Monsanto

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INDUSTRIAL BIO-TEST LABORATORIES, INC. REPORTS

Two-Year Chronic Oral Toxicity
Study With
Aroclor 1242
In Albino Rats

Histopathological Evaluation
of Additional Liver Sections

March 24, 1975

.....

Two-Year Chronic Oral Toxicity
Study With
Aroclor 1254
In Albino Rats

Histopathological Evaluation
of Additional Liver Sections

March 24, 1975

.....

Two-Year Chronic Oral Toxicity
Study with
Aroclor 1260
in Albino Rats

Histopathological Evaluation
of Additional Liver Sections

March 24, 1975

THE EPPLEY INSTITUTE REPORTS

Report on
Histopathological Re-evaluation of
Tissues from Female Sherman Rats
Fed Aroclor 1260

.....

Report on
Histopathological Re-evaluation of
Livers from Rats Treated with Aroclor

MONS 095019

Submitted by [signature]
George Roush, Jr., M. D.
Medical Director

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

C+25AM

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	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

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

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	Telangiectasia, focal
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 "											

MONS 095029

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
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 095030

acrifice 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 tunior, metastatic	Telangectasia, focal
.2 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"											

MONS 095031

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
4 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 095032

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
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"											
		697"										P	
		700"				+							
		703"	++										
		707"					P						
		708"	++	+				+++					
		711"											
		712"	+										
		682"	+										
		683"											
		691"											
		702"				+							

MONS 095033

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
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 095034

AROCLOR - 1242

Tabulation of Individual Liver Lesions in Rats

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	Cholangio-hepatoma	Reticulum Cell Sarcoma metastatic	Mammary tumor, metastatic	Telangectasia, focal
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

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

REPORT TO

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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

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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.

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	THI	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	Cholangio-hepatoma	Squamous Cell Carcinoma, metastatic	Mammary tumor, metastatic	Hepatitis/Cirrhosis
1 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"											

MONS 095045

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	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"				+							

MONS 095046

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	Hepatitis/Cirrhosis
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"		+									

MONS 095047

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	Hepatitis/Cirrhosis
24 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	Hepatitis/Cirrhosis
2 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"											

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	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

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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

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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 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

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"								

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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"								

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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"				+		+			

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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"									

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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	
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"	++			+		+			

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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)	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

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

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Report

On

Histopathological Re-evaluation of

Tissues from Female Sherman Rats

Fed Aroclor 1260

INTRODUCTION

A preliminary feeding study in which the toxicities of two PCB mixtures (Aroclor 1254 and 1260) were compared by Dr. Kimbrough (CDC, Atlanta, Ga.) resulted in no carcinogenic effect in rats. However, according to another study using Sherman strain female rats fed 100 ppm Aroclor 1260, 170 out of the 180 animals examined showed neoplastic lesions, which were classified by Dr. Kimbrough and co-workers as "neoplastic nodules" and "hepatocellular carcinomas". It was therefore concluded that Aroclor 1260 has a hepatocarcinogenic effect in female Sherman strain rats. Another study in albino rats with Aroclor also showed inconclusive results; while no carcinogenic response could be observed in a preliminary study, Dr. Gordon (Bio-Test Laboratories Inc.) reported a slight tumorigenic property of Aroclor 1242, 1254 and 1260 in rats which were fed continuously at levels of 100 ppm for 2 years. The re-evaluation of material from the latter study by myself left much doubt about carcinogenicity of the compounds tested, however a dose-dependent hepatotoxic effect was confirmed (see Report on Histopathological Re-evaluation of Livers from Rats Treated With AROCLOR). Using the same diagnostic criteria in this report the material from Dr. Kimbrough's experiment was re-evaluated and described.

MATERIALS AND METHODS

More than 550 slides from 184 experimental rats and over 360 from 173 control rats were presented. These slides consisted of tissues from the brain, pituitary gland, thyroid gland, parathyroid glands, trachea, esophagus, lungs, mammary glands, stomach, heart, liver, spleen, adrenal glands, kidneys, ovaries, uterus and bladder. Several tissues (3-5) were placed on each slide. For the most part, several liver sections were placed on 2 or 3 slides. All slides were stained with hematoxylin and eosin; additional liver sections (more than 150) were stained with AZURE eosin, Masson's Trichrome, PAS and reticulum stains. The quality of all slides were sufficient for diagnosis.

For the present report, liver, lung, and mammary gland sections were of major interest in evaluating the hepatic lesions and determining possible metastases from the mammary gland or into the lungs. The slides were evaluated in the same sequence as they were found in the plastic boxes.

The criteria for diagnostic evaluation was the same as we used in the previous report; however, two other alterations were found in the material, which were not seen in the previous material such as:

Hyperplastic nodule without atypia: This lesion was characterized by circumscribed areas of large hepatocytes (2-8 times larger than regular liver cells) showing mostly foamy, light eosinophilic, sometimes also basophilic cytoplasm occasionally with inclusion bodies (bile pigment, concentric lamellated or fibrillar structures, PAS-positive materials). These foci, in part corresponding to lesions termed "neoplastic nodules" by Dr. Kimbrough, usually occupied an area of the size of several lobules and were well-demarcated, partially suggesting a compression effect in the surrounding, regular-appearing liver parenchyma. Small foci of similar cell clusters of areas in which the alterated cells blended with surrounding liver plates without obvious architectural demarcation were not included in this category and were diagnosed as areas of cell enlargement; these areas probably correspond to lesions termed "foci or areas" by Dr. Kimbrough.

Hyperplastic nodules with atypica: An alteration, similar to hyperplastic areas, occurred showing such atypical features in either cellular or architectural behavior as abnormal nuclei and nucleoli and papillary or trabecular formations of pleomorphic cells. Binucleation or mitotic figures did not account for this alteration, since they were also seen in many regenerating hepatocytes surrounding the hyperplastic nodules or in areas remote from them.

RESULTS

The results of evaluations of experimental and control rats are given in Table 1-20. The most common findings in both animal groups are summarized in Table 21, showing that remarkable differences occurred in the experimental animals with regard to vacuolization, single and focal granular alteration, cell necrosis, cell enlargement, ductal proliferation, and Stern cell proliferation. These alterations, occurring most frequently in the experimental animals could be referred to as toxic, degenerative and regenerative effects. The degree and the extent of all lesions in experimentals was greater than that of the controls. However the extent and the degree of alteration of hyperplastic nodules in treated rats varied among the individual animals. In some sections they could be localized in small areas, while in others they were multiple and sometimes occupied more or less the entire section (i.e. 8347, 8356, 8375); in some cases the multiplicity of the lesions were so remarkable that they simulated invading lesions. However no cytologic criteria for malignancy could be found. The degree and the extent of hyperplastic nodules were greater in livers showing general toxic effects (see tables). The more advanced and severe the degenerative and regenerative process, the larger and more multiple were these nodules. Most hyperplastic nodules with atypia were associated with severe parenchymal damage. As a matter of fact among 43 animals with atypical nodules, 19 showed diffuse or almost diffuse cell alterations of the liver.

In animals with fewer and smaller nodular lesions, morphologic signs of parenchymal repair (Stern cell proliferation, pigment deposition in macrophages, basophilia of the liver cells) were obvious. In many instances, the hyperplastic nodules were surrounded by basophilic, small liver cells, which had the tendency to penetrate into the hyperplastic nodules, thus giving rise to indistinct demarcation of the nodules: this phenomenon was also seen frequently in larger nodules and was interpreted as a repair-process, rather than a sign of malignancy in terms of invasion. Such a phenomenon was also seen in a few hyperplastic

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nodules with atypia; in such instances regenerating areas were also found within the hyperplastic foci giving rise to lesions corresponding to "nodules within the nodule". In about 20 animals the nodules were large and showed such a degree of atypia that they could be considered as neoplastic; however some of these nodules showed proliferation of bile ducts of definitely normal appearance on the borderline or within the nodules. In no case were definite signs of invasion or metastases observed in the available material.

In several animals the liver lesions were moderately or only slightly damaged (i.e., 8388, 839, 8400, 8401, 8431, 8460, 8477, 9479, 8385, 8387 and 8385). In other rats (i.e., 8454, 8457, 8458, 8462, 8489) the morphologic patterns of the tissue resembled more or less regenerated liver parenchyma and in still others, the sections taken from different lobes presented different pictures. For example, in one bbethe regenerative process was dominant while in other sections, degeneration was still in process. In sections lacking degeneration, the liver plates, which were composed of small basophilic liver cells, were smaller and separated by ectatic sinuses. This feature could be observed either within or in the margin of some hyperplastic nodules.

Cholangiomatous lesions were found exclusively in experimentals and were often associated with hyperplastic alterations.

Metastatic liver lesions originating from other sites (mammary glands, uterus) were not found.

DISCUSSION

Among 148 Aroclor 1260-treated animals, 136 hyperplastic nodules without atypia were found (43 of those with atypical structures). These contrast with Dr. Kimbrough's findings of 170/184 neoplastic lesions, among which 26/184 were supposed to represent hepatocellular carcinomas. Hyperplastic nodules diagnosed by myself in controls also contrast with 28/173 reported by Dr. Kimbrough. The difference is obviously due to varying criteria used in classifying the lesions. "Focal cell enlargement" in this report obviously corresponds to lesions termed "foci or areas" by Dr. Kimbrough; however hyperplastic nodules, by my definition, encompass both "neoplastic nodules" and "hepatocellular carcinoma" of Dr. Kimbrough's terminology. The criteria used by myself in distinguishing hyperplastic nodules (with or without atypia) is of pure cyto-morphologic character and unrelated to the biologic behavior, which cannot be determined in the presented material. However, with one exception, all alterations found in control animals were, in my opinion, benign and represented foci of cell degeneration and regeneration, a process which spontaneously occurs in many rat strains. However according to Dr. Kimbrough, these lesions, termed "foci or areas" as well as lesions termed "neoplastic nodules" represent a carcinogenic response.

