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Bioassay Data and A Retention-Excretion Model For Systemic Plutonium

R. W. Leggett

Prepared for the
Division of Facility Operations
Office of Nuclear Regulatory Research
U.S. Nuclear Regulatory Commission
Under Interagency Agreement DOE 40-550-75

OPERATED BY
MARTIN MARIETTA ENERGY SYSTEMS, INC.
FOR THE UNITED STATES
DEPARTMENT OF ENERGY

Printed in the United States of America. Available from
National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road, Springfield, Virginia 22161

Available from

GPO Sales Program
Division of Technical Information and Document Control
U.S. Nuclear Regulatory Commission
Washington, D.C. 20555

NUREG/CR-3346
ORNL/TM-8795
Dist. Category RH

Health and Safety Research Division

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NOTICE: This document contains information of a preliminary nature. It is subject to revision or correction and therefore does not represent a final report.

Manuscript Completed - May 1983
Date Published - May 1984

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NRC FIN No. B0480-2

Prepared by the
OAK RIDGE NATIONAL LABORATORY
Oak Ridge, Tennessee 37831
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MARTIN MARIETTA ENERGY SYSTEMS, INC.
for the
U.S. DEPARTMENT OF ENERGY
Contract No. DE-AC05-840R21400

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ACKNOWLEDGMENT

I am grateful for the valuable assistance of Mark Cristy, who designed the computer plotting routine used to draw most of the figures in this report. Mark's excellent work is sincerely appreciated. I am also indebted to Keith Eckerman for valuable suggestions throughout the development of the model; to Dave Kocher and Mark Cristy for their helpful reviews of this report; to Allen Brodsky for his interest, encouragement, and support; and to Barbie Warren for her patience, skill, and hard work that went into the production of the final galleys of this report.

HIGHLIGHTS

The estimation of systemic burdens from urinalyses has been the most common and useful method of quantifying occupational exposures to plutonium. Problems arise in using this technique, however, because of inadequate modeling of human retention, translocation, and excretion of this element. Present methods for estimating the systemic burden from urinalyses were derived to a large extent from patterns observed in the first few months after exposure, but there is now evidence that these same patterns do not persist over long periods. In fact, recent comparisons of autopsy data with urinalyses suggest that extrapolation to extended periods based on these observed patterns usually leads to a large overestimate of the systemic burden at times more than a few years after exposure.

In this report we collect and discuss human and animal data for Pu together with general physiological properties needed for the interpretation of bioassay results. This information is used to develop a mechanistic model of the movement, retention, and excretion of systemic Pu. This model appears to be a reasonably accurate predictor of excretion for times ranging from one day to several decades after introduction of soluble Pu to blood. The model may be used in conjunction with existing models and/or case-specific information concerning translocation from the respiratory and gastrointestinal tracts or from wounds to the bloodstream.

Despite the improvements over previous retention models, significant uncertainties remain regarding some aspects of the movement of Pu in the body, particularly its transport from the liver. An attempt has been made to construct and analyze the model in such a way as to elucidate those areas needing further attention.

I. INTRODUCTION

The potential health hazards of plutonium (Pu) have been recognized since the early 1940's, when small quantities of this radioelement were first produced. For several years concern about health effects from Pu were limited primarily to occupational exposures. Because of growing inventories of Pu arising from its production in both thermal and breeder reactors, there have been increasing concerns in recent years over environmental as well as occupational exposures to this element.[1-4]

The most common and useful method of quantifying occupational exposures to Pu has been the estimation of systemic burdens from urinalyses.[5-8] Problems in using this technique arise, however, because of inadequate knowledge of human retention, translocation, and excretion of Pu. Present methods for estimating the systemic burden from urinalyses were derived to a large extent from patterns observed in the first few months after exposure.[5,6] Since there is now evidence that these same patterns do not persist over long periods,[9-14] it is important to obtain a better description of the retention of this element in the human body.

In this report we collect and discuss data needed for the interpretation of bioassay results for Pu. These data are used to develop a model that describes the movement, retention, and excretion of systemic Pu in the human body in terms of explicitly identified anatomical compartments. This model may be used in conjunction with existing models and/or case-specific information concerning the translocation of Pu from the respiratory or gastrointestinal tract or from wounds to the bloodstream. A discussion of these three modes of exposure, along with numerous references, is given by Nenot and Stather.[1] In the present report attention is restricted to the behavior of Pu after it has gained access to the bloodstream.

While we believe that there is now sufficient information on the movement of Pu among the various systemic compartments to provide an improved retention model for Pu, there remain significant uncertainties concerning some aspects of the movement of Pu, particularly its translocation from the liver. An attempt has been made to construct the model in such a way as to elucidate those areas needing further attention.

II. BACKGROUND

Biomedical studies with Pu were begun in 1944, when 11 milligrams were allocated for studies in rats. Within a few years a fairly clear picture of the behavior of Pu in rodents had developed.[3,15] Pu was removed fairly quickly from the bloodstream and was deposited principally in the skeleton, with a significant fraction also depositing in the liver. Moreover, it was clear that Pu had a long biological half-time, at least in the skeleton. Only a small fraction of ingested Pu was absorbed into the bloodstream, but a much larger fraction of inhaled Pu could reach the bloodstream over extended times following initial deposition in the lung.

In 1945 and 1946, 18 seriously ill persons were injected with tracer doses of plutonium citrate or nitrate in order to determine the relationship between urinary Pu excretion and body Pu content in humans.[5,6] Although the life expectancies of these persons were judged to be short at the time of injection, eight of them survived at least eight years and four were still alive in 1975.[16] Measurements of Pu in excretion and tissue samples of these 18 persons constitute a major portion of our direct human experience concerning the metabolism and excretion of plutonium.

Numerous measurements of Pu in urine and feces of these persons were made in the first few weeks after injection, and some measurements were made with two of the patients at times up to 1645 days.[5,17] Langham et al.[5] used these data, together with limited data from workers who had been contaminated accidentally with Pu, to determine the following urinary and fecal excretion curves for Pu:

$$Y_u = 0.20t^{-0.74} \quad (t > 1) \quad , \tag{1}$$

$$Y_f = 0.63t^{-1.09} \quad (t > 1) \quad . \tag{2}$$

Here, Y_u (Y_f) is the percentage of the injected amount of Pu in urine (feces) during day t after administration.

For over 30 years Langham's equation for Y_u has served as the basis for estimating Pu body burdens from measurements of Pu in urine. In recent years, however, evidence has accumulated that this equation may lead to large overestimates of the Pu body burden at times longer than 5 years after exposure. This is evident from Table 1, which shows two types of estimates of the systemic burden of Pu in plutonium workers, one based on application of Langham's equation to observed values of Pu in urine (generally taken over an extended period while the workers were in good health) and a second based on tissue analyses performed on these same workers after their deaths. The data in Table 1, which were taken from Refs. 13 and 18, exclude workers whose urinary Pu measurements were below the minimum detectable level. For the most part, the workers received exposures beginning 8 to 30 years before death. For such long-term body burdens, Langham's equation leads to an estimate of Pu body burden that is usually 2 to 10 times the value determined from autopsy. It should be noted that the estimates of total body Pu obtained from autopsy may also tend to be slight overestimates (but by less than a factor of 1.5, we suspect) since skeletal data are generally taken from vertebrae, sternum, or ribs, all of which tend to show concentrations higher than the skeletal average.[17,19,20]

A problem inherent in Eq. (1) is that it is simply a fit to urinary data over a relatively short period after exposure and, in effect, assumes that the continual removal of Pu from organs that occurs during this time period will maintain the same pattern throughout the exposed person's lifetime. As we shall discuss later, however, some of the Pu buried in the skeleton will become uncovered after a few years due to skeletal remodeling, and Pu throughout the skeleton may begin to become uncovered after age 40 or 50 years due to normal bone loss. Thus, Eq. (1) becomes less accurate with increasing time and age. This is illustrated by data of Hempelmann et al.[11] for Manhattan Project workers exposed to Pu around 1945. Urinary excretion of Pu by these persons remained fairly constant during the period 1953-1957 but began to increase some time after 1957 and continued to increase substantially (usually by a factor of 2 to 5) over a fifteen year period (see Table 4

Table 1. Comparison of systemic burdens as estimated from urine and autopsy samples

Estimated systemic burden (% MPSB[a])		Ratio of estimate from urinalysis to estimate from autopsy
From autopsy	From urine	
6.4	40	6.3
0.68	3.4	5.0
0.16	1	6.3
105	90	0.9
110	200	1.8
2.3	13.5	5.9
3.8	8.0	2.1
156	541	3.5
1.5	5.4	3.6
2.0	6.4	3.2
8.7	19	2.2
46	65	1.4
8.8	30	3.4
10.5	25	2.4
0.05	6	120
0.63	6.3	10
1.0	4.5	4.5
2.3	5.5	2.4
1.8	13.5	7.5
1.9	18	9.5
23.3	77.5	3.3

[a]Maximum permissible systemic burden (40 nCi). Data from McInroy[13] and Norwood and Newton.[18] Table excludes workers whose urinary Pu was below the minimum detectable level.

of Ref. 11). Since these persons reportedly experienced little or no occupational exposures to Pu after about 1946, their body burdens would be expected to decrease constantly throughout the indicated period.

In 1973 Rundo measured urinary and fecal excretion of Pu in two of the persons injected with Pu in 1945-46.[9-10] The urinary excretion rates at 10^4 days after injection were 6-12 times higher than predicted by Eq. (1), and the fecal excretion rates were 19-38 times higher than predicted by Eq. (2). It becomes evident from consideration of these and the previously discussed data that an improved description of the long-term retention and excretion of Pu by humans is needed.

III. PHYSICAL AND BIOCHEMICAL PROPERTIES OF Pu

Of the 15 known isotopes of Pu, there are eight which are produced in sufficient quantities to be of concern as a potential health hazard. Some of the physical properties of these eight isotopes are listed in Table 2.[1]

The terms "monomeric" and "polymeric" are often used in metabolic studies to describe the physical state of Pu compounds. Generally, "monomeric" refers to laboratory preparations in which any particulates formed are below about 0.01 μm in diameter, while "polymeric" particles are those of diameter 0.01 μm or greater. Pu deposited in the body has a strong tendency toward polymerization, and much or all of the Pu that enters the body in monomeric form may become converted to at least minimally polymeric form.[21]

Plutonium can exist in solutions mainly in four oxidation states: Pu(III), Pu(IV), Pu(V), and Pu(VI). Biological evidence and chemical properties of Pu suggest that most systemic Pu would be in the (IV) state.[22] The tendency to react with water (hydrolyze) decreases in the order Pu(IV) > Pu(VI) > Pu(III) > Pu(V).[22,23] Hydrolysis of Pu(IV) may result in a change from the monomeric form to an insoluble polymeric form of Pu. In high concentrations, Pu may begin to polymerize at pH 1. In fairly dilute solutions such as those that might be expected in body fluids in typical exposure situations, pseudocolloidal formation begins at pH 2.8, and genuine aggregates form above about pH 7.5.[22,23] In the human body, the pH of pure gastric juice is about 1.0, of intracellular fluid of muscle about 6.8, and of blood about 7.4, although the pH of blood can exceed 7.5 in some cases.[24]

Although it is conceivable that Pu in the body could exist in a wide distribution of solubility classes, we shall distinguish only two relative solubility classes for systemic Pu, namely, soluble Pu and particulate or colloidal Pu. When soluble Pu reaches the bloodstream, skeletal deposition is favored, and when particulate Pu enters the bloodstream, uptake by the phagocytic cells of the liver and other organs is favored.[21] There is evidence that insoluble particles containing Pu can reach the bloodstream from the lungs or from wounds.[1,25,26]

Table 2. Physical properties of the major isotopes of plutonium[1]

Isotope	Radioactive half-life (years)	Principal mode of decay	Mean alpha energy (MeV)	Specific activity[a] μCi g^{-1}
Plutonium-236	2.9E 00	α	5.8	5.3E 08
Plutonium-237	1.2E-01	E.C.		1.2E 10
Plutonium-238	8.8E 01	α	5.5	1.7E 07
Plutonium-239	2.4E 04	α	5.2	6.1E 04
Plutonium-240	6.5E 03	α	5.2	2.3E 05
Plutonium-241	1.5E 01	β		9.9E 07
Plutonium-242	3.8E 05	α	4.9	3.8E 03
Plutonium-243	5.7E-04	β		2.6E 12

[a]1 μCi = 3.7 x 10^4 Bq = 3.7 x 10^4 disintegrations per second.

IV. PROCESSES GOVERNING RETENTION AND TRANSLOCATION OF Pu IN THE BODY

Pu and Fe apparently bear sufficient chemical resemblance that Pu becomes entrapped in some of the body's iron transport and storage systems. It has been shown that Pu(IV) in blood serum complexes with transferrin, the iron-transport protein.[17,28] Thus Pu will partially trace the iron pathway, with the result that a substantial fraction of systemic Pu is carried to the bone marrow and to the liver.[5,17,22,29-34] Apparently much of the Pu is released from transferrin at these sites. It has been shown that, in vitro at physiological pH, Pu(IV) may transfer from transferrin to ferritin, the major iron storage protein in the liver, and that the ferritin complex may be more stable than the transferrin complex.[28] In the skeleton, Pu may be released mainly at sites of developing red cells.[34]

DISAPPEARANCE FROM BLOOD

A large fraction of Pu(IV) introduced into blood in monomeric form is quickly bound to transferrin.[17,28,34] Since Pu leaves blood more rapidly than it is bound to transferrin or excreted, it would appear that some of the Pu not promptly bound to protein moves into the extracellular fluid.[17] Apparently Pu slowly returns to blood; since it is nearly completely bound to protein after 1 hr, much of the binding may take place in the extravascular spaces, which contain nearly half the body's transferrin and the iron bound to it.[17] According to an analysis by Durbin of human Pu-injection data, blood volumes of patients with circulatory impairments lost Pu more slowly than those of patient with normal circulation.[17]

It appears from experimental results for laboratory animals that Pu injected in particulate or colloidal form is cleared very rapidly from blood and is deposited in cells of the reticulo-endothelial (RE) system.[21,27,28] In fact, colloidal particles of any composition are rapidly taken up by RE cells.[22] These cells are found in all tissues but are most concentrated in liver, spleen, lymph nodes, erythropoietic marrow, and lung tissues.[22]

Data describing the rate of disappearance of intravenously injected Pu from blood in four species are summarized in Table 3, where the assumption is made that retention in blood can be adequately expressed as the sum of at most five exponential terms. The exponential terms used to describe removal from blood should not be interpreted as representing a corresponding number of discrete physical compartments; this is simply a convenient mathematical description of the total result of several processes. These processes may include: (1) binding of Pu to transferrin and transfer of Pu-transferrin to the skeleton, liver, and other iron depots; (2) return to blood of that Pu released from transferrin in the bone marrow and not attaching to bone; (3) movement of both bound and unbound Pu into and out of extracellular fluids; (4) removal of a small portion of Pu into urine and bile; (5) removal of polymerized Pu by the reticulo-endothelial system.

DISTRIBUTION AMONG ORGANS

Three principle compartments will be considered in our discussion of the movement and retention of Pu: skeleton, liver, and soft tissue, where the soft tissue compartment includes only soft tissue not in the liver and skeleton. In addition to these three main compartments, several subcompartments will be considered, such as cortical bone surface, cortical bone volume, trabecular bone surface, trabecular bone volume, and compartments containing trabecular marrow and cortical marrow.

Within a few days after soluble Pu reaches the bloodstream of humans, approximately 80% of the activity is divided between the skeleton and liver, and most of the remainder is in soft tissue.[17] Only a small amount, perhaps 1%, is excreted in urine and feces during the first 2 or 3 days. These values are estimated from autopsy and excretion data for several of the persons injected with Pu in the 1940's.[8] The values are in close agreement with results of experiments with beagle dogs,[32,39,40] except that the beagles excreted Pu more rapidly than humans at early times after exposure.

Table 3. Disappearance from circulating blood of intravenously injected Pu(IV) citrate[17]

Species	Component										Day of last sample
	A		B		C		D		E		
	%	Half-time (min)	%	Half-time (hr)	%	Half-time (days)	%	Half-time (days)	%	Half-time (days)	
Rat	60.3	58	37.3	8.2			0.8	6.0			8
Dog	44	11-48	19.5	7.3	30	1.0	2.1	5.0	0.081	220	3,000
Sheep	68	24	25	2-5	5.8	1.6	1.1	4.9			10
Man	52.4	20	27.1	7.3	17.2	1.2	3.3	5.0	0.44	88	42

In the beagle experiments, the division of Pu between the skeleton and liver depended on age, with initial uptake by the skeleton averaging 68% in juveniles, 50% for young adults, and 40% for mature adults.[32,39,40] Langham et al.[7] estimated that in humans injected with Pu, approximately 66% was deposited in the skeleton and 23% in the liver. Durbin[17] reanalyzed the human data to account for the non-uniformity of Pu in samples of bone; she estimated that about 49% was in the skeleton and 31% in the liver at 4 to 457 days after injection. A few years ago, a major portion of the skeleton of one of the injected persons, a young woman injected at age 18 years and dying 17 months later (case HP-4 of Ref. 5), was analyzed and found to contain about 55% of the injected amount.[10] Since there was ample time for a small portion of the Pu to be translocated from the skeleton before this woman's death, the fraction originally deposited in her skeleton may have been higher than 55%. It is possible that the woman's age at exposure led to a higher skeletal deposition than was estimated for the older patients, although this is only conjectural.

