UNITED STATES
NUCLEAR REGULATORY COMMISSION
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MEMORANDUM FOR: Ray G. Smith, Acting Director
Office of Standards Development

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

SUBJECT: RESEARCH INFORMATION LETTER # 111 - ACUTE EFFECTS OF INHALATION EXPOSURE TO URANIUM HEXAFLUORIDE AND PATTERNS OF DEPOSITION

Introduction and Summary

This memorandum transmits the results of completed research on evaluation of the biological effects of inhalation exposure 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 Environmental Effects Research Branch of RES.

Research Request SD-77-4 stated that studies were needed on the biological effects of uranyl fluoride (UO_2F_2) in order to include a bioassay program for uranium hexafluoride (UF_6) in Regulatory Guide 8.11, "Applications of Bioassay for Uranium." Gaseous UF_6 hydrolyzes in air to form UO_2F_2 plus HF. The rates of deposition, retention and excretion of uranium were determined and indicators of acute uranium toxicity were evaluated for UF_6 and UO_2F_2.

Methodology

The experimental plan was designed to examine primarily the relationship of inhaled UO_2F_2 or UF_6 to the resulting uranium burden in the lungs, kidneys, and whole body and to the subsequent uranium elimination pattern. Two animal species, dogs and rats, were selected to reveal or verify any species differences. A range of uranium doses was used to establish the approximate level for renal injury. Other experiments were conducted to examine possibly more sensitive indicators of renal injury and to determine if the combination of HF + UO_2F_2 produces a greater effect than UO_2F_2 alone.

Dog Studies

Young adult female Beagle dogs were anesthetized with pentobarbital and intubated with an intratracheal tube for administration of UO_2F_2. Immediately after exposure, the animals were gamma counted to establish their individual initial body (lung) burdens. Catheterized urine specimens were obtained during the first day post-exposure. A limited number of intravenous administrations were performed to assist in the interpretation of the retention and elimination data.

Rodent Inhalation Studies

Young adult male rats were given nose-only exposures to UO_2F_2 while unanesthetized in a special restraining tube connected to a Lovelace exposure unit. Immediately after exposure, the heads of the rats were washed with aqueous detergent and each animal was whole-body counted. The rats were returned to their individual metabolism cages for the duration of the study (6-14 days). Selected experiments were conducted involving administration of UO_2F_2 intravenously, intratracheally, or by gavage (stomach tubes).

Rodent Intratracheal Instillation Studies

Young adult male rats were anesthetized with pentobarbital and a small area of the trachea around the larynx was exposed surgically. The solutions of UO_2F_2 and/or HF were delivered to the lungs by hypodermic syringe. The surgical opening was closed with autoclips and the animals placed into individual metabolism cages.

In the deposition pattern studies, urine and feces were collected daily and assayed for uranium content. Blood and urine samples taken from selected animals were examined for plasma urea nitrogen and urinary protein and glucose, respectively.

At death or sacrifice, each animal was necropsied and major organs were assayed for radioactivity. Samples of lungs and kidneys from selected animals were fixed and stained for histopathologic examination.

In the dose-response studies, additional measurements of body weight, water intake, food consumption, and urine volume were made daily. Sections of lung, kidney, spleen, heart, liver and trachea were fixed and stained for histopathologic examination.

Results and Discussion

The results of each experiment are given in the tables and figures of NUREG/CR-1045, which has been provided to you. The following conclusions have been drawn:

1. The principal route of excretion of absorbed UO_2F_2 is renal and the urinary excretion rate in the dog can be correlated with U^{+6} absorbed dose (uptake) as a power function relationship wherein t (time) has the exponent - 1.45. This agrees quite well with the available human data from uranyl nitrate administration and the ICRP excretion model.

2. The urinary excretion of uranium is not easily related to total intake as differences in upper respiratory tract deposition directly determine the unabsorbed fraction, which approximates that eliminated in the feces. This

effect is clearly evident when the rat and dog data are compared, where, as the result of both species and exposure-method distinctions, the fraction of the UO_2F_2 intake which is absorbed (after inhalation) is around 33 percent in the rat and virtually 100 percent in the dog. Man is expected to fall into an intermediate position depending on the particle size of the UO_2F_2, and the respiratory performance of the individual, among other things.

3. Even if the intake of UO_2F_2 is restricted to the lower airways and pulmonary parenchyma, as it was in the dogs, and the resulting intake is tantamount to uptake, the possibility of relating lung (thoracic) levels to excretion is tenuous because the absorption of UO_2F_2 is so rapid. The dog data suggest at least 70 percent of the UO_2F_2 will be absorbed with a half time of $\sim$ 15 minutes. While the clearance kinetics of the remainder of the UO_2F_2 in the lungs cannot be described precisely, the uranium appears to follow kinetics similar to those exhibited by other soft tissues, e.g., skeletal muscle and liver, suggesting the blood-borne U^{+6} levels and the urinary elimination rates are probably more important than specific pulmonary translocation processes in determining the final phase of pulmonary retention.

