Report

On

Histopathological Re-evaluation of

Tissues from Female Sherman Rats

Fed Aroclor 1260

MONS 071392

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 altered 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

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 lobe the 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 carcinoma, 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

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: 390-396, 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													+							
Stem cell proliferation							+							+	+				+	
Epithelioid cell granuloma										+										
Periportal inflammation	+	+	+				+	+		+	+			+	+	+	+	+	+	+
Hyperplastic nodules with atypia		+				+							+				+			
Hyperplastic nodules without atypia			+	+	+	+	+	+	+	+		+	+		+	+	+	+	+	
Cellular proliferous lesion																				
Lymph suppuration				+											+					

MONS 071401

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

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																			
Stem cell proliferation	+	+	+	+	+	+			+	+		+		+	+	+	+	+	+
Epithelioid cell granuloma																			
Periportal inflammation		+		+							+	+				+			
Hyperplastic nodules with atypia					+			+		+				+					
Hyperplastic nodules without atypia	+				+		+	+	+	+	+			+	+		+	+	+
Cholangiomatous lesion	+											+			+				
Lymph congestion																			

MONS 021404

Number of slide	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		+	+		+														
Stem cell proliferation	+	+	+			+			+	+			+			+	+		
Epithelioid cell granuloma																			
Periportal inflammation																			+
Hyperplastic nodules with atypia	+	+	+		+		+	+			+							+	
Hyperplastic nodules without atypia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiomatous lesion		+	+											+					
[illegible]																			
[illegible] diffuse																			
[illegible]																			

MONS 021405

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																			

A = [illegible] Diffuse
[illegible]

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																			
Stem 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 071407

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																			

[illegible] almost diffuse
[illegible] diffuse

MONS 071408

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 021409

Number of slides	8507	8508	8509	8510	8512	8513	8514	8515	8516	8517	8518	8519
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											+	
Hyperkeratosis												
Hepatocellular diffuse												

MONS 07440

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																+			
Peridural fibrosis																			
Cholangiofibrosis							+												
Stem cell proliferation	+	+		+	+			+	+	+	+	+	+		+	+	+	+	+
Epithelioid cell granuloma																			
Periportal inflammation	+			+				+			+		+		+	+	+	+	
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia																			
Cholangiomatous lesion																			
[illegible]																			

MONS 07142

Number of slides	8309	8310	8311	8312	8313	8314	8315	8316	8317	8318	8321	8151	8231	8260	8261	8263	8264	8265		
Vacuolization													+							
Focal basophilic alteration				+					+							+				
Single basophilic 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																				
Peripertal inflammation		+	+		+	+	+				+									
Hyperplastic nodules with atypia													+							
Hyperplastic nodules without atypia			+										+							
Cholangiocellular lesion													+							
Inflammation																				

MONS 07443

Controls

Number of slide	8267	8268	8269	8271	8271 (1)	8272	8273	8275	8277	8278	8281	8283	8284	8286	8289	8290	8291	8292	8293
Vacuolization					+	+			+						+				+
Focal acidophilic alteration									+	+	+								
Simple acidophilic alterations	+	-	+	+	+	+	+		+	+		+	+	+	+	+	+	+	+
Focal granular alteration					+	+													
Single granular alteration					+					+									
Perinuclear halo									+		+								
Eosinoph. homogenization																			
Single cell necrosis					+								+						+
Group cell necrosis					+														
Cell enlargement					+						+								+
Ductal proliferation																			
Peridactal fibrosis																			
Cholangiofibrosis																			
Stern cell proliferation	+	+		+									+		+	+	+	+	
Epithelioid cell granuloma																			
Peripertal inflammation				+								+							
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia					+						(+)								(+)
Cholangiomatous lesion																			
Lymphomatous lesion																			

Invaded by malignant lymphoma cells

MONS 071414

Controls

Number of slides	8294	8295	8296	8304	8172	8170	8173	8175	8176	8177	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Vacualization				+															
Focal [illegible]dophilic alteration													+						
Single [illegible]dophilic alterations	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Focal granular alteration		+		+				+	+						+				
Single granular alteration		+		+						+									
Perinuclear halo				+		+	+	+		+									
Eosinophil 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																	+		

MONS 071415

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	(+)																		
Cholangiocellous lesion																			
Lymph congestion																			

MONS 071416

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 basophilic 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																			
Stem cell proliferation	+	+		+		+	+		+						+				
Epithelioid cell granuloma																			
Periportal inflammation	+	+						+				+			+				
Hyperplastic nodules with atypia																			
Hyperplastic nodules without atypia			+!	(+)						(+)					(+)				(+)
Focal cystic lesion																			
Lymph congestion																			

MONS 071417

Controls

Number of slides	8345	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 conversion																			
Advanced fibrosis																			(+)

Diffuse Kupffer cell hyperplasia

MONS 071418

Number of slides	8131	8132	8133	8134	8135	8136	8137	8138	8139	8140	8141	8142	8144	8145	8146	8148	8149	8150	8152
			Controle																
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																			

MONS 071419

20
Controls

Number of slides	8154	8155	8156	8157	8158	8160	8162	8163	8164	8166	8167	8173
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												
Stem cell proliferation	+	+	+							+	+	
Epithelioid cell granuloma												
Periportal inflammation												
Hyperplastic nodules with atypia												
Hyperplastic nodules without atypia				(+)								
Cholangiomatous lesion												
Lymph accumulation												

MONS 071420

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