Title
238Pu(IV) IN MONKEYS: OVERVIEW OF METABOLISM

Authors
Durbin, P.W.
Jeung, N.
Schmidt, C.T.

Publication Date
1985-07-01

Lawrence Berkeley Laboratory
UNIVERSITY OF CALIFORNIA

^{238}Pu(IV) IN MONKEYS: OVERVIEW OF METABOLISM

P.W. Durbin, N. Jeung, and C.T. Schmidt

July 1985

Donner Laboratory
Biology & Medicine Division

Prepared for the U.S. Department of Energy under Contract DE-AC03-76SF00098

DISCLAIMER

NUREG/CR-4355
LBL-20022
Volume 1

^{238}Pu(IV) in Monkeys: Overview of Metabolism

Patricia W. Durbin, Nylan Jeung, and Charles T. Schmidt

Lawrence Berkeley Laboratory
University of California
Berkeley, California 94720

July 1985

Prepared for

Division of Radiation Programs and Earth Sciences
Office of Nuclear Regulatory Research
U.S. Nuclear Regulatory Commission
Washington, D.C. 20555

This work was supported by the U.S. Nuclear Regulatory Commission, through NRC FIN No. B 3041-4, under U.S. Department of Energy Contract No. DE-AC03-76SF00098.

^{238}Pu(IV) in Monkeys: Overview of Metabolism

Patricia W. Durbin,[a] Nylan Jeung,[a] and Charles T. Schmidt[b]

Lawrence Berkeley Laboratory
University of California
Berkeley, California 94720

ABSTRACT

Complete balance studies were performed using 21 adult and four adolescent Macaque monkeys (three species, both sexes) to define distribution and retention of ^{238}Pu(IV) citrate from 2 hr to 1100 d after parenteral injection. Experimental methods are described in detail. Initial distribution (6 adults, 7.5 ± 0.5 d) and retention (6 adults, 711 ± 310 d) of Pu were, respectively, as follows: skeleton and teeth 28 and 14 % ID, liver 60 and 11 % ID, other soft tissues 6 and 0.9 % ID and excretion 5 and 74 % ID. Initial Pu content of ovary and testis was 0.005 and 0.06 % ID, respectively, and both declined with $T_{\frac{1}{2}}$ ~ 1 yr. Liver Pu was cleared mainly by excretion to feces, but also by recirculation, with an average $T_{\frac{1}{2}}$ = 180 d. By 1100 d, most soft tissues lost 50 to 90% of their initial Pu content. The initial Pu concentration on trabecular bone surfaces in red marrow was calculated to be about 4.5 times greater than on compact bone surfaces. About one-half of initial skeletal Pu was eliminated in 1100 days, mainly from cancellous structures in red marrow. Implications for some changes in International Commission on Radiological Protection metabolic and dosimetric models for Pu are noted.

[a] Division of Biology and Medicine
[b] Medical Services Department

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

The invaluable assistance of Mrs. Karen Springsteen, who typed the manuscript, and Everett Harvey of the LBL Real Time Systems Group, who developed the computerized data storage system, are gratefully acknowledged. This work was supported by the U.S. Nuclear Regulatory Commission, through NRC FIN No. B 3041-4, under U.S. Department of Energy Contract No. DE-AC03-76SF00098.

EXECUTIVE SUMMARY

This study of the kinetics of ^{238}Pu in monkeys is part of a continuing effort to strengthen the base of radiation protection standards for several of the most hazardous radionuclides created in nuclear fuel cycles. Prevention of the absorption of harmful amounts of radiation from radionuclides deposited in the human body is achieved by limiting their intake. Intake limits for each radionuclide must be calculated using a kinetic (metabolic) model for the element. These biokinetic models are also applied to other important problems in radiation protection -- measurement of compliance with standards, assessment or prediction of the consequences of routine and accidental intakes, interpretation of bioassay measurements and monitoring the course of removal therapy.

