Industrial BIO-TEST Laboratories, Inc.
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REPORT TO

MONSANTO COMPANY

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

BTL-11-69 (C)

HISTOPATHOLOGICAL EVALUATION OF ADDITIONAL LIVER SECTIONS

MARCH 24, 1975

IBT NO. 641 - 06672

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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 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:

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MONS 068688

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 1260 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.

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.
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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 - Aroclor 1260

14 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 1260

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
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 "										

MONS 068695

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	Telangectasia, focal
3 Month	C-I	1011M		+	+								
	1ppm	1012"											
		1013"			+								
		1014"											
		1015"											
		1026F											
		1027"											
		1028"											
		1029"											
		1030"			+								
	C-II	1041M											
	10ppm	1042"											
		1043"											
		1045"											
		1056F											
		1057"											
		1058"											
		1059"											
	C-III	1071M											
	100ppm	1072"											
		1073"											
		1075"											
		1086F											
		1087"											
		1088"											
		1089"											
		1090"											
	Control	801M	+	+									
		802"											
		803"											
		804"											
		805"											
		816F											
		817"											
		818"											
		819"											
		820"											

MONS 068696

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	Telangectasia, focal
18 Month	C-I	71M											
	1ppm	72"	+										
		73"											
		74"											
		75"											
		76F	+										
		77"											
		78"											
		79"											
		80"											
	C-II	81M	+										
	10ppm	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"						+					

MONS 068697

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"										

MONS 068698

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
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"				+						

MONS 068699

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
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"										

MONS 068700

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"										
		Ext"	+					+				

Grading System

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