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The biokinetics of uranium migrating from embedded DU fragments

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Abstract

Military uses of depleted uranium (DU) munitions have resulted in casualties with embedded DU fragments. Assessment of radiological or chemical health risks from these fragments requires a model relating urinary U to the rate of migration of U from the fragments, and its accumulation in systemic tissues. A detailed biokinetic model for U has been published by the International Commission on Radiological Protection (ICRP), but its applicability to U migrating from embedded DU fragments is uncertain. Recently, Pellmar and colleagues (1999) conducted a study at the Armed Forces Radiobiology Research Institute (AFRRI) on the redistribution and toxicology of U in rats with implanted DU pellets, simulating embedded fragments. This paper compares the biokinetic data from that study with the behavior of commonly studied forms of U in rats (e.g., intravenously injected U nitrate). The comparisons indicate that the biokinetics of U migrating from embedded DU is similar to that of commonly studied forms of U with regard to long-term accumulation in kidneys, bone, and liver. The results provide limited support for the application of the ICRP's model to persons with embedded DU fragments. Additional information is needed with regard to the short-term behavior of migrating U and its accumulation in lymph nodes, brain, testicles, and other infrequently studied U repositories.

Keywords: Depleted uranium; Wound; Biokinetics; Model; Rat; Man

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1. Introduction

The use of depleted uranium (DU) munitions in Operation Desert Storm resulted in casualties with embedded DU fragments. An evaluation of the radiological and chemical risks from DU fragments left in the body requires estimation of the rate of mobilization of U from the fragments to blood and the time-dependent tissue concentrations of the mobilized U. The mobilization and systemic distribution of U cannot be measured directly, but must be inferred from the rate of urinary excretion of U, using a model of the biokinetics of U.

The International Commission on Radiological Protection (ICRP) recently adopted a physiologically descriptive biokinetic model for U in humans (Leggett, 1994; ICRP, 1995). A schematic of the model is given in Fig. 1, and parameter values are given in Table 1. The model is based on a sizable collection of experimental, occupational, and environmental data on the behavior of uranium in human subjects, supplemented with data from controlled studies on laboratory animals. The question arises as to the applicability of the ICRP's model to embedded DU fragments, however, due to the possibility that the form of U that migrates from the fragments may differ from the forms of injected or absorbed U considered in development of the model. For example, it is conceivable that a substantial portion of U that migrates from the

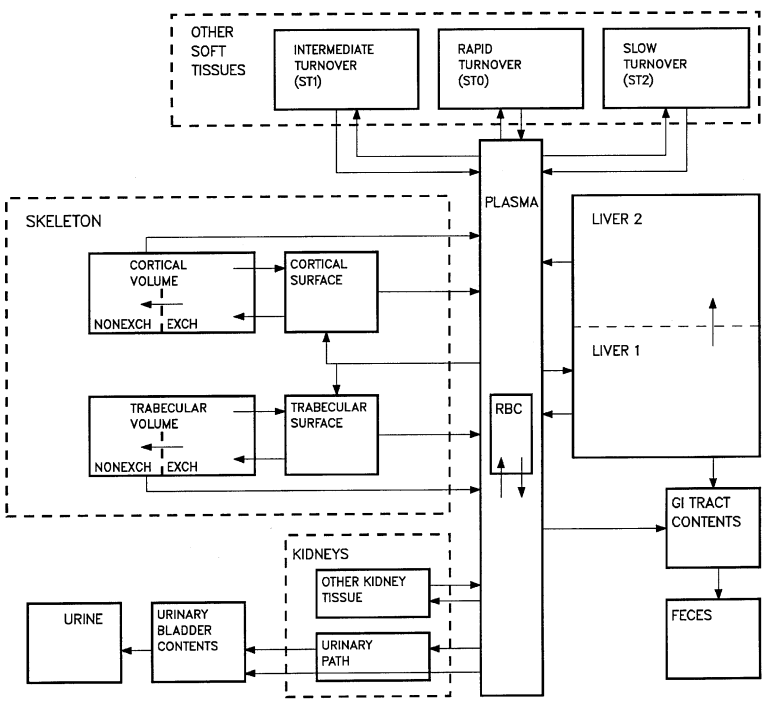

Fig. 1. Structure of the biokinetic model for U in humans (Leggett, 1994; ICRP, 1995).

Table 1
Transfer coefficients in the ICRP's biokinetic model for U in the adult human

Path	Transfer Rate (d^{-1})
From plasma to:	
ST0	1.050×10^{1}
RBC	2.450×10^{-1}
Urinary bladder contents	1.543×10^{1}
Kidney 1	2.940×10^{0}
Kidney 2	1.220×10^{-2}
Upper large intestine contents	1.220×10^{-1}
Liver 1	3.670×10^{-1}
ST1	1.630×10^{0}
ST2	7.350×10^{-2}
Trabecular bone surfaces	2.040×10^{0}
Cortical bone surfaces	1.630×10^{0}
To plasma from:	
ST0	8.320×10^{0}
RBC	3.470×10^{-1}
Kidney 2	3.800×10^{-4}
Liver 1	9.200×10^{-2}
Liver 2	1.900×10^{-4}
ST1	3.470×10^{-2}
ST2	1.900×10^{-5}
Bone surfaces[a]	6.930×10^{-2}
Nonexch. trabecular bone volume	4.930×10^{-4}
Nonexch. cortical bone volume	8.210×10^{-5}
From Kidney 1 to urinary bladder contents	9.900×10^{-2}
From Liver 1 to Liver 2	6.930×10^{-3}
From bone surfaces to exchangeable bone volume[a]	6.930×10^{-2}
From exchangeable bone volume to bone surfaces[a]	1.730×10^{-2}
From exchangeable bone volume to nonexchangeable volume[a]	5.780×10^{-3}

[a] Applies both to trabecular and cortical bone compartments.

fragments could be released as relatively insoluble particulates that are accumulated by the reticuloendothelial system, which is not addressed in the ICRP's model.

To assess the health risks associated with embedded DU fragments, Pellmar and colleagues (1999) at the Armed Forces Radiobiology Research Institute (AFRRI) conducted an experimental study in which DU pellets were implanted in rats. As part of this study, the systemic distribution and rate of excretion of U were determined at 1 day and 1, 6, 12, and 18 months after implantation of the pellets. In most cases, the U concentration was measured in urine, serum, kidney, tibia, skull, liver, spleen, brain, and muscle. More limited measurements were made in testes, heart, lungs, and teeth.

This paper compares the biokinetic data from the study of Pellmar et al. (1999)

with published findings for commonly studied forms of U in rats (e.g., injected, inhaled, or ingested U nitrate). To this end, biokinetic data on U-exposed rats are collected from the literature and used to develop a baseline biokinetic model for rats. Predictions of the baseline model are then compared with observations for the DU-implanted rats. Because the rate of migration from the DU pellets to blood is not known precisely, comparison of model predictions and observations is done only in a relative sense. Specifically, the time-dependent rate of uptake by the plasma compartment of the baseline model is set to produce the urinary excretion rates observed in the DU-implanted rats, and predicted time-dependent concentrations of U in various organs are then compared with the observed concentrations in the DU-implanted rats.