Plutonium production began more than 40 y ago, but the kinetic model recommended for its isotopes is still primitive, primarily because of the inadequacy of the human data base. Consequently, the International Commission on Radiological Protection (ICRP) in 1979 adopted simple metabolic and dosimetric models for Pu that were considered to be, but may not be conservative. The resulting new occupational limits may involve a substantial reduction of allowable Pu concentration in workroom air, and, by implication, equally severe new limits on Pu release to the environment, so it is important that all relevent data be made available promptly.

Our approach to improvement of the human kinetic models for Pu in man is to develop complete models for monkeys, and through testing and use of human data to revise the parameters, make them suitable for application to the human case. This study was conducted using three species of old World monkeys (Macaca fascicularis, Macaca mulatta, Macaca arctoides). Macaques are, in all respects, closer to human beings than any other animal that can be readily studied in the laboratory. ^{238}Pu was selected because the abundant ^{234}U L x rays accompanying its decay permit most biological samples to be assayed simply and accurately. At the average injected dosage of 1.1×10^4 Bq/kg, the x rays in excreta and most bone and tissue specimens could be detected accurately, but the radiation damage accumulated in 3 y was not expected to alter the metabolism of bone and liver significantly.

Monkeys of both sexes [20 adult (14F, 6M) and 4 late adolescent (3F, 1M] were given one intravenous (i.v.) or intramuscular (i.m.) injection of 1.1×10^4 Bq/kg of monomeric $^{238}Pu(IV)$ in 0.08 M citrate buffer, pH 3.5, that had been passed through a 0.22 μm Millipore filter. Blood was drawn periodically, beginning a few minutes after injection. Separated excreta were collected continuously. Animals were killed 2 hr to 1100 d after injection, autopsied and completely analyzed. All soft tissues, up to 35 individually assayed organs and tissue specimens, and all bones were analyzed for their ^{238}Pu content. The x rays were detected in large samples with two thin, coaxially-mounted NaI crystals. Small samples were spread and dried on glass

plates, and the alpha emissions were detected with a windowless proportional counter. Self-absorption corrections, based on ash weight, were applied to all measurements. All biological and radiochemical methods are described in detail.

Material recovery was 102 % ± 8 of the injected Pu. The non-colloidal state of the injected ^{238}Pu was confirmed by slow plasma clearance, consistently low ^{238}Pu concentrations in spleen and lymph nodes, rapid absorption from an i.m. site, and absence of alpha track stars in autoradiographs of livers from 1-, 7- or 8-day animals. Absorption of ^{238}Pu citrate from an i.m. injection was nearly complete in 10 d. Metabolic data obtained for this ^{238}Pu preparation administered by the two modes of parenteral injection were indistinguishable.

This overview is the first presentation of a body of Pu metabolic data from an animal whose physiologic attributes include both bone remodelling in adult life, as in man, and a significant excretory outlet. Reports to follow in this series will provide detailed descriptions of the distribution and retention, up to 3 y in adult monkeys, of ^{238}Pu in soft tissues and skeletal parts, clearance from plasma, excretion patterns and a complete feedback model of Pu kinetics.

The initial distribution of ^{238}Pu was defined by six monkeys killed at about one week (7.5 ± 0.5 d) after injection, and excretion and retention of ^{238}Pu were defined by six monkeys killed at 370 to 1100 d (711 ± 310 d). The ^{238}Pu was distributed at those early and late times, respectively, as follows: skeleton and teeth, 28 and 14 % ID; liver, 60 and 11 % ID; other soft tissues, 6 and 0.9 % ID; excretion, 5 and 74 % ID.

