Species differences in chemical carcinogenesis of the thyroid gland, kidney and urinary bladder

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G.A. Thomas & E.D. Williams

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Calcium phosphate-containing urinary precipitate in rat urinary bladder carcinogenesis

S.M. Cohen

Appendix 1: Agents that induce epithelial neoplasms of the urinary bladder, renal cortex and thyroid follicular lining in experimental animals and humans: Summary of data from IARC Monographs Volumes 1–69

J.D. Wilbourn, C. Partensky & J.M. Rice

Appendix 2: Chemicals associated with tumours of the kidney, urinary bladder and thyroid gland in laboratory rodents from 2000 NTP/NCI bioassays for carcinogenicity

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Swenberg and Lehman-McKeeman (see this volume) have demonstrated that if administration begins at birth, tumour response is similar to that observed in mice and rats. However, two-generation studies have not been reported for any of these other sodium salts. Only a few of these sodium salt compounds, such as FANFT or BBN, have been shown to produce transitional cell carcinomas in male rats. Although urinary bladder tumours have been reported in both male and female hamsters and guinea-pigs treated with sodium saccharin, these findings suggest that the presence of urinary tract calculi- and amorphous precipitate- and microcrystalluria-associated irritation, cell injury, and cytokine release may represent key intermediate steps in order to improve prediction of the carcinogenic response of chemicals. Overall, epidemiological data do not indicate that saccharin and other artificial sweeteners are genotoxic, although they could conceivably interfere with normal homeostatic mechanisms. Given the potential for formation of a calcium phosphate precipitate, the urinary tract changes induced by saccharin are likely to be confounding in the cohort study, these findings suggest that the presence of urinary tract irritation may be an important factor in the induction of bladder cancer in rodents. However, the relevance of urinary tract irritation to the induction of bladder cancer in humans is unknown. Critical factors essential for the formation of the urinary precipitate have not been identified. Although there are no data supporting this alternative hypothesis, it can be proposed that other factors, such as changes in urinary pH or osmolality, may be involved in the formation of urinary tract calculi and microcrystalluria. These changes may be related to the formation of calcium oxalate or uric acid calculi, which are common in rodents and humans. However, the mechanism of urinary tract irritation induced by saccharin is unknown. The contribution of these factors to the induction of urinary tract irritation in humans is also unknown. The potential for development of urinary tract stones in humans exposed to saccharin is unknown. The potential for development of urinary tract stones in humans exposed to saccharin is unknown. The potential for development of urinary tract stones in humans exposed to saccharin is unknown.
Calcium phosphate-containing precipitates in the urine of rats, such as those produced by the administration of high doses of some sodium salts, including sodium saccharin and sodium ascorbate, can result in the production of urinary bladder tumours. This sequence can be considered to be species- and dose-specific and is not known to occur in humans.

In making overall evaluations of carcinogenicity to humans, it can be concluded that the production of bladder cancer in rats via a mechanism involving calcium phosphate-containing precipitates is not predictive of carcinogenic hazard to humans, provided that the following criteria are met:

- the formation of the calcium phosphate-containing precipitate occurs under the conditions of the carcinogenicity bioassay which is positive for cancer induction;
- prevention of the formation of the urinary precipitate results in prevention of the bladder proliferative effect;
- the agent (and/or metabolites) shows a lack of genotoxic activity, based on an overall evaluation of in-vitro and in-vivo data;
- the agent being evaluated does not produce tumours at any other site in experimental animals;
- there is evidence from studies in humans that precipitate formation or cancer does not occur in exposed populations.

In situations where an agent induces tumours at other sites in rats or tumours in other laboratory animals, the evidence regarding these other tumour responses should be used independently of information on tumours associated with calcium phosphate-containing precipitates in making the overall evaluation of carcinogenicity to humans.

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<th>Table 1. Criteria for an agent causing kidney tumours through an α₂u-globulin-associated response in male rats</th>
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- Lack of genotoxic activity (agent and/or metabolite) based on an overall evaluation of in-vitro and in-vivo data
- Male rat specificity for nephropathy and renal tumorigenicity
- Induction of the characteristic sequence of histopathological changes in shorter-term studies, of which protein droplet accumulation is obligatory
- Identification of the protein accumulating in tubule cells as α₂u-globulin
- Reversible binding of the chemical or metabolite to α₂u-globulin
- Induction of sustained increased cell proliferation in the renal cortex
- Similarities in dose–response relationship of the tumour outcome with the histopathological end-points (protein droplets, α₂u-globulin accumulation, cell proliferation