ABSTRACT

Uranium is the most important element of the nuclear fuel cycle. For this reason the main experiments involving injection and inhalation of uranium compounds into several animal species as well as those associated with humans were comprehensively reviewed in this work. The literature was carefully selected to involve the intake, distribution, and excretion of uranium in humans and in mammals. The available biokinetic models for the metabolism of uranium, proposed by ICRP in Publications 2, 30 and 69, were shortly described and tested against the data. Human data which incorporates measurements of urine, autopsy and biopsy samples were also used completing the review of models associated with the systemic part.

I. INTRODUCTION

The big question on internal dosimetry remains in the way to evaluate the intakes of radionuclides by workers and members of the public as well as to establish safe limits for these intakes. The International Commission on Radiological Protection (ICRP) has been dealing with these problems for more than thirty years [1]. The intake and the internal doses can be quantitatively assessed through mathematical modeling especially made to simulate the human metabolism associated with in vivo and in vitro bioassay methods. These models are constantly being updated in order to permit good estimates of intake, retention and excretion of radionuclides by the human body. Since the success of model development as well as their reliability are strongly dependent on the quality of the data set used to construct them, a very brief description of the available data is given below. The analysis was restricted to those studies involving only injection of radionuclides or inhalation of UF₆, in order to avoid the complications associated with pulmonary retention and prolonged transfer to plasma.

The objective of this paper was to test the suitability of the ICRP pharmacokinetic systemic models for uranium in terms of reproducing published experimental data.

II. MAIN URANIUM METABOLIC STUDIES IN SEVERAL SPECIES

Metabolic Studies in Mice. Three studies in which uranium was injected are suitable for quantitative analysis of deposition in the major organs and for estimation of the rates of transfer to and from those organs to the plasma and excreta. Walinder et al.[2] administered uranyl nitrate and "uranyl tricarbonate" by intravenous and intraperitoneal injection to about 60 male CBA mice, approximately 3 months old. All animals were injected with 30 mg of uranium, about 1 mg/g for a 30 gram
mouse. Animals were killed at 1, 2, 3, 7, 14, 30, 60, 76, and 217 days post injection and uranium in liver, spleen, kidneys, sternum, tibia, urine, and feces was analyzed. This is one of the most complete sets of data on mice. Kisieleski et al.[3] injected 50 young adult female CF#1 mice weighing approximately 25 grams each with $^{233}\text{U}$ uranyl nitrate into the lateral tail vein. The animals were sacrificed at intervals of 30 minutes, 1, 3, 6, and 24 hours and at 10, 30, 60, and 120 days. Two dose levels were used, 0.05 and 0.005 mCi/g, which are equivalent to injections of 5 and 0.5 mg/g respectively. Tannenbaum et al.[4] conducted a series of experiments with $^{233}\text{U}$ on mice to determine the excretion and retention of uranium at toxic and non toxic levels and to determine the relationship between uranium excreted and uranium retained in body tissues. The number of animals, dosages, and times of sacrifice were too small to obtain a continuous picture of retention and excretion. In order to avoid the complications in renal excretion associated with nephrotoxicity the results for injected dosages of 1.5 mg/g or greater were not included in this paper.

**Metabolic Studies in Rats.** Seven separate studies on single injections of soluble uranium compounds in the rat have been analyzed. They provide sufficient information about the content of uranium in kidney, in selected bones rather than in the entire skeleton, and in other organs. These data can be used to test uranium pharmacokinetic models incorporating recirculation. Bentley et al.[5] conducted studies of uranium metabolism in female albino wistar rats (6 animals per group) aged 11 to 13 weeks. Two groups of animals were injected with natural uranyl nitrate, and 4 groups with uranium enriched in the isotope $^{235}\text{U}$ to 92.8%. The enriched material was given with injected dosages ranging from 13 to 50 mg/kg. The animals injected with natural uranium received a single parenteral dose of 50 to 500 mg/kg. Experiments previously reported by Hamilton[6][7] and Durbin [8] in mostly female adult albino rats, have been re-analyzed.$^{230}\text{U}$ and $^{235}\text{U}$ were injected intramuscularly as soluble uranyl chloride. The mass of $^{230}\text{U}$ injected was very small, on the order of 2.5x10^{-6} \text{mg/g} whereas for $^{235}\text{U}$ the mass injected was 0.1 to 0.3 mg/g. Priest et al.[9] injected fairly young female wistar, HMT strain rats, aged 50 days with uranyl citrate complex, using $^{233}\text{U}$. Groups of five rats were sacrificed at 1, 4, 14, and 32 days after injection. An unusual feature of this study was that the complete skeleton was analyzed, bone by bone, at 1 and 32 days post administration. There was rather high retention in the skeleton, which probably reflects the fact that these were very young rats, in which skeletal turnover was very rapid. This investigation is however extremely useful because of the detail given about the internal deposition, and the tendencies of uranium to be very uniformly distributed in the skeleton. Sontag[10] investigated the early distribution of $^{233}\text{U}$ in the soft tissue and skeleton of older rats. Both male and female rats, Sprague-Dawley strain aged approximately 13 months, were injected intravenously with $^{233}\text{U}$ uranyl-citrate (1.53 mCi/kg or 0.16 mg/kg) and were sacrificed 7 and 28 days post injection. Uptake was about 50% higher in male than female rats of the same age group.