I cannot follow this interpretation, since there is no way to demonstrate the definite malignant nature of said lesions in the avialable material. Therefore many pathologists, including myself, do not agree with the recent terminology of the liver lesions proposed by a group of pathologists in a workshop on rat liver tumors. Without morphologic evidence of malignancy, such as invasion and metastases, it is irrelevant to designate a lesion as malignant, unless it could be proven that its further development and progression results in malignancy. This cannot be said as to be relevant in Dr. Kimbrough's study. In contrast there is some evidence that the "neoplastic nodules" are not and cannot be precursors of carcinomas, since they may regress more or less completely under certain experimental procedures,

as shown by Dr. N. Ito of Nagoya City University in Japan and by Dr. G. M. Williams of the American Health Foundation in New York. According to Dr Ito (personal communication) a feeding experiment, conducted for a certain period of time resulted in regression of hyperplastic lesions in mice liver if the α-BHC (alpha-isomers of Benzene Hexachloride) as well as PCB, were removed from food and the animals were kept for life. A high incidence of hepatic lesions however was induced by continous feeding (2-years) of high concentration of both compounds (1500 ppm resulted in 30%, 1000 ppm in 7-8% and 500 ppm in 0%). The results of Dr. Ito's experiment will be published shortly in JNCI. By going through the material from Dr. Kimbrough's experiment and by comparison of various lesions in treated and untreated rats, I gained the strong impression that many, detectable alterations represented a degenerative and reparative, rather than a neoplastic process. Smaller hyperplastic nodules often without atypia were found in those animals, in which morphologic signs of toxic effect were minimal and that of the reparative process predominant. In contrast, larger lesions with or without atypia, (often multiple) were present in livers showing a definite diffuse toxic response. In my opinion, many of these hyperplastic lesions would have regressed if the animals had been sacrificed at a later time. Dr. Kimbrough had the same thought, however neither possible regression nor the eventual progression of these lesions can be proven in the presented material. Concerning the most hyperplastic nodules with atypia I had also the impression, that cellular atypia reflected greater toxic damage, since with a few exceptions, they failed to fullfill the proposed morphologic criteria for malignancy, such as atypical structures (thickening of liver plates, forming trabecular or papillary patterns). The basophilic cells found within some of the hyperplastic nodules were morphologically and cytologically different from basophilic foci described by Bannash in hepatocellular carcinomas. The basophilic areas seen in the presented material were composed of small basophilic cells of unique sizes and shapes forming narrow liver plates separated by ectatic sinuses, thus giving rise to pseudopapillary structures. This type of atypia is, with high

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probability, a regenerative process and was seen also remote from hyperplastic nodules within the normal-appearing liver segment. Also other atypical features such as large and bizarre cells, binucleated cells and mitotic figures (which were all of regular form) did not account for malignancy, since they were observed both within and remote from the hyperplastic nodules. The same is true for hyperplastic nodules showing regeneration or new formation of definitely normal-appearing bile ducts, the presence of which contradicts the concept of malignancy. The undefined limitation of some hyperplastic nodules in many cases was caused by the beginning of progressive cell regeneration at the periphery, or less frequently in the centrum, of hyperplastic areas, and in my opinion should not be considered invasiveness. Twenty cases of the atypical hyperplasia, I observed, presented such morphologic criteria as to be considered neoplasia, although a most significant criteria for malignancy, namely the invasion was missing and the sign of ongoing toxic, degenerative and regenerative processes in the rest of the tissues was evident. At present, the statement that these lesions may have metastasized 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,

In summary, 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 even impossible to distinguish between regeneration, hyperplasia and neoplasia, particularly when the tissue is continously exposed to a toxic substance.

In this context, Dr. Kimbrough's study (Arch. Environ. Health 27: 390-395, 1973) 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 2 months after Aroclor was removed from their 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, 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.

The different results obtained in experiments with albino and Sherman strain rats are obviously not only due to the enviromental and genetic background but also to the matter of experimental methods used in the different experiments.

Number of slides	8320	8321	8324	8324	8325	8326	8327	8329	8331	8332	8333	8334	8335	8336	8337	8338	8339	8341	8342	8343
Vacuolization	(+)	+	+	+	+	+	+		+	+	+	+	+	+	+		+	+	+	+
Focal acidophilic alteration						+														
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Focal granular alteration			+		+		+	+	+	+	+	+		+	+		+			+
Single granular alteration	+	+		+	+		+				+		+	+		+			+	
Perinuclear halo												+								
Eosinoph. homogenization																				
Single cell necrosis		+	+	+	+		+	+			+			+	+	+	+			
Group cell necrosis									+	+							+			+
Cell enlargement		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	
Ductal proliferation		+	+			+		+			+	+	+					+		
Periductal fibrosis																				
Cholangiofibrosis													+							
Stern cell proliferation							+							+	+				+	
Epithelioid cell granuloma										+										
Periportal inflammation	+	+	+				+	+		+	+			+	+	+	+	+	+	+
Hyperplastic nodules with atypia		+				+							+				+			
Hyperplastic nodules without atypia			+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	
Cholangiomatous lesion																				
Lymph congestion				+											+					

Number of slides	8344	8345	8346	8347	8350	8351	8352	8353	8354	8355	8356	8357	8358	8359	8360	8361	8362	8363	8364
Vacuolization	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+
Focal acidophilic alteration				+															
Single acidophilic alterations	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+		+
Focal granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Single granular alteration	+	+	+	+	+	+	+	+	+		+	+		+	+	+	+		+
Perinuclear halo				+															
Eosinoph. homogenization																			
Single cell necrosis	+	+		+	+	+		+	+		+					+	+		
Group cell necrosis		+			+									+					
Cell enlargement	+	+	+	+D	+AD	+AD		+	+	+	+AD	+D	+	+AD		+AD	+AD	+	+
Ductal proliferation		+		+															
Periductal fibrosis																			
Cholangiofibrosis		+			+										+				
Stern cell proliferation			+		+		+								+	+	+	+	+
Epithelioid cell granuloma																			
Periportal inflammation	+	+	+		+			+			+			+		+	+	+	
Hyperplastic nodules with atypia					+														
Hyperplastic nodules without atypia	+	+	+		+		+	+		+	+		+		+	+		+	
Cholangiomatous lesion					+														
Lymph congestion						+													

* D=diffuse
AD =almost diffuse

MONS 095077

Number of slides	8365	8366	8367	8369	8370	8371	8372	8373	8374	8375	8376	8377	8378	8380	8381	8382	8383	8384	8385
Vacuolization	+	+	+	+	+	+	+	+	+	+				+	+	+		+	+
Focal acidophilic alteration							+												
Single acidophilic alterations		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration							+	+	+	+	+	+	+		+				
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear halo																			
Eosinoph. homogenization																			
Single cell necrosis		+	+	+	+	+	+	+	+	+	+	+	+						
Group cell necrosis						+			+	+		+							
Cell enlargement	+	+	+	+AD	+	+	+	+D	+D	+AD	+	+AD	+AD	+	+AD	+	+	+	(+)
Ductal proliferation			+							+	+	+	+		+	+	+		
Periductal fibrosis																			
Cholangiofibrosis								+											
Stern cell proliferation	+	+	+	+		+	+			+	+	+	+	+	+	+	+	+	+
Epithelioid cell granuloma																			
Periportal inflammation		+		+															
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia	+	+	+		+		+					+		+			+		
Cholangiomatous lesion			+				+					+					+		
Lymph congestion																			

D=diffuse
AD=almost diffuse

Number of slides	8386	8387	8388	8389	8390	8391	8392	8393	8394	8395	8396	8397	8398	8399	8400	8401	8402	8403	8404
Vacuolization	+	+		+	+	+	+	+		+		+	+	+	+	+	+		+
Focal acidophilic alteration																			
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Focal granular alteration	+					+	+	+					+	+		+			+
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear halo																			
Eosinoph. homogenization																			
Single cell necrosis					+	+		+	+	+	+		+	+	+	+	+		
Group cell necrosis								+				+		+					
Cell enlargement	+AD	(+)	+		+AD	(+)	+	+	+	+AD	+	+AD	+D	+	+	+	+	+	+AD
Ductal proliferation	+			+					+			+			+	+		+	+
Periductal fibrosis																			
Cholangiofibrosis																			
Stern cell proliferation	+	+	+	+	+	+			+	+		+		+	+	+	+	+	+
Epithelioid cell granuloma																			
Periportal inflammation		+		+							+	+				+			
Hyperplastic nodules with atypia					+			+		+				+					
Hyperplastic nodules without atypia	+				+		+	+	+	+	+			+	+		+	+	+
Cholangiomatous lesion	+											+			+				
Lymph congestion																			

Number of slides	8405	8406	8407	8408	8411	8412	8413	8414	8415	8416	8417	8418	8419	8420	8421	8422	8423	8424	8425
Vacuolization	+	+	+	+	+	+	+	+		+	+		+			+	+	+	
Focal acidophilic alteration																			
Single acidophilic alterations	+	+	+	+		+	+		+	+	+	+	+	+	+	+		+	
Focal granular alteration	+	+	+	+		+	+	+				+				+			
Single granular alteration	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+		+	+
Perinuclear halo																			
Eosinoph: homogenization																			
Single cell necrosis	+	+	+	+	+	+	+	+	+	+	+	+							
Group cell necrosis	+				+		+												+
Cell enlargement	+	+	+AD	+	+AD	+	+	+	+	+	+	+	+	+	(+)	+	+	+	
Ductal proliferation		+	+	+														+	
Periductal fibrosis																			
Cholangiofibrosis		+	+		+														
Stern cell proliferation	+	+	+			+			+	+			+			+	+		
Epithelioid cell granuloma																			
Periportal inflammation																			+
Hyperplastic nodules with atypia	+	+	+		+		+	+			+							+	
Hyperplastic nodules without atypia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiomatous lesion		+	+											+					
Lymph congestion																			

AD=almost diffuse
D= diffuse

MONS 095080

Number of slides	8426	8427	8428	8429	8430	8431	8432	8433	8434	8435	8436	8437	8438	8439	8440	8441	8442	8443	8444
Vacuolization	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+		+
Focal acidophilic alteration																			
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+								+	+		+	+		+		+		+
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear halo																			
Eosinoph. homogenization																			
Single cell necrosis	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Group cell necrosis	+	+						+											
Cell enlargement	+	+	+AD	+	+	+	+	+AD	+	+	+AD	+	+	+	+	+AD	+	+	+
Ductal proliferation			+	+			+	+	+	+				+	+	+			
Periductal fibrosis																			
Cholangiofibrosis								+											
Stern cell proliferation	+	+	+	+	+	+	+			+		+			+	+	+		+
Epithelioid cell granuloma																			
Periportal inflammation	+			+	+														
Hyperplastic nodules with atypia		+					+	+		+				+					+
Hyperplastic nodules without atypia	+	+		+	+	+	+		+	+		+	+	+	+	+	+		+
Cholangiomatous lesion			+											+					
Lymph congestion																			

AD=almost diffuse
D=diffuse

Number of slides	8445	8446	8447	8448	8451	8452	8453	8454	8455	8456	8457	8458	8459	8460	8461	8462	8463	8465	8466
Vacuolization	+		+		+	(+)	+		+	+	(+)	+	+	+	+	+	+	(+)	+
Focal acidophilic alteration																			
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+		+				+						+	+					+
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear halo																			
Eosinoph. homogenization																			
Single cell necrosis	+		+		+	+			+	+			+	+	+	+	+		
Group cell necrosis			+			+				+			+					+	
Cell enlargement	+AD		+AD	(+)	(+)	+AD	+AD		+	+	+	+	+	+	+	+	+	+	+
Ductal proliferation													+						
Periductal fibrosis																			
Cholangiofibrosis																			
Stern cell proliferation	+	+		+	+	+	+	+	+	+	+	+			+	+	+		+
Epithelioid cell granuloma																			
Periportal inflammation						+			+										
Hyperplastic nodules with atypia		+			+														
Hyperplastic nodules without atypia	+			+	+		+		+	+				+	+		+	+	+
Cholangiomatous lesion																			
Lymph congestion																			