SKELETAL UPTAKE AND TRANSLOCATION

To describe the retention and translocation of plutonium in the skeleton, it is convenient to view the skeleton as consisting of two principal compartments: cortical (or compact) bone and trabecular (or spongy or cancellous) bone. These two bone types are usually defined by their surface to volume ratios, which are much larger for trabecular bone.[41-43] Both bone types are found in all bones, but the relative amounts of each vary greatly from one bone to another. Much of the cortical bone in the body is found in the shafts of the long bones, where it surrounds the marrow cavities. Trabecular bone is made up of a network of fine interlacing partitions (trabeculae) enclosing cavities containing red or fatty marrow. Trabecular bone is found mainly in the vertebrae, in the flat bones, and in the ends of the long bones.[44]

Each of the two principal compartments of the skeleton is further subdivided into three parts: bone surface, bone volume, and bone cavity contents, excluding blood and blood vessels (mainly bone marrow). For purposes of describing the translocation of Pu in the skeleton, it

suffices to consider bone surface as an infinitely thin layer. Bone surface includes the endosteal, periosteal, Haversian, and Volkmann surfaces of cortical bone and the endosteal surfaces of trabecular bone. Bone volume is the mineralized skeleton bounded by bone surface; it does not include the marrow or the space within Haversian or Volkmann canals, for example (cf. Ref. 41). Bone marrow consists of both red (active, blood-cell forming) and yellow or fatty (inactive) marrow. In young children, red marrow constitutes a significant portion of the marrow in both cortical and trabecular marrow cavities, but by the third or fourth decade of life, almost all of the cortical marrow and about half of the trabecular marrow is inactive.[45] In general, areas of active marrow are more highly vascularized than areas of inactive marrow.[46]

Cortical bone comprises about 80% of the adult mineralized skeleton and trabecular bone about 20%, by volume, by mass, and by mineral content.[42,47] Both bone types are constantly undergoing remodeling, which involves the elimination and replacement of bone mineral.[48-50]

Factors Affecting the Distribution of Pu on Skeletal Surfaces

Plutonium is deposited nonuniformly on bone surfaces, with the highest deposition being at sites with red marrow and the lowest at sites of yellow marrow.[46] Red marrow is more highly vascularized than yellow marrow, and the degree of vascularity may play a role in the amount of Pu deposited at a given location. For example, Humphreys, Fisher, and Thorne[51] showed that the blood flow rate is nearly linearly related to the Pu deposition in mouse femurs (see Table 4). Durbin, Horovitz, and Close[34] proposed that Pu is dissociated from transferrin to a large extent in the red marrow, specifically at the surfaces of developing red cells. Pu atoms released from transferrin in marrow could either (a) diffuse to the nearest bone surface and be bound there, (b) recombine with other transferrin molecules and recirculate, or (c) reenter blood as unbound Pu and possibly bind to bone surfaces at other sites. It has been proposed that the relatively small deposition of Pu on periosteal (exterior) surfaces may result from the centrifugal flow of blood from the bone cavity carrying some of the Pu released in the marrow and not deposited locally on bone surfaces.[52]

Table 4. Comparison of blood flow rate with Pu-239 deposition in mouse femurs (± standard error)[51]

Bone section	Pu-239 concentration 24 h after injection (% of injected amount per gram ash)	Blood flow (mg/g ash/min)
Whole femur	46 ± 4	510 ± 21
Proximal end	38 ± 5	470 ± 21
Distal end	73 ± 6	700 ± 34
Shaft	20 ± 2	320 ± 14

The strong association between sites of skeletal deposition of Pu and of Fe is illustrated in Table 5, which is derived from data of Rosenthal et al.[38]. This table compares the early distributions of Fe-59 and Pu-239 in the skeleton of the mouse. Mice injected with Fe-59 were sacrificed 5 hours after injected, when preliminary studies had shown the Fe-59 level in blood to be minimal. Mice injected with Pu were not sacrificed until 15 days after injection because Pu, particularly polymeric Pu, continues to accumulate for several days in the skeleton of the mouse and then is removed only slowly. Except perhaps in the extremeties of the body (the head, the feet, and the tail) the fraction of skeletal Fe associated with a particular bone would appear to be an excellent predictor of the fraction of skeletal Pu in the same bone, for Pu injected either in monomeric or polymeric form.

The skeletal distributions of Pu and active marrow in humans are compared in Table 6. The data for Pu are from measurements made on the skeletal remains of a woman injected with Pu in 1945 at age 18 years and dying 17 months later (subject HP-4 of Ref. 5).[20] Although this subject was suffering from Cushing's syndrome, a disease characterized by osteoporosis, it would appear that the distribution of Pu in this skeleton was not abnormal, since limited measurements on the skeleton of a man (subject HP-9 of Ref. 5) injected in 1945 at age 65 years and dying 15 months later indicated a very similar distribution of Pu.[20] The distribution of active marrow in a 20-year-old human is estimated from cellularity data presented by Cristy.[43] The distributions of Pu and active marrow in the skeletons of humans are similar, with largest differences arising for the skull and sacrum.

Rosenthal et al.[53] reported that almost none of the monomeric Pu in the skeleton of rabbits was located in marrow a few days after injection, while most of the skeletal burden of highly polymeric Pu was in marrow. Moreover, polymeric Pu was as much as 30 times more concentrated in red marrow than in fatty marrow, while monomeric Pu was 1.3-2.8 times more concentrated in red than fatty marrow. These data indicate the very different distributions of monomeric and polymeric Pu shortly after injection; however, in species such as the mouse that show a short residence time for Pu in liver, the two distributions will

Table 5. Comparison of deposition of Pu and Fe in the skeleton of the mouse[38]

Bone(s)	Percent of Fe-59 in bones after 5h	Percent of Pu-239 in bones after 15d	
		Monomeric	Polymeric
Head	2.7	5.2	4.1
Dorsal ribs	2.3	2.1	1.7
Ventral ribs	0.3	0.25	0.24
Sternum	1.2	0.77	0.44
Clavicle	0.1	0.16	0.11
Scapula	0.86	1.0	0.68
Humeri	2.0	1.4	1.1
Femora	4.1	2.8	1.9
Radius and ulna	0.34	0.64	0.53
Tibia and fibula	1.9	2.0	1.4
Feet and ankles	0.4	1.1	1.2
Cervical vertebrae	1.0	1.4	1.0
Thoracic vertebrae	2.5	3.3	2.0
Lumbar vertebrae	4.2	3.9	2.6
Sacral vertebrae	2.5	2.3	1.6
Tail vertebrae	1.3	3.2	3.2
Pelvis	3.6	2.3	1.8
Total	31.3	33.8	25.6

Table 6. Comparison of distributions of active marrow and skeletal Pu deposition using human data

Bone	Percent of Pu after 1.4 y[a]	Percent of active marrow estimated from cellularity data[b]
Skull	16.3	8.5
Mandible	0.8	0.85
Innominate	23.4	19.0
Vertebrae	20.7	29.1
Ribs	11.8	14.4
Scapula	4.7	3.1
Clavicle	1.1	0.9
Sacrum	2.9	8.9
Sternum	1.8	2.9
Femur	8.5	9.3
Humerus	2.0	3.15

[a] From data of Larsen, Oldham, and Toohey.[30]

[b] From data of Cristy.[45] Only bones assigned non-zero active marrow values in Ref. 45 are considered.

become more and more alike as the initially heavy burden of polymeric Pu in the liver is gradually relocated.

Relative deposition of Pu on various types of bone surfaces (endosteal surfaces of trabecular bone and endosteal, Haversian, and periosteal surfaces of cortical bone) has been measured in animals as well as in the human subjects HP-4 and HP-9 discussed earlier. In rabbits and dogs, the deposition onto endosteal surfaces of a given bone is usually about 3 times greater than on periosteal surfaces of the same bone.[39,44] In the distal end of the beagle femur, the relative concentrations on bone surfaces are metaphyseal trabecular, 3; endosteal, 2.6; epiphyseal trabecular, 1.5; Haversian, 1.2; and periosteal, 1.[44]

In considering the distribution of Pu on bone surfaces of human subjects HP-4 and HP-9, it must be kept in mind that these persons lived 15-17 months after injection. Thus some burial, removal, and redistribution of Pu probably occurred. Schlenker and Oltman[43] describe two distinct types of existing bone surfaces in these subjects, namely, surfaces of labeled volume and surfaces of unlabeled volume. Labeled volume (LV) is that bone volume formed while Pu was in the blood. Unlabeled volume (UV) was formed before injection and remained undisturbed until death. Also, buried surface deposits were identified; these are associated with bone surfaces that were exposed to Pu and were subsequently covered by the formation of new bone. Included in this category would probably be surfaces that were already covered by osteoid at the time of injection.

Schlenker and co-workers[45,46] found that periosteal, Haversian canal, and endosteal surfaces of unlabeled cortical bone volume in long bone midshafts showed about equal concentrations of Pu. Buried endosteal surfaces that may have been covered with osteoid at the time of injection showed about 12 times as much Pu as existing surfaces.

Relative concentrations of Pu found on the various types of bone surfaces in subject HP-4 are listed in Table 7, based on a concentration of 1.0 for Haversian canal surfaces of unlabeled volume of long-bone midshafts. It appears from this table that the original deposition may have been an order of magnitude higher on endosteal surfaces of the axial skeleton than on surfaces of long-bone midshafts. In fact, in measuring the Pu concentration in whole bones of HP-4, Larsen, Oldham, and Toohey[30] found that about two-thirds of the skeletal Pu was in the

Table 7. Concentrations of Pu on buried and existing bone surfaces of subject HP-4[44]

Type of bone	Type of surface	Relative concentration
Long-bone midshaft	Haversian canal (UV)	1.0
Long-bone midshaft	Endosteal (UV)	1.1
Long-bone midshaft	Periosteal (UV)	1.4
Proximal femur	Metaphysis	1.5
Axial skeleton	Endosteal (UV + LV)	4.2
Axial skeleton	Endosteal (buried)	9.7
Axial skeleton	Endosteal (LV)	1.7

axial skeleton, and only about 16% was in the appendicular skeleton (Table 8). These data on whole bones indicate that the relative deposition per gram of bone ash in the axial skeleton was about 10 times that in the appendicular skeleton, assuming that there was insufficient time for a substantial portion of skeletal Pu to move from one bone to another. The data in Tables 7 and 8 are in general agreement with results of beagle studies.[44] As indicated in Table 9, there is a large variation in the concentration of Pu on different trabecular surfaces of beagles soon after injection; however, this variation decreases considerably during the first year.[44] Since the skeleton remodels much more slowly in humans than in dogs, we expect that a much longer time is required for a similar decrease in variation of Pu on trabecular surfaces in humans.

For our purposes an important difference in the distribution of skeletal Pu is that between trabecular and cortical bone. These differences were measured in subject HP-9 (Table 10).[20] While the concentration on each type of surface varied widely from one bone to another, the ratio of Pu in trabecular bone to Pu in cortical bone remained between 1.9 and 4.8 in all bones (mean $\pm$S.D. = 3.3 $\pm$ 1.1). Since there is about 4 times as much cortical bone as trabecular bone by mass, this suggests that, at 1.3 years after injection, the total amount of Pu in trabecular bone may not be any greater than the total amount in cortical bone, despite initially greater deposits on some trabecular surfaces.

Attachment to Bone Surfaces

There are several substances on bone surfaces capable of binding Pu, including exposed mineral, collagen, and glycoproteins. However, the mechanisms by which Pu is released from transferrin and binds to bone surfaces are not completely understood. Herring, Vaughan, and Williamson[47] found that Pu concentrations on endosteal surfaces in skeletons of dogs are larger on resorbing surfaces than on resting surfaces and are smallest on growing surfaces. It is thought that lysosomes are ejected into resorbing regions along with citric acid and other organic acids, and it is known that Pu can be taken up by lysosomes, at least in the liver.[48-51] Moreover, increased concentrations of citrate in serum may

Table 8. Summary of plutonium distribution in the skeleton of HP-420

Bone	Percent of total		Relative Pu concentration (Pu/Ash)	
	Pu	Ash		
Frontal[a]-parietal	5.7	5.6		1.0
Occipital[a]-parietal	3.6	3.0		1.2
Temporal squamous	1.6	1.7		0.9
Sinus[a]	5.4 ± 1.3	5.0		1.1
Mandible[a]	0.8	1.8		0.4
Skull[a]	17.1 ± 1.7	17.1	Mean	1.0
Innominate	23.4	7.2		2.1
Vertebrae[a]	20.7	6.2		3.3
Ribs	11.8	5.6		2.1
Scapula	4.7	2.5		1.9
Clavicle	1.1	1.0		1.1
Sacrum[a]	2.9	0.8		3.6
Sternum[a]	1.8	0.4		4.5
Axial	66.4	23.7	Mean	2.8
Femur	8.5	20.3		0.4
Patella	0.2	0.6		0.3
Tibia	2.0	13.7		0.15
Fibula	0.5	3.4		0.15
Foot	1.8	6.2		0.3
Humerus	2.0	7.2		0.3
Radius	0.4	2.2		0.2
Ulna	0.4	2.8		0.15
Hand	0.5	2.7		0.2
Appendicular	16.3	59.1	Mean	0.27

[a]Values given are for half of this bone.

Table 9. Variation in the concentration of Pu on trabecular surfaces[a] in the beagle at times to 1 year after injection[46]

Days after injection	Maximum concentration / Minimum concentration	Mean ± standard deviation
7	5.8	5.12 ± 60%
15	6.1	5.43 ± 68%
28	8.6	5.12 ± 69%
56	4.0	2.53 ± 56%
133	2.8	3.13 ± 34%
210	4.0	2.51 ± 55%
365	3.0	1.58 ± 40%

[a]Lumbar vertebra, proximal humerus, pelvis, proximal ulna, distal humerus.

Table 10. Plutonium concentrations in the cortical and trabecular portions of selected bones from case HP-9 relative to that in the femur shaft[20]

Bone	Percent trabecular bone	Relative concentration		Concentration ratio trabecular/cortical
		Trabecular	Cortical	
Femur shaft	<10	4.5	(1.00)	4.5
Femur head	>75	2.7	1.19	2.3
Humerus shaft	<10	2.9	1.12	2.6
Tarsal	>90	1.19	a	
Clavicle	50	3.3	0.92	3.6
Rib 2	<10	25	7.1	3.5
Rib 8	<10	29	6.1	4.8
Sternum	>75	39	9.1	4.3
Vertebral body				
Cervical	>75	31	13.3	2.3
Thoracic	>75	43	22.2	1.9
Mean ± S.D.				3.3 ± 1.1

[a]No cortical portion could be isolated.

facilitate the release of Pu from proteins such as transferrin. Pu released from transferrin could be transported to bone surfaces by association with the ejected lysosomes.[39,40] Any or all of these processes may be involved in the release of Pu from transferrin and its transport to resorbing surfaces, but they do not explain the release and transport of Pu near resting and growing surfaces.

Translocation from Bone Surfaces

Deposits of Pu remain on bone surfaces until removed by bone resorption or buried by bone apposition during the bone growth and remodeling processes.[39,40] Osteoclasts resorbing bone contaminated with Pu progressively concentrate the Pu.[62] Measurements indicate that Pu is retained in osteoclasts of rats with a half-time of a few days.[63] Some Pu released from the osteoclasts may be recycled to blood, but much of it is concentrated by macrophages which may be found in the bone cavities, particularly in marrow.[40] Since there is no evidence that Pu citrate or Pu transferrin is concentrated by macrophages, it appears that Pu is released from osteoclasts in a particulate form that would be engulfed by macrophages.[64] In such an event Pu would probably remain in the macrophages until the complex is digested.[64] The length of time that Pu remains in macrophages in the marrow is not known with certainty, but experimental evidence suggests that the half-time is much less than two years in beagles.[40]

Pu released from macrophages may be carried back to the bloodstream and either recycled to bone, liver, and soft tissue, or excreted. Also, autoradiographic evidence suggests that, if Pu is released near a bone surface in a poorly vascularized area, then most of the Pu released from macrophages will be redeposited locally onto surfaces.[44,63]

UPTAKE AND TRANSLOCATION BY THE LIVER

Pu partially traces the movement of iron in the liver,[65-69] although the time course may be different for the two elements. Results of studies with beagles and rats[65-73] suggest the following scheme for hepatic uptake and translocation of Pu reaching the bloodstream in soluble form. The nuclide is first picked up by transferrin and transported to the

liver, where it may be released at the membranes of the parenchymal cells.[68] Within these cells Pu is associated at first with the soluble iron-storage protein, ferritin. Within a few weeks Pu leaves the cytosol and becomes associated with subcellular structures, principally lysosomes, microsomes, and mitochondria.[67,68,70-72] After several months the hepatic cells die and their debris, including Pu, is taken up by the reticulo-endothelial (RE) cells.[67,68] In the dog liver, Pu in RE cells is associated with hemosiderin, an iron-storage compound.[73] Pu may be retained for long periods within the RE cells.

There appear to be potentially two routes of loss of Pu from the liver: (1) in feces via bile produced in the liver, and (2) through the bloodstream. In rodents, much of the Pu in feces is apparently lost from the liver via bile.[74] The biological mechanisms by which Pu becomes incorporated in bile are not understood, but it is known that a substantial portion of systemic Fe is excreted in bile.[17]

It is also not completely understood how Pu leaves the liver through the bloodstream. Bruenger et al.[73] estimated that nearly all (perhaps 90%) of originally particulate Pu which was mobilized from the phagocytic cells of the livers of beagles was transferred to the bloodstream. This was estimated on the basis of a gradual accumulation of Pu in the skeleton, corresponding to a gradual decrease of Pu in phagocytic cells. The retention time of originally monomeric Pu in the liver of beagles varies widely after the first year from one individual to another.[73] This variation may be due to a similar variation in the iron status of the animals. Priest and Haines have shown that Pu is retained longer in the livers of rats with excess storage iron than in those with depleted circulatory iron.[69] Their results suggest that Pu in iron-depleted rats may be transported from the liver by macrophages and may be released to the blood in soluble form.