**Metabolic Studies in Dogs and Primates.** There are four sets of studies in dogs and one in a primate dealing with deposition and retention of uranium in kidney. Morrow et al.[11] investigated UF$_6$ or UF$_2$O$_2$F$_2$ administration to dogs by injection or inhalation. Sixteen dogs were exposed by inhalation of UF$_2$O$_2$F$_2$ aerosols with estimated dosages ranging from 0.1 to 1.5 mg/g. Post exposure follow-up periods were from 6 hours to 19 days. Of the 16 dogs studied, 3 were not sacrificed at the end of their post exposure period, but were re-exposed at a later time. In addition, five dogs were investigated in nine studies using intravenous injections of UF$_2$O$_2$F$_2$ in isotonic saline with dosages ranging between 0.01 to 2 mg/g. Stevens et al.[12] injected about 0.3 mg/g of body weight of $^{233}\text{U}$ intravenously in dogs and sacrificed them at times between one and 726 days post injection. In addition, a larger series of the data from kidney retention in additional animals injected with $^{233}\text{U}$ and $^{232}\text{U}$ in the same experiment has been reported by Wrenn et al.[13]. The experiments by Stevens[12] are unique in that the plasma content was measured very carefully as a function of time post injection. Uranium is rapidly eliminated from plasma. In this experiment the animals experienced some transient kidney toxicity which was indicated by increased urinary output from 7 to 10 days post injection after which it decreased gradually to normal pre-injection volumes. One day post injection, the average concentration of uranium in the kidney was approximately 15 mg/g. Cumulative urinary excretion after one day was in the range from 22 to 58%. At the end of three weeks the cumulative urinary excretion was 83%. Fecal excretion was small, only 2 to 3 % of the injected dose during the first week. Tannenbaum[4] injected 0.0033, 0.0036 and 0.318 mg/g of uranium as uranyl-233 nitrate in 3 separate female dogs, from which 42, 78 and 90% was excreted in urine during the first 24 hours. One dog was sacrificed at 59 days and the other two at 74 days, post injection. Lipszeit[14] injected 0.01865 mg/g of $^{235}\text{U}$ and 0.00334, 0.000685, 0.01013, 0.000143 mg/g of $^{237}\text{U}$ intravenously as nitrate in five separate young female Papio "Kenya" baboons. Urine, feces and blood samples were collected on daily basis for times varying from one to 49 days after the injection depending on the animal. Percentages of uranium injected were determined also separately in plasma and red blood cells; red cells accounted for 0.7% of initial deposition with a half-time of 1.2 days. One animal was sacrificed four days after the injection and 5.3% of the injected activity was found in kidneys, followed by liver and spleen with 0.53, 0.16% respectively.

**Human Studies.** Nine brain tumor patients injected with uranyl nitrate in Boston were originally reported by Bernard and Struxness[15]. These cases have been re-
analyzed resulting in new evaluations of the percentage of uranium present in kidney, liver, spleen, muscle, other tissues, skeleton and urine (Durbin[16]). These cases were injected with natural and enriched uranium. The dosages injected ranged from 47 to 1,050 mg/kg. It appears however that the human data were deficient in several respects. First, the patients were completely non ambulatory, comatose, bedridden and in the terminal phase of life. Second, the number of data points (time to death) at different times post injection was not under the control of the investigators and therefore the data is missing in critical time periods where the animal work indicated the need to understand more about the removal rates in man.