MONS 095082

AD=almost diffuse
D=diffuse

Number of slides	8467	8468	8469	8470	8471	8472	8473	8474	8475	8476	8477	8478	8479	8480	8481	8482	8483	8484	8485
Vacuolization	+	+	(+)	+	+	+	+	+	+	+	+		(+)	+		+	+	+	+
Focal acidophilic alteration																			
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+		+	+	+		+				+	+		+			+		+
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear halo																			
Eosinoph. homogenization																			
Single cell necrosis	+	+	+	+	+	+	+	+			+	+		+			+	+	+
Group cell necrosis				+							+							+	+
Cell enlargement	+	+	(+)	+AD	+	+AD	+	+	+	+	+	+	+	+AD	+	+AD	+	+AD	+AD
Ductal proliferation						+			+					+				+	
Periductal fibrosis																			
Cholangiofibrosis																			
Stern cell proliferation		+	+	+	+		+		+	+		+	+	+	+	+	+	+	+
Epithelioid cell granuloma																			
Periportal inflammation	+		+	+	+		+		+					+	+	+	+	+	
Hyperplastic nodules with atypia			+					+	+					+		+	+	+	
Hyperplastic nodules without atypia	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Cholangiomatous lesion						+			+										
Lymph congestion																			

AD=almost diffuse
D=diffuse

MONS 095083

Number of slides	8486	8488	8489	8490	8491	8492	8493	8494	8495	8496	8497	8498	8499	8500	8501	8502	8504	8505	8506
Vacuolization	+	+	(+)	+			(+)	+	+		+	+	+	+	+	+	+	+	+
Focal acidophilic alteration																			
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+	+		+	+	+	+	+	+	+		+	+			+			
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear halo																			
Eosinoph. homogenization																			
Single cell necrosis	+	+		+	+	+	+	+	+	+	+	+	+	+	+		+	+	
Group cell necrosis		+				+													
Cell enlargement	+AD	+AD	(+)	+AD	+	+	+AD	+	+	+	+	+	+	+AD	+	+AD	+AD	+	+
Ductal proliferation	+	+		+											+	+			
Periductal fibrosis																			
Cholangiofibrosis																	+		
Stern cell proliferation	+	+	+	+	+	+		+	+	+		+	+	+	+	+			+
Epithelioid cell granuloma																			
Periportal inflammation			+						+						+				
Hyperplastic nodules with atypia		+					+			+				+		+	+		
Hyperplastic nodules without atypia	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiomatous lesion																+			
Lymph congestion																			

AD=almost diffuse

MONS 095084

Number of slides	8507	8508	8509	8510	8512	8513	8514	8515	8516	8517	8518	8319
Vacuolization	+	+	+		+	+	+	+	+	+	+	+
Focal acidophilic alteration												
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration			+	+		+	+		+	+	+	+
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear halo												
Eosinoph. homogenization												
Single cell necrosis	+			+	+	+	+	+	+	+	+	+
Group cell necrosis									+		+	+
Cell enlargement	+AD	+	+AD	+	+	+	+AD	+D	+AD	+	+AD	+AD
Ductal proliferation	+						+				+	
Periductal fibrosis												
Cholangiofibrosis												
Stern cell proliferation	+		+	+	+	+	+	+	+	+	+	+
Epithelioid cell granuloma												
Periportal inflammation								+	+	+	+	+
Hyperplastic nodules with atypia	+						+		+		+	+
Hyperplastic nodules without atypia	+	+	+		+	+	+		+	+		
Cholangiomatous lesion											+	
Lymph congestion												

AD=almost diffuse

MONS 095085

Number of slides	8165	8167	8169	8178	8174	8181	8185	8193	8194	8202	8206	8215	8225	8227	8228	8230	8237	8240	8242
Vacuolization																+		(+)	
Focal acidophilic alteration										+	+	+				+	+		
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration														+			+		+
Single granular alteration	+	+		+	+										+				+
Perinuclear halo																			
Eosinoph. homogenization																			
Single cell necrosis																	+		
Group cell necrosis																			
Cell enlargement						+													
Ductal proliferation							+												
Periductal fibrosis																			
Cholangiofibrosis																			
Stern cell proliferation				+	+			+					+			+	+		+
Epithelioid cell granuloma																			
Periportal inflammation							+		+										
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia																			
Cholangiomatous lesion																			
Lymph congestion																			

Number of slides	8244	8245	8246	8247	8249	8250	8259	8266	8279	8280	8282	8299	8199	8285	8300	8301	8303	8306	8307
Vacuolization																			
Focal acidophilic alteration	+		+	+															
Single acidophilic alterations	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration			+			+											+		
Single granular alteration	+	+	+	+		+	+	+		+	+								
Perinuclear halo																			
Eosinoph. homogenization																			
Single cell necrosis	+	+		+		+													
Group cell necrosis																			
Cell enlargement	+																		
Ductal proliferation																+			
Periductal fibrosis																			
Cholangiofibrosis							+												
Stern cell proliferation	+	+		+	+			+	+	+	+	+	+		+	+	+	+	+
Epithelioid cell granuloma																			
Periportal inflammation	+			+				+			+		+		+	+	+	+	
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia																			
Cholangiomatous lesion																			
Lymph congestion																			

Number of slides	8309	8310	8311	8312	8313	8314	8315	8316	8317	8318	8321	8151	8231	8260	8261	8263	8264	8265		
Vacuolization													+							
Focal acidophilic alteration				+					+							+				
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Focal granular alteration			+					+		+			+							
Single granular alteration				+			+	+			+		+	+	+		+	+		
Perinuclear halo																				
Eosinoph. homogenization																				
Single cell necrosis					+		+	+												
Group cell necrosis													+							
Cell enlargement			+										+							
Ductal proliferation													+							
Periductal fibrosis																				
Cholangiofibrosis													+							
Stern cell proliferation		+	+	+	+	+	+	+	+	+	+			+	+			+		
Epithelioid cell granuloma																				
Periportal inflammation		+	+		+	+	+				+									
Hyperplastic nodules with atypia													+							
Hyperplastic nodules without atypia			+										+							
Cholangiomatous lesion													+							
Lymph congestion																				

Controls

Number of slides	8267	8268	8269	8271	8271 (?)	8272	8273	8275	8277	8278	8281	8283	8284	8286	8289	8290	8291	8292	8293
Vacuolization					+	+			+						+				+
Focal acidophilic alteration									+	+	+								
Single acidophilic alterations	+	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+
Focal granular alteration					+	+													
Single granular alteration					+					+									
Perinuclear halo									+		+								
Eosinoph. homogenization																			
Single cell necrosis					+								+						+
Group cell necrosis					+														
Cell enlargement					+						+								+
Ductal proliferation																			
Periductal fibrosis																			
Cholangiofibrosis																			
Stern cell proliferation	+	+		+									+		+	+	+	+	
Epithelioid cell granuloma																			
Periportal inflammation				+								+							
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia					+						(+)								(+)
Cholangiomatous lesion																			
Lymph congestion																			

Invaded by malignant lymphoma cells

Controls

Number of slides	8294	8295	8296	8304	8172	8170	8173	8175	8176	8177	8179	8180	8182	8184	8186	8187	8188	8190	8191
Vacuolization				+															
Focal acidophilic alteration													+						
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration		+		+				+	+						+				
Single granular alteration		+		+						+									
Perinuclear halo				+		+	+	+		+									
Eosinoph. homogenization																			
Single cell necrosis																			
Group cell necrosis																			
Cell enlargement																	+		
Ductal proliferation																			
Periductal fibrosis																			
Cholangiofibrosis																			
Stern cell proliferation	+											+	+						
Epithelioid cell granuloma																			
Periportal inflammation												+	+					+	
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia																			
Cholangiomatous lesion																			
Lymph congestion																	+		

Controls

Number of slides	8192	8195	8196	8197	8198	8200	8201	8203	8204	8207	8208	8209	8210	8211	8212	8213	8214	8217	8218.
Vacuolization																			
Focal acidophilic alteration													+						
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration								+										+	
Single granular alteration				+		+	+	+					+					+	
Perinuclear halo				+															
Eosinoph. homogenization																			
Single cell necrosis																			
Group cell necrosis																			
Cell enlargement	+																		
Ductal proliferation																			
Periductal fibrosis																			
Cholangiofibrosis																			
Stern cell proliferation			+	+					+	+	+		+	+		+	+	+	
Epithelioid cell granuloma																			
Periportal inflammation					+											+			
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia	(+)																		
Cholangiomatous lesion																			
Lymph congestion																			

Controls

Number of slides	8219	8220	8221	8222	8223	8224	8226	8228	8229	8232	8233	8234	8235	8236	8237	8238	8239	8241	8243
Vacuolization																			
Focal acidophilic alteration		+	+	+	+												+		+
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration			+														+		
Single granular alteration																			
Perinuclear halo																			
Eosinoph. homogenization																			
Single cell necrosis																			
Group cell necrosis																			
Cell enlargement		+	+							+	+				+				
Ductal proliferation																			
Periductal fibrosis																			
Cholangiofibrosis																			
Stern cell proliferation	+	+		+		+	+		+						+				
Epithelioid cell granuloma																			
Periportal inflammation	+	+						+				+			+				
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia		+	(+)							(+)					(+)				(+)
Cholangiomatous lesion																			
Lymph congestion																			

Controls

Number of slides	8245	8248	8251	8252	8253	8254	8255	8257	8258	8119	8120	8122	8123	8124	8126	8127	8128	8129	8130
Vacuolization					+				(+)									+	
Focal acidophilic alteration	+									+		+		+	+		+		
Single acidophilic alterations	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+		+															+	
Single granular alteration	+												+						
Perinuclear halo										+						+		+	
Eosinoph. homogenization																			
Single cell necrosis							+												
Group cell necrosis																			
Cell enlargement																		+	
Ductal proliferation																			
Periductal fibrosis																			
Cholangiofibrosis																	+		
Stern cell proliferation		+	+			+	+	+	+			+	+	+	+				
Epithelioid cell granuloma																			
Periportal inflammation	+						+	+			+	+							
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia																			
Cholangiomatous lesion																			
Lymph congestion																			
Advanced fibrosis																		(+)	

Diffuse Kupffer cell hyperplasia

Controls

Number of slides	8131	8132	8133	8134	8135	8136	8137	8138	8139	8140	8141	8142	8143	8145	8146	8148	8149	8150	8152
Vacuolization			(+)																
Focal acidophilic alteration			+				+	+	+										
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration								+						+			+	+	+
Single granular alteration		+	+						+			+							
Perinuclear halo			+									+							
Eosinoph. homogenization																			
Single cell necrosis					+					+							+		
Group cell necrosis																			
Cell enlargement																		+	
Ductal proliferation																			
Periductal fibrosis																			
Cholangiofibrosis																			
Stern cell proliferation					+	+				+			+		+	+	+	+	+
Epithelioid cell granuloma																			
Periportal inflammation				+															
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia																			
Cholangiomatous lesion																			
Lymph congestion																			

20
Controls

Number of slides	8154	8155	8156	8157	8158	8160	8162	8163	8164	8166	8167	8168
Vacuolization												
Focal acidophilic alteration			+	+		+						
Single acidophilic alterations	+	+	+	+	+	+	+	+	+	+	+	
Focal granular alteration		+		+								
Single granular alteration	+			+		+					+	
Perinuclear halo												
Eosinoph. homogenization												
Single cell necrosis	+		+									
Group cell necrosis												
Cell enlargement				+								
Ductal proliferation												
Periductal fibrosis												
Cholangiofibrosis												
Stern cell proliferation	+	+	+							+	+	
Epithelioid cell granuloma												
Periportal inflammation												
Hyperplastic nodules with atypia												
Hyperplastic nodules without atypia				(+)								
Cholangiomatous lesion												
Lymph congestion												

Table 21: Differences of liver lesions in control and experimental rats treated with Aroclor 1260

	Experimentals	Controls
Vacuolization	155	13
Focal granular alteration	100	31
Single granular alteration	169	45
Single cell necrosis	125	17
Group cell necrosis	36	2
Cell enlargement	175	17
Ductal proliferation	52	3
Cholangiomatous lesion	7	-
Stern cell proliferation	121	87
Hyperplastic nodules:		
without atypia	136	9
with atypia	43	1

3315 South 104th Street
Omaha, Nebraska 68124
August 1, 1975

Paul. L. Wright, Fh.D.
Monsanto Company
800 North Lindbergh Boulevard
St. Louis, Missouri 68166

Dear Dr. Wright:

Enclosed please find the report on histopathological re-evaluation of the slides you sent to me on May 30, 1975.

