

## COMMENTS ON CYSTIC DEGENERATION/SPONGIOSIS HEPATIS IN THE RAT LIVER

By  
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### INTRODUCTION

I am currently the Scientific Director of Pathology at Covance Laboratories, a contract research organization. My curriculum vita is attached. In brief, I am board certified in veterinary pathology and have more than 30 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 chronic and subchronic toxicity 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,
- monitoring ongoing toxicity/carcinogenicity studies at contract toxicology laboratories.

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).

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). The documents provided to me included:

- Karbe, E. & R.L. Kerlin (2002). Review Article: Cystic Degeneration/Spongiosis Hepatitis in Rats. *Toxicol. Pathol.* 30: 216-227.



## **CYSTIC DEGENERATION/SPONGIOSIS HEPATIS IN RATS**

Cystic degeneration or spongiosis hepatitis is a lesion that is commonly observed in the liver of 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 and generally increases in incidence with age. Histopathologically, it is characterized by the presence of cystic spaces or vacuoles, often multiloculated in appearance, occurring between hepatocytes, with no compression of adjacent hepatic parenchyma. The cystic spaces are not usually lined by endothelium or only partially lined by endothelium. The spaces may appear empty or filled with eosinophilic proteinaceous fluid, or eosinophilic flocculent or fibrillar material. Erythrocytes (red blood cells) may also be present, although usually to a limited degree.

It is generally accepted that cystic degeneration/spongiosis hepatitis represents a non-neoplastic lesion of the perisinusoidal lining (Ito) cells of the liver. It has been proposed that cystic degeneration/spongiosis hepatitis 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, all referring to the same carcinogen. The term spongiotic pericytoma to replace cystic degeneration/spongiosis hepatitis has not been widely accepted nor has the view that this lesion represents a benign neoplasm, as indicated by the fact that this entity was not included in the International Harmonization of Rat Nomenclature, Final Version, 2000. This 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. The STP guidelines published in 1994 use the term 'cystic degeneration' for this lesion and it is considered a non-neoplastic lesion. These guidelines are considered the reference standard for terminology for the evaluation of safety toxicology studies by toxicologic pathologists in the Society of Toxicologic Pathologists.

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. Because of the focal nature of these lesions and degree of severity observed, they are unlikely to compromise hepatic function. When found in association with proliferative hepatocellular lesions (foci, neoplasms), cystic degeneration/spongiosis hepatitis

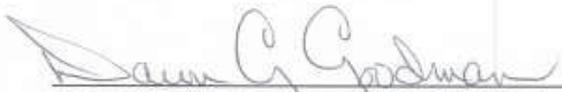
generally appears to be a relatively small component of these lesions and it is much more likely that any perturbation of liver function is related to the presence of these other hepatocellular lesions. When observed independent of proliferative lesions, cystic degeneration/spongiosis hepatitis still remains, in and of itself, a relatively insignificant toxic lesion, unlikely to seriously compromise hepatic function or cause the death of the rat.

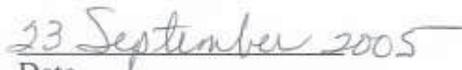
#### CYSTIC DEGENERATION/SPONGIOSIS HEPATIS IN CHRONIC TOXICITY/ONCOGENICITY STUDIES WITH DINP IN RATS

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 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. 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. It is unlikely that such lesions had an adverse affect on liver function or the overall health of the animal. It did, however, increase in incidence at the higher dose levels.

In summary, increased incidences of 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 toxic effect in the rat with no significant effect on liver function or the general health of the animals.

  
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