The average retention of ^{238}Pu in the whole body, liver and skeleton can be described from 7 to 1100 d by the following equations, time is in days:

$$\text{Body, \% ID}(t) = 19e^{-0.693t/42} + 50e^{-0.693t/980}$$

$$\text{Liver, \% ID}(t) = 56.6e^{-0.693t/180}$$

$$\text{Skeleton, \% ID}(t) = 12.4e^{-0.693t/204} + 14.8e^{-0.693t/4076}.$$

The distribution of Pu in the soft tissues of adult monkeys was not substantially different from other animals studied. Initially, Pu was prominent in hepatic cells, non-skeletal mineralized structures, arteries and arterioles, renal tubular structures, and occasionally, in involuting ovarian follicles and corpora lutea: Pu was consistently present at low concentrations in the reticulum of all tissues. Within 3 y, Pu in the soft tissues had been reduced to 10% to 50% of initial values. Clearance of liver Pu, as inferred from plasma and excretion data, occurred variably by both biliary excretion and recirculation. In most cases, clearance of liver Pu was nearly complete at 1 y, however, in two cases clearance was only about 50% complete at

1.5 y; autoradiographs showed that much of the retained Pu was in large aggregates associated with hemosiderin in reticulo-endothelial cells.

Initial Pu deposition in the adult monkey skeleton is skewed to cancellous bone in red marrow sites. Initial ^{238}Pu concentrations in cancellous bone (lumbar vertebral bodies and sternum) and compact bone (long bone shafts) imply an average deposition of ^{238}Pu at least four and one-half times more intense on cancellous than on compact surfaces.

In 3 y about 50% of the Pu initially deposited in the bones was lost; most of the Pu lost from either bone or liver was recovered in excreta (mainly feces); but some Pu, recirculated from either liver or skeleton, was redeposited as is suggested by small increases in Pu content of teeth and long bone shafts. Different rates of loss of ^{238}Pu from cancellous and compact bone structures were demonstrated by the significant decreases in the ^{238}Pu concentrations in lumbar vertebral bodies and sternum accompanied by slight increases in the ^{238}Pu concentrations in long bone shafts and paw bones between 7 d and 3 y.

With respect to current ICRP recommendations, these results indicate that: (i) The initial deposition fraction for Pu in testis is reasonable, but that for liver is low, and those for bone and ovary are high; (ii) The net rates of Pu loss from all tissues recommended by ICRP are probably conservative; (iii) The bone surface dosimetry scheme needs adjustment to account for the preferential deposition of Pu on cancellous surfaces in red marrow sites in the adult skeleton and the more rapid rate of Pu loss from cancellous than from compact bone; (iv) The dosimetrically important recirculation and redistribution of Pu between liver and various parts of skeleton needs to be explicitly taken into account.

INTRODUCTION

These studies of ^{238}Pu in monkeys are part of a continuing effort to improve the scientific base of radiation protection standards for several of the most hazardous radionuclides created in nuclear fuel cycles. The nuclides under study -- isotopes of plutonium, americium and strontium -- are produced in large amounts in all conventional fission and breeder cycles (1,2). Their isotopes are long-lived and dominate the long-term hazard of both spent fuel and reprocessing wastes (2,3).

When encountered in the workplace or the environment, these radioelements may enter the body by inhalation or ingestion, and their decay energy will be absorbed in tissues. Prevention of the absorption of harmful amounts of radiation is a fundamental principle of radiation protection, and control of radiation doses from radionuclides deposited within the body is achieved by limiting intake. Intake limits for each radionuclide are calculated using its physical properties and a metabolic model for the element. Thus, models of radioelement metabolism in man are essential components of the radiation protection process -- both for setting protection standards (intake limits) and for monitoring compliance with standards. The permissible body burdens of many radionuclides are too small to be detected accurately by external measurements, so proof of compliance with standards for them often rests on interpretation (through a metabolic model) of radionuclide excretion patterns (bioassay results). For both safety and scientific validity, the metabolic models should be based on human experience, but when human data are not available, the best animal data must be substituted.

The biokinetic models recommended for the actinide elements in man are primitive. The model recommended by the International Commission on Radiological Protection (ICRP) in 1959 was based on data from rodents and a few dogs, a small collection of short-term human excretion data (mainly urine) and a few autopsy tissue analyses obtained from five very ill Pu-injected people (4,5). The actinide model recently recommended by ICRP relies on those same data plus newer data from dogs injected with tissue-damaging dosages of ^{239}Pu and a physiologically inappropriate relationship of hepatic and skeletal Pu retention to body size (6,7). Neither model takes account of what is known about the intraskeletal distribution of individual actinides (8-15) or the physiology of the human and animal skeletons providing the data. The simplicity of the currently recommended models for actinides in man, which are based on retention in individual organs and do not explicitly include feedback to plasma, causes them to be inadequate for assessing accident consequences and incompetent for interpretation of bioassay results (excreta analysis).