The report includes illustrations of my findings and my opinion regarding the interpretation of the results, as well as some recommendations for additional studies. If you have some questions in this regard, please don't hesitate to call me at your convenience.

Sincerely,

P. POUR, M.D.

Tel. (402) 541-4495

jfm

Report On

Histopathological re-evaluation of livers from rats treated with AROCLOR

MONS 095098

SUMMARY

A review of slides from rats fed chronically with three doses of AROCLOR 1242, 1254, and 1260 for different time intervals 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. The results are discussed and suggestions for further studies have been made.

INTRODUCTION

A total of 549 slides, submitted for consultation from Monsanto Company, were said to represent liver tissues from 540 albino rats continuously fed diets containing 1 (T-1), 10 (T-11), or 100 (T-111) ppm AROCLOR 1242 (A group=157 liver sections), 1254 (B group=176 liver sections) and 1260 (C group-211 liver sections), and sacrificed at intervals of 3,8,14, and 24 months. A study with AROCLOR 1260 in albino rats revealed no carcinogenic effects. However, investigators conducted another experiment with AROCLOR 1260 and reported induction of hepatocellular carcinoma in 26 of 184 experimentals, while the ration in controls was 1 out of 173 In addition in the same study 146 of 184 experimental rats showed neoplastic nodules. From this study, Dr. Kimbrough and other NCI consultants (Dr. Robert Squire and Morton Levitt) concluded that AROCLOR 1260 had a hepatocarcinogenic effect when fed in the diet of female Sherman strain rats.

Histopathologic evaluation of additional liver sections from rats of a 2-year chronic oral toxicity study of AROCLOR 1242, 1254 and 1260 by Dr. Gordon of Industrial BIO-TEST Laboratories Inc. indicated that all 3 lots of AROCLOR were slightly tumorigenic at levels of 100 ppm, when fed continuously in the diet for 2 years. Additional material from the latter experiments has been submitted for re-evaluation as to whether there are apparent reasons for the varying results obtained by the two laboratories and suggestions regarding possible additional animal testing.

MATERIALS AND METHODS

For the most part, one slide per rat was submitted, and there were 1-3 slices of liver tissues per slide. However, in the case of 4 rats, there were 2 slides each. Therefore in the final accounting, the number of liver slides exceeded the number of animals by four. Tissues were stained with hematoxylin

and eosin, placed in conventional plastic slide boxes for transport, and were of sufficient quality for evaluation. Some slides were not adequately identified, with regard to sex or treatment groups. In some cases, tissues other than of the liver (i.e., of the mammary glands or pancreas) were found in a few slides, and these were not subjected to histologic evaluation. Four of the liver slides could not be evaluated because of: (1) advanced autolysis in 2 cases ($A_2$230F and $A_3$272M) and (2) severe infiltration by malignant lymphoma cells in 2 other tissues($C_1$569M, $C_1$589M). The slides were evaluated in the same sequence as they were found in the plastic slide boxes. However, the final analysis was performed according to the submitted information with regard to the groups of rats per each dose level and the data was summarized in tables.

The following criteria were used in the evaluation process:

Vacuolization: Small or large vacuolar changes in the hepatocytes (Fig. 1) indicative of fatty metamorphosis.

Focal acidophilic alteration: Focal degeneration of the hepatocytes characterized by intense eosinophilia of cytoplasm and pyknosis of nuclei (Fig. 2).

Single acidophilic alteration: Scattered eosinophilic alteration of hepatocytes (Fig. 3).

Focal granular alteration: Group of hepatocytes with a granular or vacuolar foamy appearance (Figs. 4 and 5).

Single granular alteration: The same cell alteration as above, but in scattered areas rather than in groups.

Perinuclear halo: Vacuolar alteration of cytoplasm in areas near the nuclei. This alteration was distinguishable from fatty metamorphosis, and seems to indicate the location of glycogen, which was extracted by processing (Fig. 6). Such a change was often associated with

eosinophilic homogenization of the cytoplasm around the nuclei of the hepatocytes (Fig. 7) and seems to represent the cell-bounded glycogen.

Single cell necrosis: Necrosis and degeneration of individual cells found throughout the tissue or as

group cell necrosis of a certain area. This alteration was found in 2 forms: a lytic form (Fig. 8), indicative of acute toxic effect with or without minimal inflammatory reaction and coagulative form (coagulative necrosis) (Fig. 9) associated with epithelioid cell reaction (see below).

Cell enlargement: Enlargement of the hepatocytes up to 8-fold of their normal size in localized form as a so-called "hyperplastic nodule" (Fig. 10) or in a more or less diffuse form (Fig. 11; see also A_3: 311F, 287F, 291F, B_3: 982M, 983M, B_2x: 59F, 60F, B_3: 443F, 445F, 484M, 491M, 499M, 507F, 522F, 524F, 527F, 541F, Extra 1F, Extra 4F, 529F, Extra 1F, 2F, 3F). The enlarged cells showed usually eosinophilic, vacuolar or granular alterations (Figs. 12 and 13) and were often associated with bile duct formation (transformation) (Figs. 14 and 15), or with fibrosis (Fig. 16).

Ductual proliferation: Formation of new ducts or proliferation of principal ducts (Figs. 1, 12-16), sometimes associated with

periductal fibrosis in the form of connective tissue manchettes around the individual bile ducts, in contrast to

cholangiofibrosis, which was characterized by both bile duct proliferation and fibrosis (Fig. 17).

Stern cell proliferation: Activation or proliferation of Von Kupffer cells in localized area. Extramedullary hemopoeitic foci were

included in this category.

Epithelioid cell granuloma: Focal inflammation, often with coagulative cell necrosis (Fig. 19). These lesions were often found in areas close to periportal triads or central veins (Figs. 18 - 20). In one case, this inflammatory reaction was present around a foreign body (Fig. 21), which probably represents a parasite. In another section, structures reminiscent of fungeal hyphen (aspergillus fumigatus?) were seen (Fig. 22).

Periportal inflammation: This inflammation occurred in varying degrees of severity, and often in cases with epithelioid cell granulomas (Fig. 18).

Lymph congestion: A peculiar lesion, characterized by formation of spaces lined with endothelial cells and filled with amorphous or granular material or erythrocytes (Fig. 23-25). These occurred in livers, without marked alteration of hepatocytes (Fig. 23), in livers with fatty metamorphosis (Fig. 24), or in areas with enlarged hepatocytes (Fig. 25). This alteration might correspond to fatty cysts or peliosis, as described by other investigators.

Crystal deposition: Light-polarizing material in the sinusoids, which probably represent fatty crystals.

Other lesions: In 4 animals, marked proliferation and cystic distention of the ducts (adenomatous ductal proliferation; cystic proliferation of bile ducts) were seen (Fig. 26). The non-neoplastic character of these lesions was evident by the uniform cytologic appearance of cells and identification of normal hepatocytes between the ducts, indicating a

glandular origin from the principal bile ducts. In one slide (B_3: 527F), atypical glands invading liver parenchyma were found. This lesion seems to represent a metastatic tumor (probably a mammary gland carcinoma of the same animal from which his tumor was submitted), rather than a cholangiocarcinoma. In the same animal localized cellular enlargements of hepatocytes were found; the cells showed a marked pleomorphism, and occasionally contained bile pigment (Fig. 30). There was no ductal proliferation and no periportal traid in this area, but there were hemopoietic foci.

RESULTS:

The histocytologic findings for individual slide(s) are listed on pages 13-37 and the summary of lesions, according to dose levels on pages 38-41 The grouping and subgrouping was based on the report of March 24, 1975, by Industrial Bio-Test Laboratories.

DISCUSSION:

The pathological changes in the livers of both experimental animals and controls varied in quantitative but not qualitative aspects. As the dose level increased, the lesions progressed in severity, indicating AROCLOR'S dose-dependent toxic effect. No marked differences could be found among rats treated with 3 different lots of AROCLOR.

The epithelioid cell granulomas often associated with coagulative cell necrosis and periportal round cell infiltration seem to reflect an endogenous disease, such as parasitic or fungeal infestation (as found in 2 animals) in this colony of rats. The same might be true for the focal bile duct proliferation, periductal fibrosis, and cholangiofibrosis. The apparently higher incidence of this inflammatory condition in the experimental animals might be sought as an

enhancing effect of the compound in the development and course of the disease. However, since their incidence in 24-month-old control rats was even higher than in corresponding experimentals, such an iatrogenic effect of the compound should be ruled out. It should be also pointed out that much liver alteration in animals, as well as in man, is distributed unevenly in the parenchyma and therefore might not be detected in a single section. Examination and comparison of several different liver sections from the same rat will verify this fact. Besides their inflammatory reaction, many other liver lesions found seem unrelated to drugs, and represent, rather, spontaneous age-related alterations, since they appeared in a higher incidence in rats kept for 24 months. However, the more pronounced character of vacuolication and degenerative and regenerative changes is attributed to the toxic effect of the compound. The most frequent finding in rats treated with 100 ppm of compound was cell enlargement, mostly in localized areas which resembled so-called "hyperplastic nodules". We prefer the term "cell enlargement" to cell hypertrophy, since the enlargement of the hepatocytes in the sumbitted material is obviously due to degenerative effect(s) resulting in vacuolization, granulation and hydropic changes. The term hypertrophy should be reserved for describing regenerating or activated cells. The focal response of liver parenchyma to infectious or toxic agents is a known characteristic of this organ, and is in most cases, unspecific. Therefore, focal cell alterations do not always represent a "hyperplastic nodule" or premalignant and malignant lesions. The presence of many necrotic cells, sometime in form of piecemeal necrosis in areas of "hyperplastic nodules" definitely indicates their degenerative changes, associated with some regenerative process. The compression of surrounding tissue, due to focal enlargement of cells (which were sometimes 8 times larger than normal liver cells), is self-explanatory and is in no way indicative of malignant growth. A special staining would be of help in distinguishing non-neoplastic from neoplastic lesions, which usually destroy the normal structures, such as the reticular network. In our opinion, liver lesions should be

considered non-neoplastic, unless otherwise proven. Cytologic criteria, such as cellular pleomorphism and nuclear atypia, are uncharacteristic features and could be seen in any damaged cell, particular in those of organs with a tendency to rapidly regenerate. The criteria of the non-neoplastic lesions in the submitted slides can be summarized as follows:

1. No evidence of destruction

2. In several cases, cell enlargement was not limited to a certain area, but had largely or completely involved the entire liver lobe.

