

[Arch Toxicol.](#) 2006 Nov 24; [Epub ahead of print]

Uranium induces oxidative stress in lung epithelial cells.

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Uranium compounds are widely used in the nuclear fuel cycle, antitank weapons, tank armor, and also as a pigment to color ceramics and glass. Effective management of waste uranium compounds is necessary to prevent exposure to avoid adverse health effects on the population. Health risks associated with uranium exposure includes kidney disease and respiratory disorders. In addition, several published results have shown uranium or depleted uranium causes DNA damage, mutagenicity, cancer and neurological defects. In the current study, uranium toxicity was evaluated in rat lung epithelial cells. The study shows uranium induces significant oxidative stress in rat lung epithelial cells followed by concomitant decrease in the antioxidant potential of the cells. Treatment with uranium to rat lung epithelial cells also decreased cell proliferation after 72 h in culture. The decrease in cell proliferation was attributed to loss of total glutathione and superoxide dismutase in the presence of uranium. Thus the results indicate the ineffectiveness of antioxidant system's response to the oxidative stress induced by uranium in the cells.

PMID: 17124605 [PubMed - as supplied by publisher]

[Biochim Biophys Acta.](#) 2006 Oct 19; [Epub ahead of print]

In vivo effects of chronic contamination with depleted uranium on vitamin D(3) metabolism in rat.

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The extensive use of depleted uranium (DU) in today's society results in the increase of the number of human population exposed to this radionuclide. The aim of this work was to investigate in vivo the effects of a chronic exposure to DU on vitamin D(3) metabolism, a hormone essential in mineral and bone homeostasis. The experiments were carried out in rats after a chronic contamination for 9 months by DU through drinking water at 40 mg/L (1 mg/rat/day). This dose corresponds to the double of highest concentration found naturally in Finland. In DU-exposed rats, the active vitamin D (1,25(OH)(2)D(3)) plasma

level was significantly decreased. In kidney, a decreased gene expression was observed for *cyp24a1*, as well as for *vdr* and *rxralpha*, the principal regulators of CYP24A1. Similarly, mRNA levels of vitamin D target genes *ecac1*, *cabp-d28k* and *ncx-1*, involved in renal calcium transport were decreased in kidney. In the brain lower levels of messengers were observed for *cyp27a1* as well as for *lxrbeta*, involved in its regulation. In conclusion, this study showed for the first time that DU affects both the vitamin D active form (1,25(OH)(2)D(3)) level and the vitamin D receptor expression, and consequently could modulate the expression of *cyp24a1* and vitamin D target genes involved in calcium homeostasis.

PMID: 17118558 [PubMed - as supplied by publisher]

Toxicology. 2006 Oct 17; [Epub ahead of print]

Effect of acetaminophen administration to rats chronically exposed to depleted uranium.

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The extensive use of depleted uranium (DU) in both civilian and military applications results in the increase of the number of human beings exposed to this compound. We previously found that DU chronic exposure induces the expression of CYP enzymes involved in the metabolism of xenobiotics (drugs). In order to evaluate the consequences of these changes on the metabolism of a drug, rats chronically exposed to DU (40mg/l) were treated by acetaminophen (APAP, 400mg/kg) at the end of the 9-month contamination. Acetaminophen is considered as a safe drug within the therapeutic range but in the case of overdose or in sensitive animals, hepatotoxicity and nephrotoxicity could occur. In the present work, plasma concentration of APAP was higher in the DU group compared to the non-contaminated group. In addition, administration of APAP to the DU-exposed rats increased plasma ALT ($p<0.01$) and AST ($p<0.05$) more rapidly than in the control group. Nevertheless, no histological alteration of the liver was observed but renal injury characterized by incomplete proximal tubular cell necrosis was higher for the DU-exposed rats. Moreover, in the kidney, CYP2E1 gene expression, an important CYP responsible for APAP bioactivation and toxicity, is increased ($p<0.01$) in the DU-exposed group compared to the control group. In the liver, CYP's activities were decreased between control and DU-exposed rats. These results could explain the worse elimination of APAP in the plasma and confirm our hypothesis of a modification of the drug metabolism following a DU chronic contamination.

PMID: 17126469 [PubMed - as supplied by publisher]

J Toxicol Environ Health A. 2006 Sep;69(17):1613-28.

Short-term effects of depleted uranium on immune status in rat intestine.

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In the event of ingestion, the digestive tract is the first biological system exposed to depleted uranium (DU) intake via the intestinal lumen. However, little research has addressed the biological consequences of a contamination with depleted uranium on intestinal properties such as the barrier function and/or the immune status of this tissue. The aim of this study was to determine if the ingestion of depleted uranium led to changes in the gut immune system of the intestine. The experiments were performed at 1 and 3 d following a per os administration of DU to rats at sublethal dose (204 mg/kg). Several parameters referring to the immune status, such as gene and protein expressions of cytokines and chemokines, and localization and density of immune cell populations, were assessed in the intestine. In addition, the overall toxicity of DU on the small intestine was estimated in this study, with histological appearance, proliferation rate, differentiation pattern, and apoptosis process. Firstly, the results of this study indicated that DU was not toxic for the intestine, as measured by the proliferation, differentiation, and apoptosis processes. Concerning the immune properties of the intestine, the ingestion of depleted uranium induced some changes in the production of chemokines and in the expression of cytokines. A diminished production of monocyte chemoattractant protein-1 (MCP-1) was noted at 1 day post exposure. At 3 d, the increased gene expression of interferon gamma (IFN γ) was associated with an enhanced mRNA level of Fas ligand, suggesting an activation of the apoptosis pathway. However, no increased apoptotic cells were observed at 3 d in the contaminated animals. There were no changes in the localization and density of neutrophils, helper T lymphocytes, and cytotoxic T lymphocytes after DU administration. In conclusion, these results suggest that depleted uranium is not toxic for the intestine after acute exposure. Nevertheless, DU seems to modulate the expression and/or production of cytokines (IFN γ) and chemokines (MCP-1) in the intestine. Further experiments need to be performed to determine if a chronic contamination at low dose leads in the long term to modifications of cytokines/chemokines patterns, and to subsequent changes in immune response of the intestine.

PMID: 16854789 [PubMed - indexed for MEDLINE]