III. RETENTION IN KIDNEY

Fig. 1 shows the retention of uranium in kidney at different time intervals post administration expressed as the percentage of injected activity retained in kidney as a function of time using the main mammalian kidney data including humans. Individually and collectively the rat studies show that there is a rapid component of loss from rat kidney; some of them indicate that a second component exists composed of a small fraction of the activity initially deposited in kidney with a longer half-time. The information in the dog is consistent with that in the rat and mouse to the extent that retention in kidney appears to be a two component process with the bulk of the activity being excreted with a short half-time on the order of 3 days. The human studies also reveal that particularly for being excreted with a short half-time on the order of 3 days. An additional longer term with a smaller fraction of deposition was included as pointed out by the metabolic studies in dogs. An earlier study by Wrenn et al.[13] based on the data by Stevens et al.[12] indicated a fraction of 27.5% for the short term component with a half-time of 3 days and a fraction of 1.8% with a corresponding half-time of 67 days for this longer term.

IV. RETENTION IN SKELETON

Fig. 2 depicts the data on skeletal retention for all experiments. Wallinder’s[2] data, not shown in this figure, clearly indicate a declining retention in skeleton leveling off after about 10 days, whereas the data from Kisieleski et al.[3] , depicted in Fig. 2, show a flat retention with almost no decrease with time at all. These clearly inconsistent results are puzzling, especially in view of the fact that the deposition in and rates of loss from kidney appeared to be comparable. Possibly the bolus reaching the kidney in the experiment by Kisieleski et al.[3] was more concentrated because of the intravenous injection, and recirculation may have been more prolonged due to decreased excretion by the kidney, resulting in a greater and more persistent deposition in the skeleton. None of the studies in rats indicates a short term component of loss from bone.
The skeletal content observed is persistent in the studies conducted by Bentley et al., Priest et al., and Sontag. The data from all studies in rats suggests that once uranium is deposited in the skeleton it is persistent to the extent that the rate of release is measured in period of months or longer. Even though uranium is redistributed by processes of remodeling in bone, it remains strongly bound after initial deposition on bone surface. The studies in dogs also show that there is no evidence for a short term component in the skeleton. The single measurement at the longest time post injection made by Stevens et al. in the dog was at 726 days post injection. The data seem to support a single exponent declining with a half-time of 883 days and an initial extrapolated value of 7.7 ± 0.3%. The initial content in skeleton of all studies in dogs appears to be below 10%, with an average of 7%, with the exception of a single data point by Tannenbaum et al.

V. RETENTION IN OTHER ORGANS

The retention of uranium in other soft tissues excluding kidney was also studied. Since less than 2% of the initial activity in plasma is distributed to all other tissues, the dog and the human data for liver, spleen, muscle and others could be grouped into a single compartment. Studies in mice show a small retention in liver, initially about 3%, declines with a half-time of about 3 days, and the content in spleen and other tissues which is even smaller is also lost rapidly. There are no measurements in plasma for the mouse, but Kisieleski's work shows that distribution by plasma is apparently complete within 30 minutes. Studies in rats show that in general the estimates of initial deposition in liver and in other organs range between 1 and 20%, with most of the estimates being less than 4% and declining rapidly.

VI. MAIN SYSTEMIC MODELS FOR URANIUM

The literature shows a great variety of systemic models describing the uranium metabolism. However, due to space limitation, only the official ICRP models will be very shortly described here since they have been forming the bases for international radiation protection regulations. These models are depicted in Fig. 3.

A very comprehensive description of the evolutionary process until 1984 can be found elsewhere. A later literature review can be found in ICRP Publication 69. The first ICRP retention model for systemic uranium was issued in the Publication no. 2 in 1959. At that time ICRP was concerned in relating concentrations of radionuclides in the air and water as a way to assess internal doses in the several body organs. The objective was the establishment of Maximum Permissible Concentrations (MPC) for radionuclides in air and water related to maximum permissible weekly doses in body organs. According to this model, 56% of the injected activity is directly excreted with a half-time of 0.25 day, 11% of the activity goes to kidney and is removed with a half-time of 15 days and 33% goes to skeleton with a half-time of 300 days.