3. In many of the lesions, regular liver structures were found, such as periportal triads, central viens, stinusoids as well as bile ducts often showing a tendency to proliferate. These criteria are in favor of the benign character of these lesions (see Farber: Methods in cancer Research 7, 345, 1973). Since, as mentioned before, the liver lesions might show highly irregular distribution patters, the absence of some regular structures within the pathologic areas is anticipated, and the examination of step section(s) of such tissues pertinent.

4. The cells in an area encompassing enlarged cells (the so-called "hyperplastic nodules") show the same cytologic alteration, as in surrounding tissue or in areas remote from it. This is in contrast to the effect of well-known hepatogenic carcinogens, such as aflatoxin and ethionin in which following treatment, the tissue surrounding the hyperplastic nodules is little different from that of normal liver (Farber, Ibid.). In only one of the present cases were there cytologic alterations which could justify a diagnosis of malignancy. However, even in that lesion regular sinusoids with hempoeitic foci (which are very unusual features for a hepatoma) were present, so that the malignant character of the lesion is questionable. It seems possible that the atypical cytologic alteration of this lesion is due to a response to a tumor metastasis, which was found in its borderline. The latter liver lesion could be interpreted as a cholangiocarcinoma. However, on comparing the histologic pattern of this tumor with the mammary carcinoma from the same

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rat, it becomes obvious that the liver lesion is a metastatic lesion, rather than a primary neoplasm. Nevertheless, interpretation of these particular lesions is difficult and further study is required. Other bile duct lesions, which we called adenomatous lesions, have been described and observed in many species and were considered cystic hyperplsia of the bile duct. The non-neoplastic character of these alterations is evident by their uniform histocytologic patterns and by the presence of normal liver cells between the ducts, indicating alteration of pre-existing ducts.

The question as to whether or not these lesions represent a premalignant alteration cannot be answered, using the present material, and further discussion could only be speculative. Since most liver carcinogens induce tumors during the 8-12 months from the beginning of the experiment, it seems doubtful that AROCLOR will cause neoplasms at a time later than 24 months, which is virtually the terminal age of many rat strains. However, additional study is needed to clarify the problem, particularly because different opinions exist about the nature of the liver lesions induced by AROCLOR. We might recommend the following:

1. Step-sectioning of the present material and special straining of some of the tissues. If this procedure would not clarify the situation, a new experiment should be started (see below).

2. The new set of experiments should compare findings in the same colony with those of other rat colonies, since apparently some strains of rats are unusually sensitive to certain compounds (Farber, Ibid.). For example the rats used in this study seemed to have an endogenous liver disease, which might influence the effect of the AROCLOR. The experiment should also include additional groups with different feeding periods - - (i.e., including rest periods), as proposed by Teebor and Becker. (Cancer Res. 31, 1, 1971).

3. The use of special stains under certain experimental conditions might also deliver additional information (Epstein et al: Cancer Res. 27, 1702, 1967).

Legend:

Fig. 1: Vacuolization of hepatocytes and focal bile duct proliferation: A3-275M, 250x.

Fig. 2: Focal eosinophilic alteration characterized by dense, ioseinophilic cytoplasm and pyknotic nuclei: B1-938F, 250x.

Fig. 3: Scattered, iosinophilic alteration of hepatocytes: B3-68F, 250x.

Fig. 4: Focal granular alteration, associated with cell-enlargement. Two hepatocytes showing eosinophilic alteration are seen within the granulated cells. Note atrophy of surrounding liver-tissue, probably due to compression of enlarge cells: B1x-43M, 250x.

Fig. 5: Different types of granular alteration of hepatocytes, interspersed with eosinophilic alteration. The granulated cells are often 8 times larger than normal hepatocytes: A3-271M, 250x.

Fig. 6: Perinuclear halo in hepatocytes: B1x-43M, 500x.

Fig. 7: Eosinophilic homogenization of cytoplasm. The eosinophilic material probably represents cell-bounded glycogen, which usually will be extracted during histologic processing, giving rise to structures shown in Fig. 6: B3-Extra 2F, 250x.

Fig. 8: Lyric form of group cell necrosis. No inflammatory reaction is seen: B1-338M, 250x.

Fig. 9: Congulative group cell necrosis associated with inflammatory reaction: B3-70F, 250x.

Fig. 10: Focal cell enlargement of hepatocytes. The sinusoidae structure is still present. Note pale nuclei with enlarged, but uniform nuclei: B1-343M, 100x.

Fig. 11: Diffuse enlargement of hepatocytes with characteristic nuclei and nucleoli. A portal triad is seen in middle of photo: A3-314F, 100x.

Fig. 12: Focal cell enlargement with tendency toward bile-duct formation, A3-314F, 250x.

Fig. 13: Focal cell enlargement with vacuolic and granular alteration, as well as bile-duct formation: A3-275M, 250x.

Fig. 14: Focal cell enlargement showing proliferation of bile-duct epithelium: B2-60F, 250x.

Fig. 15: Glandular sturctures of hepatocytes within areas of enlarged hepatocytes. Note apparent pleomorphisum of the cells; however no atypia is present: B3-Ext.F, 250x.

Fig. 16: Fibrosis and proliferation of bile-duct epithelium within area of regenerating and degenerating liver cells: A3-314F, 100x.

Fig. 17: Cholangiofibrosis surrounded by enlarged liver cells showing group cell necrosis (upper left corner): B3-541F, 100x.

Fig. 18: Epithielioid cell granuloma with coagulative cell necrosis, adjacent to a periportal triad, showing marked round cell infiltration: B3-70F, 250x.

Fig. 19: Epithelioid cell granuloma with a multi-nucleated giant cell. Vascuolar degeneration, cell necrosis and cell enlargement are seen in the surrounding tissue. B3-539F, 250x.

Fig. 20: Epithelioid cell granuloma with multiple giant-cells in area close to central vein (left lower corner): C2-707F, 250x.

Fig. 21: Foreign body probably representing a section of a parasite of the liver associated with cell necrosis and few inflammatory cells: C2-707F, 250x.

Fig. 22: Cystic degeneration containing structures similar to <u>aspergillus fumigatus</u>. B3-Extra 3F, 250x.

Fig. 23: Cystic degeneration. The cystic spaces are lined endothelial-like cells and are filled with homogenous eosinophilic or granular material. Minimal enlargement of the sourrounding liver cells: B3-489M, 250x.

Fig. 24: Cystic alteration resembling lymphangiectasia in a liver showing severe vacuolization: B3-459M, 250x.

Fig. 25: Cystic alteration in area of focal cell enlargement giving rise to papillary structures of the hepatocytes. Some of these spaces contain erythrocytes: A3-275M, 250x.

Fig. 26: Cystic proliferation of bile-ducts (adenomatous bile-duct proliferation) A3-243M, 100x.

Fig. 27: High magnification of the same lesion in Fig. 26 showing liver cell groups between proliferated ducts. Note completely benign appearance of the cells. 250x.

Fig. 28: Adenocarcinoma of the liver composed of tall columnar cells, interspersed with mucous-producing cells. Morphologically similar tumor was found in the mammary glands of the same rat: B3-527F, 250x.

Fig. 29: Area of focal cell enlargement displaying pleomorphism of the nuclei. B3-527, 500x.

Fig. 30: Another area of the same lesion showing intracytoplasmic bile-pigment (arrow). 500x.

Code	C_1								C_2										C_3			
Sex	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	F	M	M	?	?
No	596	598	599	636	637	638	639	640	676	677	678	679	680	716	717	718	719	720	756	757	758	759
Vacuolization	+	+	+	+	+	+	+		+	+		+	+		+			+				
Focal acidophilic alteration																						
Single acidophilic alteration	+			+	+	+	+	+	+	+		+	+	+		+	+	+	+	+	+	+
Focal granular alteration																						
Single granular alteration		+											+	+			+	+		+	+	+
Perinuclear holo		+	+						+	+	+	+				+	+	+	+	+	+	+
Eosinoph.homogenization	+		+							+	+	+	+			+			+	+	+	+
Single cell necrosis																						
Group cell necrosis																						
Cell enlargment																						
Ductal proliferation															+							
Periductal fibrosis																						
Cholangiofibrosis																						
Stern cell proliferation					+			+			+					+	+			+	+	+
Epithliod-cell granuloma								+							+							
Periportal inflamation					+	+		+			+	+			+	+	+	+	+	+		
Lymph congestion																						

Code	C_3				C_0										C_1				
Sex	M	F	F	F	M	M	M	M	M	F	F	F	F	F	M	M	M	M	M
No	760	796	797	798	800	36	37	38	39	40	76	77	78	79	80	1011	1012	1013	1014	1015
Vacuolization					+				+	+						+	+	+		
Focal acidophilic alteration																				
Single acidophilic alteration	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration				+	+									+						
Single granular alteration	+	+	+	+	+		+	+	+	+	+	+	+	+	+					
Perinuclear halo	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eosinoph.homogenization	+	+	+		+	+	+	+	+	+				+			+			
Single cell necrosis									+							+		+		
Group cell necrosis																				
Cell enlargment																				
Ductal proliferation	+						+													
Periductal fibrosis																	+			
Cholangiofibrosis																				
Stern cell proliferation		+		+		+			+		+				+					
Epithliod cell granuloma													+			+	+	+	+	
Periportal inflamation													+			+	+	+	+	+
Lymph congestion																				

MONS 095112

Code	C_1					C_2								C_3				
Sex	F	F	F	F	F	F	M	M	M	F	F	F	F	M	M	M	M	F
No	1026	1027	1028	1029	1030	1041	1042	1043	1045	1056	1057	1058	1059	1071	1072	1073	1075	1080
Vacuolization	+			+										+	+			
Focal acidophilic alteration																		
Single acidophilic alteration	+		+	+	+		+	+	+	+	+	+	+			+	+	+
Focal granular alteration	+					+	+	+	+	+	+	+	+			+		+
Single granular alteration	+	+		+	+									+	+		+	
Perinuclear holo	+	+	+	+	+	+	+	+	+	+	+		+		+	+	+	
Eosinoph homogenization						+		+	+							+		
Single cell necrosis					+	+	+	+	+			+				+		+
Group cell necrosis																		
Cell enlargment																		+
Ductal proliferation																		
Periductal fibrosis				+			+	+										
Cholangiofibrosis																		
Stern cell proliferation					+	+						+		+				
Epithliod cell granuloma	+		+		+	+	+		+	+	+	+						
Periportal inflamation	+	+	+	+	+			+	+	+	+	+	+					
Lymph congestion																		

MONS 095113

Code	C_3				C_0										C_1										C_2
Sex	F	F	F	F	M	M	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	F	M
No	1087	1088	1089	1090	801	802	803	804	805	816	817	818	819	820	71	72	73	74	75	76	77	78	79	80	81
Vacuolization					+													+							
Focal acidophilic alteration																									
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+			+														+							
Single granular alteration		+	+		+	+	+	+	+	+	+		+		+	+	+		+	+	+	+	+	+	+
Perinuclear holo					+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eosinoph.homogenization					+		+	+	+							+	+	+	+	+				+	
Single cell necrosis	+		+	+	+	+	+	+					+	+		+	+	+		+		+	+	+	
Group cell necrosis																									
Cell enlargment	+																								
Ductal proliferation				+																					
Periductal fibrosis		+	+																						
Cholangiofibrosis																									
Stern cell proliferation		+			+	+	+																		
Epithliod cell granuloma	+					+								+			+			+		+		+	
Periportal inflamation					+	+			+	+			+	+	+		+	+	+	+		+		+	
Lymph congestion																									