2. The baseline biokinetic model for U in rats

2.1. Model structure

A "baseline" biokinetic model for U in rats was developed from collected data on the behavior of commonly studied forms of U in rats. A schematic diagram of this baseline model is given in Fig. 2. The structure resembles that used in the bioki-

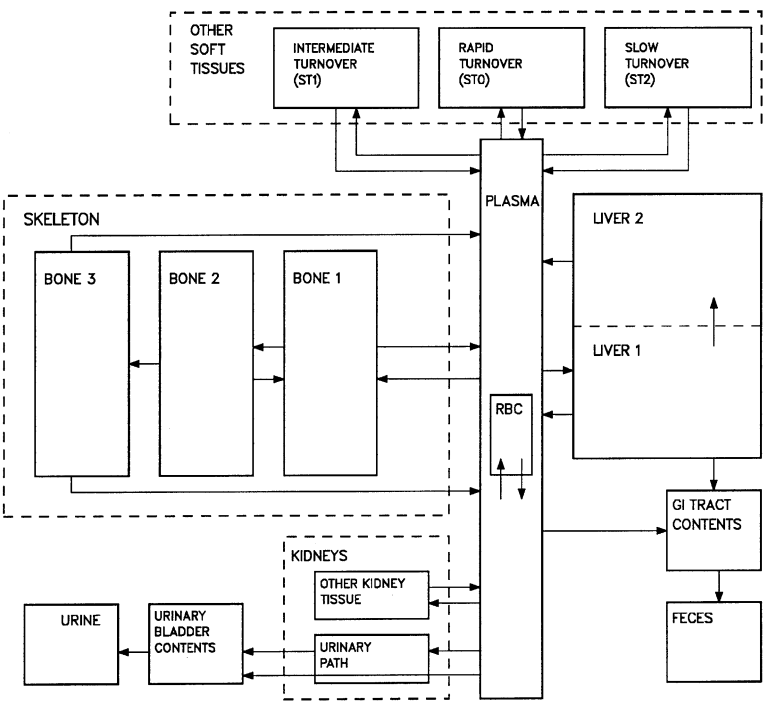

Fig. 2. Structure of the biokinetic model for U in rats. The structure is similar to that of the ICRP's model for man (Fig. 1), but the sub-model of the skeleton has been simplified.

netic model for U in humans (Fig. 1), but the representation of the skeleton has been modified in view of limitations in the available data on the behavior of U in the rat skeleton. Essentially, the difference between the skeletal model for rats and that for humans is that the rat skeleton is not divided into anatomically identifiable compartments. In both models, however, retention of U in the rat skeleton is described in terms of a tri-layered model, with deeper layers representing longer retention times.

Parameter values of the baseline model for rats are given in Table 2. The basis for these values is described below.

2.2. Definitions

Transport of U between compartments is assumed to follow first-order kinetics. Parameter values are expressed as transfer coefficients (d^{-1}) (sometimes called rate

Table 2
Transfer coefficients in the biokinetic model for U in adult rats

Path	Transfer rate (d^{-1})
From plasma to:	
ST0	6.000×10^{1}
RBC	2.800×10^{-1} (0.2%)[a]
Urinary bladder contents	7.000×10^{1} (50%)
Kidney 1	2.800×10^{1} (20%)
Kidney 2	7.000×10^{-1} (0.5%)
Upper large intestine contents	7.000×10^{0} (5%)
Liver 1	1.120×10^{0} (0.8%)
ST1	3.500×10^{0} (2.5%)
ST2	1.400×10^{0} (1%)
Bone 1	2.800×10^{1} (20%)
To plasma from:	
ST0	8.320×10^{0}
RBC	6.930×10^{-1}
Kidney 2	1.386×10^{-2}
Liver 1	9.603×10^{-2}
Liver 2	6.930×10^{-3}
ST1	2.311×10^{-1}
ST2	6.930×10^{-3}
Bone 1	6.930×10^{-2}
Bone 3	3.000×10^{-3}
From Kidney 1 to Urinary bladder contents	1.733×10^{-1}
From Liver 1 to Liver 2	2.970×10^{-3}
From Bone 1 to Bone 2	6.930×10^{-2}
From Bone 2 to Bone 1	1.730×10^{-2}
From Bone 2 to Bone 3	5.780×10^{-3}

[a] Percentages given in parentheses correspond to deposition fractions, i.e., portions of U leaving the circulation that deposit in the indicated compartments.

coefficients) between compartments, that is, fractional transfers (or compartment volumes) per day from one compartment to another. Most of the derived transfer coefficients in this model are secondary values calculated from selected removal half-times and deposition fractions. The removal half-time from a compartment refers to the biological half-time that one would observe, theoretically, if outflow from that compartment continued while feeds from all other compartments were stopped. The removal half-time as used here generally is shorter than the apparent half-time (or half-time of disappearance) in the presence of recycling. A deposition fraction for a compartment refers to the fraction of instantaneous outflow from the circulation that deposits in that compartment. As described later, U is assumed to leave plasma at a rate of 200 d^{-1}. ST0, an extracellular fluid compartment assumed to be in rapid exchange with plasma, is assigned 30% of the instantaneous outflow from plasma, but is regarded as part of the circulation. Therefore, only 70% of the activity leaving plasma is considered to "leave the circulation", and the transfer coefficient describing instantaneous removal from the circulation is $0.7\times200\ d^{-1}=140\ d^{-1}$. The transfer coefficient from plasma to a compartment is $F\times140\ d^{-1}$, where F is the deposition fraction for that compartment.

2.3. Limitations in reported biokinetic data for U in rats

Numerous studies of the fate of inhaled, ingested, or injected U in rats have addressed the rate of urinary excretion of U as well as uptake and retention by the skeleton, kidneys, and liver, but data for other tissues are sparse. Therefore, the only tissues addressed explicitly in the model are the skeleton, kidneys, and liver. Remaining tissues are lumped together as "other soft tissues".

With regard to rat studies involving inhalation, ingestion, or injection of U(VI), no evidence was found to suggest that the systemic biokinetics of U depends strongly on the chemical form administered or the route of exposure. On the other hand, there are indications in the literature that uptake and retention of U by the kidneys and skeleton of rats depends to some extent on age, gender, and the mass U administered (Neuman, 1949; Jones, 1966; Sontag, 1984). To examine the effects of these factors on the biokinetics of U, data were grouped as follows (Figs. 3–6): young females receiving a relatively low mass of U (Muir et al., 1960; Jones, 1966; Cooper et al., 1982; Priest et al., 1982; Stradling et al., 1985; Ellender, 1987); young females receiving a relatively high mass (Jones, 1966; Neuman, 1949; Bentley et al., 1985); old females receiving a relatively high mass (Sontag, 1984); young males receiving a relatively high mass (Neuman, 1949); old males receiving a relatively high mass (Sontag, 1984); mixed genders receiving a relatively low mass (Durbin, 1984); and mixed genders receiving a relatively high mass (Hamilton, 1948). "Mass" refers here to the mass of U that reaches blood, with 0.01 μg U g^{-1} or less defined as a "relatively low mass" and values substantially greater than 0.01 μg U g^{-1} defined as "relatively high mass". In these studies, "young" animals were typically 50–120 days old and "old" animals were slightly more than a year old at the time of exposure. By these definitions, the rats used in the study of Pellmar et al. (1999) were young at the beginning of the study, but were old during the last few months of the study.

