UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D. C. 20555

FEB 7 1983

MEMORANDUM FOR: John G. Davis, Director
Office of Nuclear Material Safety and Safeguards

FROM: Robert B. Minogue, Director
Office of Nuclear Regulatory Research

SUBJECT: RESEARCH INFORMATION LETTER #133 - METABOLIC FATE AND EVALUATION OF INJURY IN RATS AND DOGS FOLLOWING EXPOSURE TO THE HYDROLYSIS PRODUCTS OF URANIUM HEXAFLUORIDE

Introduction

This memorandum transmits the results of the completed research project on biological studies of inhalation exposures to uranium hexafluoride. The work was performed by the Department of Radiation Biology and Biophysics at the University of Rochester under the direction of the Health Effects Research Branch.

The project was begun in order to develop the technical base for including a bioassay program for uranium hexafluoride (UF_6) in Regulatory Guide 8.11, "Applications of Bioassay for Uranium." RIL #111, addressed to the former Office of Standards Development, transmitted the results of the first year's study as given in NUREG/CR-1045, "Acute Effects of Inhalation Exposure to Uranium Hexafluoride and Patterns of Deposition."

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While the results of the first year's study supported the ICRP's formulation of the relation between absorbed dose and urinary elimination rate, it was decided that retention functions for bone and kidney should be obtained out to several weeks post-exposure. It was also thought desirable to obtain additional information on the possible synergism between the hydrolysis products of UF_6 (viz, UO_2F_2 + 4 HF) and on the behavior of the kidney which has been exposed to U^{+6} previously. Finally, further work on renal injury indicators was desired.

Methodology

The experimental plan was described in RIL #111 and was subsequently extended to lower doses, longer times and additional renal injury indicators. It was designed to examine the relationships of inhaled UO_2F_2 and HF and a) the resulting uranium burden in the lung, kidneys, and whole-body, and b) the subsequent uranium elimination patterns. As before, two species, the rat and the dog, were used as were multiple exposure routes; i.e., inhalation, intratracheal instillations, and intravenous injection.

Results and Discussion

The results of each experiment are given in the tables and figures of NUREG/CR-2268, which has been provided to you. The following results have been found:

1. The principal route of excretion of absorbed UO_2F_2 is renal. The urinary uranium excretion rate in the dog follows nearly exactly the current ICRP excretion model for humans for U^{+6}: the fraction eliminated in the first 24 hours is 0.82 compared to 0.80 for the human; and 0.18 is eliminated as a power function $t^{-1.5}$ compared to 0.20 in the human. The total amount of uranium eliminated in the urine is 0.78 of the total absorbed dose.

2. Because the nasal deposit and a lesser amount translocated from the tracheobronchial airways are transported to the gastrointestinal tract well before significant absorption occurs, nearly two-thirds of the inhaled UO_2F_2 appeared in the feces. The new ICRP model for aerosol particle deposition should not overestimate the nasal deposition of UO_2F_2 for a given particle size, but it may underestimate it due to the hygroscopic character of UO_2F_2. Thus, fecal uranium measurements might be useful as an index of UO_2F_2 exposure but not as a predictor of systemic dose.

3. Intake into the pulmonary region of the lung leads to very rapid and nearly complete absorption. In the dog pulmonary retention of UO_2F_2 was mainly (about 90%) characterized by a 0.3 hour half-time. At necropsy measurements showed a small persistent fraction (about 5%) with a half-time of days.

4. On the basis of the first weeks's pattern of uranium distribution, the rat kidney and bone contained 74 and 20 percent of the body burden, respectively, and the dog 71 and 26 percent, respectively, a very similar finding. Renal retention in the dog peaked before six hours and declined with a 9.3 day half-time.

5. Following multiple UO_2F_2 exposures, both species showed increased renal uranium concentration and decreased urinary uranium excretion.

6. The indicators of renal injury tested included urinary protein, urinary glucose, urinary N-acetyl-glucosaminidase, urinary α -NH nitrogen, urinary phosphate, urinary citrate, creatinine and inulin clearance (glomerular filtration rate), and plasma urea nitrogen. These studies indicate multiple sites of uranium-induced dysfunction; i.e., involving both glomeruli and tubules. The most advantageous test was determined to be urinary glucose.

7. Intravenous doses of 0.01 mg U kg^{-1} as UO_2F_2 were nephrotoxic to the dog; in the rat an intravenous dose of 0.1 mg U kg^{-1} produced transient elevations in several urinary biochemical indices of renal injury. Data from other studies indicate that man is intermediate in sensitivity.

8. While many biochemical criteria returned to "normal" during the first 14 days post-exposure, some such as glomerular filtration rate do not, and others such as diminished urine concentrating function persist for many weeks. Even when the repair process is described histologically as well advanced, areas of recognizable injury persist, and the regenerated tubular epithelium appears basophilic and flattened.

9. Both species appear to show slightly greater urinary indicator response following exposure to combined UO_2F_2 + HF than when the same amount of UO_2F_2 was inhaled alone. The results indicate simple combined action rather than synergism.

Conclusions and Recommendations

The results from the numerous experiments done for this study show that urinary excretion of uranium can be mathematically related to the amount of uranium absorbed systemically. We recommend use of the ICRP excretion model for humans for calculation of uranium burdens.

Several findings can be put into use before the Occupational Radiation Protection Branch has completed the regulatory guide on bioassay. Fecal monitoring can be useful to detect the occurrence of a recent airborne exposure, since uranium in urine could be the result of prior exposures. Testing of urine for the presence of glucose (in individuals not diabetic and whose normal excretion is known) can be implemented to screen for renal injury.

The old concept of "reversible" renal injury has been proved wrong both for functional tests and histopathological changes. This finding along with the lower levels found to cause renal damage puts into question the currently used NRC action level of 30 $\mu g\ U\ l^{-1}$ of urine. We recommend (while the Occupational Radiation Protection Branch is developing the regulatory guide) action levels of 1 $\mu g\ U\ l^{-1}$ Monday morning urinary excretion rate and an exposure-associated urinary output of 100 $\mu g\ U\ l^{-1}$ during the first 24 hours post-exposure.

For further information on this study, please contact Dr. Judith D. Foulke (427-4563).

Robert B. Minogue, Director
Office of Nuclear Regulatory Research

RIL #133 SUMMARY

Rats and dogs were exposed to UF_6 and its hydrolysis products UO_2F_2 and HF by inhalation, intratracheal instillation, or intravenous injection. Pulmonary retention was characterized by a 0.3 hour half-time and renal retention by a 9.3 day half-time. During the first 24 hours post-exposure, 82% of the absorbed uranium was excreted. After one week the rat kidney and bone contained 74 and 20% of the body burden, respectively, and the dog 71 and 26%, respectively. Intravenous doses of 0.01 milligrams of uranium per kilogram were nephrotoxic to the dog and 0.1 milligrams per kilogram to the rat; man is judged to be intermediate in sensitivity. The urinary excretion rate confirmed the current ICRP excretion model for humans. Both biochemical and histopathological evidence proved that the old concept of "reversible" renal injury was wrong. Evaluation of urinary indicators of renal injury indicated urinary glucose was the most advantageous.

RES Files

Subject File No. 2813.03
2813.04
Reg. Guide 8.11
Task No.
Research Request No.
FIN No. A-4083
NUREG No./CR 2268
Docket No.
Rulemaking No.
Other RIL 133
Return NRC-318 to RES, Yes ✓ No

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Original Signed by

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for Robert B. Minogue, Director
Office of Nuclear Regulatory Research

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