Supplemental Materials: Pathology Opinions

1. Klaunig (2016) states that “The induction of liver tumors in mice and rats by 1,4-dioxane appears to be through the nongenotoxic, dose responsive and threshold based induction of cytotoxicity with resulting compensatory hyperplasia. While the mouse data is less robust than that available in the rat to support the cytotoxicity mode of action, based on the 1) absence of other possible modes of action, 2) the observed necrosis seen in the mouse liver and 3) the similar biological and pathological effects of 1,4-dioxane to that seen in the rat, the cytotoxicity mode of action appears to be in force for the induction of the observed mouse liver tumors.”

2. McConnell (2016) states that “Based on my review (2 January 2013) of the histopathology observed in the livers of mice in the NTP study, I think it is appropriate to view 1,4-dioxane as a classic non-genotoxic liver carcinogen, e.g. dose-related changes that progress from hepatocellular tinctorial changes and hypertrophy to focal hepatocellular hyperplasia to adenoma to carcinoma. Additionally, I think it is probable that the same morphologic steps (progression) that were observed in the mice in the NTP study would be present in rats at an equivalent toxic dose. That has been my experience with other hepatocellular toxins, albeit mice seem to be more sensitive than rats to the same chemical at the same dose.”

3. Jayne Wright (2016) states that “In my experience once a MOA has been hypothesised it is usual to substantiate this. Particularly in a situation such as rodent liver tumors, and where a MOA has been well documented. It is common for a similar MOA to operate across both rodent species and sometimes for the so-called precursor events to be more apparent in one species than the other. And indeed sometimes even when the same MOA is operating in both species, tumors are only seen in one species (exposure/thresholds). In the absence of the expected so-called precursor events, the same MOA could still be operating. With low grade cell damage one does not always see histopathology evidence of cell damage and repair. In my opinion, with or without the expected histopathology, the MOA would need to be demonstrated – in recent times microarrays to demonstrate cell damage and proliferation pathways, and labeling index to measure cell proliferation rates have been commonly used. Such work would mean additional live animal studies.”

References

Klaunig, J. E. 2016. Personal communication with M. L. Dourson on June 10.

McConnell, G. 2016. Personal communication with M. L. Dourson on March 3.

Wright, Jayne. 2016. Personal communication with M. L. Dourson June 22, 2016.