There are more recent actinide data (mainly Pu) for man, but as yet they do not form a coherent pattern (13-25). Analysis of that body of data is confounded by individual variation and uncertainty about mode and time of exposure. The human data are not yet

sufficient by themselves to construct metabolic models for Pu and other actinides, but they are of great value in testing and revising theoretial and animal models.

Objective of Study

The immediate aim of this program to develop complete biokinetic models for $^{238}Pu(IV)$, $^{241}Am(III)$ and $^{90}Sr(II)$ in Macaca, a genus of Old World monkeys phylogenetically close to man.

The long-range goal is to update the biokinetic models used for those radionuclides in radiation protection practice -- for setting intake limits, measuring compliance with standards, assessing or predicting consequences of accidental intakes or exposures, monitoring the course of chelation therapy and interpretation of bioassay results. Our approach to improvement of the human biokinetic models is to extend and revise the models developed for monkeys in this program, and through testing and use of human data to revise parameters, make them suitable for radiation protection purposes.

Experimental Approach

Among non-human primates, Macaca are the most easily obtained and amenable to laboratory conditions. The similar morphology and growth patterns of the human and Macaque skeletons make these animals uniquely appropriate models for the human skeleton (26-29).

The experimental approach was the metabolic balance method; each animal was managed as an individual case; all excreta and tissues were analyzed to obtain a material balance. Serial sacrifices of animals, with detailed tissue and bone sampling and radiochemical analysis, define the distribution and retention of the radionuclides in the tissues, and radiochemical analysis of plasma and separated excreta aid in defining the turnover rates of tissue pools.

This report is an expanded summary of the large body of metabolic data that we have developed for ^{238}Pu in monkeys; condensations of some of this material have been presented (30,31). Descriptions of the animals, their history in the experiment and summaries of the distribution of Pu in their tissues are included as an Appendix. Reports to follow in this series will present, analyze and interpret the detailed data for individual monkeys, including: (i) intraskeletal distribution, i.e., Pu content of all sampled bones and bone parts, (ii) Pu content of all sampled soft tissues, (iii) Pu content of periodic plasma samples and calculated total plasma Pu, (iv) Pu content of urine and fecal specimens.

PROCEDURES

This is the first of a series of reports concerning the metabolism of some important bone-seeking radionuclides in non-human primates, so the preparation of the $^{238}Pu(IV)$ citrate solution, the

animals and their management, the sampling procedures and the radioanalytical procedures for ^{238}Pu are described in detail. Most of the biological techniques described herein have been used in this Laboratory for many years, and they apply also to previously published summary reports of the metabolism of ^{90}Sr, ^{238}Pu and ^{241}Am in monkeys (9,10,32-36).

Plutonium Isotope

The ^{238}Pu isotope [$T_{1/2}$ = 87.7 y, mean alpha energy = 5.49 MeV (37)] was chosen for these studies. Its high specific alpha activity (1.54×10^{-6} µg/Bq) permits the administration of small masses of plutonium. Dilute solutions of complexes are stable and reproducible, and colloid formation is suppressed. The mass of Pu required for accurate radiochemical analysis in an animal experiment is close to what might be encountered in human occupational or environmental exposures. The occupational maximum permissible body burden of ^{239}Pu is 1480 Bq in a 70 kg man (0.0092 µg/kg) (4); most of the experimental animals received 11,100 Bq/kg of ^{238}Pu (0.016 µg/kg). About 10% of the alpha decays of ^{238}Pu are accompanied by detectable 17 keV ^{234}U L x rays; for ^{238}Pu and ^{239}Pu there are 0.115 and 0.0465 detectable x rays/alpha (38). A sensitive, low background photon detector was available with which to determine the ^{238}Pu activity of the large tissue and excreta samples with a minimum of chemical processing.