Code	C_2									C_3									C_0									C_1				
Sex	M	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	M	M	M	M	M	F	F	F	F	M	M	M	M	M
No	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	1	2	3	4	5	6	7	8	9	564	566	591	567	569
Vacuolization		+		+						+	+	+		+	+	+	+	+	+		+										
Focal acidophilic alteration																																
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+	+	+	+	
Focal granular alteration			+		+	+					+	+	+	+	+	+	+	+		+					+			+				
Single granular alteration	+	+		+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		
Perinuclear holo	+	+	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eosinoph.homogenization			+	+								+	+	+	+				+	+	+	+	+						+	+		
Single cell necrosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+				+		
Group cell necrosis																																
Cell enlargment											+	+	+		+	+	+	+														
Ductal proliferation			+	+	+						+	+					+									+	+	+	+	+	+	
Periductal fibrosis			+								+	+				+	+	+		+	+				+				+	+	
Cholangiofibrosis																																
Stern cell proliferation			+		+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+						
Epithlioid cell granuloma	+		+	+	+	+				+	+	+	+			+	+	+			+			+					+	+		
Periportal inflamation	+		+	+	+					+	+	+	+	+		+	+				+		+	+	+	+	+			+		
Lymph congestion											+																					

MILGNANT LYMPHOMA

MONS 095115

Code	C_1																						
Sex	M	M	M	M	M	M	F	F	F	F	M	F	F	F	F	F	F	F	F	F	F	F	F
No	572	576	580	588	589	595	601	604	605	582	583	607	608	609	613	621	627	628	631	634	635	606	610
Vacuolization								+	+	+	+	+	+	+	+		+	+	+	+	+		+
Focal acidophilic alteration				+																			+
Single acidophilic alteration	+	+	+	+		+	+		+		+			+			+	+	+	+	+		+
Focal granular alteration								+		+		+		+						+			
Single granular alteration	+	+	+	+		+	+																
Perinuclear holo	+	+		+		+	+	+	+		+	+	+			+	+						
Eosinoph homogenization	+			+							+												
Single cell necrosis	+			+		+	+		+	+		+			+				+		+		+
Group cell necrosis																							
Cell enlargment																			+				
Ductal proliferation	+	+		+		+	+			+		+			+	+						+	+
Periductal fibrosis	+	+	+	+		+	+			+		+				+					+	+	+
Cholangiofibrosis				+			+																
Stern cell proliferation		+					+							+						+			+
Epithliod cell granuloma		+																+					
Periportal inflamation		+					+							+					+				
Lymph congestion																		+					

MILGNANT LYMPHOMA

MONS 095116

Code	C_1			C_2													C_3						
Sex	F	F	F	M	M	M	M	M	M	M	M	M	M	M	M	M	F	F	F	F		F	F
No	620	626	633	655	657	662	667	640	641	643	644	645	646	649	651	673	775	Ext.	733	765	776	773	780
Vacuolization	+	+			+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+
Focal acidophilic alteration		+	+																				
Single acidophilic alteration	+	+	+	+		+	+	+					+	+	+		+	+	+		+	+	
Focal granular alteration			+			+			+	+							+	+			+	+	
Single granular alteration		+		+	+			+	+		+								+				
Perinuclear halo									+	+				+			+						
Eosinoph. homogenization								+				+											
Single cell necrosis		+	+	+	+	+		+		+			+				+			+	+	+	
Group cell necrosis								+															
Cell enlargment								+				+					+	+	+	+	+	+	
Ductal proliferation			+	+	+		+	+			+	+	+				+		+		+	+	
Periductal fibrosis			+	+			+		+		+	+	+				+	+	+		+	+	
Cholangiofibrosis																			+		+	+	
Stern cell proliferation	+				+	+				+	+		+			+							
Epithliod cell granuloma																				+			
Periportal inflamation			+	+		+		+		+		+	+									+	+
Lymph congestion						+					+												

MONS 095117

Code	C_3				
Sex	M	F	F	F	F
No	724	766	767	771	789
Vacuolization	+	+	+	+	+
Focal acidophilic alteration					+
Single acidophilic alteration	+	+	+	+	+
Focal granular alteration		+	+	+	+
Single granular alteration	+	+	+	+	+
Perinuclear holo			+		+
Eosinoph. homogenization					+
Single cell necrosis	+	+	+	+	+
Group cell necrosis			+		+
Cell enlargment		+	+	+	+
Ductal proliferation		+	+	+	+
Periductal fibrosis			+		+
Cholangiofibrosis			+		+
Stern cell proliferation	+		+	+	+
Epithliod.cell granuloma					
Periportal inflamation					
Lymph congestion					
Fibrosis			+		+
cholangiomatous lesion				+	

Code	C_3		C_0							C_2														
Sex	F	F	M	M	M	M	M	M	M	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
No	793	Ext.	8	8	11	12	21	23	33	686	687	689	685	690	695	697	700	703	707	708	711	712	682	683	691
Vacuolization	+	+	+			+		+		+	+	+	+	+		+	+	+	+	+	+	+	+		+
Focal acidophilic alteration																	+								
Single acidophilic alteration			+	+	+	+	+	+	+	+	+							+	+	+		+		+	+
Focal granular alteration		+		+			+	+	+			+							+			+	+	+	
Single granular alteration			+	+	+					+						+	+			+	+	+			
Perinuclear holo		+	+			+			+	+	+	+	+				+		+		+	+	+	+	+
Eosinoph. homogenization		+					+											+				+			
Single cell necrosis		+												+					+			+	+		
Group cell necrosis																				+					
Cell enlargment		+		+													+								
Ductal proliferation	+	+	+	+		+	+	+	+		+									+					+
Periductal fibrosis			+	+	+		+	+	+	+			+							+		+			
Cholangiofibrosis		+			+																				
Stern cell proliferation		+	+		+						+					+	+				+	+		+	
Epithliod cell granuloma									+					+		+	+		+		+	+		+	
Periportal inflamation																+	+	+			+	+		+	
Lymph congestion																									

MONS 095119

Code	C_2	C_0																	A							
Sex	F	M	M		F	F	F	F	F	F	F	F	F	F	F	F	F	F	M	M	M	M	M	M	F	F
No	702	34	35	Ext.	46	47	49	51	52	56	59	62	63	64	66	70	71	Ext.	116	117	118	119	120	147	156	157
Vacuolization	+				+		+	+			+	+					+		+		+	+			+	+
Focal acidophilic alteration		+				+					+	+														
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+				+		+	+							+									+		
Single granular alteration		+	+	+	+	+	+	+		+	+	+	+	+		+	+	+	+	+		+	+	+	+	+
Perinuclear holo	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eosinoph homogenization	+	+	+			+	+	+	+				+		+	+	+	+				+	+	+	+	+
Single cell necrosis		+	+	+	+		+	+				+	+	+		+	+						+	+		+
Group cell necrosis										+				+												
Cell enlargment										+		+														
Ductal proliferation		+			+		+	+	+	+			+		+	+	+	+							+	+
Periductal fibrosis		+					+	+	+	+		+	+	+	+		+							+	+	+
Cholangiofibrosis												+					+									
Stern cell proliferation		+	+	+	+		+	+				+	+		+			+	+							+
Epithliod cell granuloma		+		+	+		+					+		+									+			
Periportal inflamation		+		+	+		+	+				+				+	+									
Lymph congestion																		+								

MONS 095120

Code	A													A_3		A_2	A_3				
Sex	F	F	F	M	M	M	M	M	F	F	F	F	F	M	M	M		F	F	F	F	F
No	158	159	160	195	196	198	200	Ext.	236	237	238	239	240	276	277	279	280	315	317	318	319	320
Vacuolization	+			+	+	+	+						+		+							
Focal acidophilic alteration																						
Single acidophilic alteration	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration														+	+	+	+		+			
Single granular alteration		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear holo	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+	+	+	+
Eosinoph. homogenization				+	+	+	+	+		+	+	+	+	+	+	+		+				
Single cell necrosis		+		+	+	+	+				+	+	+		+		+			+		+
Group cell necrosis																						
Cell enlargment														+	+	+				+		
Ductal proliferation										+	+	+		+		+			+			
Periductal fibrosis		+	+							+	+	+	+		+	+						
Cholangiofibrosis																						
Stern cell proliferation		+			+	+	+			+	+	+	+						+	+	+	+
Epithliod. cell granuloma		+							+	+	+											
Periportal inflamation						+															+	
Lymph congestion																						

MONS 095121

Code	?																				A1		
Sex	?	?	?	?	?	?	?	?	?	?	?	M	M	M	M	?	F	F	F	F	M	M	M
No	832	835	834	846	848	849	864	865	873	878	879	891	893	894	895	906	907	908	909	910	11	12	13
Vacuolization												+		+		+							+
Focal acidophilic alteration																							
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+							+	+	+		+	+	+		+						+	+
Single granular alteration	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear holo	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Eosinoph homogenization			+		+	+	+	+	+			+	+	+	+	+	+			+	+	+	+
Single cell necrosis	+	+	+			+	+	+	+	+		+	+	+		+							+
Group cell necrosis																							
Cell enlargment								+					+	+									
Ductal proliferation		+				+		+	+			+			+								
Periductal fibrosis	+	+				+		+	+	+		+	+		+		+					+	+
Cholangiofibrosis																							+
Stern cell proliferation	+	+	+	+	+		+	+	+														
Epithliod cell granuloma	+	+	+	+	+	+		+		+											+	+	+
Periportal inflamation	+	+	+	+		+	+	+	+				+							+	+		+
Lymph congestion																							
* Crystal deposition									**														

MONS 095122

Code	?	A_1			?	A_1	?											A_3					A_1		?	
Sex	M	M	F	F	F	F	M	M	M	M	M	F	F	F	F	F	?	?	?	M	F	F	F	F	?	?	?	?
No	14	15	16	17	18	19	21	22	23	24	25	26	27	28	29	30	31	32	33	34	36	37	38	39	40	85	86	87	101
Vacuolization					+					+	+		+									+							
Focal acidophilic alteration																													
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+	+		+		+	+	+	+	+	+	+	+			+	+	+	+	+		+	+	+	+	+	+	+	
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear holo		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+	+	+	+	+	+	+		+
Eosinoph. homogenization		+	+				+		+	+	+	+	+		+	+		+		+	+	+	+	+	+	+	+		+
Single cell necrosis		+					+	+	+	+			+							+		+	+	+	+	+	+		
Group cell necrosis																												+	
Cell enlargment																		+		+	+	+	+	+	+				+
Ductal proliferation	+													+								+	+	+	+	+		+	+
Periductal fibrosis	+																+			+		+	+	+	+	+		+	+
Cholangiofibrosis																													
Stern cell proliferation		+	+	+				+		+			+				+		+	+						+		
Epithliod. cell granuloma		+						+			+		+							+						+	+		
Periportal inflamation	+	+		+				+			+		+	+												+	+		+
Lymph congestion																										+			
*Crystal deposition						++							++																

