing of milk from many producers in relatively few processing facilities. In addition, most cull dairy cattle are used for hamburgers and processed meat products that would also receive wide distribution. Thus, the marketing system diluted the degree of exposure for the individual; however, it increased the number of those exposed. In 1978, the distribution of PBBs was comprehensively studied in a probability sample of 1,738 persons. PBB levels in serum were determined, and 844 adipose tissue samples were also analyzed for PBBs. PBBs were detected in 97.3% of the adipose tissue samples, in 68% of the adult serum samples, and in 72.7% of the serum samples from children. The mean PBB concentration in adipose tissue was 400 ppb (μg/kg); in serum it was 1.3 ppb (μg/kg) for adults and 1.8 ppb (μ/gkg) for children. The highest adipose tissue concentration was 37 ppm (mg/kg) (18). In additional studies, when cohorts of PBB-exposed residents of Michigan were compared with residents of the state of Wisconsin, a higher prevalence of a variety of symptoms and complaints was noted in the Michigan residents (106). Similarly, in comparative neurobehavioral studies, the Michigan population was found to be affected more than that in Wisconsin (107).

Since the findings were not correlated with body burdens of PBB in any of these studies, determining whether other factors may be responsible for these differences is difficult. In 1976, the Michigan Department of Public Health established a cohort of farmers who had been exposed to varying concentrations of PBBs in their products and their environment. A total of 3,877 persons were enrolled. They included farm residents, direct recipients of farm products, chemical workers and their families, and a few persons who had been originally studied in a smaller previous study.

The serum PBB levels in this entire group ranged from no detectable levels to 1,900 ppb (μg/l), with a mean of 21.2 ppb (μg/l) and a median of 3 ppb (μg/l). Because of the wide range of exposure and because results could be analyzed by regression analyses with exposure as a variable, a comparison group for acute health effects was not included. This cohort was found to have various symptoms and conditions; however, these symptoms did not correlate with PBB body burdens. Symptom prevalence rates were slightly higher in persons with no detectable PBBs in serum than in those with measurable quantities. In all groups, including chemical workers and quarantined farm residents, the highest prevalence rates were in persons with the lowest serum PBB levels (22).

Similarly, in this study and in a previous immunologic study (108) no dose-related depression of lymphocyte function in persons exposed to PBBs could be demonstrated. All these findings suggest that there may be no causal

relationship between the abnormal lymphocyte functions observed in some persons or the prevalence of other symptoms and exposure to PBBs. This cohort of Michigan residents is still being followed by the Michigan Department of Health in collaboration with the Centers for Disease Control. Several studies of subgroups of this population and surveys for chronic health effects have been conducted since the cohort was first assembled (109, 19). When serum and adipose tissue concentrations were compared, a significant correlation was found. The serum:adipose tissue concentration ratios ranged from 1 to 140 to 1 to 260 for pregnant women and male chemical workers, respectively. Males from farms had a significantly different ratio of 1 to 325 to 329. Potential transplacental passage of PBBs was demonstrated, since they could also be found in the fetus and newborn. Cord blood contained one-tenth of the concentration found in the maternal serum, which indicated partial placental passage. Human milk contained PBBs at 107–119 times the quantity found in maternal serum. PBBs were also detected in bile and feces, which indicates that these materials can be transferred into the intestinal tract. All of these concentrations were measured long after the population had first been exposed to PBBs (19). Concentrations of PBBs observed in bile and feces were about one half to seven-tenths of the serum levels and are probably about 0.5% of the adipose tissue levels. These findings indicate that PBBs are very slowly excreted, which is consistent with the findings of Tuey & Matthews in rats (110). The estimated half-life for PBB is 6.5 years.

More recently, two groups of Michigan residents—those with high PBB serum levels and those with PBB serum levels around 1 ppb—were matched for age, sex, and smoking. For both groups, various clinical laboratory tests were conducted, blood pressure was measured, and height and weight were determined. In this study, 83 participants had PBB serum levels of 50 ppb (μg/l) or more. In the middle group, 83 had PBB levels of 5–49 ppb and 96 had PBB levels of 0–44 ppb (μg/l) in serum. Urinary porphyrins were also measured in all of the participants. Thus far, the final results of this study have not been reported. For most of the parameters studied—which included serum glucose, triglycerides, high-density lipoproteins, various liver functions, creatinine, uric acid, thyroid function, proteins, calcium and phosphorus in serum, and also measurement of various porphyrins—no differences of clinical significance were found among different groups (M. Barone, personal communication). (Note: Even though significantly more women in the high PBB group used birth-control pills than women in the low PBB group, too few were using them to affect urine porphyrin levels.) In none of a variety of other studies conducted on this population as well as other groups in Michigan did any findings indicate that exposure to PBB had impaired the health of the exposed group. All of these studies have been reviewed by Fries (105).

Although this population was exposed during a 9-month period in 1973 and 1974, whether it will have chronic health effects is unknown. This particular cohort needs to be followed for 30 to 40 years before the question of chronic health effects can be intelligently addressed. Two problems with assessing chronic health effects are that the cohort, in spite of its size, is still relatively small and that the amount of exposure it has received varied widely. Although some members of the group exposed to PBBs have relatively high body burdens, these burdens are still appreciably lower than those of rats in which liver cancer developed.

In the study by Kimbrough et al (111), liver cancer developed in the rats that received a dose of 1,000 mg/kg body weight. This dose for humans would roughly translate into a dose of 70 grams per person. These amounts are much greater than the estimated mean total exposure per person. The highest exposure was about 11.7 grams, and the mean was 170 mg per person. In rats given 200 mg/kg, a dose that for humans would be between 12 and 14 grams, only neoplastic nodules developed in their livers; there was no evidence of hepatocellular carcinomas. Of course, whether humans would be more or less susceptible to the toxic effects of PBBs and whether their response would be similar to that of rats is not known.

In conclusion, various toxic effects of PBBs and PCBs have been described in laboratory animals. In humans, acute poisoning outbreaks have only occurred following exposure to a combination of PCBs and PCDFs. When humans were exposed only to PCBs or PBBs, the only observed acute effects have generally been minor. So far, no significant chronic health effects have been causally associated with exposure to PCBs or PBBs.

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