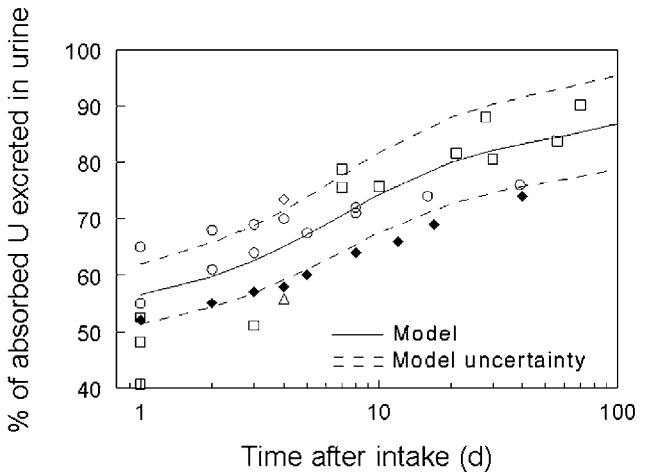

Fig. 3. Observations and model predictions of cumulative urinary excretion of U (commonly studied forms) as a function of time after acute uptake to blood. *Squares*, young females receiving low mass of U; *open circles*, young females, high mass; *plus signs*, old females, high mass; *closed diamonds*, young males, high mass; *closed circles*, old males, high mass; *open diamonds*, mixed genders, low mass; *triangles*, mixed genders, high mass. Data sources given in the main text.

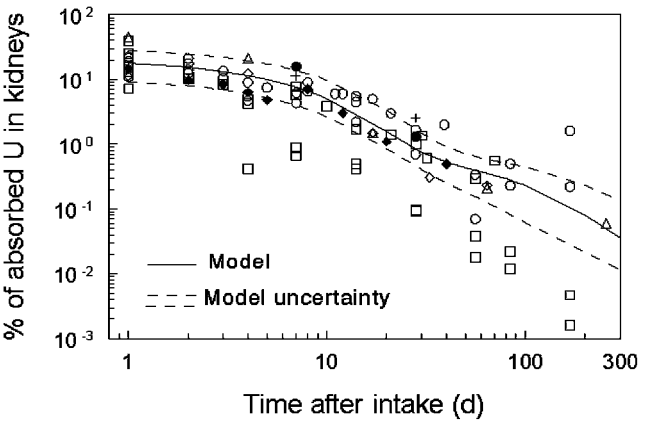

Fig. 4. Observations and model predictions of retention of U (commonly studied forms) in kidneys of rats after acute uptake to blood. Symbols defined in Fig. 3. Data sources given in main text.

Attempts were made to introduce age, gender, and dosage dependence into model parameters on the basis of these separated data sets, but this did not prove to be feasible due to the relatively small sizes and inconsistencies in the separated data sets. In the end, model parameters were based on the lumped data, although some data sets were excluded without regard to age, gender, or mass because they were inconsistent with the preponderance of the data.

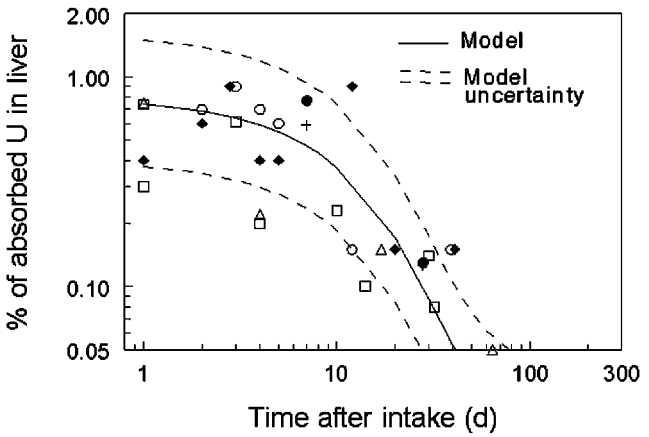

Fig. 5. Observations and model predictions of retention of U (commonly studied forms) in rat liver after acute uptake to blood. Symbols defined in Fig. 3. Data sources given in the main text.

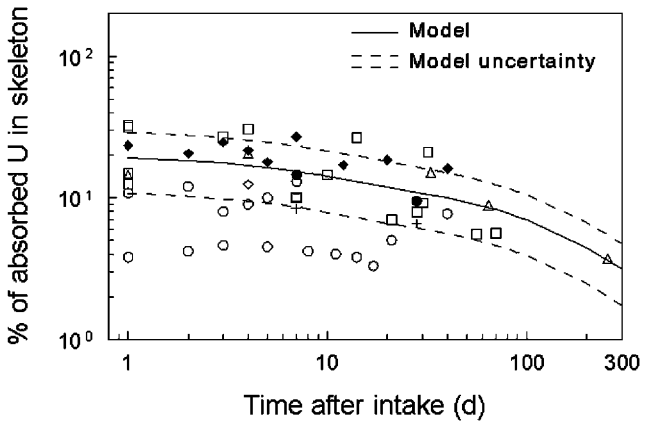

Fig. 6. Observations and model predictions of retention of U (commonly studied forms) in rat skeleton after acute uptake to blood. Symbols defined in Fig. 3. Data sources given in main text.

2.4. The model for blood and rapid-turnover soft tissues

Data for several species, including rats, indicate a rapid phase of clearance of a substantial portion of injected U from blood, followed by slower clearance of the remaining few percent over the following hours or days (Leggett, 1994). The initially rapid clearance is associated with a high rate of filtration by the kidneys, together with a high rate of diffusion from plasma into extravascular fluids. The slower clearance at later times appears to be due to binding to plasma proteins and red blood cells, and to return from the extravascular spaces.

Two compartments are used to describe circulating U: plasma and a rapid-turnover soft-tissue compartment called ST0 that returns U to plasma over a period of hours.

It is assumed that U leaves plasma with a transfer coefficient of 200 d^{-1}, that the rapidly exchanging extracellular fluid compartment ST0 receives 30% of U leaving plasma, and that the removal half-time from ST0 back to plasma is 2 h. These values, which were used in a more detailed model of the human circulation described in an earlier paper (Leggett, 1994), yield reasonable agreement with data on the early behavior of circulating U in rats (Neuman, 1949). The derived transfer coefficient from plasma to ST0 is $0.3\times200\ d^{-1}=60\ d^{-1}$ and the transfer coefficient from ST0 to plasma is $0.693/2\ h=0.347\ h^{-1}=8.32\ d^{-1}$.

Limited data on retention of U in blood of rats (Neuman, 1949; Galibin, 1971) are consistent with a deposition fraction for RBC on the order of 0.2% and a removal half-time to plasma on the order of 1 d. Neither of these values can be estimated with much confidence, but model predictions for other compartments are not sensitive to the uncertainties in parameter values for RBC. The transfer coefficient from plasma to RBC is $0.002\times140\ d^{-1}=0.28\ d^{-1}$. The transfer coefficient from RBC to plasma is $\ln(2)/(1\ d)=0.693\ d^{-1}$.

2.5. The model for kidney retention and urinary excretion

The kidney is assumed to consist of two compartments, Kidney 1 and Kidney 2, representing short-term retention (days) and long-term retention (months), respectively. It is assumed that a portion of U filtered at the glomerulus deposits in Kidney 1, but that most of the filtered amount goes directly to the urinary bladder contents and subsequently to urine. Uranium leaving Kidney 1 is assigned to the urinary bladder contents. The longer-term compartment, Kidney 2, is assumed to be fed directly by plasma and to lose U to plasma rather than urine.