Code	?			A_1			?				A_1												A_2
Sex	?	?	?	M	?	?	F	?	?	?	?	?	F	F	F	F	F	F	F	F	F	F	?
No	106	112	114	105	107	109	122	125	127	129	130	138	141	147	151	155	144	131	132	135	139	16
Vacuolization					+		+					+				+						
Focal acidophilic alteration						+														+	+	+
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration				+	+	+	+				+									+		+
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
Perinuclear holo	+	+	+	+	+	+			+	+	+		+	+	+	+	+	+	+			+
Eosinoph. homogenization	+	+	+	+	+	+			+	+	+			+	+	+						+
Single cell necrosis				+		+	+		+		+	+										
Group cell necrosis																						
Cell enlargment							+													+		
Ductal proliferation	+	+		+	+	+	+	+	+	+					+				+	+		+
Periductal fibrosis	+	+			+	+	+	+	+	+					+			+		+		+
Cholangiofibrosis	+		+					+		+										+	+	
Stern cell proliferation																		+	+			
Epithliod.cell granuloma				+			+												+			
Periportal inflamation				+			+							+				+	+			+
Lymph congestion																						
* Crystal deposition											*+											

Code		A_2		?		A_2		?			A_2									?	A_2	?	?
Sex	?	?	?	?	?	M	?	?	?	F	F	F	F	F	F	F	F	F	F	F	F	F	F
No	168	179	182	184	187	Ext.	205	208	210	212	213	220	221	224	233	234	219	230	203	204	206	207
Vacuolization	+	+	+	+					+	+	+	+		+			+	AUTOLYTIC CHANGES			+	+
Focal acidophilic alteration			+				+					+				+						
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+	+	+
Focal granular alteration	+	+	+	+	+	+	+	+	+	+		+		+		+	+					+
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Perinuclear holo	+	+			+		+		+	+	+	+	+	+		+	+				+	+
Eosinoph. homogenization	+	+		+		+	+		+	+		+		+			+				+	+
Single cell necrosis	+	+	+		+	+	+	+	+	+	+	+		+		+	+					
Group cell necrosis											+											
Cell enlargment	+	+	+			+	+		+			+	+	+		+						
Ductal proliferation	+	+	+	+	+	+	+		+		+	+		+	+	+	+		+		+	
Periductal fibrosis	+	+	+	+	+	+	+		+		+	+		+		+			+		+	
Cholangiofibrosis	+																				+	
Stern cell proliferation																						
Epithliod.cell granuloma												+				+						
Periportal inflamation	+					+						+									+	
Lymph congestion		+																				

MONS 095125

Code	A_3		?		A_3		?	A_3							?	?	A_3						
Sex	M	?	M	?	M	M	M	M	M	M	M	?	M	M	?	?	F	F	F	F	F	F	F
No	241	253	261	264	270	271	272	275	243	244	312	231	274	275	294	297	302	306	308	311	314	240	245
Vacuolization	+	+		+	+		+			+	+		+	+	+	+			+	+	+	+	+
Focal acidophilic alteration		+																					
Single acidophilic alteration	+	+	+	+	+	+		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Single granular alteration	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear holo	+			+	+					+		+	+			+			+	+	+	+	+
Eosinoph. homogenization	+			+	+	+				+		+	+			+	+		+	+	+	+	+
Single cell necrosis	+	+	+	+	+	+		+			+	+	+	+	+	+	+		+	+	+	+	+
Group cell necrosis	+	+	+	+										+	+	+	+			+	+	+	+
Cell enlargment	+	+		+	+	+		+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Ductal proliferation	+		+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Periductal fibrosis	+	+	+	+	+	+		+		+	+	+	+	+	+	+			+	+	+	+	+
Cholangiofibrosis	+		+		+						+				+						+	+	+
Stern cell proliferation						+																	+
Epithliod.cell granuloma										+								+					
Periportal inflamation	+	+	+	+	+	+				+	+							+					
Lymph congestion	+	+		+						+				+									

AUTOLYTIC CHANGES

MONS 095126

Code	A_3	A_3	?	?	A_3
Sex	F	F	?	?	F
No	281	287	291	291	309
Vacuolization	+	+	+	+	+
Focal acidophilic alteration		+			
Single acidophilic alteration	+	+	+	+	+
Focal granular alteration	+	+	+	+	+
Single granular alteration	+	+	+	+	+
Perinuclear holo		+	+		+
Eosinoph. homogenization	+	+	+	+	
Single cell necrosis	+	+	+	+	+
Group cell necrosis			+	+	+
Cell enlargment	+	+	+	+	+
Ductal proliferation	+	+	+	+	+
Periductal fibrosis	+	+	+	+	+
Cholangiofibrosis	+	+	+		+
Stern cell proliferation					
Epithliod.cell granuloma					
Periportal inflamation					
Lymph congestion					+

Code	B_1										B_2										B_3	
Sex	M	M	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	F	M	M
No	356	357	358	359	360	396	397	398	399	400	436	437	438	439	440	476	477	478	479	480	516	517
Vacuolization	+	+											+								+	
Focal acidophilic alteration																						
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration		+					+														+	
Single granular alteration	+	+	+	+	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear holo	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eosinoph. homogenization	+	+	+	+	+	+	+		+		+	+	+	+	+	+		+	+	+	+	+
Single cell necrosis																+					+	
Group cell necrosis																						
Cell enlargment																					+	
Ductal proliferation																						
Periductal fibrosis		+			+		+			+												
Cholangiofibrosis																						
Stern cell proliferation	+				+		+	+	+				+	+		+	+	+	+	+	+	
Epithliod.cell granuloma							+					+				+						
Periportal inflamation	+	+					+									+					+	
Lymph congestion																						

Code	B_3								B_1										B_2			
Sex	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	F	M	M	M	M
No	518	519	520	555	557	558	559	560	921	922	923	924	925	936	937	938	939	940	950	951	952	953
Vacuolization	+	+	+													+	+					+
Focal acidophilic alteration																+						
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+			+	+		+															
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear holo	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Eosinoph. homogenization	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Single cell necrosis				+			+		+		+					+	+	+			+	
Group cell necrosis	+																					
Cell enlargment	+	+	+																			
Ductal proliferation											+						+					
Periductal fibrosis							+				+			+	+					+		
Cholangiofibrosis																						
Stern cell proliferation	+	+	+	+	+		+				+	+	+		+		+	+			+	+
Epithliod.cell granuloma	+			+			+		+		+			+			+	+			+	
Periportal inflamation				+					+	+	+				+		+	+			+	
Lymph congestion																						

MONS 095129

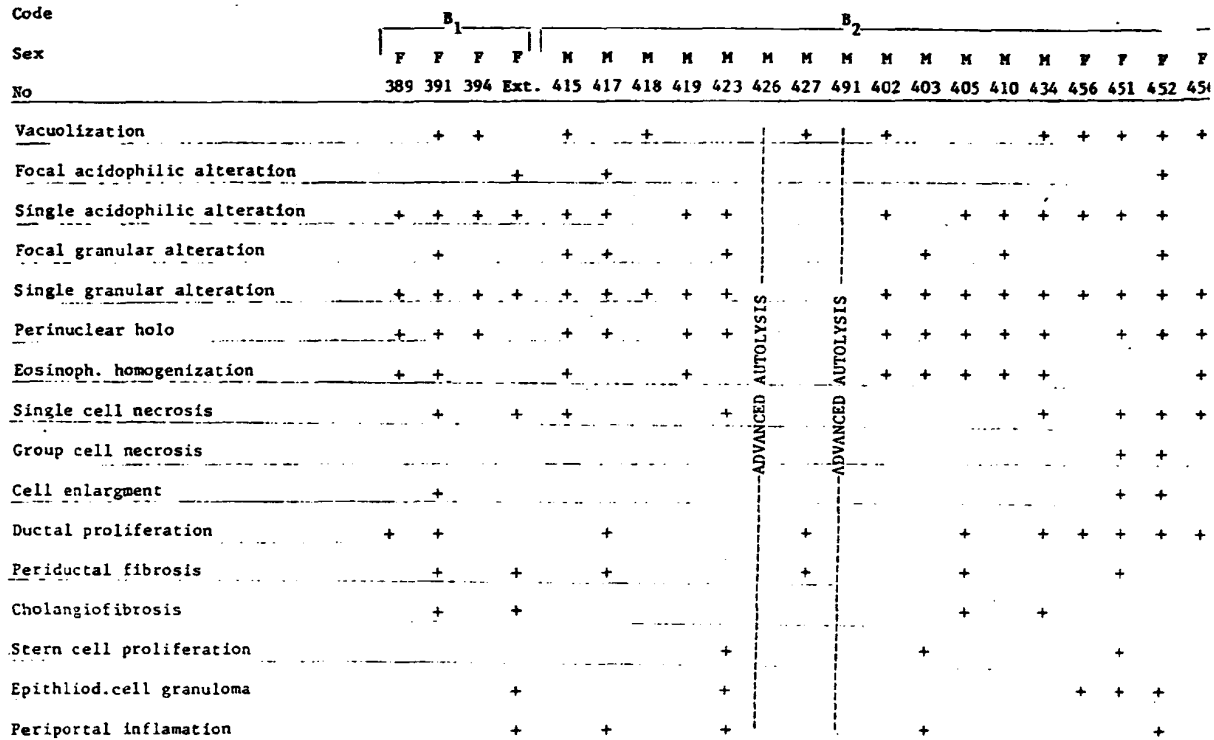
Code	B_2						B_3										B_1x							
Sex	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F
No	954	966	967	968	969	970	981	982	983	984	985	996	997	998	999	1000	41	42	43	44	45	46	47	48
Vacuolization	+						+	+	+	+	+	+					+	+	+					
Focal acidophilic alteration								+	+								+					+		
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration									+		+		+	+	+		+	+	+	+	+	+	+	
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear holo	+				+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+		+	+
Eosinoph. homogenization	+				+	+	+	+	+	+	+	+					+	+	+	+	+		+	
Single cell necrosis	+		+	+		+	+	+	+	+	+	+	+		+									
Group cell necrosis										+														
Cell enlargment							+	+	+	+	+	+		+	+	+								
Ductal proliferation			+			+	+	+	+				+		+		+	+						+
Periductal fibrosis					+	+	+	+	+	+	+													
Cholangiofibrosis																								
Stern cell proliferation	+	+	+	+	+	+	+	+	+			+	+										+	
Epithliod.cell granuloma			+	+		+	+	+	+	+	+				+									
Periportal inflamation	+		+	+	+	+	+	+	+	+	+								+					
Lymph congestion																								

MONS 095130

Code	B_1x		B_2x									B_2	B_3										B_1					
Sex	F	F	M	M	M	M	M	F	F	F	F	F	M	M	M	M	M	M	F	F	F	F	M	M	M	M	M	M
No	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	326	330	335	338	351	323
Vacuolization	+	+		+	+	+	+	+	+		+	+	+			+	+				+		+		+	+	+	
Focal acidophilic alteration	+			+												+				+							+	
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear holo	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
Eosinoph. homogenization			+	+	+	+	+	+	+	+	+		+		+	+	+	+			+		+	+	+	+	+	+
Single cell necrosis				+	+	+	+	+			+	+	+	+		+	+	+	+	+	+	+	+	+			+	
Group cell necrosis																+						+				+	+	
Cell enlargment											+	+					+											
Ductal proliferation	+					+			+			+					+		+			+		+	+		+	+
Periductal fibrosis									+													+	+	+	+			
Cholangiofibrosis																												
Stern cell proliferation			+	+		+	+		+					+			+		+		+	+	+				
Epithliod.cell granuloma						+	+	+				+	+	+					+	+		+						
Periportal inflamation				+		+	+	+					+	+			+		+			+	+					
Lymph congestion																	+											