4. In the dog, approximately 75 percent of the absorbed dose was excreted in the urine during the first post-exposure day. There is some indication for greater urinary elimination of uranium at lower absorbed doses, although the evidence is far from substantial. This suggests occupational exposures would result in somewhat higher 24 hour values, and this view is consistent with the ICRP excretion model for U^{+6} which predicts 80 percent urinary elimination during the first day. All of the available studies, both human and animal, provide excretion data at slightly or definitely nephrotoxic dose levels of U^{+6}.

5. Retention data from UO_2F_2 studies are somewhat variable and must be considered tentative. On the basis of the first study, the dog and rat retention data for uranium in the kidney are quite harmonious. The dog experiments (inhalation and intravenous) suggest 5 to 10 percent of the absorbed dose is present in the kidneys at 6 days post-exposure, and the kidney levels exhibit a fairly protracted retention time. Consequently, the 5 to 10 percent retention level in rodent kidneys from 6 to 14 days is in general agreement with the dog data.

6. The bone and kidneys are the two major retention sites for U^{+6}, but more data are needed on both before more definitive retention functions are available.

7. Absorbed doses of UO_2F_2 down to 0.05 mg kg^{-1} give clear evidence of uranium-induced nephrotoxicity. Whereas previously reported human and animal studies suggest 0.1 mg kg^{-1} as an approximate threshold dose for renal injury, the current study suggests the threshold is nearer 0.01 mg kg^{-1} in the previously-unexposed (novice) subject.

8. The indicators of renal injury initially tested were urinary protein and glucose, and plasma urea nitrogen (PUN). Of these, urinary glucose appeared to be the most sensitive early indicator, i.e., when comparing pre-exposure and post-exposure values. PUN's were typically slower to change; consequently, they peaked several days after the glucosuria and albuminuria.

9. Possible synergism of UO_2F_2 aerosol and stoichiometric amounts of HF gas, which would typify a UF_6 release, was investigated. Findings to date are inconclusive.

Future Work

The first year of this experimental study did not address sufficiently the possibility of synergistic effects when the hydrolysis products of UF_6 (viz, UO_2F_2 + 4HF) were present together in the exposure. This will be investigated in the second year of the project, especially in relation to U^{+6} retention, urinary excretion and renal toxicity.

The available data on UO_2F_2 excretion and that on other U^{+6} compounds has been acquired from subjects, both man and laboratory animals, at dose levels > 0.01 mg kg^{-1}, i.e., at certainly nephrotoxic levels. Also, there is an important information gap on the behavior of the kidney which has been exposed to U^{+6} previously. This could range from tests for possible predispositional effects from subliminal doses, up to tests on the response of severely injured and "recovered" kidneys to further uranium exposure. This research area has important implications in plant experience and for potential bioassay and injury assessment procedures. Currently, limited numbers of evaluations of previously-exposed animals are being undertaken insofar as nephrotoxic indicators are concerned and in relation to renal injury thresholds and retention functions.

Associated with the foregoing is need for further work on renal injury indicators. Since the first year's study, the scope has been broadened to include inulin clearance and urinary phosphate, α-amino acid nitrogen and N-acetyl β-glucosaminadase.

Distinctions between the normal and exposed kidneys should ultimately be expressed in terms of the dose modification producing nephrotoxicity. It is conceivable, for example, that the so-called regenerated nephron ("tolerant" kidney) does return to normal insofar as proteinuria is concerned, but there may be more persistent renal effects and indicators of renal dysfunction, and these should be assessed in terms of minimally effective doses or thresholds.

Retention functions for bone and kidney are needed for at least 8 weeks post-exposure so that current estimations regarding the return of exposed persons to work can be verified. The distribution and retention data from the first year's study were limited to 1 week in the dog and 3 weeks in the rat. These data provided an excellent basis for some current exposure protocols which are designed to produce 3 μg U g^{-1} kidney levels at 60 days post-exposure.

Conclusions and Recommendations

Results to date support the relation between absorbed dose and urinary elimination rate proposed by the ICRP for U^{+6} compounds. The completed studies indicate pulmonary retention of UO_2F_2 is extremely short and suggest that the threshold absorbed dose for producing renal injury is of the order of 10 $\mu g\ kg^{-1}$ body weight.

However, we suggest revision of Regulatory Guide 8.11 be delayed until the additional studies discussed above are completed. The final report is expected by the end of this fiscal year.

For further information on this study, please contact Dr. Judith D. Foulke (427-4358).

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