RETENTION OF Pu IN THE SOFT TISSUE COMPARTMENT

Concentrations of Pu in various soft tissues were measured in six Pu-injected persons who died from 4 to 456 days after injection.[8,17] These concentrations are listed in Table 11 for various organs in the soft tissue compartment, along with the percent of total-body iron per

Table 11. Concentrations of Pu in soft tissues in humans at 4 to 456 days after injection, compared with typical Fe concentrations

Organ	Fe concentration[a]	Pu concentration[b]					
		4 d	5 d	17 d	151 d	160 d	456 d
Spleen	0.0066	0.0048	0.0019	0.0012	0.0007	0.0025	0.0015
Kidneys	0.0018	0.0015		0.0054	0.0002	0.00038	0.0002
Lungs	0.004	0.0016		0.0016	0.0005	0.00058	
Pancreas	0.0009			0.0022	0.0002		0.0002
Intestines	0.00046	0.00045		0.00065	0.00015		
Testes	0.0006	0.0012			0.0003	0.00052	
Thyroid	0.0015	0.0009		0.0034	0.0001		
Adrenals	0.0007	0.0022			0.0004		
Muscle	0.0009	0.0002	0.0004	0.0006	0.0002	0.00025	0.0002
Skin	0.0003	0.0002	0.00058	0.0006			
Heart	0.001			0.001		0.00028	

[a] Percent total body Fe per gram tissue.[47]
[b] Percent injected Pu per gram tissue.[5,17]

gram tissue in each organ of a typical adult human.[47] It appears from the data in Table 11 that the distribution of Pu in soft tissue at early times is very similar to the distribution of Fe. Also, it is apparent that a substantial portion of Pu is lost from soft tissues during the first 5 months after injection.

EXCRETION

For bioassay purposes it is important to estimate the amount U of circulating activity that is excreted each day in urine and the amount F excreted each day in feces. For plutonium, the ratio U:F appears to vary with time after contamination of blood.[8,17,33] It is convenient to relate U and F to the amount of Pu in blood and express clearances as fractions of circulating Pu. This is done in Table 12, which summarizes the renal and gastrointestinal clearance of circulating Pu in Langham's subjects during the first few weeks after injection. This table is taken from an article by Durbin,[17] who pointed out that the renal clearance of Pu was initially lower for persons with anemia or abnormal kidney function, and that fecal clearance was lower for persons on restricted diets or having abnormal livers.

Voelz et al.[13] recently investigated the urinary and fecal clearance of Pu in several persons who worked with Pu during the Manhattan Project. A summary of renal and GI clearance of circulating Pu for these persons is given in Table 13. Urinary clearance (as a fraction of circulating Pu) was not markedly different in these persons, who had been exposed approximately 30 years earlier, than from Langham's patients at 3 weeks after exposure. Fecal clearance at late times, however, appears to be much lower than at early times after exposure, so that the ratio U:F appears to be much higher at later times than soon after Pu initially reaches blood.

In 1973, measurements of Pu in blood, urine, and feces were made in two of the persons (cases HP-3 and HP-6) injected in 1945-46.[9,10] Urinary and fecal clearance rates in these two persons compare reasonably well with those estimated for the Manhattan Project workers. The urinary clearance was about 0.04 d^{-1} and the fecal clearance was about 0.015 d^{-1}; again, these are expressed as fractions of circulating Pu.

Table 12. Renal and gastrointestinal clearance of circulating Pu in human subjects, expressed as fraction of circulating Pu^{17}

Subject	Group	Renal clearance		Group	Fecal clearance		(U/F)		
		1 to 6 days	19 to 24 days		1 to 6 days	19 to 24 days	1 to 6 days	19 to 24 days	35 to 65 days
HP-1	A[a]	0.008		R[a]	0.009		0.9		
HP-2		0.017	.031		0.020	0.061	0.8	0.5	
HP-3		0.020	.070	Ab.L.[a]	0.011	0.037	1.8	1.9	
HP-4	Ab.K.[a]	0.009	.029		0.010	0.030	0.9	1.0	
HP-5		0.021	.098		0.034	0.095	0.6	1.0	
HP-6		0.020	.130		0.020	0.100	1.0	1.3	
HP-7	A	0.011	.025	R	0.008	0.027	1.4	0.9	
HP-8		0.019	.066	R	0.017	0.056	1.1	1.2	1.3
HP-9	A	0.007	.034		0.024	0.055	0.3	0.6	
HP-10		0.013	.090	R	0.006	0.051	2.2	1.8	
HP-12	A						0.4	0.7	1.2
Kidney and erythropoiesis normal				G.I. function normal					
Mean		0.018	0.081	Mean	0.022	0.068			
± S.D.		0.003	0.034	±S.D.	0.009	0.029			
Anemia and/or abnormal kidney				Restricted diet and/or abnormal liver					
Mean		0.0088	0.029	Mean	0.010	0.034			
±S.D.		0.0007	0.004	±S.D.	0.004	0.017			

[a]A = anemic, Ab.K. = abnormal kidney, R = restricted diet, Ab.L. = abnormal liver.

Table 13. Renal and gastrointestinal clearance of circulating Pu in Manhattan Project workers, approximately 30 years after exposure (expressed as fraction of circulating Pu)[12]

Subject number	Renal clearance (d^{-1})	Fecal clearance (d^{-1})	U/F
1	0.04	0.04	1.0
3	0.39	0.02	17.2
5	0.05	0.007	7.4
6	0.13		
7	0.07	0.02	2.9
8	0.06	0.008	7.3
9	0.06	0.015	4.1
12	0.04	0.005	8.0
17	0.05		
18	0.20		
19	0.05	0.023	2.2
22	0.06	0.02	3.0
Mean ± S.D.	0.10 ± 0.10	0.02 ± 0.01	5.9 ± 4.9
Mean ± S.D. without subject #3	0.07 ± 0.05	0.02 ± 0.01	4.5 ± 2.7
Value considered most likely at times remote from contamination of blood based on these data and Refs. 5, 9, 10, 17	0.06	0.024	2.5

Iron may be excreted in urine after filtration of low-molecular weight chelates, exfoliation of kidney, bladder, or urethra cells, leakage of transferrin-bound iron through the glomerulus or tubules, and possibly transferrin catabolism in the kidney.[17] Pu transferrin is less stable than Fe transferrin;[35] hence one might expect that a higher fraction of Pu than Fe could be filtered through the kidney. The daily urinary clearance of iron is about 0.015-0.03 times plasma iron,[76,77] which appears to be less than the urinary clearance of Pu.[9,10,12,17]

Fecal clearance of iron may be about 0.10 times plasma iron,[17] which is higher than fecal clearance of Pu,[9,10,12,17] particularly at times long after injection. About one-third of fecal iron stems from biliary secretions, with the remainder arising from desquamated intestinal epithelial cells, and other digestive secretions.[17] In rodents, much of the fecal Pu comes from bile.[74]

V. A MODEL FOR THE RETENTION AND EXCRETION OF Pu BY HUMANS

In this section a mathematical model is described that quantifies the processes described in the preceding section. A schematic diagram of the major compartments in the model and the main pathways among these compartments is given in Fig. 1. The model applies to persons 18 years of age and older. Except where indicated by additional references, justification for model components and parameters can be found in Section IV. In this section we attempt to assign a most likely or most reasonable "base case" value to each model parameter, and in the following section we examine the sensitivity of the model to those parameters that appear to be the most uncertain. Whenever a parameter appears to be a function of the adult age, a separate value is assigned to the set of ages 18, 24, 30, 40, 45, 55, 65, and 75 years; intermediate values are estimated by linear interpolation between values at bounding ages from this set.

DISAPPEARANCE FROM BLOOD

Blood is regarded as a transfer compartment which feeds the skeleton, liver, and soft tissue compartments, and which receives Pu lost from those compartments (except for a small amount of Pu lost in excretion from the liver and from the cells of the urinary system). Although blood is regarded as a single pool, removal of Pu from blood cannot be approximated by a single exponential term; this may result mainly from the movement of Pu into and out of the extracellular fluids, and to a lesser extent from recycling of Pu from the major organs. Retention R(t) of Pu in blood t days after introduction is estimated as

$$R(t) = 0.52\ \exp(-50t) + 0.271\ \exp(-2.28t) + 0.172\ \exp(-0.58t) + 0.033\ \exp(-0.14t) + 0.004\ \exp(-0.0087t)\ .$$

This retention function is based on data for humans as given in Table 3, but the coefficients were adjusted slightly to sum to 1.0, and a long-term half-time of 80 days (rather than 88 days) was used since this

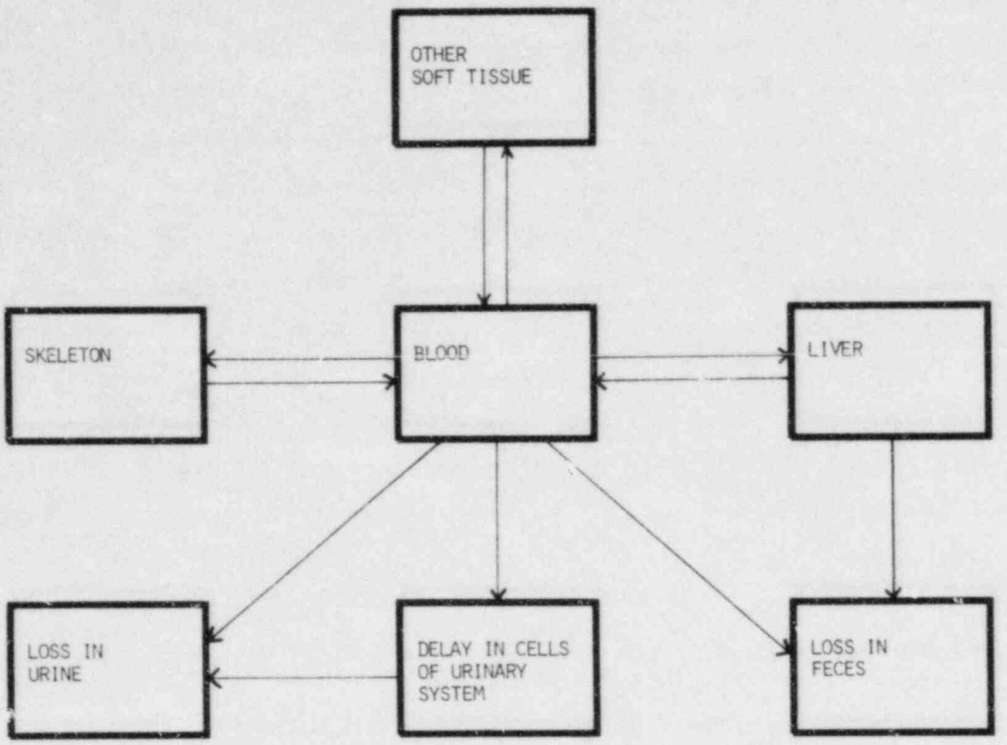

Figure 1. Major compartments and pathways in the model for the retention and excretion of systemic Pu.

half-time would produce an apparent long-term half-time of about 88 days when recycling from skeleton, liver, and soft tissue is considered explicitly.

INITIAL DEPOSITION FRACTIONS IN THE THREE MAIN COMPARTMENTS

For a given quantity of Pu reaching the bloodstream, a small fraction is excreted in urine and feces. It is assumed that eighty percent of the non-excreted Pu is divided between the skeleton and liver, with the remainder going to soft tissue.

The skeletal deposition fraction is assumed to vary slightly with age before age 30 years. This feature is of marginal significance for present purposes but is included for the sake of consistency with an extension of this model that applies to children. (This extension will appear elsewhere.)

It is assumed that the skeletal deposition fraction decreases linearly from 60% at age 18 years to 50% at age 30 years and remains at 50% thereafter. These values also apply to Pu recycled from blood after translocation from skeleton, liver, and soft tissues.

THE MODEL FOR Pu IN THE SKELETON

Processes governing the uptake and translocation of Pu in the skeleton, as discussed in Sect. IV, are summarized schematically in Fig. 2. This figure shows the skeletal compartments used in the model, and the pathways among these compartments. The model of the skeleton will be described through reference to the pathways indicated in this figure.

Pathways L and K

It is assumed that 60% of the initial deposit in skeleton is on trabecular surfaces and 40% is on cortical surfaces. These values involve some arbitrariness but reflect the following considerations. There is at least as much trabecular surface in the skeleton as cortical surface, and possibly more.[41-43] Thus, if Pu deposited uniformly on all surfaces, then at least 50% of the initial deposit in the skeleton

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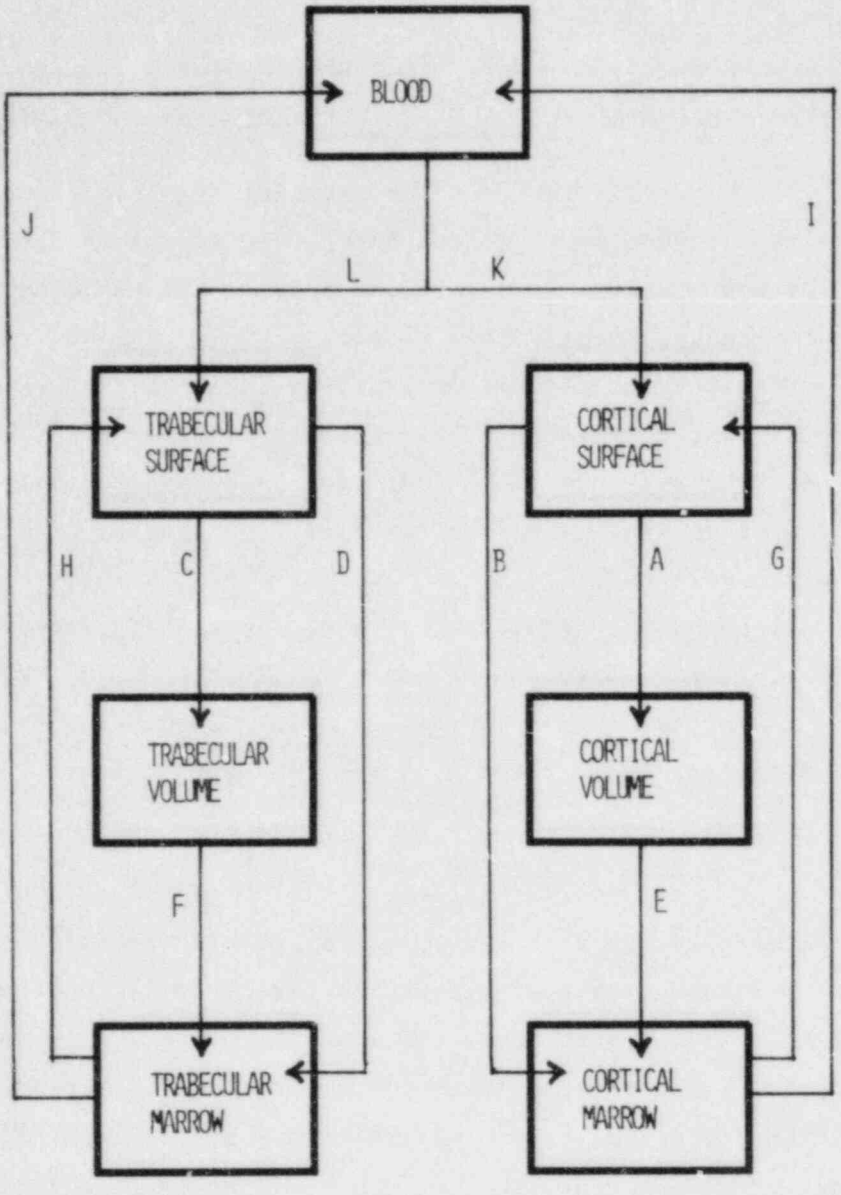

Figure 2. Compartments and pathways in the model for the retention and translocation of Pu in the skeleton.

should be assigned to trabecular surfaces. Since it is known that Pu deposits more heavily in areas of active marrow and since almost all active marrow in adults is in trabecular bone, it seems reasonable to assign more than 50% of the initial deposit to trabecular surfaces. On the other hand, the data in Table 10 suggest that trabecular bone may not contain any more Pu than cortical bone after 1.3 years in a 65-year-old man. Although there has been time for some translocation to occur (cf. Table 9 for beagles), the turnover rate for trabecular bone in humans (as discussed later) is probably not high enough to have led to a massive relocation during 1.3 years. Thus a 60%-40% division between trabecular and cortical surfaces seems reasonable.

Pathways A, B, C, and D

Plutonium may be removed from surfaces either through burial by formation of new bone (A and C) or through resorption by osteoclasts (B and D). The rate of removal from surfaces by burial or resorption depends on the age of the individual and on the bone-surface type (trabecular or cortical). There seems to be general agreement that cortical turnover rates in adult humans average about 3% per year (but may vary with age) and that trabecular turnover rates are at least 4 times higher than cortical rates.[41,48,54] These are volume turnover rates; it is assumed throughout that the surface turnover rate is the same as the volume turnover rate for a given bone type.

Bone formation rates used in this model are listed in Table 14 for various ages. Formation rates chosen for cortical bone are based on tetracycline studies of Frost for the sixth human rib.[48] Cortical formation rates in the rib may be higher than in the long bones[17,41] and not much different than in the ilium.[79] The rib may be a fairly representative bone for our purposes, considering that most of the initial deposit of Pu is in the axial skeleton.

For ages 30 years and greater, it is assumed that trabecular bone forms at a rate five times that of cortical bone. This approach is similar to that used in Publication 20 of the International Commission on Radiological Protection,[42] where it was assumed that trabecular formation rates are four times cortical formation rates on the basis of

Table 14. Estimated bone formation and net bone loss rates at various ages

Age (y)	Formation rate (y^{-1})[a]		Net bone loss rate (y^{-1})[b]	
	Cortical bone	Trabecular bone	Cortical bone	Trabecular bone
18	0.135	0.285	0.0	0.0
24	0.067	0.255	0.0	0.0
30	0.018	0.09	0.0	0.0
40	0.018	0.09	0.0	0.0
45	0.037	0.185	0.007	0.007
55	0.036	0.180	0.02	0.02
65	0.040	0.20	0.01	0.01
75	0.044	0.22	0.005	0.005

[a]Based on data of Frost[48] for cortical bone and on the assumptions given in the text for trabecular bone.

[b]Crude estimates based on Refs. 82-86.

similar differences in surface-to-volume ratios in the two bone types. The higher value of five used here considers that some researchers now estimate an even higher surface-to-volume ratio for trabecular bone.[42,43] This value also leads to reasonable agreement with trabecular turnover rates estimated using other approaches.[17,41,48,54,80] For ages younger than 30 years, the assumption that the trabecular formation rate is a constant multiple of the cortical formation rate at all ages does not seem valid.[80] For ages 18-30 years we have used trabecular formation rates based indirectly on strontium turnover rates in vertebrae (see Refs. 80, 81).