Data on cumulative urinary excretion and renal retention of U in acutely exposed rats are summarized in Fig. 3 and Fig. 4, respectively (data sources given in a previous section). In these two figures as well as in Fig. 5 (retention of U in the liver) and Fig. 6 (retention of U in the skeleton), attention has been restricted to studies involving either intravenous injection of U or relatively rapid absorption of reasonably well known quantities of U to blood, in order to avoid uncertainties associated with the level and time course of absorption of U to blood. The model uncertainty bands in Figs. 3–6 and subsequent figures were determined by examining the sensitivity of model predictions to uncertainty in parameter values. Uncertainties in parameter values were assessed on the basis of inconsistencies and gaps in the data from which parameter values were selected and potential inadequacies in the methods used to extrapolate available data to times or situations outside the region of observation.

Most of the U introduced to blood at time zero is lost to urine over a relatively short period. As an average, about half of acutely absorbed U is lost in urine the first day, about 70% is lost in the first ten days, and about 85% is lost during the first three months.

A reasonably good fit to the preponderance of the data on cumulative urinary excretion and renal retention of U in rats is obtained if it is assumed that 50% of U leaving the circulation goes directly to the urinary bladder contents and subsequently to urine, 20% goes to the short-term kidney compartment Kidney 1 and

is lost from this compartment to urine with a half-time of 4 d, and 0.5% goes to the long-term kidney compartment Kidney 2 and is lost from this compartment to plasma with a half-time of 50 d. The resulting transfer coefficient from plasma to bladder urine is $0.5\times140\ d^{-1}=70\ d^{-1}$, from plasma to Kidney 1 is $0.2\times140\ d^{-1}=28\ d^{-1}$, from plasma to Kidney 2 is $0.005\times140\ d^{-1}=0.7\ d^{-1}$, from Kidney 1 to bladder urine is $\ln(2)/4\ d=0.1733\ d^{-1}$, and from Kidney 2 to plasma is $\ln(2)/50\ d=0.01386\ d^{-1}$.

2.6. The model for fecal excretion

Although rats show high biliary secretion of many metals, there appears to be little endogenous fecal excretion of U in rats (Neuman, 1950). Based on data of Neuman (1949, 1950) and Cooper et al. (1982), it is assumed that 5% of U leaving the circulation is secreted into the contents of the gastrointestinal tract and is subsequently excreted in feces. The transfer coefficient from plasma to the intestinal contents is $0.05\times140\ d^{-1}=7\ d^{-1}$.

2.7. The model for liver

The liver is viewed as consisting of two compartments, called Liver 1 and Liver 2, representing, respectively, short- and long-term retention of U. Liver 1 receives U from plasma. Outflow from Liver 1 occurs over a period of days and is mainly to plasma, but a small percentage of outflow enters Liver 2, from which it is transferred to plasma over a period of months.

Data on retention of U in the liver in acutely exposed rats are summarized in Fig. 5 (data sources given in a previous section). A reasonably good fit to the data is obtained by assuming that 0.8% of U leaving the circulation deposits in Liver 1; the removal half-time from Liver 1 is 7 d; of U leaving Liver 1, 3% transfers to Liver 2 and 97% returns to plasma; and the removal half-time from Liver 2 to plasma is 100 d. Under these assumptions, the transfer coefficient from plasma to Liver 1 is $0.008\times140\ d^{-1}=1.12\ d^{-1}$; the total transfer coefficient from Liver 1 is $\ln(2)/7\ d=0.099\ d^{-1}$; the transfer coefficient from Liver 1 to Liver 2 is $0.03\times0.099\ d^{-1}=0.00297\ d^{-1}$; the transfer coefficient from Liver 1 to plasma is $0.97\times0.099\ d^{-1}=0.09603\ d^{-1}$; and the transfer coefficient from Liver 2 to plasma is $\ln(2)/100\ d=0.00693\ d^{-1}$.

2.8. The model for the skeleton

The early distribution of U in the skeleton is similar to that of Ca (Leggett, 1994). There is evidence that UO_2^{++} exchanges with Ca^{++} at the surfaces of bone mineral crystals (Neuman et al., 1948; Neuman, 1953). Perhaps depending on the microscopic structure of the bone of each species, U on bone surfaces may gradually diffuse into bone volume. Such diffusion has been demonstrated in dogs (Rowland and Farnham, 1969; Stevens et al., 1980), but not in rats (Priest et al., 1982) or mice (Kisieleski et al., 1952).

In the biokinetic model for U in humans (Leggett, 1994; ICRP, 1995), bone is divided into cortical and trabecular bone, and each of these bone types is further

divided into compartments representing bone surface, exchangeable bone volume, and non-exchangeable bone volume. Uranium is assumed to deposit on bone surface, from which it is transferred over a period of days to plasma and exchangeable volume. Uranium in exchangeable bone volume transfers to bone surface and non-exchangeable volume over a period of months. Uranium in non-exchangeable bone volume is transferred to plasma over a period of years, at the rate of bone resorption.

The model structure for rats (Fig. 2) differs from that for humans (Fig. 1) in two main ways. First, no distinction is made between trabecular and cortical bone in the rat skeleton due to a paucity of data for the separate bone types in rats. Second, compartments within the rat skeleton are not divided into surface and volume due to uncertainties regarding the rate or extent of migration of U from bone surfaces to bone volume in rats.

On the other hand, the model for U in the rat skeleton is similar to that for humans in three important ways. First, retention is described in terms of a tri-layered model, with deeper layers representing longer retention times. Second, parameter values used in the model for humans to describe early and intermediate-term removal of U from the skeleton (removal from the first two layers) are reasonably consistent with retention data for rats and hence are used in the model for rats. Third, the removal half-time for the long-term retention component is consistent with reported bone resorption rates for rats.

Data on skeletal retention of U in acutely exposed rats are summarized in Fig. 6 (data sources given in a previous section). The data generally indicate an initial skeletal deposit in the range 10–30% of the injected or absorbed amount, a noticeable early decline, and a long-term retention component representing a substantial portion of the initial deposit.

In the baseline model for rats, the skeleton is assumed to consist of three compartments, called Bone 1, Bone 2, and Bone 3. These compartments represent fast, intermediate, and slow turnover, respectively. Data on skeletal retention of U in rats over the first several weeks after uptake to blood are reproduced reasonably well, if it is assumed that 20% of U leaving plasma deposits in Bone 1; the removal half-time from Bone 1 is 5 d; 50% of U leaving Bone 1 goes to Bone 2 and 50% returns to plasma; the removal half-time from Bone 2 is 30 d; and 25% of U leaving Bone 2 goes to Bone 3 and 75% returns to Bone 1. Therefore, the transfer coefficient from plasma to Bone 1 is $0.2\times140\ d^{-1}=28\ d^{-1}$; from Bone 1 to plasma is $0.5\times\ln(2)/(5\ d)=0.0693\ d^{-1}$; from Bone 1 to Bone 2 is $0.5\times\ln(2)/(5\ d)=0.0693\ d^{-1}$; from Bone 2 to Bone 1 is $0.75\times\ln(2)/(30\ d)=0.0173\ d^{-1}$; and from Bone 2 to Bone 3 is $0.25\times\ln(2)/(30\ d)=0.00578\ d^{-1}$. The skeletal deposition fraction is a rounded central estimate based on reported data for rats, excluding presumably anomalous data points. The transfer coefficients for Bone 1 and Bone 2 are taken from the model for humans, with Bone 1 and Bone 2 identified kinetically with the short- and intermediate-term retention compartments in the model of the human skeleton. In the development of the model for humans (Leggett, 1994), transfer coefficients for the short- and intermediate-term compartments (called bone surfaces and exchangeable bone volume in that model) were based on collective data for mammalian species and hence were assumed, in effect, to be independent of species.