A 300 mg source of nearly pure $^{238}PuO_2$ was obtained from storage at the Lawrence Berkeley Laboratory (LBL). That ^{238}Pu source had been separated on the Oak Ridge National Laboratory mass spectrograph (Calutron) on Dec. 20, 1965, and as of that date the composition by weight was as follows: ^{238}Pu, 99.48%; ^{239}Pu, 0.46%; ^{240}Pu, 0.036%; ^{241}Pu, 0.016%; ^{242}Pu, 0.002%. A 2.6×10^8 Bq portion of the $^{238}PuO_2$ was shipped to D.R. Atherton at the University of Utah Radiobiology Laboratory, Salt Lake City. It was dissolved in concentrated HNO_3 and HCl, reduced with SO_2 and taken to dryness; it was redissolved and oxidized to the (IV) state with a small amount of HNO_3 (conc) and diluted in 0.08 M citric acid-sodium citrate buffer. The final pH was 3.5, and the ^{238}Pu concentration was 84×10^6 Bq/l. Additional details of this method of preparation of Pu(IV) solutions suitable for animal injection have been published (39).

A fraction of the stock solution was transferred to four rubber-capped serum bottles, pasteurized and shipped by air to LBL. Upon receipt, the ^{238}Pu was frozen. It had been shown earlier that similar solutions of ^{239}Pu(IV) citrate stored for 3 mo at 6°C were stable to both disproportionation [98% of the ^{238}Pu remained in the (IV) state, and 2% was present as Pu(III) and/or Pu(VI)] and hydrolysis (absorption spectra and dialysis showed no evidence of Pu(IV) colloid formation) (39). Since its receipt in Aug. 1973, the ^{238}Pu(IV) citrate solution has been maintained in the frozen state, and during that time there has been no biological or radiochemical evidence of colloid formation; analyses of freshly removed batches agree within 5% of the first analysis; there have been no demonstrated

losses of activity on the filters used to resterilize portions thawed for animal injections; colloidal aggregates have not been observed in autoradiographs of soft tissues prepared from animals killed within a few days after injection of filtered solutions.

In preparation for animal injections, one bottle was thawed at room temperature. The required amount of solution was withdrawn with a syringe, and the stock bottle was refrozen. The withdrawn solution was forced through a 0.22 μm Millipore filter (Millipore Corp., Bedford, MA 01730) into a new, washed and sterilized serum bottle covered with a new sterilized rubber dam. Individual disposable syringes were loaded with an amount predetermined for each animal from its most recent body weight. The loaded syringes were weighed to ± 0.01 g and reweighed immediately after injection into the animal. Similarly weighed portions of the ^{238}Pu solution were expressed into volumetric flasks for use as counting standards.

Animals

Experimental subjects were three species of Macaque: Macaca is a genus of Old World Monkeys of the family Cercopithedicae, which also includes the mandrill and baboon.

On the scales of morphological and behavioral evolution of primates, only the Apes stand closer to man than the Cercopithecine monkeys. Like man, these highly developed monkeys have long periods of gestation (about 180 d) and growth (5 to 6.5 y for females and males, respectively), and compared with most other mammals of similar size, they have long life spans (about 30 y). The Macaques are generally omnivorous, and the structures of their teeth and gastrointestinal tracts (GI), like those of man, are general rather than specialized. The differences in digestive tract structures among the higher primates are chiefly of size rather than of function and appear to be adaptations to local dietary habits. All of the anthropoid primates share a common skeleton (which in fact defines the anthropoid families of the Primate order and sets it apart from other mammals): There are five free digits on both hands and feet with an apposable thumb and large toe; claws have been replaced by nails; the clavicle is retained; radius and ulnae and tibia and fibula are separate; the muzzle or snout is reduced; vision is binocular and visual fields overlap; olfactory apparatus is reduced; total cranial capacity is enlarged. The skeletons of monkeys differ most from that of man in that the monkeys have an apposable big toe, variable numbers of caudal vertebrae (man has none), a lumbar spine that contains seven vertebrae (man has five), a pelvic structure and limb lengths that are adapted to quadrupedal gait and, proportionally, a more massive mandible and a smaller cranial capacity. The available evidence indicates a common pattern of skeletal development among the primates as well as many gross and microscopic structural similarities of their bones (26).