Bone resorption rates are calculated from Table 14 as bone formation rates plus net bone loss rates as estimated from various studies.[82-86] Thus net bone loss is assumed to stem from resorption rates being higher than formation rates. Cortical bone loss is assumed to equal trabecular bone loss, and bone loss is assumed to be occur primarily from the middle of the fifth decade to the middle of the seventh decade of life.[82-86]

In order to estimate rate constants for pathways A, B, C, and D, it is necessary to understand the relationship between bone formation and bone resorption. There are two somewhat different pictures of this relationship presented in the literature, depending (perhaps) on the focus of the articles. In some articles, bone addition and resorption are described as occurring on opposite sides of a bone (or bone trabecula), so that the bone is continually "drifting" in a given direction.[49,87] Other authors describe resorption and addition as occurring in the same location; first an area of bone is excavated by osteoclasts, and then the same area is refilled with osteoid which is later mineralized.[48,50] We believe that a suitable model that describes bone formation, loss, and replacement throughout life should involve some combination of these models. Bone drift may be the predominant process during growth and perhaps into young adulthood, but bone remodeling may not involve a great deal of drift after the skeleton has matured fully.

If bone formation and resorption always occurred on opposite surfaces of a bone segment, then the removal rate for Pu on bone surface would be approximately the sum of the resorption rate λ_1 and the formation rate λ_2. On the other hand, if formation represented only the immediate replacement of resorbed bone, then the removal rate would be

approximately λ_1 and Pu would be buried in volume only by depositing in unmineralized osteoid and moving to the mineralized surface underneath the osteoid. In this model, an intermediate scenario is assumed as a "base case," with the burial rate in bone volume being estimated as $0.5\ \lambda_2$, and the removal rate from bone surface being estimated as $\lambda_1 + 0.5\ \lambda_2$.

Plutonium resorbed by osteoclasts may be released and concentrated by macrophages in bone cavities, particularly in marrow.[29] The length of time that Pu remains in these macrophages is not known. In beagles receiving low doses of Pu, peak labeling of macrophages in bone marrow was at two years post injection, and all labeled macrophages had disappeared at four years post injection.[30] This suggests a half-time in beagles that is very short compared with two years, perhaps 0.25 years or less. For lack of better information we have arbitrarily assigned a "base case" value of 90 days as the half-time in this compartment.

Some fraction of the Pu in resorbed bone may be dissolved and recycled systemically without being taken up by macrophages, and with little or no sojourn time in the marrow. Since our model channels all resorbed Pu through the marrow with a 90-day half-time and since bone marrow receives much of its absorbed dose from Pu on bone surfaces (at least for the important Pu isotopes), the assumed half-time probably would not lead to a significant underestimate of dose to marrow. Moreover, as we shall discuss later, estimates of activity in other sensitive tissues are fairly insensitive to the estimate of the half-time in marrow, provided this half-time is relatively short compared with residence times in other compartments of the skeleton.

Pathways E and F

Pu buried in bone volume may eventually become volume distributed as the bone section "drifts" due to remodeling. The time required for Pu to become volume distributed is assumed to depend on the bone turnover rate. If the resorption rate for trabecular bone is k per year (see Table 14), then some buried Pu might be resorbed in about $1/k$ years, and it is assumed that all buried Pu is equally likely to be resorbed by $2/k$ years after exposure. Here account must be taken of the

fact that k varies with age. Because of the slow turnover time for cortical bone, much of the Pu buried in cortical bone may never be recycled.

Pathways G, H, I, and J

Autoradiographs suggest that both local (G and H) and systemic (I and J) redeposition onto bone surfaces occurs.[46,63] If Pu is released in a highly vascularized area and more remote from bone surfaces, then removal in the bloodstream and possible systemic redeposition is likely. If Pu is released in a less vascularized area, it is likely that some local redeposition will occur. The short time required for redistribution of Pu on bone surfaces in beagles (see Table 9, for example) is one indication of the large amount of systemic redeposition that apparently occurs. For a "base case" value we assume that 100% of the Pu in the transfer compartments is carried back to the bloodstream, from where it may still be deposited on bone surfaces. Any error inherent in this assumption is partially negated by the model because some of the Pu assumed to be recycled via blood will be assigned to surfaces that should have been assigned local redeposition.

THE MODEL FOR Pu IN THE LIVER

The retention and removal of Pu by the liver cannot be quantified with much confidence on the basis of available data. However, the major pathways for Pu in the liver are known; these pathways are shown schematically in Fig. 3. It is known from animal studies that some Pu may leave the liver in bile, that Pu is taken up by hepatocytes but later transferred to RE cells, and that Pu may reside for years in the RE system, with the residence time possibly depending on the iron status of the animals.[64-72] It is also suggested by autopsies of persons exposed to Pu several years previously that this nuclide may reside for many years in the human liver.[13,18]

In this model three subcompartments are associated with the liver, two associated with the hepatocytes, and the third with the reticuloendothelial system. Pu is transferred initially from the bloodstream to the hepatocytes, where it may be released and taken up by the first

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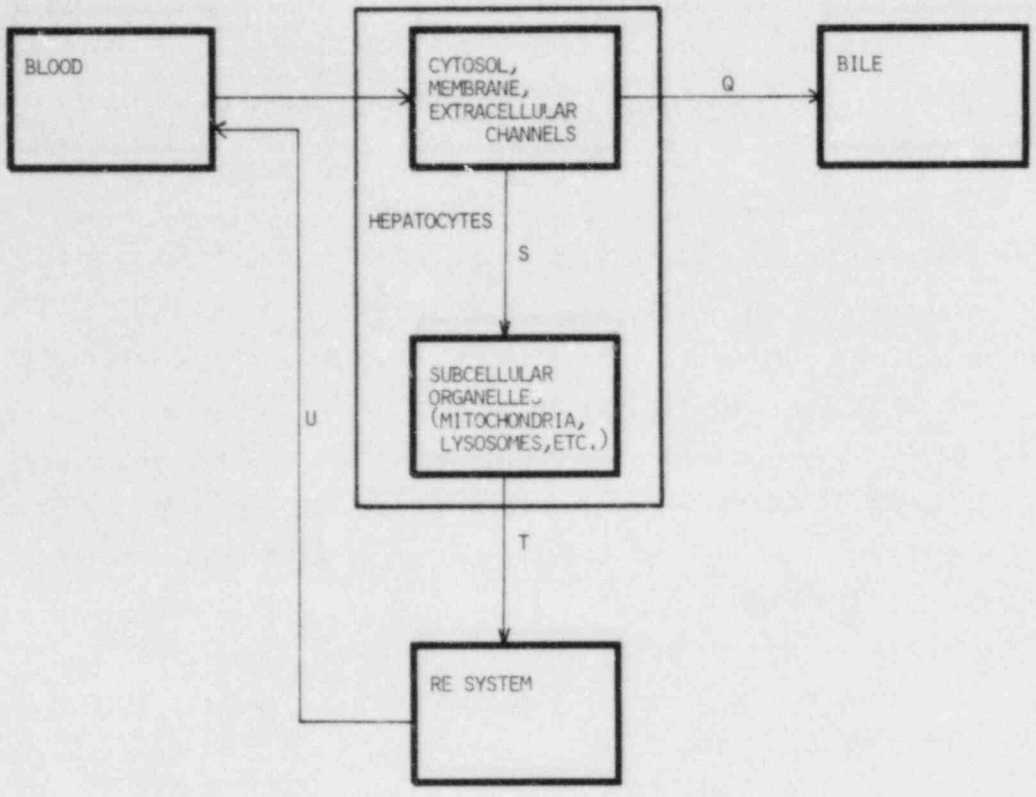


Figure 3. Compartments and pathways in the model for the retention and translocation of Pu in the liver.

subcompartment, consisting principally of the cytosol but also including the cell membrane and extracellular spaces. Pu may leave this subcompartment either in bile at some rate α day^{-1}, or through its movement into the second subcompartment, consisting of the subcellular organelles (particularly the mitochondria, microsomes, and lysosomes), at a rate of about 30α day^{-1}. The ratio of removal rates (1:30) was determined from a differential equation describing the rate of change of activity in the "cytosol" compartment, assuming steady-state conditions. To determine the ratio in this way, one needs to apply the following assumptions or estimates: (1) at times remote from injection, the effective removal rate from blood is about 0.9 day^{-1}, and about 30% of Pu removed from blood enters the "cytosol" compartment; this compartment includes the cytosol and cell membranes of the hepatocytes, plus extracellular spaces around the hepatocytes; (2) one-third of fecal Pu reaches feces via bile formed in the cytosol compartment; (3) the daily clearance of Pu in feces represents about 0.024 times the activity in blood at times remote from injection. The second assumption arises from the observations that, even in rodents, much of the injected Pu reaches feces by non-biliary secretions and, in humans, about one-third of fecal iron stems from biliary secretions. (Whenever overriding evidence is absent, it is assumed that Pu behaves the same as Fe.) The third assumption is based on data in Refs. 5, 9, 10, 12, and 17. Data on beagles indicate that the removal of Pu from cytosol occurs with a half-time of a few days or weeks.[71,72] Since the particular choice of α is not important as long as the removal rate from the first compartment is large compared with that from the RE cells, we have arbitrarily assumed that the first compartment clears to the subcellular organelles at a rate of 20 times per year. It is assumed that Pu leaves the subcellular organelles and enters the third subcompartment, the RE system in the liver, upon death of the hepatocytes, which is assumed to occur with a half-time of one year; this approximates the turnover time of hepatic cells in rats and mice.[88,89] The value chosen for retention half-time in the subcellular organelles is also not particularly important, as long as it remains small compared with the half-time in the RE cells.

The biological half-time of Pu in the liver in general, and in the RE cells in particular, is not known but appears to be at least 5 or 10 years and possibly more on the basis of autopsy data. The net half-time of Pu in the liver of beagles exposed to low levels of Pu is about 10 years,[90] and since the liver may receive Pu released from the skeleton and other organs (including the liver itself), the actual half-time for a single sojourn in the liver may be much less than 10 years. In this model we assume that Pu is released from the RE cells to the bloodstream with a half-time of 10 years, as a "base case" estimate (cf. Ref. 75).

THE MODEL FOR Pu IN THE SOFT TISSUE

Soft tissue is assumed to consist of a single compartment which receives approximately 20% of the Pu in the blood compartment. Pu is assumed to be removed from soft tissue back into blood with a half-time of 500 days (cf. Refs. 5, 17).

THE MODEL FOR RECYCLING OF SYSTEMIC Pu

Pu reaching the bloodstream after removal from skeleton, liver, or soft tissue is assumed to behave the same as the initial deposit in blood.

THE MODEL FOR URINARY AND FECAL EXCRETION OF Pu

Pu in urine is assumed to come from two sources. Each day 2% of the integrated activity in blood is assumed to pass directly into urine, and 4% of the integrated activity in blood is assumed to move into tissues of the urinary pathway (kidneys, bladder, urethra), from which Pu is eventually removed to urine with a half-time of 500 days (the half-time of the soft tissue compartment). These values arise from the observations that, at equilibrium, perhaps 6% of the activity of blood is excreted daily in urine (see Table 13), but soon after injection only 2% of the activity in blood is removed daily in urine (see Table 12). Although removal from blood to urine is assumed to be independent of age, the marked decrease in renal blood flow and glomerular filtration rate that begins at about age 30 years[91,92] could lead to some age dependence in this process.

Pu in feces is assumed to come from two sources. First, 1.6% of the integrated activity in blood is assumed to be removed via feces. Second, approximately 3.5% per day of the activity removed from the cytosol compartment of the liver is assumed to be removed to feces via bile. Removal rates from blood to feces and from cytosol to feces were determined from the conditions that, at times remote from injection, (1) two-thirds of the Pu in feces should arise from non-biliary secretions, and (2) an amount equivalent to 2.4% of the integrated activity in blood should be removed each day in feces. These conditions were discussed earlier.

The "base case" values for all pathway fractions and rate constants appearing in the model are given in Table 15 for selected ages. The ages chosen are those which are considered explicitly in the computer code corresponding to our model; that is, the ages and "base case" parameter values given in Table 15 are entered explicitly into the computer code, and parameter values for intermediate ages are calculated by linear interpolation. The uncertainties involved in choosing the "base case" values have been emphasized throughout the report. In the following section we attempt to gain some understanding of the sensitivity of model predictions to estimates of pathway fractions and rate constants.

Table 15. Base case values of parameters for various ages.

Parameter	Age (years)							
	18	24	30	40	45	55	65	75
Cortical bone formation rate (y^{-1})	0.135	0.067	0.018	0.018	0.037	0.036	0.040	0.044
Trabecular bone formation rate (y^{-1})	0.285	0.255	0.09	0.09	0.185	0.18	0.20	0.22
Removal rate from marrow (y^{-1})	2.77	2.77	2.77	2.77	2.77	2.77	2.77	2.77
Removal rate from soft tissue (y^{-1})	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Rate of net loss of cortical bone (y^{-1})	0.0	0.0	0.0	0.0	0.0067	0.02	0.01	0.005
Rate of net loss of trabecular bone (y^{-1})	0.0	0.0	0.0	0.0	0.0067	0.02	0.01	0.005
Fraction of non-excreted Pu in blood going to the skeleton	0.6	0.55	0.5	0.5	0.5	0.5	0.5	0.5
Fraction of non-excreted Pu in blood going to liver (hepatocytes)	0.2	0.25	0.3	0.3	0.3	0.3	0.3	0.3
Fraction of non-excreted Pu in blood going to other soft tissue	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Fraction of bone remodeling attributed to "drift"	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Fraction of skeletal Pu going to trabecular surfaces	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Fraction of Pu released from marrow going to blood	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Removal rate from liver (y^{-1})	0.0693	0.0693	0.0693	0.0693	0.0693	0.0693	0.0693	0.0693
Removal rate from cytosol to subcellular organelles in liver (y^{-1})	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Removal rate from cytosol to bile (y^{-1})	0.71	0.71	0.71	0.71	0.71	0.71	0.71	0.71
Removal rate from subcellular organelles in liver to RE cells (y^{-1})	0.693	0.693	0.693	0.693	0.693	0.693	0.693	0.693
Removal rate from cells of urinary system to urine (y^{-1})	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Fraction per day of integrated activity in blood removed in urine (equilibrium)	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Fraction per day of integrated activity in blood removed in feces (equilibrium)	0.024	0.024	0.024	0.024	0.024	0.024	0.024	0.024

VI. SENSITIVITY ANALYSIS

The model describing the retention, translocation, and excretion of Pu is a mechanistic model as opposed to a model derived simply from curve-fitting techniques. We first identified the processes governing the translocation of Pu, and we then identified several physical entities, called compartments, that play some part in these processes. Finally, we appealed to experimental data and physiological considerations to quantify the movement of Pu among these compartments. There are sufficient experimental studies on both humans and non-humans to justify the basic framework of our model, but in many cases there are substantial uncertainties involved in assigning pathway fractions and rate constants. To emphasize these uncertainties, we have referred to our estimates of the various model parameters only as "base case" values. In order to understand how reliable the model is, it is necessary to first determine how sensitive model output is to the various model parameters, particularly those that are most uncertain.

In Figs. 4-12 we have attempted to illustrate graphically the sensitivity of model output to the various model parameters. In each case we have allowed one or two model parameters to vary among conceivably realistic values (indicated in the legends) while holding all other parameters at the base case values given in the preceding section. Clearly this method does not give a complete picture of the uncertainties associated with model predictions. However, the model involves several parameters, and it would be prohibitive to vary more of the model parameters simultaneously in any meaningful way.

In each of the figures, the "base case" value(s) of the varied parameter(s) is given first, and this value is used to produce the solid curve in the figure. Thus, in each of the figures, the solid curve represents model predictions based on all the "base case" parameter values. Model predictions are expressed as fractions of an original activity of 1.0 unit in blood (of a young adult, age 25 years) at time zero.

The names of the input parameters in the following discussion correspond to the names in Figs. 4-12 and in the computer program used to calculate model output. These names are descriptive to some extent.

