COMMENTS ON CYSTIC DEGENERATION/SPONGIOSIS HEPATIS IN THE RAT LIVER (updated July 30, 2012)

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INTRODUCTION

I am currently an independent consultant in Toxicologic Pathology. My curriculum vita is attached. In brief, I am board certified in veterinary pathology and have more than 35 years of experience in veterinary and toxicologic pathology. Since 1975, I have specialized in toxicologic pathology and oncology. In various capacities, I have provided pathology support and toxicology data evaluation to numerous private clients and to government scientific advisory and regulatory agencies. Much of my work has included such activities as:

- organizing and chairing independent peer reviews or Pathology Working Groups on both subchronic toxicity studies and carcinogenicity studies,
- performing histopathologic evaluations for numerous toxicity/carcinogenicity studies involving a variety of strains of rats and mice as well as other species,
- serving as an expert witness,
- conducting independent data evaluations of toxicology studies, and
- managing a large Pathology Department in a contract research laboratory.

I also served as the chairman for the Subcommittee on Proliferative Lesions of the Liver in the Rat for the Standardized System of Nomenclature and Diagnostic Criteria Committee, Society of Toxicologic Pathologists from 1989 to 1994 and co-authored the paper Proliferative and Selected Other Lesions of the Liver in Rat in Guides for Toxicologic Pathology (1994). Currently, I am serving as a member of the Global Editorial Steering Committee (GESC), International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice (INHAND), Society of Toxicologic Pathologists. The GESC has oversight for all of the Organ Working Groups responsible for development of the manuscripts for each organ system, including the liver.

In 2005, I was asked by the American Chemistry Council Phthalate Esters Panel to review several scientific papers and documents and to comment on the occurrence and significance of cystic degeneration/spongiosis hepatitis in the rat liver in general and on its occurrence in several long-term studies with di(isononyl)phthalate (DINP). Recently, I was asked by ExxonMobil Chemical Company to update my comments based on current literature. I was also asked to
comment on the occurrence and significance of cystic degeneration/spongiosis hepatis in a long-term study with di-isodecyl phthalate (DIDP).

The documents originally provided to me in 2005 by the American Chemistry Council Phthalate Esters Panel included:


I participated in the Pathology Working Group (PWG) that reviewed selected lesions of the liver and spleen in rats exposed to DNOP as reported in Hardisty (1999) so I am familiar with the lesions of spongiosis hepatis/cystic degeneration observed in the studies reviewed by the PWG.

For the initial preparation of this document, I also obtained the following articles:


In preparation for updating my initial comments, I conducted a literature review and found the following additional relevant articles:


CYSTIC DEGENERATION/SPONGOYSIS HEPATIS IN RATS

Cystic degeneration or spongiosis hepatis is a lesion that is often observed in the liver of untreated rats of many strains, particularly in male rats. It has not been reported in other laboratory rodents, dogs or primates. The lesion is uncommon in young rats (Dixon, et al, 1995) and generally increases in incidence with age. Histopathologically, it is characterized by the presence of cystic spaces lined by fine septa, often multiloculated in appearance, occurring between hepatocytes, with no compression of adjacent hepatic parenchyma. The cystic spaces are not lined by endothelium and may appear empty or filled with eosinophilic flocculent or fibrillar material. Erythrocytes (red blood cells) may occasionally be present, although usually to a limited degree. It is generally accepted that cystic degeneration/spongiosis hepatis represents a nonneoplastic lesion of the perisinusoidal lining (Ito) cells of the liver.

It has been proposed that cystic degeneration/spongiosis hepatis may be a benign neoplasm and that a more appropriate term for this entity would be spongiotic pericytoma to indicate the proposed benign neoplastic nature of the lesion (Stroebel, et al, 1995). However, there are only a few articles in the literature referring to this entity. Karbe & Kerlin (2002) conducted an extensive review of the literature on cystic degeneration/spongiosis hepatis and spongiotic pericytoma and provide cogent arguments against considering the lesion a benign neoplasm. The term spongiotic pericytoma to replace cystic degeneration/spongiosis hepatis has not been widely accepted nor has the view that this lesion represents a benign neoplasm, as indicated by the fact that this entity has not been included over the years in the various guidelines for nomenclature
that are considered reference standards for terminology to be used for the evaluation of safety toxicology studies by toxicologic pathologists internationally. The STP guidelines published in 1994 (Goodman, et al) use the term ‘cystic degeneration’ for this lesion and consider it a nonneoplastic lesion. The International Harmonization of Rat Nomenclature, Final Version, 2000 document addresses preferred terminology for hyperplastic and neoplastic lesions of a variety of organ systems and is a harmonization of guidelines from the STP, WHO/IARC/RITA and NACAD. Their preferred term for this lesion is ‘cystic degeneration’ and it is considered a nonneoplastic lesion. The most recent guideline (Thoolen, et al, 2010), published under the auspices of the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) Committee of the American, British, European, and Japanese Societies of Toxicologic Pathology, recommends ‘cystic degeneration’ as the preferred term and includes the term under nonneoplastic lesions.

Cystic degeneration/spongiosis hepatitis may occur in otherwise normal appearing livers or may be found occurring within foci of cellular alteration or hepatocellular neoplasms, both adenomas and carcinomas. These lesions may also occur in livers with various types of hepatotoxicity. Cystic degeneration/spongiosis hepatitis has been reported to increase in incidence with the administration of a number of compounds (Karbe & Kerlin, 2002; Bannasch, 2003), many, but not all of which also cause an increase in hepatocellular neoplasms.