MONS 095131

Code	B_1																				
Sex	M	M	M	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
No	325	343	340	342	362	368	374	375	376	475	366	367	372	377	378	379	380	381	384	387	388
Vacuolization				+										+	+	+			+		
Focal acidophilic alteration		+																			
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Focal granular alteration	+			+	+	+	+	+	+					+			+		+	+	
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Perinuclear holo	+	+	+	+			+	+	+	+	+		+		+	+	+	+	+	+	
Eosinoph. homogenization	+	+	+				+	+			+				+	+	+	+	+	+	
Single cell necrosis	+	+	+	+	+	+	+	+	+	+				+		+				+	+
Group cell necrosis														+							
Cell enlargment		+	+				+		+						+			+			
Ductal proliferation		+	+	+		+	+	+		+	+		+			+					
Periductal fibrosis		+	+	+		+	+	+	+	+	+		+			+			+		
Cholangiofibrosis			+	+		+			+	+	+		+			+					
Stern cell proliferation									+					+		+					
Epithliod.cell granuloma			+		+		+		+											+	+
Periportal inflamation									+							+				+	+
Lymph congestion														+	+						


Code
B1
B2
Sex
F F F F M M M M M M M M M M M M F F F F
No
389 391 394 Ext. 415 417 418 419 423 426 427 491 402 403 405 410 434 456 451 452 45
Vacuolization
Focal acidophilic alteration
Single acidophilic alteration
Focal granular alteration
Single granular alteration
Perinuclear holo
Eosinoph. homogenization
Single cell necrosis
Group cell necrosis
Cell enlargment
Ductal proliferation
Periductal fibrosis
Cholangiofibrosis
Stern cell proliferation
Epithliod.cell granuloma
Periportal inflamation
Lymph congestion
ADVANCED AUTOLYSIS
ADVANCED AUTOLYSIS

MONS 095133

Code	B_2									B_3												
Sex	F	F	F	F	F	F	F	F	F	M	M	M	M	M	F	M	M	M	M	M	F	F
No	459	463	469	470	471	478	443	445	448	484	491	497	499	499	507	509	510	512	483	489	522	52
Vacuolization	+	+	+			+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Focal acidophilic alteration						+										+	+					
Single acidophilic alteration	+	+	+	+	+	+	+	+		+	+	+		+	+	+	+	+	+	+	+	+
Focal granular alteration	+	+	+	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear halo	+	+	+		+	+	+	+	+		+			+	+	+	+					
Eosinoph. homogenization	+	+	+		+	+	+	+	+													•
Single cell necrosis		+	+			+		+		+	+	+	+	+	+	+	+	+	+	+	+	+
Group cell necrosis				+						+	+			+	+						+	
Cell enlargment	+	+				+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Ductal proliferation	+	+		+	+	+	+			+	+	+			+	+	+	+	+	+	+	
Periductal fibrosis			+			+				+	+	+				+	+	+		+	+	
Cholangiofibrosis						+					+							+	+	+	+	
Stern cell proliferation			+							+												+
Epithliod.cell granuloma			+												+					+		
Periportal inflamation			+	+						+								+		+	+	
Lymph congestion														+						+		
Advanced fibrosis															+							

Code	B_3															
Sex	F	F	F	1F	2F	3F	4F	5F	5F	F	F	F	F	1F	2F	3F
No	527	541	547	Ext.	Ext.	Ext.	Ext.	Ext.	Ext.	536	537	539	441	Ext.	Ext.	Ext.
Vacuolization	+	+	+	+	+	+	+	+		+		+		+	+	+
Focal acidophilic alteration														+	+	
Single acidophilic alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration	+	+	+	+	+	+	+	+	+	+			+	+	+	+
Single granular alteration	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perinuclear halo			+	+					+		+	+		+		+
Eosinoph. homogenization									+					+		
Single cell necrosis	+	+	+	+	+	+	+	+		+	+	+		+	+	+
Group cell necrosis	+	+	+	+	+	+	+	+	+	+	+	+			+	
Cell enlargment	+	+	+	+	+	+	+	+				+		+	+	+
Ductal proliferation	+	+	+	+	+		+	+	+	+		+	+	+	+	+
Periductal fibrosis	+	+	+	+	+	+	+	+	+	+		+		+	+	+
Cholangiofibrosis		+		+			+	+		+		+	+	+	+	
Stern cell proliferation	+			+												
Epithliod.cell granuloma												+				
Periportal inflamation	+			+												
Lymph congestion																
Hepatoma(?)	+															
Cholangiocarcinoma (?)	+															
Cholangomatous lesion					+										+	

A GROUP

Sacrifice Interval	3 Months			8 Months			14 Months			24 Months		
Dose Level	AI	AII	AIII	AI	AII	AIII	AI	AII	AIII	AI	AII	AIII
No. of Animals	11	10	9	6	5	9	9	10	9	25	22(23)	27(28)
Vacuolization	6	5	1	0	0	3	2	3	1	4	12	20
Focal acidophilic alteration	0	0	0	0	0	0	0	0	0	3	5	2
Single acidophilic alteration	11	8	9	6	5	9	9	10	9	25	21	26
Focal granular alteration	1	0	5	1	3	4	6	8	8	9	16	26
Single granular alteration	7	9	9	6	4	9	9	10	9	24	22	27
Perinuclear holo	11	9	8	6	4	9	8	10	5	19	15	15
Eosinoph. homogenization	5	9	4	3	3	7	5	8	7	15	13	18
Single cell necrosis	4	7	4	4	4	4	2	5	5	9	14	24
Group cell necrosis	0	0	0	0	0	0	0	0	0	1	1	15
Cell enlargment	0	0	4	0	1	2	0	0	7	3	10	25
Ductal proliferation	2	3	3	2	2	2	1	1	4	15	17	26
Periductal fibrosis	5	4	2	3	3	4	3	0	6	14	15	24
Cholangiofibrosis	0	0	0	0	0	0	1	0	0	6	2	12
Stern cell proliferation	2	7	4	5	3	0	3	3	3	3	0	2
Epithliod. cell granuloma	2	3	0	6	2	0	4	3	1	5	2	2
Periportal inflamation	0	1	1	5	3	2	5	4	0	8	5	9
Lymph congestion	0	0	0	0	0	0	0	0	0	1	1	6
Crystal deposition	0	0	0	0	1	0	1	2	0	1	0	0

MONS 095136

B GROUP

Sacrifice Interval	3 Months			8 Months			14 Months			24 Months		
Dose Level	1ppm	10ppm	100ppm	1ppm	10ppm	100ppm	1ppm	10ppm	100ppm	1ppm	10ppm	100ppm
No. of Animals	10	10	10	10	10	10	10	10	10	31	26	29
Vacuolization	2	1	3	2	2	6	5	8	4	11	15	26
Focal acidophilic alteration	0	0	0	1	0	2	3	1	2	3	3	4
Single acidophilic alteration	10	10	10	10	10	10	10	10	10	30	19	28
Focal granular alteration	2	0	5	0	0	5	9	9	9	17	13	27
Single granular alteration	8	10	10	10	10	10	10	10	10	31	23	29
Perinuclear holo	10	10	10	9	7	9	9	10	9	25	20	12
Eosinoph. homogenization	8	9	7	10	7	6	6	9	6	20	16	2
Single cell necrosis	0	1	3	5	5	8	0	7	9	19	10	26
Group cell necrosis	0	0	1	0	0	1	0	0	2	3	3	18
Cell enlargment	0	0	4	0	0	9	0	2	1	7	8	24
Ductal proliferation	0	0	0	2	2	5	4	3	3	16	14	24
Periductal fibrosis	4	0	1	3	3	5	0	1	1	17	6	22
Cholangiofibrosis	0	0	0	0	0	0	0	0	0	10	3	14
Stern cell proliferation	5	7	7	5	8	5	1	5	5	4	4	4
Epithliod. cell granuloma	1	2	3	4	4	6	0	4	5	7	5	2
Periportal inflamation	3	1	2	5	5	5	1	4	5	6	6	6
Lymph congestion	0	0	0	0	0	0	0	0	1	3	1	2
Advanced fibrosis												1
Hepatoma (?)												1
Cholangiocarcinoma (?)												1
Chp[illegible]ions												2

MONS 095137

C GROUP

Sacrifice Interval	3 Months				8 Months				14 Months			
Dose Level	1ppm	10ppm	100ppm	control	1ppm	10ppm	100ppm	control	1ppm	10ppm	100ppm	control
No. of Animals	8	10	9	10	10	8	9	10	10	10	9	9
Vacuolization	7	6	1	2	5	0	0	1	1	2	8	2
Focal acidophilic alteration	0	0	0	0	0	0	0	0	0	0	0	0
Single acidophilic alteration	6	8	9	9	9	7	7	10	10	10	9	7
Focal granular alteration	0	0	2	1	1	8	4	0	1	3	8	2
Single granular alteration	1	4	8	9	4	0	5	8	9	7	9	9
Perinuclear holo	2	7	8	10	5	7	3	10	10	7	9	9
Eosinoph. homogenization	2	5	8	6	5	3	1	4	6	2	5	5
Single cell necrosis	0	0	0	1	3	4	5	6	7	9	9	5
Group cell necrosis	0	0	0	0	0	0	0	0	0	0	0	0
Cell enlargment	0	0	0	0	0	0	2	0	0	0	7	0
Ductal proliferation	0	1	1	1	0	0	1	0	0	3	3	1
Periductal fibrosis	0	0	0	0	2	2	2	0	0	1	5	3
Cholangiofibrosis	0	0	0	0	0	0	0	0	0	0	0	0
Stern cell proliferation	2	3	5	4	2	2	2	3	0	4	9	7
Epithliod. cell granuloma	1	1	0	1	7	6	1	2	4	5	7	2
Periportal inflamation	3	6	2	1	10	6	0	6	7	4	7	6
Lymph congestion	0	0	0	0	0	0	0	0	0	0	1	0

MONS 095138

C GROUP

Sacrifice Interval	24 Months			
Dose Level	1ppm	10ppm	100ppm	control
No. of Animals	29(31)	30	14	24
Vacuolization	16	25	14	9
Focal acidophilic alteration	4	1	1	4
Single acidophilic alteration	22	16	10	24
Focal granular alteration	7	9	9	8
Single granular alteration	9	11	6	18
Perinuclear holo	12	15	4	20
Eosinoph. homogenization	5	5	1	12
Single cell necrosis	14	10	10	11
Group cell necrosis	0	2	2	2
Cell enlargment	1	3	12	4
Ductal proliferation	16	11	10	17
Periductal fibrosis	15	10	7	16
Cholangiofibrosis	2	0	6	3
Stern cell proliferation	6	12	5	12
Epithliod. cell granuloma	4	7	1	7
Periportal inflamation	7	6	2	8
Lymph congestion	1	2	0	1
Advanced fibrosis			2	
Cholangiomatous lesion			1	

MONS 095139