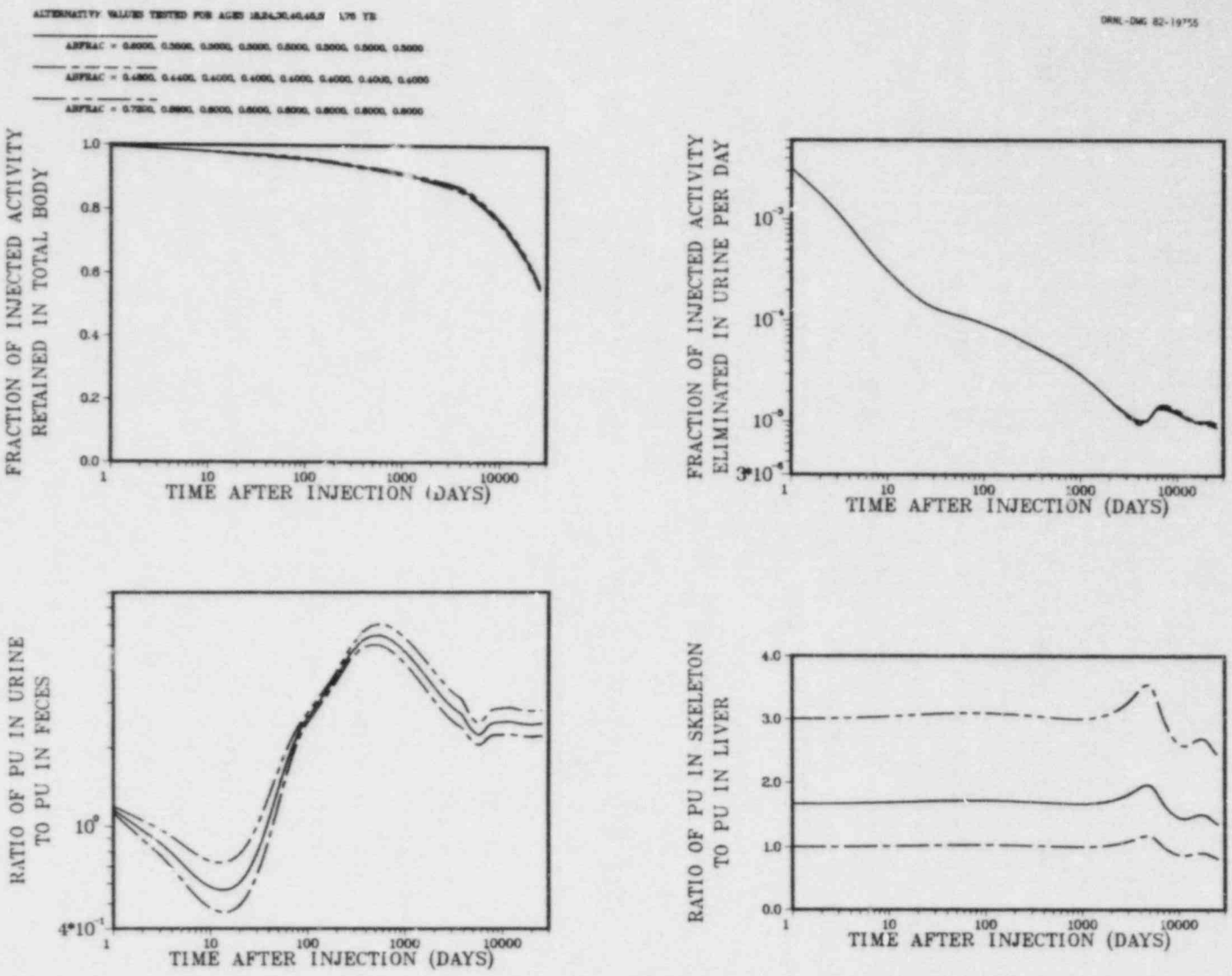


Figure 4. Sensitivity of model predictions to changes in ABFRAC, the fraction of non-excreted activity in blood deposited in the skeleton.

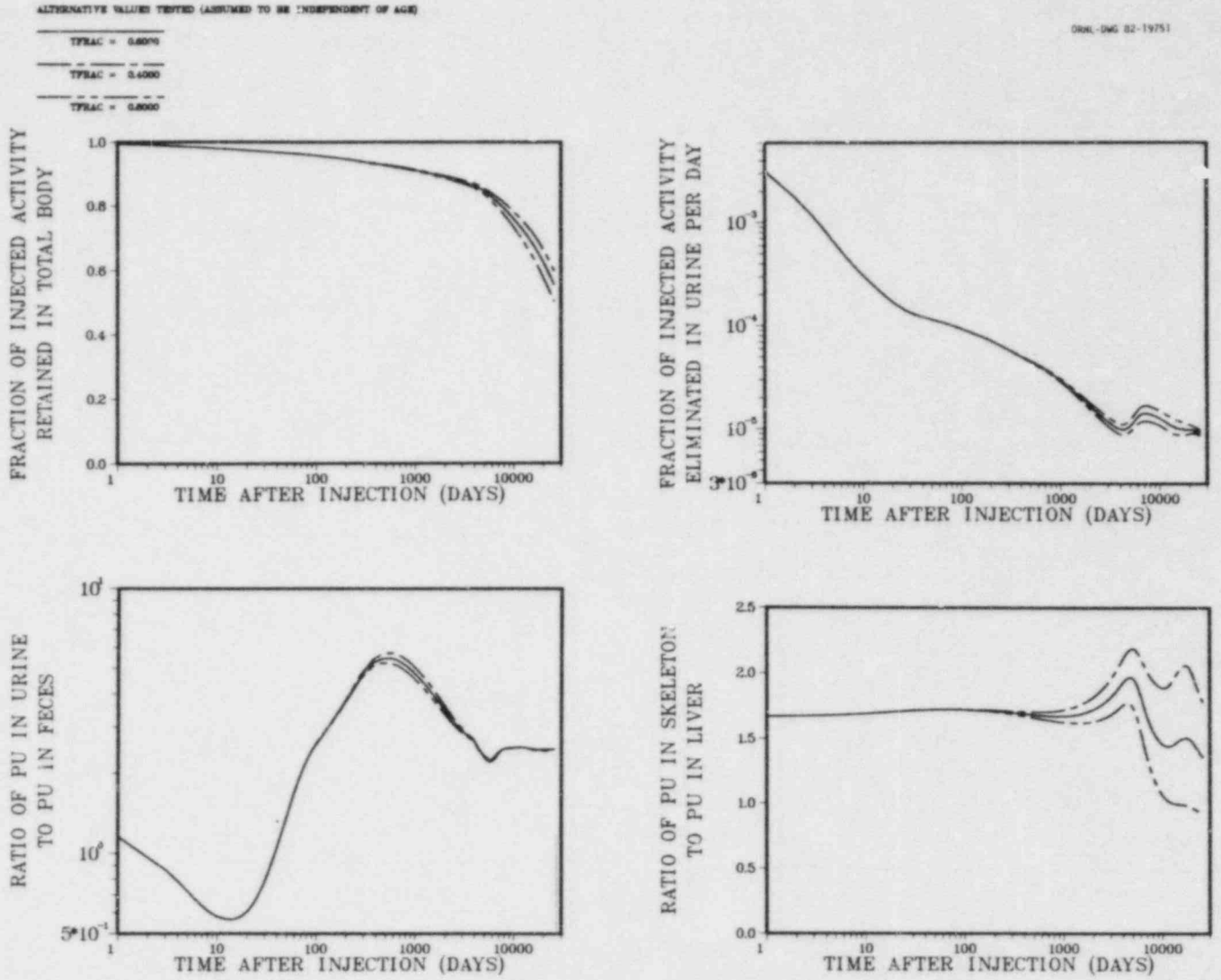


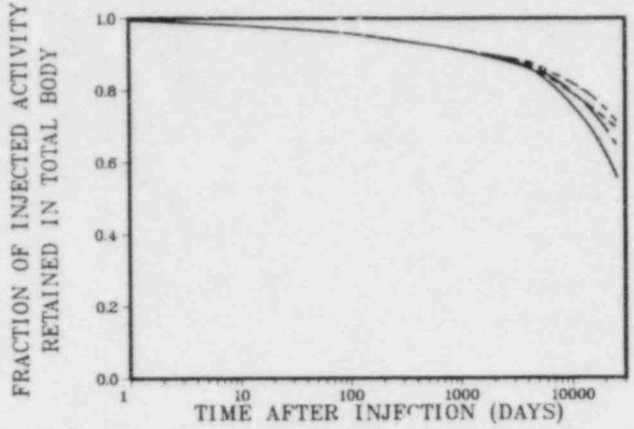
Figure 5. Sensitivity of model predictions to changes in TFRAC, the fraction of activity deposited in the skeleton that goes to trabecular bone.

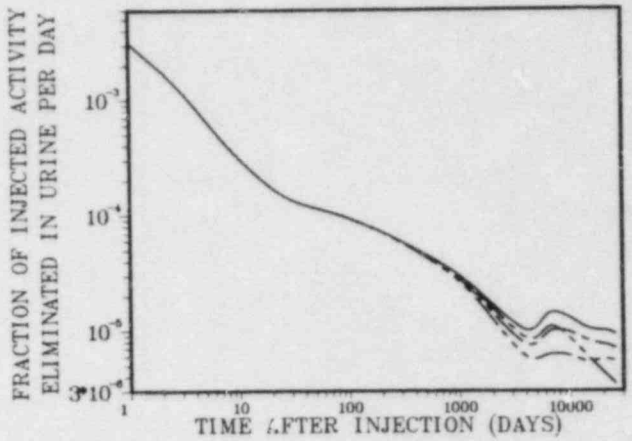
IFRAC = 1.0000
JFRAC = 1.0000

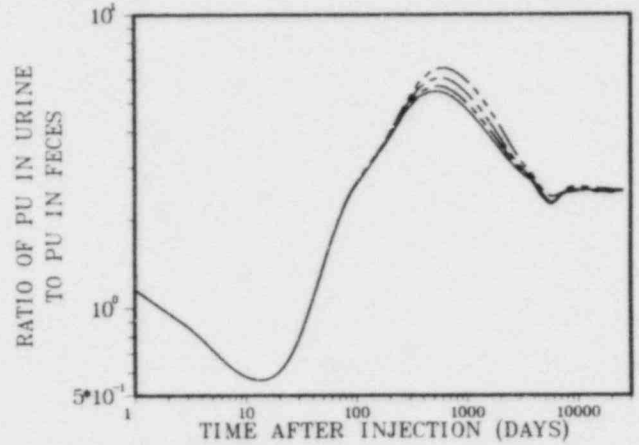
IFRAC = 0.5000
JFRAC = 0.5000

IFRAC = 0.1000
JFRAC = 0.3000

IFRAC = 0.9000
JFRAC = 0.1000







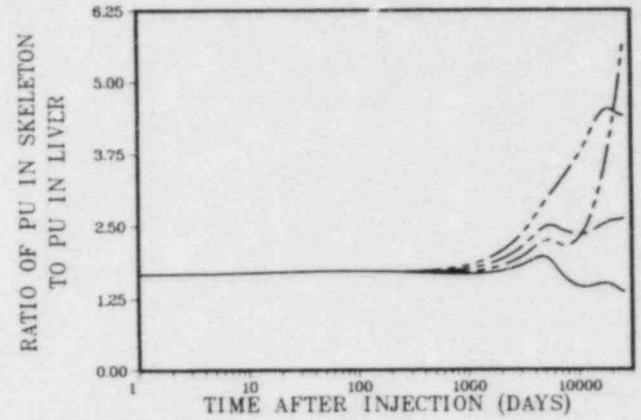


Figure 6. Sensitivity of model predictions to changes in IFRAC and JFRAC, the fractions of activity removed from cortical and trabecular bone, respectively, that are returned to blood rather than locally redeposited.

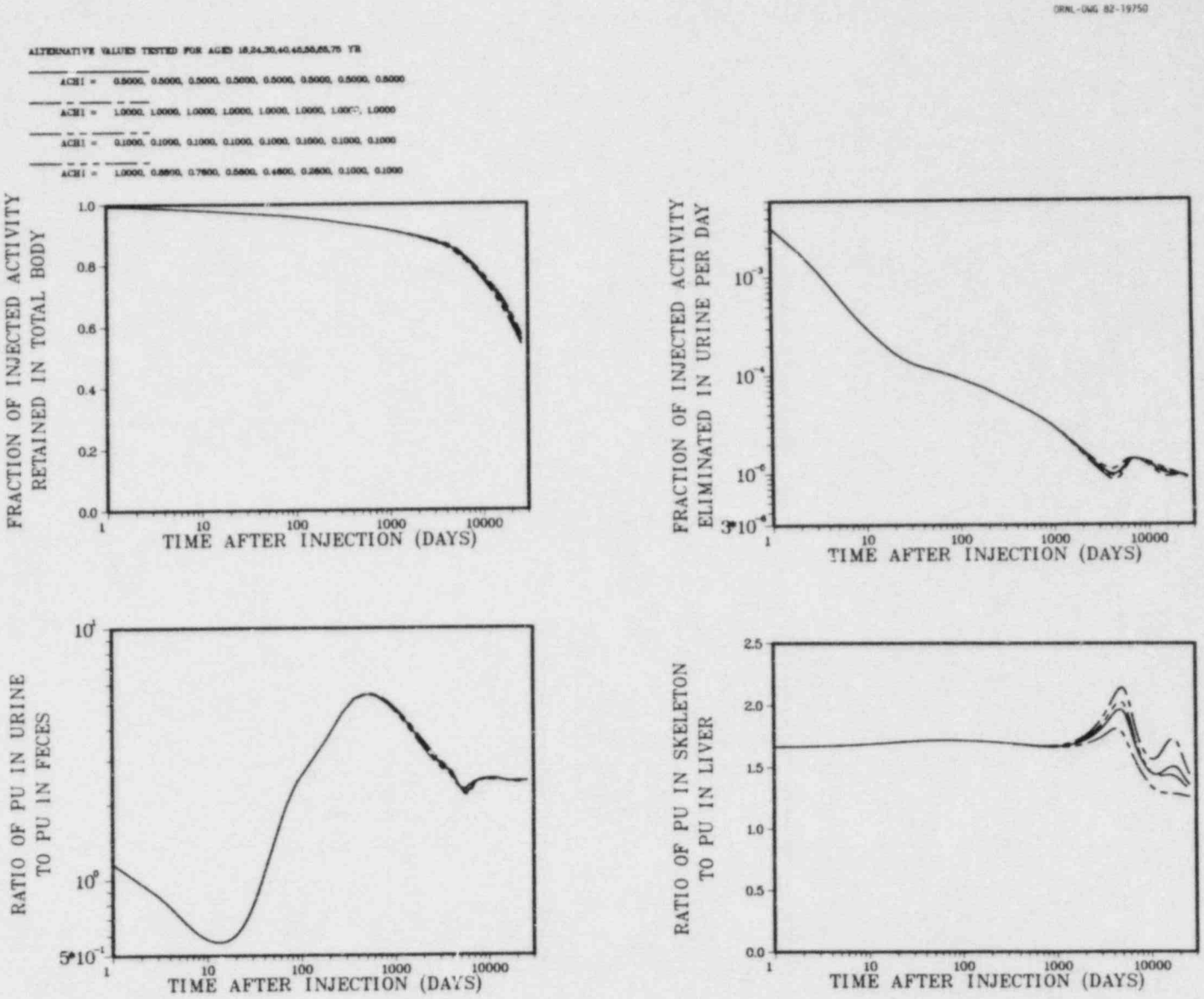


Figure 7. Sensitivity of model predictions to changes in ACHI, the fraction of remodelling attributed to "drift."

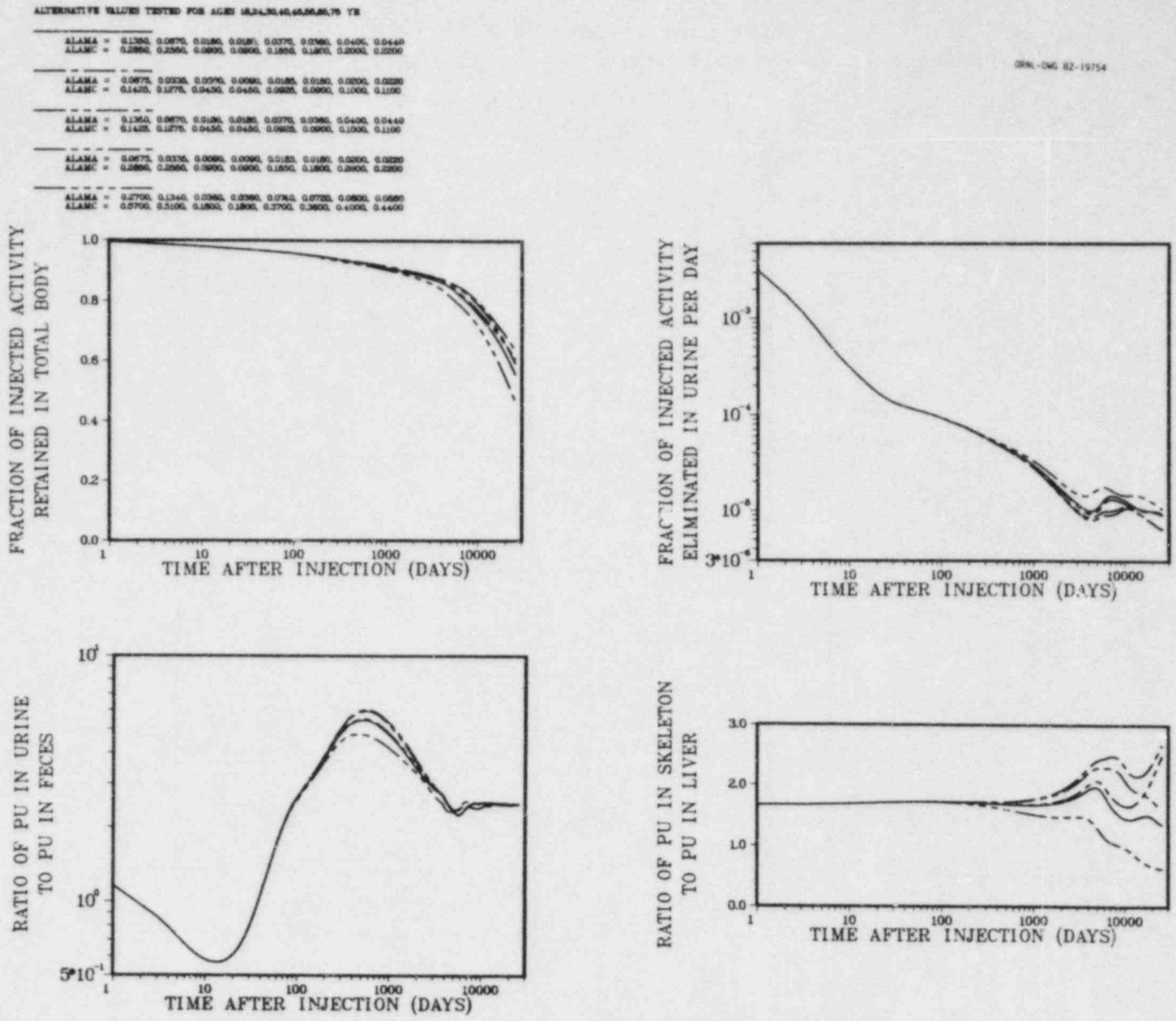


Figure 8. Sensitivity of model predictions to changes in ALAMA and ALAMC, the formation rates (yr^{-1}) of cortical and trabecular bone, respectively.

