

Distinguishing Modes-of-Action for Chemically-Induced Male Rat Renal Carcinogens

Susan Borghoff. CIIT Centers for Health Research.

A number of chemicals cause a low incidence of renal tumors in male rats. One of the major contributors to this response is the ability of the chemical to cause α 2u-globulin (α 2u) nephropathy, a syndrome unique to male rats. Recently, a number of male rat renal carcinogens have been identified to cause a mild α 2u-globulin nephropathy response. With several of these chemicals, this weak response does not appear to account for the increase in cell proliferation observed. Tertiary-butyl alcohol (TBA), a chemical that has been shown to induce a mild increase in α 2u and increased renal cell proliferation in male rats, has recently been shown to be metabolized similarly in male and female rats. This suggests that α 2u is most likely responsible for the increase in renal cell proliferation measured in TBA-exposed male rats. Recently, protein overload in kidney cells has been shown both in vivo and in vitro to stimulate apoptosis. This project was to examine whether apoptosis or necrosis secondary to protein overload contribute to the toxicity of α 2u inducers. This project ended in early 2002 in response to CIIT's research reorganization.

Start and end date: January 2001 – February 2002.

Presentation(s):

Williams, T. M., Parkinson, H. D., Sumner, S. J., and Borghoff, S. J. (2001). Elimination of ¹⁴C-tert-butyl alcohol-derived radioactivity from male and female F-344 rats following single and repeated administration. *Toxicol. Sci.* 54 (1), 293. Supplement–*The Toxicologist*. (Abstract 1394).

Williams, T. M., Howell, E. R., Mooney, E. C., and Borghoff, S. J. (2000). Characterization of tert-butyl alcohol binding to α 2u-globulin. *Toxicol. Sci.* 54 (1), 401. Supplement–*The Toxicologist*. (Abstract 1884).

Peer-reviewed publication(s):

Borghoff, S. J., Prescott, J. S., Janszen, D. B., Wong, B. A., and Everitt, J. I. (2001). α 2u-globulin nephropathy, renal cell proliferation, and dosimetry of inhaled tert-butyl alcohol in male and female F-344 rats. *Toxicol. Sci.* 61, 176–186.

Licata, A. C., Dekant, W., Smith, C. E., and Borghoff, S. J. (2001). A physiologically based pharmacokinetic model for methyl tert-butyl ether in humans: implementing sensitivity and variability analyses. *Toxicol. Sci.* 62, 191–204.

Williams, T. M. and Borghoff, S. J. (2001). Characterization of tert-butyl alcohol binding to α 2u-globulin in F-344 rats. *Toxicol. Sci.* 62, 228–235.

Other publication(s): None to date.

Sponsors in addition to the LRI: None.

Abstract revision date: January 2006.