Transcriptional profile of diuron-induced toxicity on the urinary bladder of male Wistar rats to inform mode of action.

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ABSTRACT

Diuron (3-(3,4-dichlorophenyl)-1,1-dimethylurea) is a substituted urea herbicide that induces rat urinary bladder urothelial tumors at high dietary levels (2500 ppm). The specific mode of action and molecular alterations triggered by diuron, however, have not been clarified. The present study evaluated the dose-dependent effects of mucosal alterations and transcriptional changes in the urinary bladder of rats exposed to diuron. Six-week old male Wistar rats were treated with 0, 60, 125, 1250, 2500 ppm of diuron in the diet for 20 weeks. Histologic examination showed urothelial hyperplasia present in rats treated with either 1250 or 2500 ppm diuron, but not 60 or 125 ppm. Comprehensive gene expression analyses of urothelial cell RNA were conducted using Affymetrix microarrays. The numbers of differentially expressed transcripts (DETs) between each treatment group and controls increased with diuron dose. Based on similar histology and gene expression responses, the treatment groups were re-grouped into a high dose (1250 and 2500 ppm) and low dose group (60 and 125 ppm). The major categories of altered pathways after treatment with 1250 and 2500 ppm included genes involved in amino acid, lipid, xenobiotic metabolism and stress response and correlated with diuron's toxic effects in the rat urinary bladder.