In my experience, when present as an aging spontaneous lesion, the lesions of cystic degeneration/spongiosis hepatitis are usually small and minimal to mild in severity and may be solitary or multiple. Because of the focal nature of these lesions and degree of severity observed, they do not appear to compromise hepatic function. When found in association with proliferative hepatocellular lesions (foci, neoplasms), cystic degeneration/spongiosis hepatitis generally is a small component of these lesions and any perturbation of liver function is most likely related to the presence of these other hepatocellular lesions. When observed independent of proliferative lesions, cystic degeneration/spongiosis hepatitis is an insignificant toxic lesion, unlikely to compromise hepatic function or cause the death of the rat and thus is not considered to be adverse.

CYSTIC DEGENERATION/SPONGIOSIS HEPATIS IN CHRONIC TOXICITY/ONCOGENICITY STUDIES WITH DINP IN RATS

Two chronic toxicity/oncogenicity studies were conducted with DINP in F344 rats (Exxon, 1986 and Moore, 1998). The Exxon study was also reported by Lington, et al (1997). In both of these studies, test article related effects were observed in the liver. In the Moore (1998) study, effects were also present in the kidney. This document is restricted to a discussion of the test article related effects reported in the liver, principally cystic degeneration/spongiosis hepatitis. Both studies reported an increased incidence of cystic degeneration/spongiosis hepatitis in male rats at the higher dose levels (3000 ppm and above). Increased incidences of mononuclear cell leukemia, which usually affects the liver and spleen, were reported in both studies in the higher dosed animals and an increased incidence in hepatocellular neoplasms was reported in one study (Moore, 1998) at the highest dose level. In 1999 (Hardisty), a PWG was held to review selected liver lesions from both studies, including cystic degeneration/spongiosis hepatitis, mononuclear
cell leukemia, foci of cellular alteration (liver) and hepatocellular neoplasms. The results of this review were similar to those reported originally. It was further determined that the incidence of cystic degeneration/spongiosis hepatitis was increased independently of the presence of mononuclear cell leukemia in the same liver. The conclusion reached by the PWG was that cystic degeneration/spongiosis hepatitis was increased in incidence in both studies at doses of 3000 ppm and greater compared to controls.

Subsequently, Brown (2000) reviewed liver slides from male rats diagnosed with spongiosis hepatitis (cystic degeneration) in the Exxon (1986) study in order to assess the severity of the lesion and its distribution among the various liver lobes. This review found that the severity of the lesions ranged from minimal to moderate in severity with the vast majority being rated as minimal or mild, regardless of dose. The average severity for each dose group was minimal to mild. There was a marginal increase in the severity in the higher dosed rats which was likely related to the increased number of foci observed/rat with increasing dose rather than an increase in severity of the individual lesions within the liver. Similarly in the Moore (1998) study, the average severity of spongiosis hepatitis (cystic degeneration) was minimal to slight (mild). The number of foci per rat was not determined in this study. Regardless of dose in either study, cystic degeneration/spongiosis hepatitis remained a mild lesion affecting the liver. Minimal to mild cystic degeneration/spongiosis hepatitis is unlikely to have an adverse affect on liver function or the overall health of the animal. My expert opinion is that the increases in liver weight and liver enzymes noted in these studies are unlikely to be related to the presence of minimal to mild cystic degeneration/spongiosis hepatitis and are more likely related to other histopathologic findings in the liver. It should be noted that the increases in liver weight and liver enzymes occurred in both male and female rats while the increases in cystic degeneration/spongiosis occurred only in males.

CYSTIC DEGENERATION/SPONGIOSIS HEPATIS IN A CARCINOGENICITY STUDY WITH DIDP IN RATS

A 2 year carcinogenicity study was conducted with DIDP in Fischer 344 rats (Cho, et al, 2008). Test article related increases of several nonneoplastic lesions were observed in the liver, including cystic degeneration/spongiosis hepatitis which was increased in male rats given the highest dose of 8000 ppm. The actual incidences of cystic degeneration/spongiosis, although statistically significantly different between control and high dose animals (0/40 vs. 5/39) were quite low. The severity and multiplicity of these lesions were not reported. Increased incidences of mononuclear cell leukemia, although not considered test article related, were also noted in males and females at this dose level. Significant increases in liver weights were reported in both sexes; liver enzymes were not evaluated. The low numbers of males with cystic degeneration/spongiosis hepatitis and the fact that increases in liver weight were seen in females as well as males make it unlikely that cystic degeneration/spongiosis hepatitis is related to the increased liver weights. The increased liver weights are more likely related to the other lesions observed in the liver. My expert opinion is that the cystic degeneration/spongiosis hepatitis reported by Cho, et al (2008) most likely represents a non-adverse test article related lesion.
CONCLUSION

In summary, increased incidences of minimal to mild cystic degeneration/spongiosis hepatitis of the male rat liver are associated with DINP administration for 104 weeks. The increase in incidence was observed primarily in animals killed at the end of the study. Any increase in severity with dose was marginal at best, although there may have been a slight increase in the number of foci per rat. There were no tumors of the perisinusoidal lining (Ito) cells observed in either study even after two years of treatment, and thus no reason to suppose that cystic degeneration/spongiosis hepatitis was a preneoplastic lesion. In short, the increased incidences of cystic degeneration/spongiosis hepatitis associated with DINP administration represent a mild, non-adverse test article related effect in the rat.

The results from the two year carcinogenicity study with DIDP were similar to those found in the DINP studies. In the DIDP study, cystic degeneration/spongiosis hepatitis is associated with test article administration in male rats at the highest dose level and most likely represents a non-adverse test article related effect.

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Date