Reported half-times of the long-term component of retention of U in the rat skeleton generally are in the range 150–400 d (Galibin and Parfenov, 1970; Galibin, 1971; Seidel, 1982; Durbin, 1984; Ballou et al., 1986), corresponding to removal rates in the range 0.0017–0.0046 d^{-1}. A central value of 0.003 d^{-1} is selected as the transfer coefficient from Bone 3 to plasma. This is consistent with estimates of the rate of bone resorption in mature rats (O'Flaherty, 1991).

2.9. The model for "other soft tissues"

Data on the behavior of U in soft tissues other than kidneys and liver (Neuman, 1949; Maynard and Downs, 1959; Galibin, 1971; Bentley et al., 1985) indicate that retention can be described in terms of three components. The short-term component represents 20% or more of the injected amount and has a removal half-time of, at most, a few hours. The intermediate-term component represents about 2–3% of the injected amount and appears to have a removal half-time on the order of 2–3 d. The long-term component represents roughly 1% of the injected amount and appears to have a half-time of at least a few months.

In this model these three retention components are represented by compartments ST0, ST1, and ST2, respectively. Parameter values for ST0 were described earlier, in connection with the circulation. Compartments ST1 and ST2 are assumed to receive, respectively, 2.5% and 1% of U leaving the circulation and to have removal half-times to plasma of 3 d and 100 d, respectively. Therefore, the transfer coefficient from plasma to ST1 is $0.025\times140\ d^{-1}=3.5\ d^{-1}$, from plasma to ST2 is $0.01\times140\ d^{-1}=1.4\ d^{-1}$, from ST1 to plasma is $\ln(2)/3\ d=0.2311\ d^{-1}$, and from ST2 to plasma is $\ln(2)/100\ d=0.00693\ d^{-1}$.

3. Comparison of baseline model with data for DU-implanted rats

Three dosage levels, referred to as L (low dose), M (medium dose), and H (high dose), were used in the study by Pellmar et al. (1999). Groups L, M, and H were implanted with 4, 10, and 20 cylindrical pellets, respectively. The pellets had a diameter of 1 mm and a height of 2 mm and consisted of 99.25% DU and 0.75% titanium by weight.

For purposes of the present analysis, the data for Groups L, M, and H were reduced to a common basis by normalizing to one pellet. That is, the measured concentration of uranium in tissues or fluids of rats in Groups L, M, and H were divided by 4, 10, and 20, respectively, giving the uranium concentration per implanted DU pellet. This allows simultaneous graphical comparison of data for all three groups with model predictions. Normalized values were labeled by dosage level, however, in view of the possibility of dosage dependence in the biokinetics of U in these animals.

As illustrated in Fig. 7 for the case of daily urinary excretion of U, the DU-implanted rats exhibited considerable variability with regard to the time-dependent concentration of U in tissues, fluids, and excreta. Because of the large scatter in the data, it was decided that model predictions should be compared only with the central

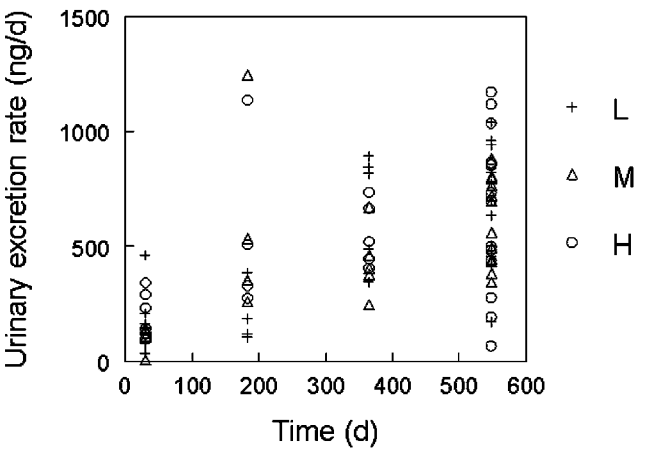

Fig. 7. Variability in normalized urinary excretion rates in DU-implanted rats, at 1, 6, 12, and 18 months after surgery.

tendency of the observations. The median rather than the mean was used as the central value for a set of observations because the mean often was strongly influenced by a small number of extreme values.

Reference organ masses or volumes at different ages were needed to convert model predictions of organ contents to concentrations, for comparison with the data for DU-implanted rats. Reference values (Table 3) were based, as far as practical, on measurements on the animals used in this study, but due to the infrequency of such measurements it was necessary to supplement these observations with information from the literature (Caster et al., 1956; Bard, 1961; Durbin, 1973; Sontag, 1983).

Table 3
Reference organ weights and fluid volumes for rats at different adult ages

Tissue or fluid	Assumed mass or volume of total body and organs at different ages[a]			
	3 months	9 months	15 months	21 months
Total body (g)	470	700	800	900
Kidneys (g)	3.1	4.6	5.2	5.2
Skeleton (g)	28	42	48	50
Liver (g)	16	23	26	26
Spleen (g)	0.9	1.4	1.6	1.6
Muscle (g)	210	320	360	360
Brain (g)	2.8	4.2	4.8	4.8
Serum (ml)	14	21	24	24

[a] The following percentages of body weights were assumed through age 15 months, Kidneys, 0.65% (reported values, 0.65–0.78%); Skeleton, 6% (5.5–10.9%); Liver, 3.3% (3.1–4.2%); Spleen, 0.2% (0.14–0.25%); Muscle, 45% (44–45.5%); Brain, 0.6% (0.46–0.8%); Blood, 5% (5–5.5%); Serum=60% of mass of blood.

For comparisons of model predictions with observations for the DU-implanted rats, model input (i.e., the time-dependent uptake rate to blood) was adjusted, as described below, so that model predictions of the urinary excretion rate agreed with the median time-dependent urinary excretion rates determined for the DU-implanted rats. Model predictions of the time-dependent concentrations of U in the skeleton (based on the average of values for tibia and skull), kidneys, liver, and other tissues and fluids of the rat were then compared with observations for the DU-implanted rats. For an organ such as the spleen that is not addressed explicitly in the model, predictions were derived by assuming a uniform distribution of U in "other soft tissues" and multiplying by the mass fraction of the organ.