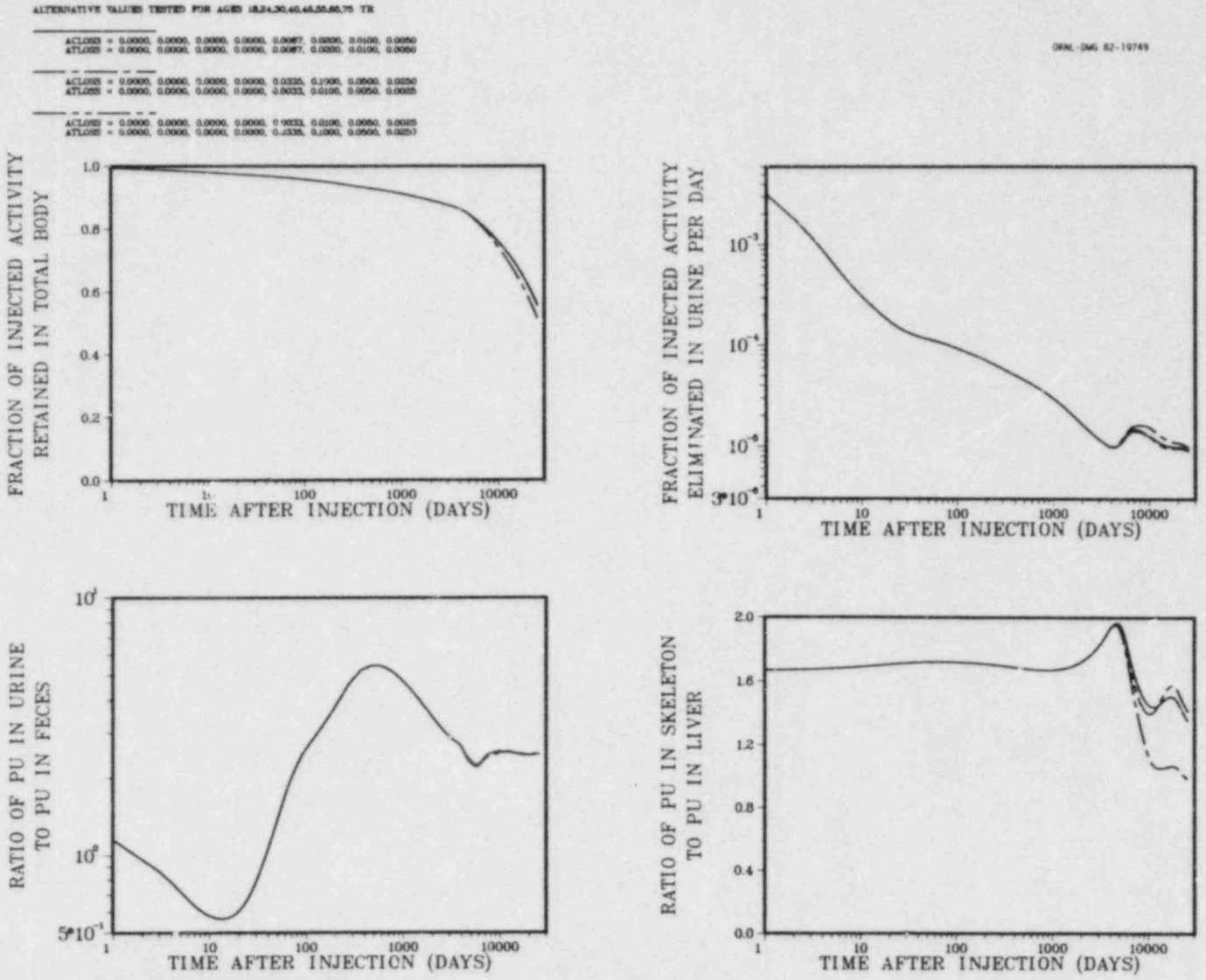


Figure 9. Sensitivity of model predictions to changes in ACLOSS and ATLOSS, the rate of net loss (yr^{-1}) of cortical and trabecular bone, respectively.

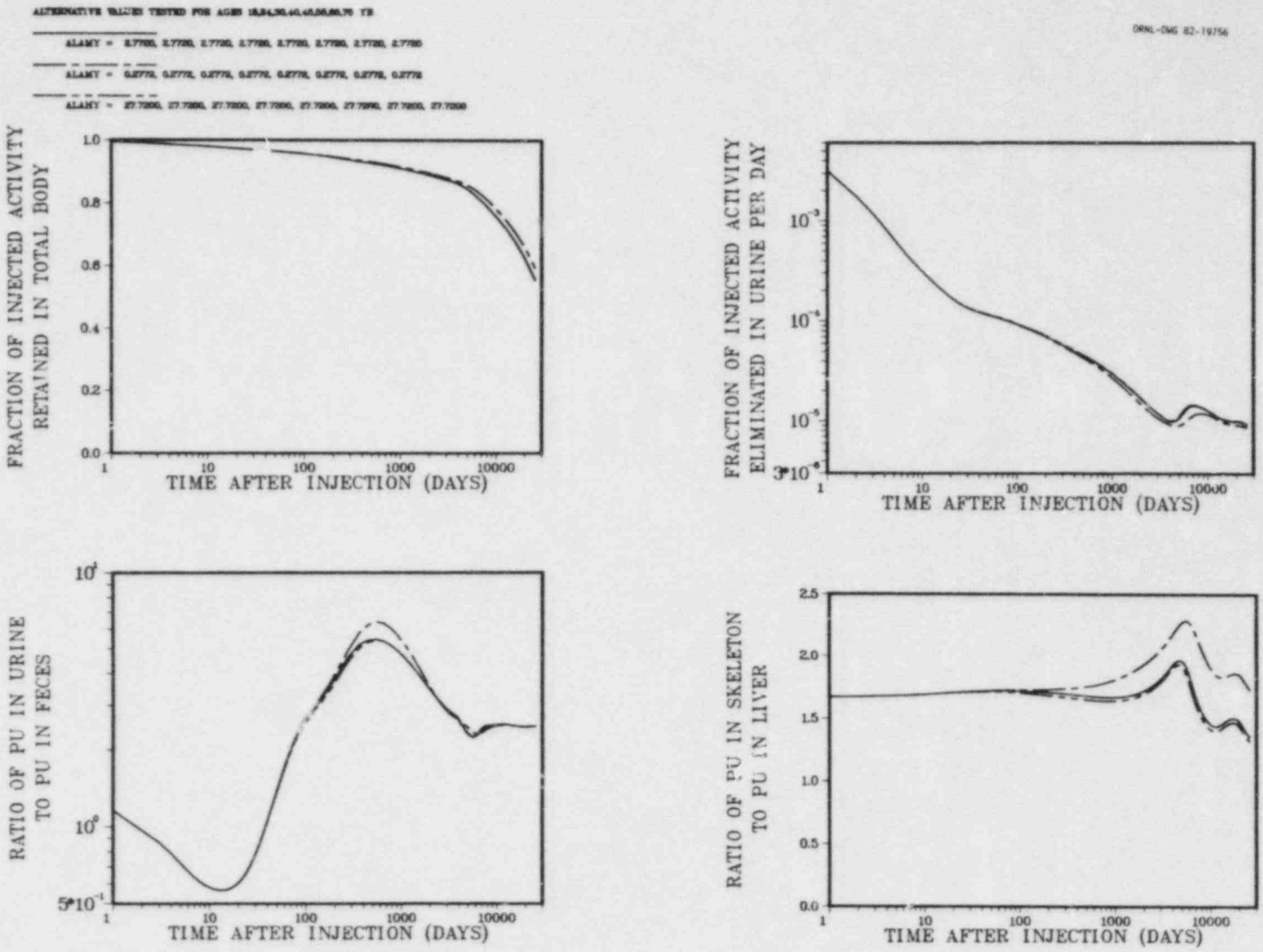


Figure 10. Sensitivity of model predictions to changes in ALAMY, the rate of removal (yr^{-1}) of activity from bone marrow.

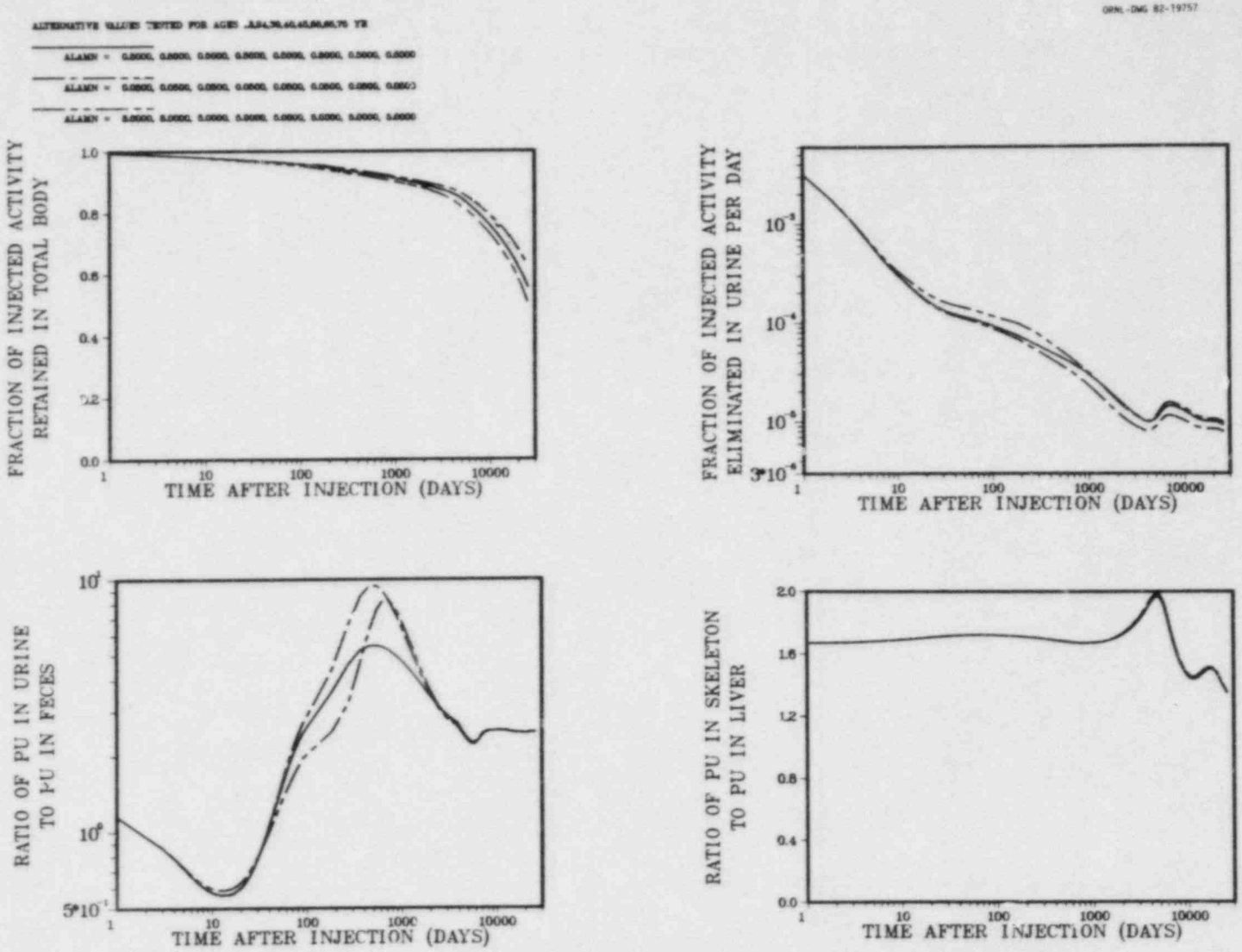


Figure 11. Sensitivity of model predictions to changes in ALAMN, the rate of removal (yr^{-1}) of activity from soft tissue.

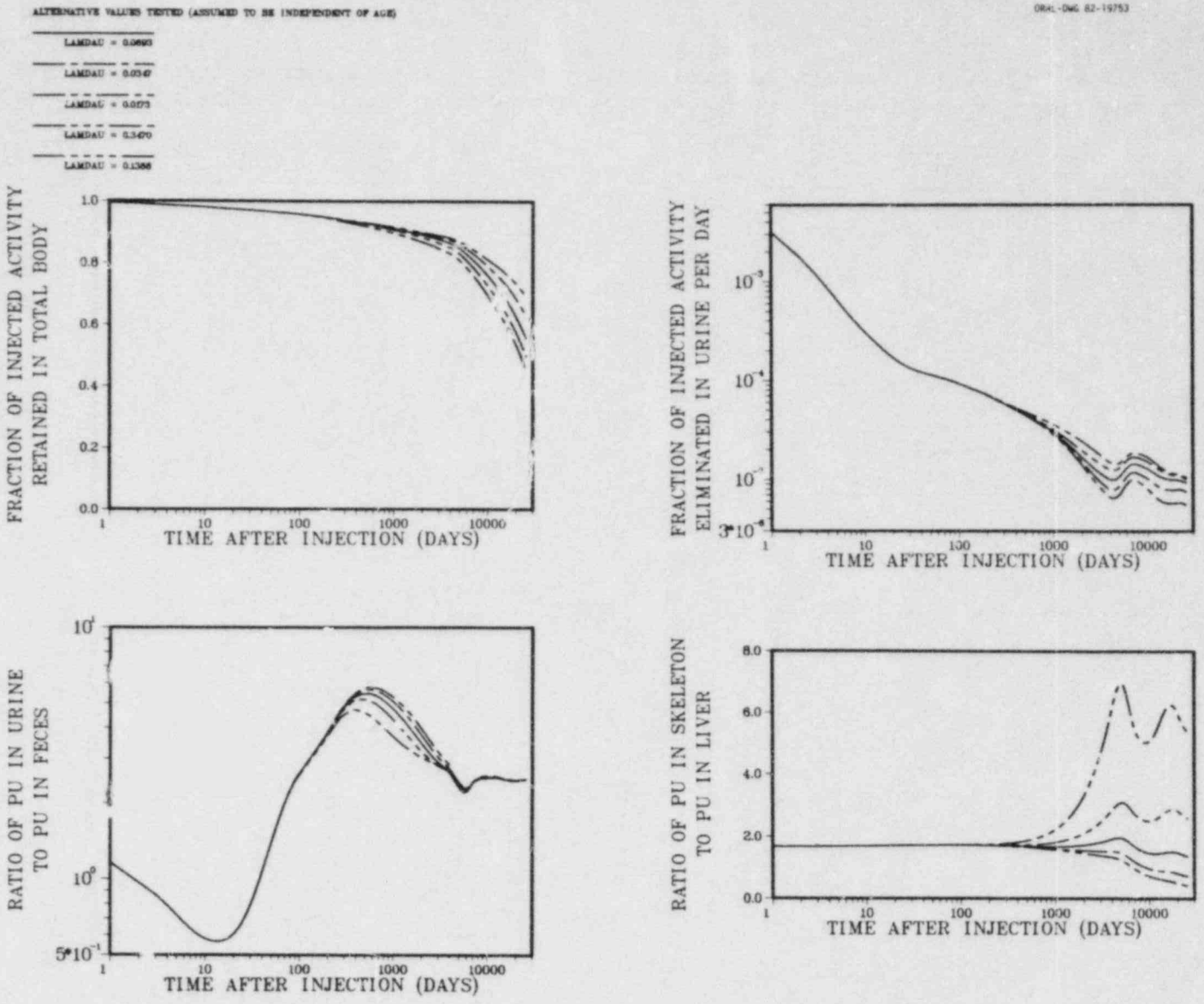


Figure 12. Sensitivity of model predictions to changes in LAMDAU, the rate of removal (yr^{-1}) of activity from RE cells of the liver.

An "A" at the beginning of a name indicates that the parameter is assumed to be age dependent. Names involving "LAM" (for lambda) indicate removal rates, and the last letter in such names indicate a pathway indicated in Fig. 2 or 3. Names involving "FRAC" are pathway fractions.

ABFRAC

ABFRAC (Fig. 4) is the fraction of (non-excreted) activity in blood deposited in the skeleton. It is not surprising that an increase or decrease in ABFRAC results in a corresponding increase or decrease in the activity in the skeleton throughout life following exposure. Activity in the liver would vary in the opposite direction, since it is assumed that the sum of the skeletal and hepatic depositions is constant at all times. Variation in ABFRAC has little effect overall on activity in urine or total body under our assumptions, because of the large amount of recycling between skeleton and liver and the fairly similar biological half-times for a large portion of activity in the two organs.

TFRAC

TFRAC (Fig. 5) is the fraction of activity deposited in the skeleton that goes to trabecular bone. Higher values of TFRAC result in more rapid loss of activity from skeleton and total body but generally higher activity in liver. These effects stem from the much higher turnover rate for trabecular bone than for cortical bone. The larger the fraction that goes to cortical bone (1.0 - TFRAC), the longer activity will be retained in the skeleton and kept out of the recycling and excretion pathways.

IFRAC, JFRAC

IFRAC is the fraction of resorbed activity leaving cortical marrow and spaces and being returned to blood, with 1.0 - IFRAC being redeposited locally on cortical surfaces. This is the pathway fraction corresponding to pathway I in Fig. 2. JFRAC is the analogous value for activity removed from trabecular marrow and spaces. Only qualitative information is available concerning IFRAC and JFRAC, and it is suggested

that both IFRAC and JFRAC are closer to 1.0 than to 0.0. As "base case" values, we have chosen IFRAC = JFRAC = 1.0. Because of recycling from blood to bone, any error in estimating local redeposition as zero is overridden to some extent. Decreasing both IFRAC and JFRAC leads to higher activity in the skeleton and total body and lower activity is liver and urine (Fig. 6).

ACHI

ACHI (Fig. 7) is the fraction of remodelling attributed to "drift." Thus, if ACHI = 0.2, then 80% of bone remodelling presumably would involve bone addition at a recently resorbed location, while 20% would involve addition on one side of a bone element (such as a trabecula) and resorption on the opposite side. Perhaps surprisingly, the general location of activity as a function of time after exposure is affected only slightly by the assumption concerning the particular form of bone remodelling.

