Report On

Histopathological re-evaluation of

livers from rats treated with AROCLOR

NEV 011146

710398

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, characterised 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-neoplaatic 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 structurea 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

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 prs-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).

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Legend:

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

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

Fig. 3: Scattered, ioeinophilic 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 nucleol A portal triad is seen in middle of photo: A3-314F, 100x.

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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 pleomorphism 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 call 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.

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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 aourrounding liver cells: B3-489M, 250x.

Fig. 24: Cystic alteration resembling lymphangiectasis 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																						
Cholsngiofibrosis																						
Stern cell prolifaration					+		+				+					+	+			+	+	+
Epithliod-cell granuloma							+								+							
Periportal inflamation					+	+	+				+	+			+	+	+	+	+	+		
Lymph congestion																						

NEV 011159

710411

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 lolo	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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_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 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																			

NEV 011101

710413

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 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																									

NEW 011162

710414

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											+																					

MALIGNANT LYMPHOMA

NEV 011103

710415

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
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																		+					

MALIGNANT LYMPHOMA

NEV 011164

710416

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 holo									+	+				+			+						
Eosinoph. homogenization								+				+											
Single cell necrosis		+	+	+	+	+		+		+			+				+			+	+	+	
Group cell necrosis								+															
Cell enlargment								+				+					+	+	+	+	+	+	
Ductal proliferation			+	+	+		+	+			+	+	+				+		+		+	+	
Periductal fibrosis			+	+			+		+		+	+	+				+	+	+		+	+	
Cholangiofibrosis																			+		+	+	
Stem cell proliferation	+				+	+				+	+		+			+							
Epithliod cell granuloma																				+			
Periportal inflamation			+	+		+		+		+		+	+									+	+
Lymph congestion						+					+												

NEV 011165

710417

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	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																									

NEV 01107

710419

Code	C_2	C_0																A							
Sex	F	M	M		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																		+								

NEV 011168

710420

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 halo	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+	+	+	+
Eosinoph. homogenization				+	+	+	+	+		+	+	+	+	+	+	+		+				
Single cell necrosis		+		+	+	+	+				+	+	+		+		+			+		+
Group cell necrosis																						
Cell enlargment														+	+	+				+		
Ductal proliferation										+	+	+		+		+			+			
Periductal fibrosis		+	+							+	+	+	+		+	+						
Cholangiofibrosis																						
Stem cell proliferation		+			+	+	+			+	+	+	+						+	+	+	+
Epithliod cell granuloma		+							+	+	+											
Periportal inflamation						+															+	
Lymph congestion																						

NEV 011169

710421

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									*+														

NEV 011170

710422

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	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	?
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											**											

NEW 011172

710424

Code	A_2			?	A_2		?			A_2									?	A_2	?	?
Sex	?	?	?	?	?	M	?	?	?	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	+	+	+	+					+	+	+	+		+			+				+	+
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

NEV 011173

710425

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	24
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

NEV 011174

710426

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 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					+

NEW 01175

710427

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																						

NEW 01176

710428

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																						

NEV 011177

710429

Code	B_2						B_3										$B_1{}^x$							
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																								

NEV 01178

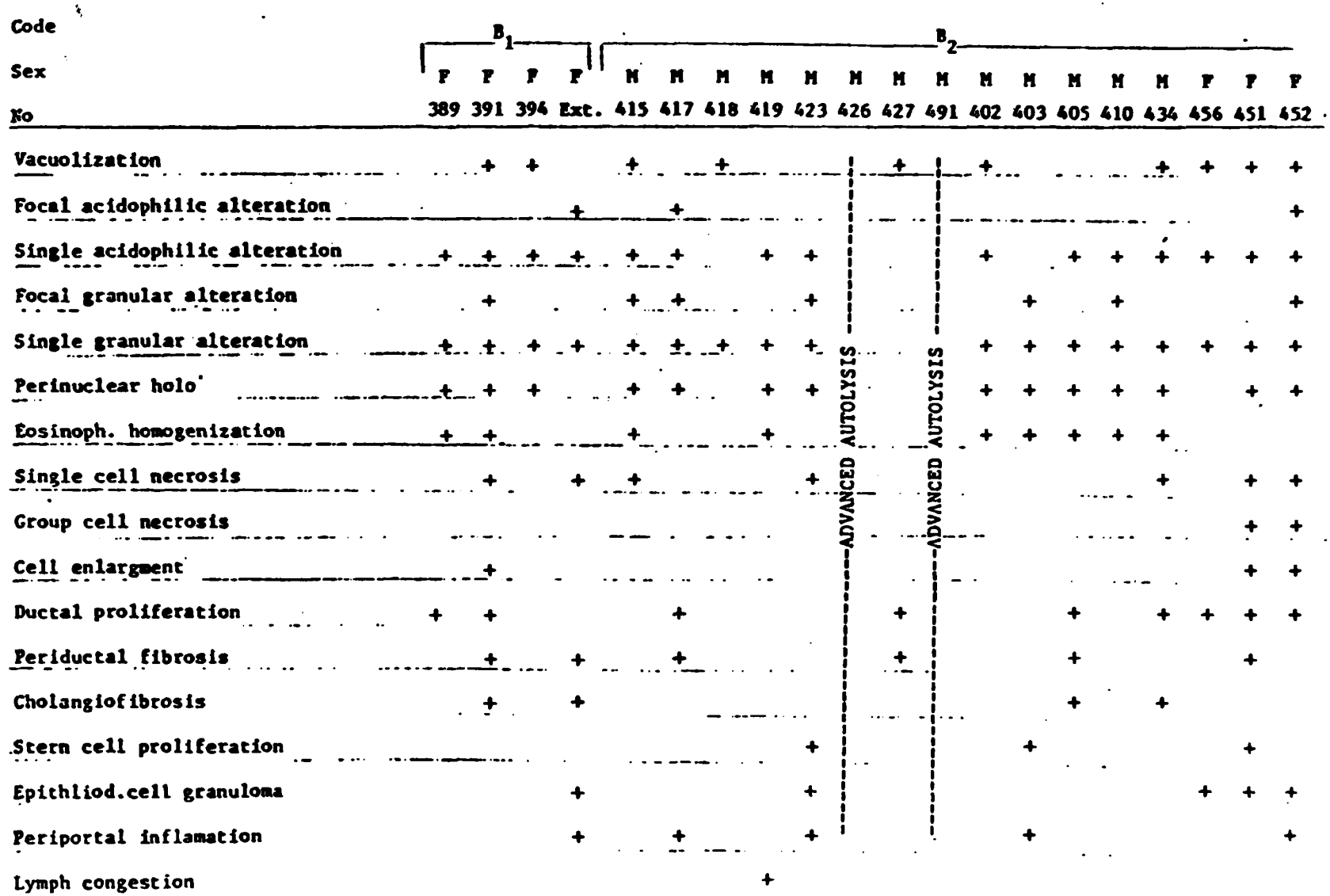
710430

Code	B_1^x		B_2^x									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																	+											

NEV 011179

710431

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	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 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 fibrosis															+							

NEW 01182

710434

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 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																
Hepatoma(?)	+															
Cholangiocarcinoma (?)	+															
Cholangomatous lesion					+										+	

NEV 011103

710435

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

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 halo	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

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

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	