Estimation of the time-dependent rate of uptake to blood required to reproduce an observed urinary excretion rate is a two-step process (that may also be applied in interpretation of urinary excretion data for human subjects with embedded DU fragments):

- Step 1: Suppose urinary excretion rates $u(t_i)$ have been determined at times t_i, i=1, 2, …, n. The model is run, using these urinary excretion rates as uptake rates to blood at these times and basing uptake rates for times other than t_i, i=1, 2, …, n, on linear interpolation between observed urinary excretion rates. For example, if the first three observation times are 10, 20, and 30 days and the observed urinary excretion rates at these times are 500, 600, and 620 ng d^{-1}, respectively, then the assumed rates at 4, 5, 15, 25, and 29 days are the linearly interpolated values, 440, 450, 550, 610, and 618 ng d^{-1}, respectively. The model run yields a new, generally lower, set of predicted urinary excretion rates $v(t_i)$, i=1, 2, …, n. Because a substantial portion of U reaching plasma will be excreted in urine within a short time, the values $v(t_i)$ may not differ greatly from the urinary excretion rates $u(t_i)$. The important pieces of information revealed in this step are the ratios, $u(t_i)/v(t_i)$, which indicate the sizes of the errors in the assumed uptake rates.
- Step 2: Each observed urinary excretion rate $u(t_i)$ is multiplied by $u(t_i)/v(t_i)$. The product, $[u(t_i)]^2/v(t_i)$, is the final estimate of the uptake rate to blood. Again, uptake rates at times other than t_i, i=1, 2, …, n, are estimated by linear interpolation. With the revised uptake curve, the urinary excretion rates predicted by the model are nearly identical to the observed urinary excretion rates, $u(t_i)$.

The accuracy of this two-step process for matching model predictions with observed urinary excretion rates is illustrated in Fig. 8. The "observed" urinary excretion rates in this figure are central values for the DU-implanted rats. The urinary excretion rates were measured at 1, 6, 12, and 18 months after surgery. The central values were derived by finding median urinary excretion rates for each of the dose groups L, M, and H, and then taking the median of the three median values for each of the four times. The derived urinary excretion rates at 1, 6, 12, and 18 months were 141.7, 414.4, 520.4, and 665.9 ng d^{-1}, respectively; these are called the "observed" rates. The assumed central urinary excretion rates for times between measurement periods were determined by linear interpolation of the observed values. For the period prior to the first measurements (between surgery and 1 month), the

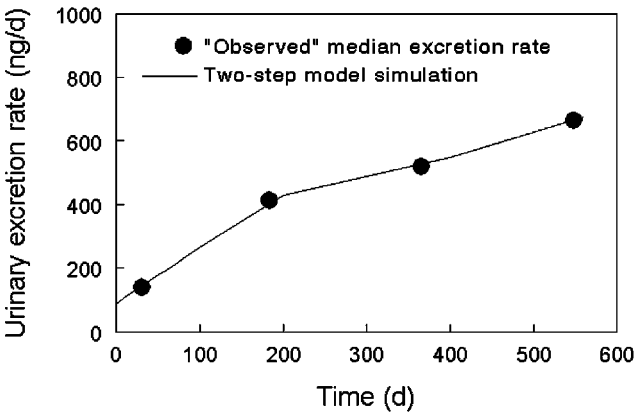

Fig. 8. Illustration of the accuracy of the two-step method for determining a time-dependent uptake rate to blood that yields the observed urinary excretion rates.

urinary excretion rates were estimated by extending the line determined by the first two measurement points, that is, the line determined by the order pairs (a_1,b_1) and (a_2,b_2), where a_1=one month, a_2=six months, and b_1 and b_2 are the central urinary excretion rates at one month and six months, respectively.

Model predictions for serum are compared in Fig. 9 with observations for the DU-implanted rats. For purposes of this comparison it is assumed that the concentration in serum, which is not considered as a separate compartment in the model, is the same as that in plasma, which is considered as a separate compartment. Uncertainties in model predictions for serum have not been characterized, but despite the reasonably good fit to the data for DU-implanted rats, are judged to be large in view of the sparsity of information on the kinetics of U in plasma or serum of rats.

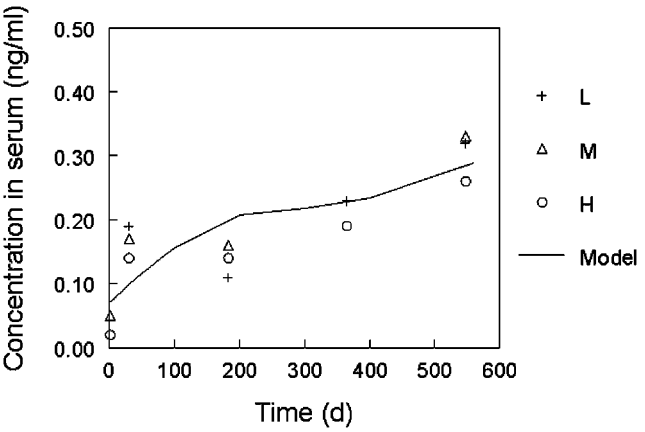

Fig. 9. Comparison of model predictions for serum with observations for the DU-implanted rats. It is assumed that the concentration of U in plasma is the same as that in serum.

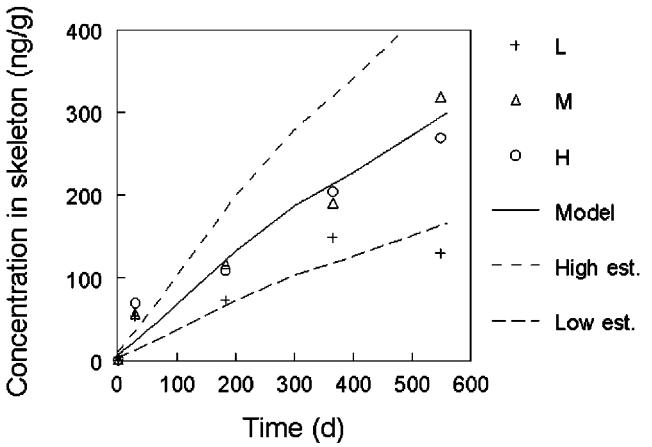

Fig. 10. Comparison of model predictions of the time-dependent concentration of U in the skeleton with observations for the DU-implanted rats.

Comparisons of model predictions and observations of the median U concentrations in skeleton (based on the average of measured concentrations in tibia and skull), kidneys, and liver of the DU-implanted rats are shown in Figs. 10, 11 and 12, respectively. Here and in the following, the "high" and "low" estimates are uncertainty bounds extrapolated from bounds shown earlier (Figs. 4–6) for the case of acute uptake of U to blood. Recall that, for purposes of this comparison, data for Groups L, M, and H were reduced to a common basis by normalizing to one pellet, but were not lumped due to the possibility of a dosage dependence in the biokinetics of U. As it turned out, normalized data for the three dosage groups were reasonably consistent in most instances, with data for individual animals typically showing con-

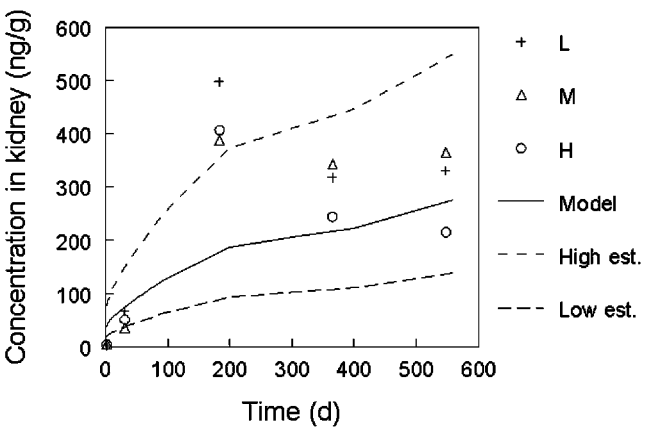

Fig. 11. Comparison of model predictions of the time-dependent concentration of U in kidneys with observations for the DU-implanted rats.