ALAMA, ALAMC

ALAMA is the formation rate (yr^{-1}) of cortical bone and ALAMC is the formation rate (yr^{-1}) for trabecular bone. Activity in skeleton and liver are fairly sensitive to these parameters (Fig. 8), which are known only within a factor of perhaps two for most ages. It would not be surprising, for example, if the model predictions for activity in skeleton are too high or too low by a factor of 1.5 at times remote from exposure because estimated bone turnover rates are too low or too high by a corresponding factor.

ACLOSS, ATLOSS

ACLOSS is the rate of net loss (yr^{-1}) of cortical bone; it is assumed to be the difference between cortical formation and resorption rates. ATLOSS is the analogous value for trabecular bone. Higher values of ACLOSS and ATLOSS lead to lower activity in skeleton and total body and higher activity in liver and urine after age 40 years (Fig. 9).

ALAMY

ALAMY (Fig. 10) is the removal rate (yr^{-1}) of activity from both yellow and red marrow. Within a reasonable range of values, activities in skeleton, liver, total body, and urine are all fairly insensitive to ALAMY since removal rate from marrow is fairly rapid compared with removal rates from the major compartments.

ALAMN

ALAMN (Fig. 11) is the rate of removal (yr^{-1}) of activity from soft tissue. Within a reasonable range of values of ALAMN, model output is not particularly sensitive to ALAMN since this value is short compared with removal rates of the preponderance of activity in skeleton and liver.

LAMDAU

LAMDAU (Fig. 12) is the rate of removal (yr^{-1}) of activity from the liver (RE system) to blood. The value of LAMDAU is perhaps the most significant uncertainty among all model parameters. Activities in liver, skeleton, total body, and urine are all strongly influenced by LAMDAU.

VII. COMPARISON OF MODEL PREDICTIONS WITH HUMAN DATA

There are three main sources of human data on the distribution, retention, and excretion of plutonium: (1) excretion and autopsy data for humans injected with Pu for experimental purposes; (2) excretion and autopsy data for persons occupationally exposed to Pu; (3) and autopsy data for persons exposed only to extremely low levels of plutonium fallout from nuclear weapons tests. Much of this collection of data, particularly that from the experimental injection cases, was used in choosing values of model parameters. Thus, in evaluating the model on the basis of comparing observed data with model predictions, the dependence (if any) of predictions on corresponding observations must be kept in mind.

THE RATIO OF Pu IN SKELETON TO Pu IN LIVER

A crude estimate of the ratio of activity in the skeleton to activity in the liver several years after exposure to Pu can be made from autopsy data for persons occupationally exposed or exposed only to low levels of radioactive fallout. Of course, these data have the problem that the exposures were generally not acute and the time-course of exposure is not known with much precision. (The preponderance of the exposure to fallout occurred in the mid-1960's, and some estimate of the time and amount of occupational exposure is sometimes available.) A related problem is the inhomogeneity of Pu distribution in the skeleton. Autopsy samples from the skeleton are generally small and are usually taken from the vertebrae, ribs, or sternum. Depending on the time since exposure, the concentration of Pu in these bones may be much higher than the skeletal average, or they may be fairly close to the skeletal average. In fact, data for beagles indicate that the distribution of skeletal Pu tends toward uniformity within a few years of exposure;[49,90,93,94] a similar occurrence in humans might be expected to require many years, however, because of slower skeletal remodeling in humans. Some estimates of skeletal burden of Pu have been adjusted for skeletal inhomogeneity using data from humans, monkeys, and dogs,[17,19,20] while others have been based on the assumption of a uniform distribution in the skeleton. Thus it would not be surprising if any estimate of the ratio

of skeletal burden to liver burden were in error by a factor of as much as two. (The estimates for the human injection cases should be reasonably accurate, considering the extensive theoretical and experimental analyses that have been done for those cases.[5,17,20,55]) A third problem is that Pu concentrations in the autopsy samples, particularly those for exposures from fallout, are extremely small and may approach limits of detectability in many cases. Because of these various problems, it is clear that one should not attempt any detailed comparison of model predictions with these autopsy data, although some broad comparisons may be instructive.

Nenot and Scather[1] compiled a table of Pu concentrations in autopsy tissues of occupationally exposed workers. It can be estimated from their raw data that, as an average, the skeletons of these autopsy cases contained about 1.6 times as much Pu as the livers, assuming uniform distribution of Pu in the skeleton. Since the time from possible first exposure to death varied from 1 to 30 years, it is probable that the assumption of uniform distribution in the skeleton leads to an overestimate of the skeletal burden in many of these cases (those whose primary exposures occurred only a few years before death).

An extensive study of the distribution of fallout plutonium in persons in the United States was performed by McInroy et al.[95,96] It is apparent from these studies that the ratio of Pu in skeleton to Pu in liver depends on the stage of life at which exposure occurred, being near 1.0 for persons whose median age at death was about 60 years but lying between 2.0 and 4.0 (depending on assumptions concerning uniformity of distribution in the skeleton) for persons whose mean age at death was near 28 years. Similar results for median age 28 years were found by Fisenne et al.[97]

The autopsy data suggest the following: for persons exposed to Pu during childhood or early adulthood, the quotient R = Pu in skeleton/Pu in liver may remain much greater than 1.0 for several years; for persons exposed after early adulthood, R may not vary too far from 1.0 after most of the activity has first reached blood. As indicated in Fig. 13, these rather weak conditions are met by the model predictions.

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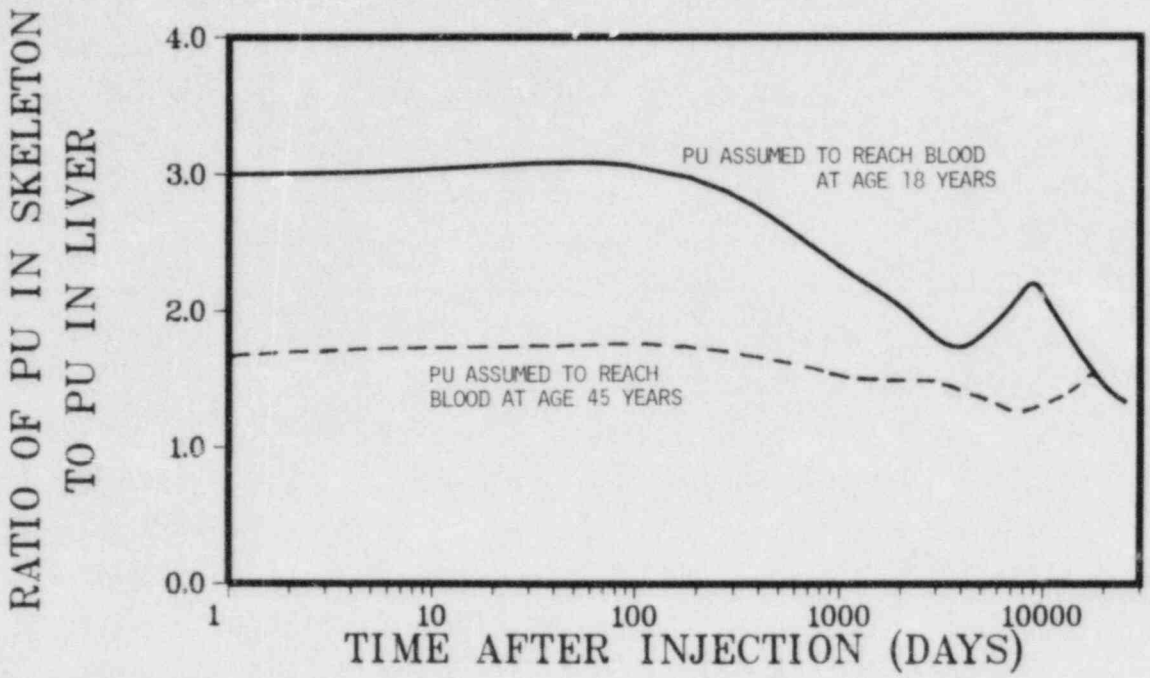

Figure 13. Model predictions of the ratio of Pu in skeleton to Pu in liver as a function of time after injection, for two different ages at injection.

Pu IN URINE AND FECES

Parameter values for clearance of Pu in urine and feces were based on data for Manhattan Project workers taken approximately 30 years after exposure, together with data for injected humans taken the first several weeks after injection. Comparison of model predictions for the first 138 days after injection with data from the injected patients are shown in Figs. 14 and 15. Since data points in these figures played some role in the choice of model parameters, the curves (predictions) are not completely independent of the data. On the other hand, the curves are produced by a mechanistic model and involve considerably more information than is furnished by the data, so that the curves should not be considered empirical fits to the data.

Urinary and fecal clearance data have been obtained from one of the injected patients at approximately 1.5, 4.5, and 27 years after injection and for a second patient at approximately 4.5 and 27 years after injection.[9,10] Measured values are compared with model predictions in Table 16. It appears from these limited comparisons that the model is a reasonably good predictor of Pu excretion through 27 years after exposure.

Voeltz *et al.*[12] estimated body burdens, amounts in blood, and urinary and fecal clearance of Pu in Manhattan Project workers at approximately 32 years after exposure. Although estimates of total body activity were based partially on Langham's equations, "calculations were revised to give a more favorable comparison of body burdens based on urinalysis data and on available autopsy tissue values."[12] Voelz and co-workers estimated that daily urine excretion of Pu ranged from 0.0002% to 0.0015% and averaged 0.0007% of the current body burdens. Assuming approximately 75% of the original body burden of Pu is still retained three decades after exposure (cf. the "base case" for total body retention in Fig. 4), these estimates would correspond to a range of 0.00015% to 0.0011% of the original body burdens currently being cleared each day in urine. Our model would predict a daily urinary clearance that is near the upper limit of the estimates by Voelz and co-workers.

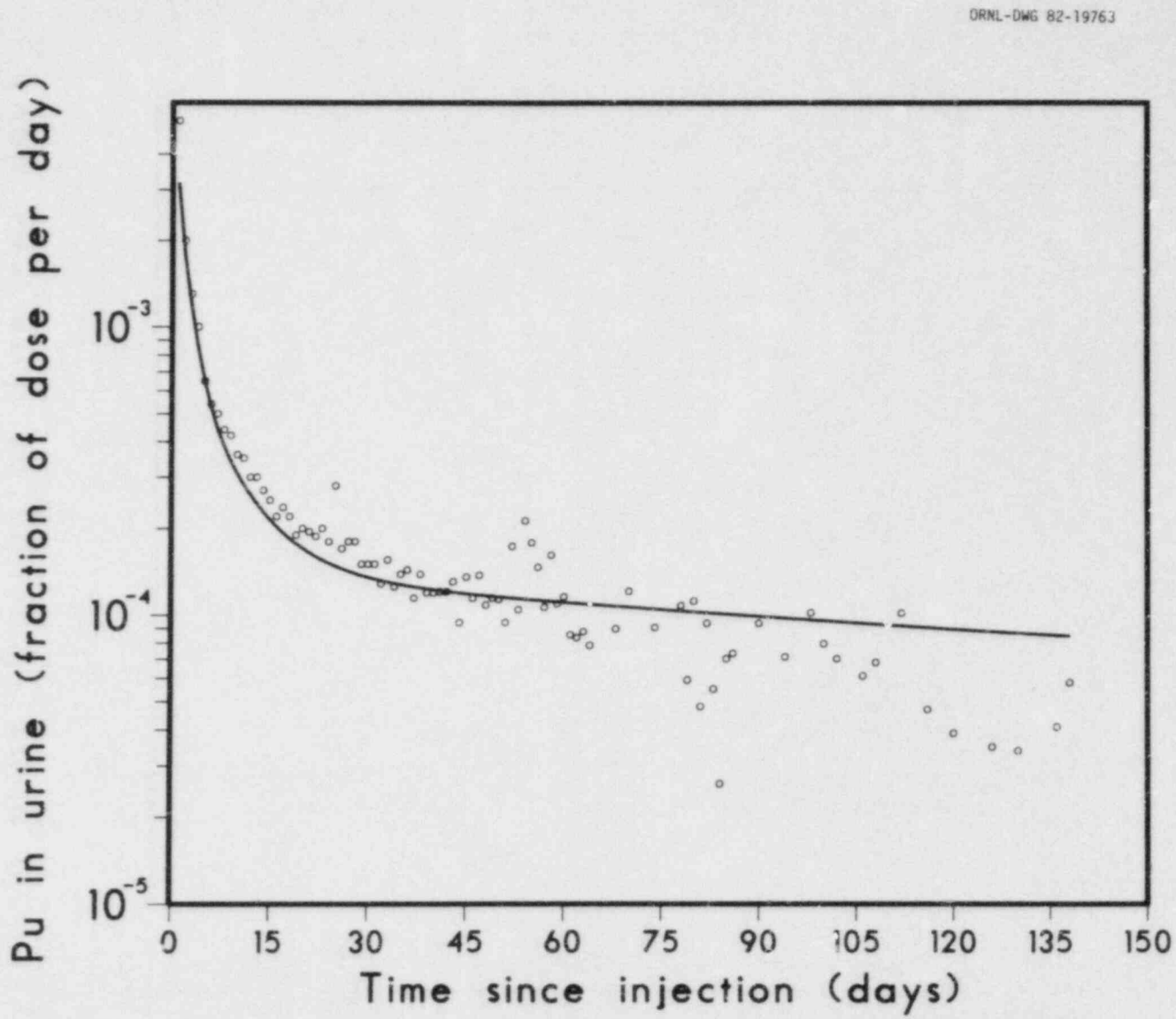

Figure 14. Comparison of model predictions of Pu in urine with data from human subjects (circles) during first 138 days after injection.

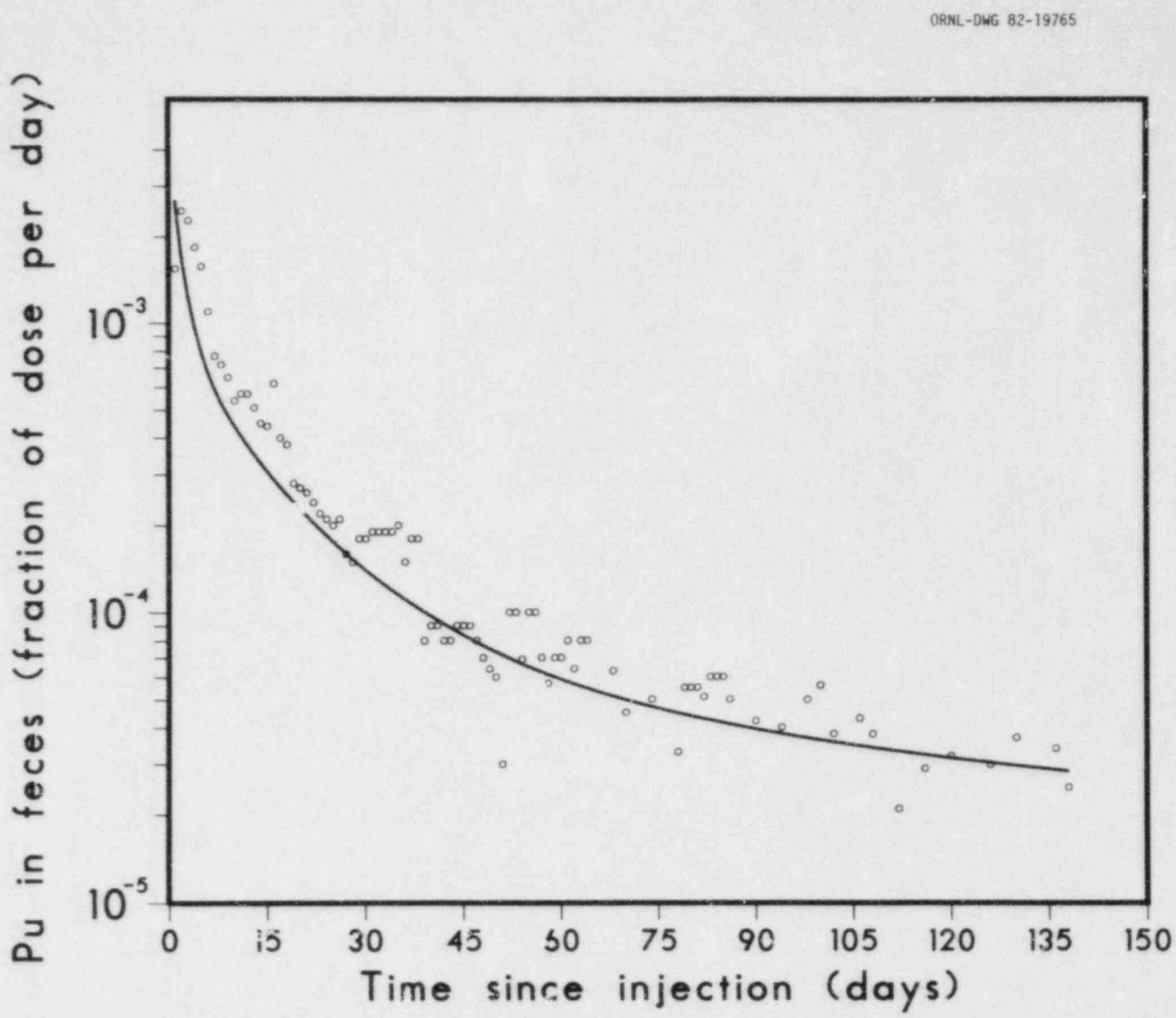

Figure 15. Comparison of model predictions of Pu in feces with data from human subjects (circles) during first 138 days after injection.

Table 16. Comparison of model predictions of urinary and fecal excretion of Pu with observations on injected patients at 1.4 to 27 years after injection

Age of subject at time of measurement (yr)	Days after injection	Percent of injected Pu in urine per day		Percent of injected Pu in feces per day	
		Measured	Predicted by model	Measured	Predicted by model
46	532	0.0020	0.0029	----	----
49	1,610	0.0011	0.0017	----	----
53	1,645	0.0008	0.0017	----	----
76	9,934	0.0025	0.0012	0.0011	0.0005
72	10,008	0.0014	0.0012	0.0005	0.0005

It is interesting that our model predicts a temporary rise in excretion of Pu beginning a few years after introduction to blood. In fact, such a rise has been observed in Manhattan Project workers. A comparison of the trend in the observed data for one subject[12] with that predicted by the model is made in Fig. 16. Since the total body burdens of the Manhattan Project workers are not known very accurately, we have normalized the curve to agree with the data at age 40, which is near the minimum value of both observations and predictions.