ICRP proposed the second uranium systemic model in its Publication 30. In this case it is assumed that of uranium entering the transfer compartment, fractions of 0.2 and 0.023 are assumed to go to mineral bone and be retained there with half-times of 20 and 5000 days.
respectively, fractions of 0.12 and 0.00052 are assumed to go to the kidneys and to be retained with half-times of 6 and 1500 days respectively and fractions 0.12 and 0.00052 are assumed to go to all other tissues of the body and be retained with half-times of 6 and 1500 days respectively. Uranium is assumed to be uniformly distributed amongst these other tissues. The remainder of uranium entering the transfer compartment is assumed to go directly to excretion.

The third and last ICRP uranium systemic model was proposed in ICRP Publication 69[19]. This very sophisticated model has been used to describe the metabolisms of alcaline earths and lead as well. This is not the first published uranium biokinetic model presenting recycling, but it is the first one of this kind adopted by ICRP. The activity entering blood is retained by bone surfaces and soft tissues or excreted. The bone was divided into cortical and trabecular portions, which were divided into bone surface and bone volume. According to ICRP[19] 15% of the activity leaving the plasma is deposited on bone surfaces. It is assumed that 50% of this returns to plasma and the other half migrates to exchangeable bone volume with a half-time of 5 days. A portion of 75% of activity leaving exchangeable bone volume is assumed to return to bone surfaces and 25% migrates to regions of bone that loses activity to plasma more slowly. These processes are represented by the pathways leaving the EXCH and NONEXCH compartments respectively. Despite the numerous studies described above, substantial uncertainties are associated with the long-term retention of uranium in the skeleton. The compartments ST0, ST1 and ST2 serve to provide the balance of the model in terms of material distribution. The liver was assumed to have two compartments. LIVER1 is assumed to receive 1.5% of uranium leaving the circulation having a removal half-time of 7 days, 93% of uranium leaving liver is assumed to return to plasma and 7% goes to LIVER2, from which it is removed with a half-time of 10 years. Is is assumed that 63% of the uranium leaving the circulation moves directly to the urinary bladder and that 12% of the uranium leaving the circulation is removed from the renal tubules to the urinary bladder with a half-time of 7 days. OTHER KIDNEY TISSUE compartment is assumed to receive 0.05% of uranium leaving the circulation and to be removed from there with a half-time of 5 years. Smaller portions of 0.7% and 0.35% go to Red Blood Cells (RBC) and Gastro Intestinal Tract Contents respectively.

VII. SIMULATION OF URANIUM RETENTION AND EXCRETION USING THE OFFICIAL ICRP SYSTEMIC MODELS

The ICRP metabolic models were entered in a computer program which calculates activities in body organs and excreta after intakes of radionuclides[21]. A case of a single injection of soluble uranium in blood was simulated. Figures 1 and 2 show the results for kidney and skeletal retention respectively. In both figures the dotted lines correspond to the simulation using the model proposed in ICRP Publication 2. The simulations using the ICRP Publications 30 and 69 are represented by the dashed and solid lines respectively. It can be seen that the kidney retention is much better predicted by the ICRP-69 model, not only at short times down to less than one day, but also for much longer times after exposure, when compared to those predicted using the ICRP-2 and ICRP-30 models. Moreover, the ICRP-69 model is the only pharmacokinetic model proposed by ICRP, which was meant to be used in bioassay and dosimetry of uranium. The other two needed to be complemented by excretion functions, which were not necessarily associated with pharmacokinetic compartments. The same can be observed for the skeletal retention shown in Figure 2.

The cumulative urinary excretion after a single injection of soluble uranium was also simulated to test the predictions of the systemic models against the human urinary excretion data obtained from the Boston and Rochester cases[16].

Figure 4 clearly shows that the ICRP-69[19] systemic model describes the urinary excretion better than the others. The ICRP-30[20] model underpredicts the urinary excretion for early times after the intake while the ICRP-2[1] model underpredicts the urinary excretion for latter times.

All these observations suffice to show that the use of the ICRP69[19] systemic model should be encouraged when interpreting in vivo and in vitro bioassay data from intakes of uranium compounds.
ACKNOWLEDGMENTS

The authors express their gratitude to the Brazilian National Council for Scientific and Technological Development (CNPq), to the Atomic Energy Control Board of Canada for supporting this study and to the Colombian Institute for Development of the Science and Technology (COLCIENCIAS) for supporting A. Puerta at the Institute of Radiation Protection and Dosimetry of the Brazilian Nuclear Energy Commission.

REFERENCES


