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

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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 $\alpha_2u$-globulin ($\alpha_2u$) nephropathy, a syndrome unique to male rats. Recently, a number of male rat renal carcinogens have been identified to cause a mild $\alpha_2u$-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 $\alpha_2u$ and increased renal cell proliferation in male rats, has recently been shown to be metabolized similarly in male and female rats. This suggests that $\alpha_2u$ 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 $\alpha_2u$ inducers. This project ended in early 2002 in response to CIIT’s research reorganization.

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