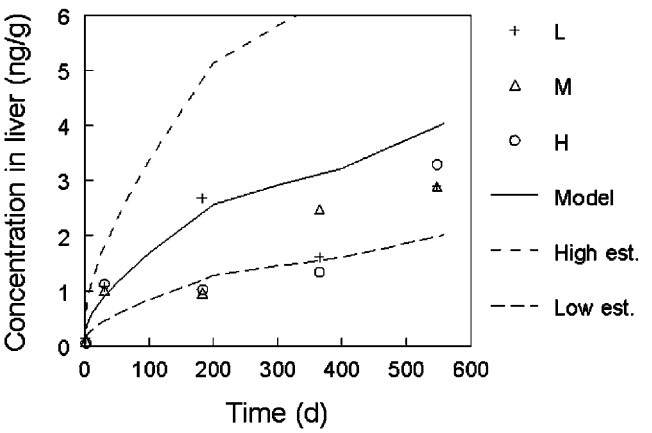

Fig. 12. Comparison of model predictions of the time-dependent concentration of U in liver with observations for the DU-implanted rats.

siderable overlap. Although some degree of dosage dependence in the data is suggested in some cases (for example, Group L showed lower central skeletal concentrations than the other two groups at most times), differences in median values for the three groups may be attributable to the small number of measurement times, small sample sizes, and typically high variability of individual data points within dosage groups.

The comparisons of model predictions and observations in Figs. 10–12 suggest that, with regard to kidneys, bone, and liver, the biokinetics of U in the DU-implanted rats did not differ greatly from the biokinetics that may be expected for more commonly encountered forms of U. In most cases the observed values fell within the uncertainty bands around model predictions. Generally, agreement between predictions and observations is better at times remote from surgery than at times from one day to six months after surgery.

One of the more conspicuous differences between predictions and observations occurs for the kidneys at six months after surgery. At this time, the medians of observed values fall above the upper end of the uncertainty range for model predictions. Also, the model predicts that the kidney concentration at six months should be lower than that for 12 months, whereas the observed values fall sharply from 6–12 months. At measurement times other than six months, model predictions of the U concentration in the kidneys agree closely with observations. The discrepancy between observations and predictions at six months may have resulted from a peculiarity in the biokinetics of U migrating from embedded DU metal or may be associated with a limitation of the model simulation that is not reflected in the uncertainty bands in the figure. That is, the urinary excretion rates in the DU-implanted rats may have actually been highly variable during the first few months after exposure, but rates for 0–6 months have been simulated here by a simplistic linear model based on observations at only two times.

4. A model-independent check for unusual aspects of the biokinetics of U In the DU-implanted rats

Morris et al. (1990) determined the time-dependent distribution of U in systemic tissues of male rats over a two year period following inhalation of highly insoluble UO_2 at age 3 mo. The data indicate slow removal of U from the lungs to the gastrointestinal tract and blood over the study period. Thus, as in the DU-implanted rats, the time-dependent systemic burden of U results from chronic uptake from a slowly feeding source. Although the time-course of uptake of U to blood would not be identical to that in the study of Pellmar et al. (1999), it was expected that comparison of the time-dependent distribution of U in the two groups of rats might reveal unusual aspects in the biokinetics of U migrating from implanted DU pellets.

For comparison of the distributions of U in the two groups of rats, the total contents of U in skeleton, kidneys, and liver were normalized to the content of the skeleton. That is, the average U burden in an organ at a given time was divided by the U burden in the skeleton.

Time-dependent distributions in the two groups are compared in Fig. 13. The greatest differences between the two groups occur soon after the beginning of exposure. Also, over the long term, there is somewhat greater accumulation of U in the liver in the inhalation study than in the study of Pellmar et al. (1999). Overall, however, the comparisons indicate reasonably similar systemic biokinetics of U in the two groups.

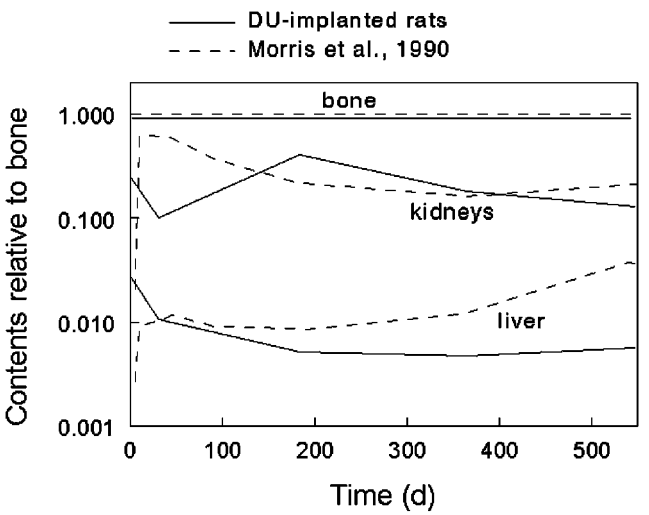

Fig. 13. Comparison of the time-dependent systemic distribution of U in the DU-implanted rats with that in rats with slow uptake of U to blood from the lungs (Morris et al., 1990).

5. Summary and conclusions

The applicability of the ICRP's updated biokinetic model for U to cases with embedded DU fragments has been evaluated indirectly by comparing the biokinetics of U in rats implanted with DU pellets with the biokinetics of U in rats exposed by inhalation, ingestion, or injection to more commonly encountered forms of U. The data for DU-implanted rats were developed in an experimental study by Pellmar et al. (1999). The data for rats exposed by inhalation, ingestion, or injection to other forms of U were collected from the literature and summarized in the form of a baseline biokinetic model.

Because the rate of migration from the DU pellets to blood was not known precisely, comparison of model predictions and observations could be done only in a relative sense. Specifically, the time-dependent rate of uptake to the plasma compartment of the baseline model was adjusted to reproduce the urinary excretion rates observed in the DU-implanted rats, and predicted time-dependent concentrations of U in various organs were then compared with the observed concentrations in the DU-implanted rats.

Generally, agreement between model predictions, representing the biokinetics of commonly studied forms of U, and the observed biokinetics of U in DU-implanted rats is better at times remote from surgery than at times from one day to six months after surgery. Discrepancies between model predictions and observations over the first six months could result from a peculiarity in the biokinetics of U migrating from embedded DU metal or may be associated with a limitation of the model simulation. That is, the urinary excretion rates in the DU-implanted rats may have actually been highly variable during the first few months after exposure, but excretion over the first six months was simulated by a simplistic linear model based on observations at only two times.

In conclusion, results of the present analysis suggest that the biokinetics of U that migrates from embedded DU metal is generally similar to that of commonly encountered forms of U with regard to long-term accumulation in the kidneys, bone, and liver. More information is needed on the short-term biokinetics of migrating U and its accumulation in lymph nodes, brain, and testicles, three typically minor repositories for U that are suggested by the study of Pellmar et al. (1999) to have potential toxicological significance for embedded DU fragments. Until such information is available, it seems reasonable to apply the ICRP's recently updated biokinetic model for U to assessments of radiological or chemical risk for soldiers with embedded DU fragments.

