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.

DEPOSITION EXHIBIT
LEVINSKAS-41
5-22-87 WK

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.

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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.

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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.

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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

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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

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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

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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

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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	Hupatoma	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"				+						

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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"		+								

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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	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"			++							

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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	Cholangio-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"										

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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	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

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