Monsanto TECHNOLOGY

DATA
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

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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.

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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

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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

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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).

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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

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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".

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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]

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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.

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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.

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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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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.

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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.

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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.

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

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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.

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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.

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