

Reply to Comments of Dr. Lawrence H. Lash

I'm writing in response to the comments of Dr. Lawrence H. Lash and his response to my comments regarding CPN in rats and its relevance to humans. I am not saying that the CAAC's recommendations are without merit, but I am saying that the confusion and division amongst the CAAC clearly results from a lack of pathology expertise. As indicated in the EPA guidance for composition of the CAAC, appropriate expertise is necessary to be represented on these reviews to provide a comprehensive assessment.

All of the findings in the kidneys of TBA and ETBE-treated can be explained by  $\alpha_{2u}$ -globulin nephropathy and CPN as I detailed in my earlier comments for the 2016 and 2017 presentations by IRIS and my comments to this CAAC review. Either  $\alpha_{2u}$ -globulin nephropathy or CPN would result in increased kidney weight. In addition, either of these can result in an increased incidence of renal cell tumors. Dr. Lash, like the IRIS, continues to rely extensively on the review by Melnick et al. (2012), but does not discuss the comments by Hard et al. (Toxicol. Sci., 132: 268-275, 2013) concerning the fallacies of the Melnick publication. Dr. Lash indicates that if CPN did lead to an increased incidence of tumors it should be seen in controls. Only high grade CPN is associated with tumor induction. This was demonstrated in an extensive review of NTP control rats by Hard et al. (Toxicol. Pathol., 40: 473-481, 2013), with approximately 24% of control male rats with the highest grade of CPN developing renal tubule atypical hyperplasia (a precancerous lesion) or tumors. Furthermore, the differences between CPN in rats and renal diseases in humans are described in detail in Hard et al., Toxicol. Pathol., 39: 332-346, 2009. I encourage Dr. Lash, and other members of the CAAC that have concerns about CPN, to read the comments that I and others have made and the numerous other publications on the subject.

Another issue that concerns IRIS and some on the CAAC members is transitional (urothelial) cell hyperplasia as a separate endpoint from CPN. As was stated explicitly in the NTP report on TBA, this lesion is part of CPN, not separate from it. This was specifically evaluated in the PWGs on TBA (Hard et al., Regul. Toxicol. Pharmacol., 59:430-436, 2011) and ETBE (Cohen et al., PWG report, 2011). This is not transitional cell hyperplasia but is an increase in cell number on the lining epithelium of the papilla. As we have recently demonstrated (Souza et al., Toxicologic Pathology, 2018), this epithelium is not transitional (urothelial) cell, and the lesion is likely not hyperplasia but rather a vesicular outpouching of the epithelium from the papilla. Most importantly, this lesion is part of CPN and it is a lesion that does not exist in humans.

Dr. Lash raises public health concerns, noting the increasing incidence of kidney cancer in the United States. To some extent this is true, but the reasons for this are well-known: 1) an increased incidence of incidentally detected small tumors by increased imaging studies for other reasons (such as gallbladder disease); and 2) the increasing incidence of obesity, the leading cause of kidney cancer in the United States.

In science, appropriate expertise is essential. To study PBPK, metabolism, or statistics, individuals with appropriate expertise are critical. Likewise, to understand pathology, it is important to have somebody trained in pathology, in the present instance, someone who is expert in kidney pathology. The lack of such expertise has resulted in a sharply divided CAAC

evaluation of the IRIS assessments of TBA and ETBE. I strongly support the recommendation by the CAAC to suggest that EPA convene a panel of experts to discuss the role of CPN in kidney toxicity and carcinogenicity, so that a more standardized evaluation can be reached and appropriate policy decisions attained. This same recommendation was made to the IRIS program at the 2016 and 2017 reviews.