

## **Urothelial proliferation induced by Diuron (3-(3,4-Dichlorophenyl)-1,1-Dimethylurea) in the urinary bladder of Wistar rats does not depend on DNA damage (comet assay) and/or urinary pH changes**

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Background: Diuron (3-(3,4-Dichlorophenyl)-1,1-dimethylurea), a substituted urea herbicide, is used on many agricultural crops such as soy, cotton and sugar cane. In long term study, this herbicide presented carcinogenic potential to the urinary bladder of male Wistar rats and was considered by US-EPA as potentially carcinogenic for humans. The genotoxicity and mutagenicity of Diuron, as evaluated *in vitro* and *in vivo* tests, are uncertain. However, it can be a non-genotoxic carcinogen that acts predominantly by epigenetic mechanisms in the urothelium. Design: The aim of this study was to evaluate the Diuron carcinogenic mode of action in the urothelium of male Wistar rats. After treatment with high doses of Diuron the genotoxic potential of this herbicide on urothelial cells was evaluated by the comet assay; urinary pH and histologic mucosal lesions were also analysed. Six weeks old male Wistar rats were fed pelleted Nuvilab diet mixed with 125, 500 and 2500ppm of Diuron. As a positive control Sodium Saccharin (NaS) was mixed with a commercial Nuvilab diet at 8,3%. Results: The incidence of simple epithelial hyperplasia (HS) was 2/10, 2/10 and 7/10 ( $p < 0,004$ ) in the 125, 500 and 2500ppm fed groups respectively. Simple epithelial hyperplasia (HS) and papillary/nodular hyperplasia (HPN) occurred respectively at incidences of 3/10 and 2/10 in the NaS group. Urinary pH was comparable to controls in all Diuron

groups but in the NaS group it was lower. Conclusions: The results suggest that genotoxicity and changes in urinary pH are not related to the Diuron carcinogenic mode of action on the urinary bladder mucosa. The increased incidence of urothelial hyperplasia in the Diuron high dose group suggests that other factors are involved with the induction of proliferative response of male Wistar rats urothelium.

Key words: Diuron, Urinary bladder, male Wistar rats, simple hyperplasia, comet assay, urinary pH