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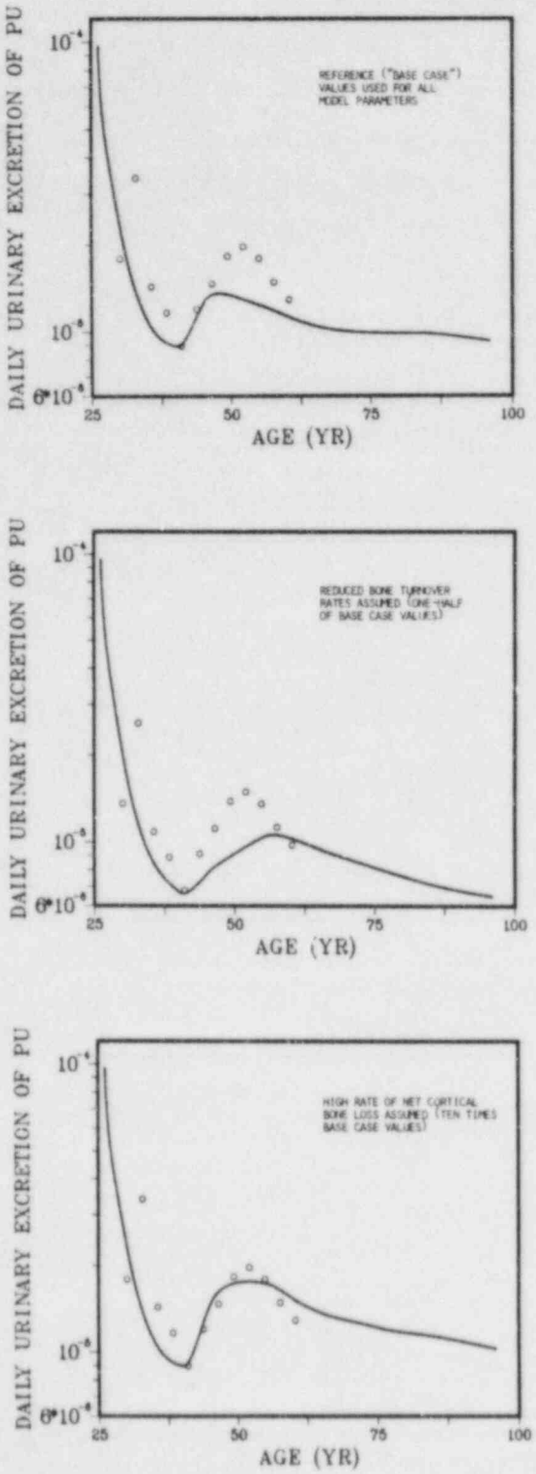

Figure 16. Trend with time (or age) in urinary excretion of Pu. Circles represent data for a Manhattan Project worker. Curves are model predictions resulting from indicated assumptions. Units on y-axis are arbitrary, and curve has been normalized to data at age 40 yr.

VIII. SUMMARY AND CONCLUSIONS

For several years occupational exposures to Pu have been estimated using Langham's urinary excretion curve

$$Y_u = 0.20t^{-0.74} \quad (t > 1) \quad ,$$

where Y_u is the percentage of the injected quantity of Pu in urine during day t after introduction to blood. This power function is an empirical fit to data obtained principally from injected humans up to 138 days after exposure and to a lesser extent from occupationally exposed persons up to 1750 days after exposure. Thus, this curve should yield fairly accurate estimates of systemic burdens of Pu at times up to a few months and reasonable estimates at times up to a few years after Pu has first reached the bloodstream.

In recent years it has become evident from a variety of excretion and autopsy data that Langham's equation will usually yield large overestimates of the systemic burden of Pu at times much greater than five years after exposure. The failure of this equation at times remote from injection results from radical quantitative changes with time in the processes governing the retention and excretion of Pu.

In the first few months after injection most of the injected Pu resides on the bone surfaces and in the parenchymal cells of the liver (hepatocytes). Activity on bone surfaces is gradually removed by bone remodelling which serves to bury part of the activity in bone volume and remove part of the activity to blood. Activity in the hepatocytes gradually transfers to the reticuloendothelial system of the liver although a small fraction of this activity may be lost in feces via bile. Activity initially taken up by other soft tissues is returned to blood with an average half-time of perhaps a few months or years, and this activity is available for early urinary or fecal excretion, or for transfer to skeleton, liver, or other soft tissue.

Langham's equation was derived from data obtained principally during the time that these initial processes were dominating, so that this equation reflects a gradual receding of much of the activity from potential excretion pathways into the bone volume and liver RE system. After a few years, however, much of this "buried" Pu may regain access to

blood, thereby increasing the urinary and fecal excretion rates. In particular, the continual remodeling of bone gradually results in the uncovering of Pu buried in the thin trabeculae on which much of the skeletal Pu first deposited. Also, depending on the age of the exposed person, there may be a significant amount of osteoporosis (net bone loss) that leads to removal of Pu from both cortical and trabecular bone. Less is known about the removal of Pu from the RE cells in the liver, but evidence suggests that, eventually, much of the activity will be removed from these cells to blood, perhaps in response to iron needs.

In this report we have attempted to develop a mechanistic model for the retention and excretion of systemic Pu that quantifies these controlling processes throughout adult life after introduction of Pu into blood. It is evident from our discussion and sensitivity analysis that there are substantial uncertainties related to some model parameters. However, with our "best estimates" of model parameters, model predictions compare well with observations at times from one day to 32 years after exposure.

Our model predicts a total body retention of Pu that agrees well with that predicted by Langham's equations up to about one year after exposure. Beginning at about one year after injection, our model predicts a higher excretion rate than do Langham's equations. A comparison of total body retention of Pu over several years as predicted by our model and Langham's equations is made in Fig. 17.

As we have indicated throughout this report, the fraction R(t) of systemic Pu retained t days after introduction into the bloodstream depends to some extent on the age of the individual at exposure. Differences in R(t) with age at exposure, as estimated using our model, are indicated in Fig. 18. The major differences with age that are accounted for in our model are the decreased bone resorption rate in the fourth decade of life and the increased net bone loss after the fifth decade, both of which result in generally larger values of R(t) for younger (adult) ages at exposure. However, since much of the decrease in R(t) occurs during the first year after exposure, due largely to processes which are assumed to be independent of age, the effect of age at exposure on R(t) is not great.

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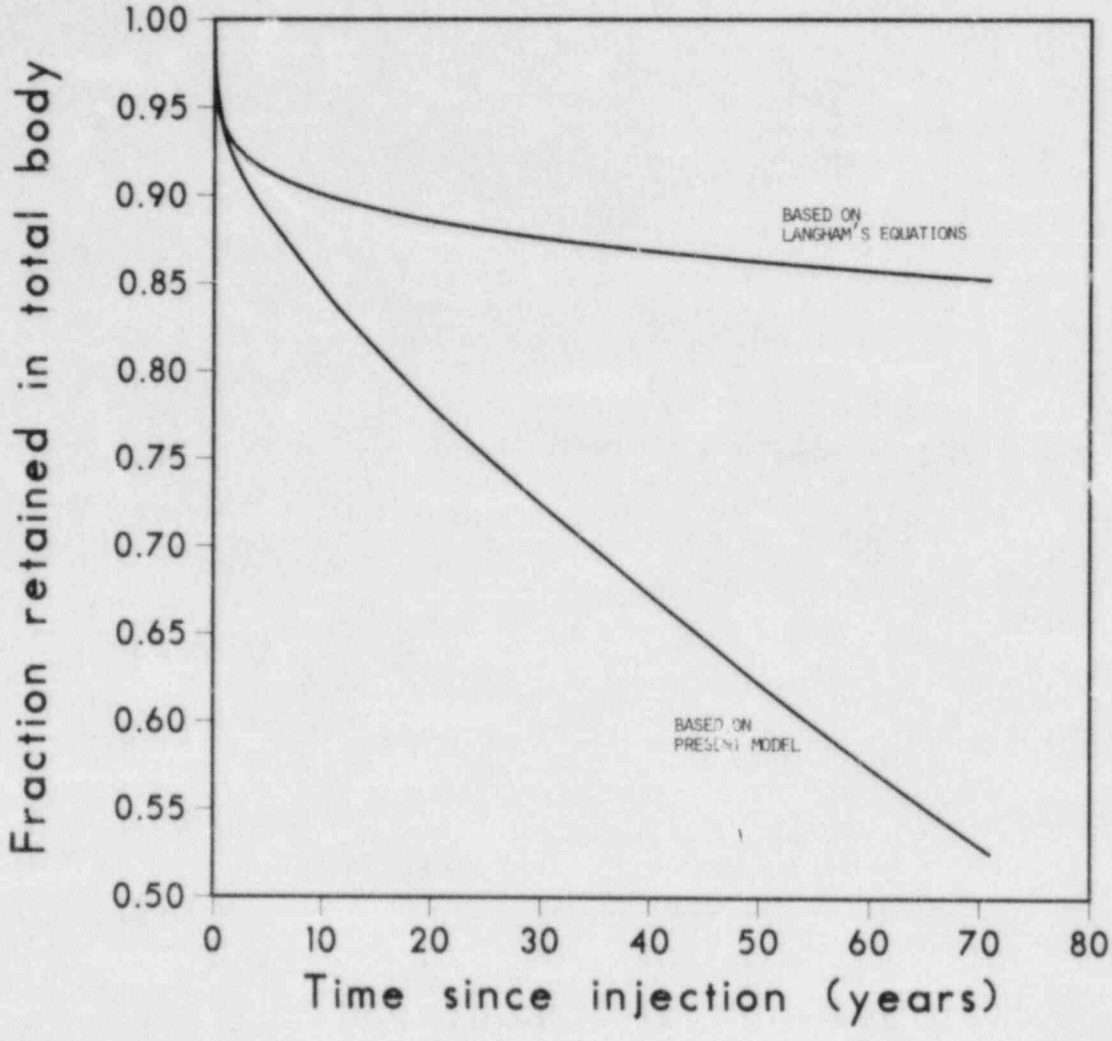

Figure 17. Total body retention of systemic Pu as predicted by present model and by Langham's equations.

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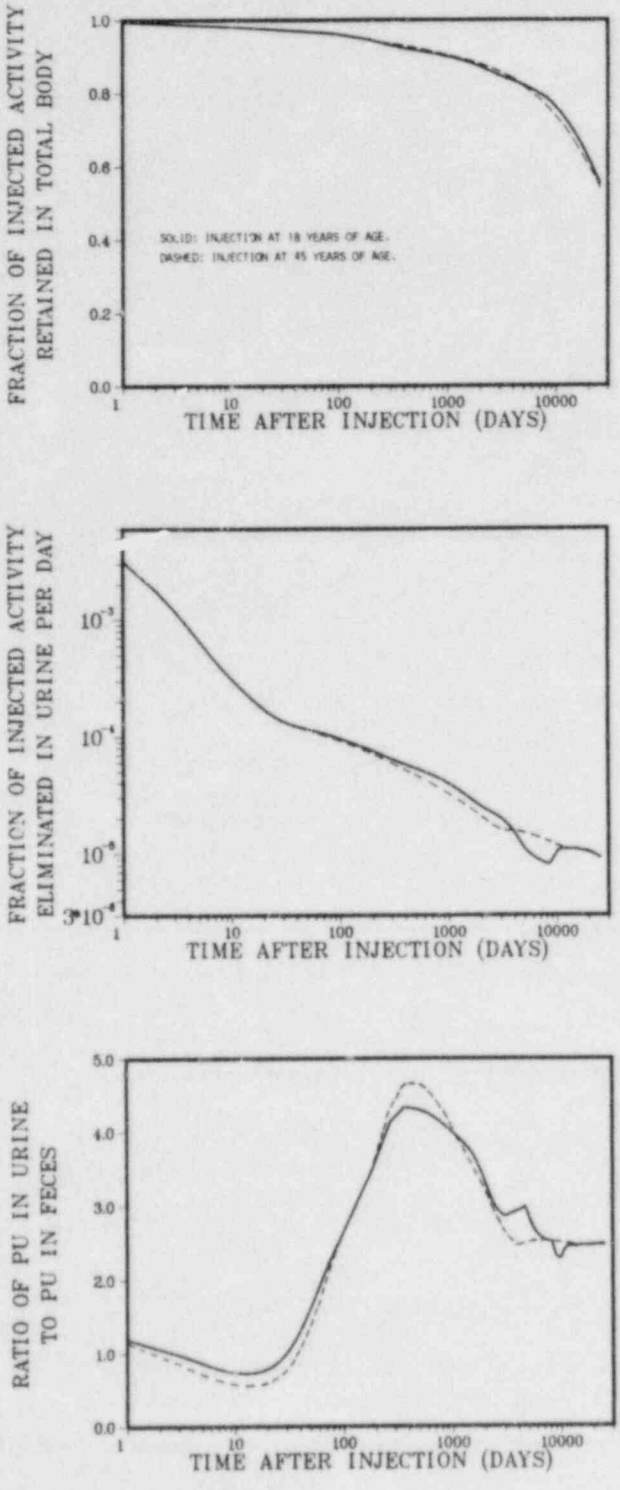

Figure 18. Dependence of Pu retention and excretion on age at injection, as estimated using the model.

It will be convenient for many purposes to provide a single explicit retention function R(t) for systemic Pu that is fairly representative of all adult ages at exposure. The function

$$R(t) = 0.012 \exp(-0.693t) + 0.02 \exp(-0.03t) + 0.042 \exp(-0.0028t) + 0.926 \exp(-0.0000216t)$$

is a good approximation to model predictions of the retention of systemic Pu any time t days after an injection which occurs during the middle years of life. Thus this expression might be assumed to hold for an average adult. We emphasize strongly that this expression is simply a fit to model predictions and that the individual terms have no apparent physical meaning whatever. The last term, which accounts for 92.6% of the initial activity, would indicate a total body retention halftime of about 90 years for the preponderance of injected Pu.

In this report we have dealt only with the retention and excretion of Pu after its entry into the bloodstream. Typical occupational or public exposures to Pu will be through inhalation or ingestion, or through wounds. Thus, after exposure there will be some delay before Pu reaches the bloodstream. In the case of ingestion this delay is short and may be ignored. However, the fraction of ingested Pu that is absorbed into the bloodstream appears to depend strongly on chemical form and other factors, and is not known very accurately even under the most favorable conditions. In any case of exposure through wounds, the delay in reaching the bloodstream and the amount that reaches the bloodstream depend totally on the conditions of the given case and cannot be discussed meaningfully in a general setting. Inhalation is by far the most common and important exposure pathway for Pu. Retention of three different solubility classes of Pu in the respiratory tract and their translocation to blood can be estimated using the Task Group Lung Model of the ICRP, which was described in Ref. 98 and modified in ICRP Publication 19.[22] Discussions of the transport of Pu from the respiratory or gastrointestinal tract or from wounds to the bloodstream, along with numerous references, can be found in Refs. 1, 21, and 22.

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NRC FORM 335 (11-81)

U.S. NUCLEAR REGULATORY COMMISSION

BIBLIOGRAPHIC DATA SHEET

1. REPORT NUMBER (Assigned by DDC)
NUREG/CR-3346
ORNL/TM-8795

4. TITLE AND SUBTITLE (Add Volume No., if appropriate)
BIOASSAY DATA AND A RETENTION-EXCRETION MODEL FOR SYSTEMIC PLUTONIUM

2. (Leave blank)

3. RECIPIENT'S ACCESSION NO.

7. AUTHOR(S)
R. W. Leggett

5. DATE REPORT COMPLETED
MONTH: May YEAR: 1983

9. PERFORMING ORGANIZATION NAME AND MAILING ADDRESS (Include Zip Code)
Oak Ridge National Laboratory
Health and Safety Research Division
P. O. Box X
Oak Ridge, TN 37831

DATE REPORT ISSUED
MONTH: April YEAR: 1984

6. (Leave blank)

8. (Leave blank)

12. SPONSORING ORGANIZATION NAME AND MAILING ADDRESS (Include Zip Code)
Division of Facility Operations
Office of Nuclear Regulatory Research
U.S. Nuclear Regulatory Commission
Washington, DC 20555

10. PROJECT/TASK/WORK UNIT NO.

11. FIN NO.
B0480-2

13. TYPE OF REPORT
Topical

PERIOD COVERED (Inclusive dates)

15. SUPPLEMENTARY NOTES

14. (Leave blank)

16. ABSTRACT (200 words or less)

The estimation of systemic burdens from urinalyses has been the most common and useful method of quantifying occupational exposures to plutonium. Problems arise in using this technique, however, because of inadequate modeling of human retention, translocation, and excretion of this element. Present methods for estimating the systemic burden from urinalyses were derived to a large extent from patterns observed in the first few months after exposure, but there is now evidence that these same patterns do not persist over long periods. In fact, recent comparisons of autopsy data with urinalyses suggest that extrapolation to extended periods based on these observed patterns usually leads to a large overestimate of the systemic burden at times more than a few years after exposure. In this report we collect and discuss human and animal data for Pu together with general physiological properties needed for the interpretation of bioassay results. This information is used to develop a mechanistic model of the movement, retention, and excretion of systemic Pu. This model appears to be a reasonably accurate predictor of excretion for times ranging from one day to several decades after contamination of blood.

17. KEY WORDS AND DOCUMENT ANALYSIS

17a. DESCRIPTORS

bioassay
mechanistic model
plutonium
retention
translocation
excretion
urinary excretion
fecal excretion
skeleton
liver
soft tissue

17b. IDENTIFIERS/OPEN-ENDED TERMS

18. AVAILABILITY STATEMENT
Unlimited

19. SECURITY CLASS (This report)
Unclassified

21. NO. OF PAGES
96

20. SECURITY CLASS (This page)
Unclassified

22. PRICE
$

NRC FORM 335 (11-81)