REPORT TO

MONSANTO COMPANY

THREE-GENERATION REPRODUCTION STUDY WITH
AROCLOR 1254
IN ALBINO RATS

NOVEMBER 1, 1971

IBT NO. B7297

I. Introduction

At the request of Monsanto Company, a reproduction study was initiated in order to ascertain potential toxicological effects of subacute oral administration of Aroclor 1254, Lot No. AK-18, upon the fertility and offspring of three consecutive generations of albino rats.

This report presents the data collected from the initiation of the investigation to the weaning of the second (F3b) litters obtained from the third (F2) parental generation.

PLAINTIFF'S EXHIBIT 681

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II. Summary

A three-generation reproduction study employing albino rats fed diets containing 1, 10 or 100 ppm Aroclor 1254 was conducted. The following results were obtained during the investigation.

A. Parental Animals

1. Body Weights

Body weights and body weight gains revealed no differences between test and control animals which could be attributed to the ingestion of Aroclor 1254.

2. Mortality and Reactions

Several animals succumbed during each of the three generations. None of these deaths could be attributed to the ingestion of Aroclor 1254.

3. Pathologic Studies

Gross pathologic examination revealed no differences between test and control rats.

The liver weights and liver to body weight or brain weight ratios were significantly elevated in males fed 100 ppm Aroclor 1254. The liver weights for females in the same group (T-III) were not elevated; however, liver to brain weight ratios were significantly higher than control values. Statistical evaluations of other organ weights, organ to body weight and organ to brain weight ratios disclosed several randomly occurring intergroup differences. The lack of any consistent dose or

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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	Hepato-cellular Carcinoma	Cholangio-Hepatoma	Reference
48	Kanechlor 400	Donryu	M	23-62 wks	38.5-616	5	0	-	-	-	-	-	-	Kimura + Ba. (1973)
						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	23	-	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'-tetra-chlorobiphenyl[3]	-	-	24 mos.	100	-	-	-	-	-	-	-	-	Weltman & Horback (197?)

[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.

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TABLE 1

SUMMARY OF CO-CARCINOGENESIS STUDIES WITH PCBs

Product	Mode	Time	Other Treatment[1]	Mode	Species	Observations	Ref.
Kanechlor 400	Diet	With	20-MeCh	Uterine implant	dd mouse	Hepatocellular carcinoma with 20-MeCh. None with combination.	Uchiyama, 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

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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	MSB cells	Intra-muscular	C57BL/6 mouse	Enhanced growth of MSB tumor.	Kerkvliet and Koller, 1978
Aroclor 1254	Diet	Before	Moloney leukemia virus	Intra-peritoneal	Balb/c mouse	Did not affect oncogenesis of Moloney leukemia virus.	Koller, 1977

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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-DMA = 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 B6 mice.

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TABLE 6

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.	•	•	•	Meddle and Bruce 1977
AROCLOR 1254	• •		•	•	•	•	•	•	•	Pos[?]	•	•	Wyndham, et al. 1976
Kanechlor 500[2]	• •		•	•	•	•	Neg.	Neg.	Neg.	Neg.	•	•	Odashima, 1976
Kanechlor 500	• •		•	Neg.	Neg.	•	•	•	•	•	Neg.[•]	•	Sugimura, et al. 1976
2,2',5,5-tetra-chlorobiphenyl	• •		•	•	•	•	•	•	•	Neg.	•	•	Wyndham, et al. 1976
2,2'5,5'-tetra-chlorobiphenyl	• •		•	Neg[•]	Neg[•]	•	Neg[•]	•	Neg[•]	•	•	•	Hsia, et al. 1978
Kanechlor 300[2]	• •		•	•	•	•	Neg.	Neg.	Neg.	Neg.	•	•	Odashima, 1976
Kanechlor 300	• •		•	Neg.	Neg.	•	•	•	•	•	Neg.[•]	•	Sugimura, et al. 1976
AROCLOR 1221	• •		•	•	•	•	•	•	•	Pos[•]	•	•	Wyndham, et al. 1976
4-chlorobiphenyl	• •		•	•	•	•	•	•	•	Pos[•]	•	•	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[•] = Only tested without activation.

Neg[+] = Only tested with activation.

Pos[+] = Positive only with activation.

Pos[?] = Uncertain. See text.

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