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References

Ballou, J.E., Gies, R.A., Case, A.C., Haggard, D.L., Buschbom, R.L., Ryan, J.L., 1986. Deposition and early disposition of inhaled $^{233}UO_2(NO_3)_2$ and $^{232}UO_2(NO_3)_2$ in the rat. Health Phys. 51, 755–771.

Bard, P., 1961. Medical Physiology. 11th ed. C.V. Mosby Co, St. Louis, MO, p. 302.

Bentley, K.W., Stockwell, D.R., Britt, K.A., Kerr, C.B., 1985. Transient proteinuria and aminoaciduria in rodents following uranium intoxication. Bull. Environ. Contam. Toxicol. 34, 407–416.

Caster, W.O., Poncelet, J., Simon, A.B., Armstrong, W.D., 1956. Tissue weights of the rat. I. Normal values determined by dissection and chemical methods. Proc. Soc. Exp. Biol. Med. 91, 122–126.

Cooper, J.R., Stradling, G.N., Smith, H., Ham, S.E., 1982. The behaviour of uranium-233 oxide and uranyl-233 nitrate in rats. Int. J. Radiat. Biol. 41, 421–433.

Durbin, P.W., 1973. Metabolism and biological effects of the transplutonium elements. In: Hodge, H.C., Stannard, J.N., Hursh, J.B. (Eds.), Uranium, Plutonium, and Transplutonium Elements, Handbook of Experimental Pharmacology 36. Springer-Verlag, Berlin, pp. 739–896.

Durbin, P.W., 1984. Metabolic models for uranium. In: Moore, R.H. (Ed.), Biokinetics and Analysis of Uranium in Man. United States Uranium Registry, USUR—05, HEHF—47. Available from National Technical Information Service, 5285 Port Royal Road, Springfield, VA, pp. F1-F65.

Ellender, M., 1987. The clearance of uranium after deposition of the nitrate and bicarbonate in different regions of the rat lung. Human Toxicol. 6, 479–482.

Galibin, G.P., 1971. Distribution of uranium in the body of rats under a single administration of ammonium diuranate to the stomach. In: Moskalev, Yu.I. (Ed.), Radioactive Isotopes and the Body, Moscow, Meditsina Publishing House, 1969. AEC-tr-7195, 1971.

Galibin, G.P., Parfenov, Yu.D., 1970. Inhalation study on metabolism of insoluble uranium compounds. In: Walton, W.H., (Ed.), Inhaled particles III, Proceedings of an international symposium, organized by the British Occupational Hygiene Society, London, September 14–23, 1970, Surrey, England. The Gresham Press, London, pp. 201–208.

Hamilton, J.G., 1948. The metabolic properties of the fission products and actinide elements. Rev. Modern Phys. 20, 718–728.

ICRP, 1995. Age-dependent doses to members of the public from intake of radionuclides, Part 3. Ingestion Dose Coefficients. Publication 69 of the International Commission on Radiological Protection. Pergamon Press, Oxford.

Jones, E.S., 1966. Microscopic and autoradiographic studies of distribution of uranium in the rat kidney. Health Phys. 12, 1437–1451.

Kisieleski, W., Faraghan, W.G., Norris, W.P., Arnold, J.S., 1952. The metabolism of uranium-233 in mice. J. Pharmacol. Exp. Therap. 104, 459–467.

Leggett, R.W., 1994. Basis for the ICRP's age-specific biokinetic model for uranium. Health Phys. 67, 589–610.

Maynard, E.A., Downs, W.L., 1959. Toxicology and pharmacology—animal data. In: HASL-58. Symposium on occupational health experience and practices in the uranium industry, held in New York City, Oct. 15–17, 1958. Health and Safety Laboratory, US Atomic Energy Commission, pp. 30–33.

Morris, K.J., Khanna, P., Batchelor, A.L., 1990. Long-term clearance of inhaled UO_2 particles from the pulmonary region of the rat. Health Phys. 58, 477–485.

Muir, J.R., Fish, B.R., Jones, E.S., Gillum, N.L., Thompson, J.L., 1960. Distribution and excretion of

uranium. In: Health Physics Division annual progress report for period ending July 31, 1960, ORNL-2994. Oak Ridge National Laboratory, Oak Ridge, TN, pp. 272-273.

Neuman, W.F., Fleming, R.W., Dounce, A.L., Carlson, A.B., O'Leary, J., Mulryan, B., 1948. The distribution and excretion of injected uranium. J. Biol. Chem. 173, 737–748.

Neuman, W.F., 1949. The distribution and excretion of uranium. In: Voegtlin, C., Hodge, H.C. (Eds.), Pharmacology and Toxicology of Uranium Compounds. National Nuclear Energy Series, Division VI—vol. I, Part II. McGraw-Hill, New York, pp. 701–727.

Neuman, W.F., 1950. Urinary uranium as a measure of exposure hazard. Industrial Medicine and Surgery 19, 185–191.

Neuman, W.F., 1953. Deposition of uranium in bone. In: Voegtlin, C., Hodge, H.C. (Eds.), Pharmacology and Toxicology of Uranium Compounds. National Nuclear Energy Series, Division VI—vol. I, Part IV. McGraw-Hill, New York, pp. 1911–1991.

O'Flaherty, E.J., 1991. Physiologically based models for bone-seeking elements. Toxicol. Appl. Pharmacol. 111, 313–331.

Pellmar, T.C., Fuciarelli, A.F., Ejnik, J.W., Hamilton, M., Hogan, J., Strocko, S., Emond, C., Mottaz, H.M., Landauer, M.R., 1999. Distribution of uranium in rats implanted with depleted uranium pellets. Toxicological Sciences 49, 29–39.

Priest, N.D., Howells, G.R., Green, D., Haines, J.W., 1982. Uranium in bone, metabolic and autoradiographic studies in the rat. Human Toxicol. 1, 97–114.

Rowland, R.E., Farnham, J.E., 1969. The deposition of uranium in bone. Health Phys. 17, 139–144.

Seidel, A., 1982. Biological behavior, effects, and decorporation of uranium. In: Handbook of Inorganic Chemistry, vol. U, Uranium, Suppl. A7, Springer, Berlin, pp. 300–341.

Sontag, W., 1983. The early distribution of ^{239}Pu, ^{241}Am, and ^{233}U in the soft tissues and skeleton of old rats. A comparative study. Human Toxicol. 2, 91–100.

Sontag, W., 1984. Long-term behaviour of 239-Pu, 241-Am and 233-U in different bones of one-year-old rats, macrodistribution and macrodosimetry. Human Toxicol. 3, 469–483.

Stevens, W., Bruenger, F.W., Atherton, D.R., Smith, J.M., Taylor, G.N., 1980. The distribution and retention of hexavalent ^{233}U in the beagle. Radiat. Res. 83, 109–126.

Stradling, G.N., Stather, J.W., Strong, J.C., Sumner, S.A., Towndrow, C.G., Moody, J.C., Lennox, A., Sedgwick, D., Cooke, N., 1985. Metabolism of some industrial uranium tetrafluorides after deposition in the rat lung. Human Toxicol. 4, 159–168.