The genus, Macaca, comprises 12 species ranging in body size from

1.5 kg (female, M. fasicularis) to 18 kg (male, M. arctoides). The comparative anatomy of the Macaques is remarkably similar considering the diversity of their habitats. The differences that define the individual species are largely of external appearance, such as color and texture of coat, color and hairiness of face and crown and characteristics of tail and external genitalia (26). The Macaques appear to be genetically homogeneous. All have 42 chromosomes with a common karyotype, except for variability of the X chromosome; their serum proteins are structurally similar as demonstrated by immune-precipitin reactions (26); with the possible exception of M. arctoides, interspecies crosses yield fertile hybrids (27).

The three species of Macaques used in these studies were M. mulatta (Rhesus), M. fasicularis (Cynomolgus) and M. arctoides (Stump-tail). The species were mixed for practical rather than scientific reasons, namely, the difficulty in obtaining adults (especially males) of one species in a reasonable period of time and the time and expense involved in raising immature monkeys (more easily obtained) to adulthood. The animals were acquired from several sources: retired breeding Rhesus females and the four Rhesus adolescents were obtained from the Regional Primate Center at the University of California at Davis; young adult M. fasicularis males were obtained from local zoos; M. arctoides and Rhesus males were obtained from other investigators who no longer needed them; female M. fasicularis (adults and one adolescent) were obtained from a commercial supplier (Primate Imports, New York, no longer in business). Some were born in captivity, but most had been caught in the wild and had been held for varying periods of time. Skeletal maturity was verified roentgenographically (40) and by dental examination (41). Age past maturity was estimated from weight charts and laboratory histories.

Animal Care: The animals were housed according to body size in individual heavy duty metal cages 0.7 to 0.9 m tall with 0.37 to 0.65 m^2 of floor area (Research Equipment Co., P.O. Box 1151, Bryan, TX 77801). The animals were shifted to clean sterilized cages every other week. The flooring consisted of steel rods (1 cm diameter) on 4-cm centers reinforced against sagging by two or three evenly spaced cross bars. Excreta were collected in a closely fitting 8.5-cm tall stainless steel catch pan locked in place just below the flooring. A rough separation of urine and feces was obtained by inserting into the excreta catch-pan a closely fitting 0.6-cm mesh stainless steel screen that was raised 2.5-cm above the pan bottom by corner posts.

Diet consisted of commercial monkey chow (Purina #5038, Ralston Purina Co., St. Louis, MI 63164), whole wheat bread, fresh fruit and vegetables and tap water. Amounts of food were adjusted to the body size of each animal so as to maintain a constant and reasonably lean body mass. Dietary supplements included one tablet daily of an iron and B and C vitamin preparation ("Zentron," chewable, Eli Lilly and Co., 307 E. McCarty St., Indianapolis, IN 46285) and an occasional egg

nog (raw egg, reconstituted non-fat dry milk and sugar) when needed as a vehicle for medications or to encourage fluid intake.

Upon arrival, monkeys were placed in quarantine where they remained until they were demonstrated to be free of tuberculosis and intestinal worms and protozoa. Standards of housing, care and cleanliness changed and improved over the years; the animal colony at LBL is presently accredited by the American Association for Accreditation of Laboratory Animal Care and is a Registered Research Facility (USDA Animal and Plant Health Inspection Service, license No. 93-210).

The upper canine teeth were extracted from adult males, and the long tails of the Cynomolgus monkeys were docked to about 10 cm length. All animals in the colony were examined two to four times a year; physical examinations included the following: body weight, hemogram, TB test, inspection of eyes, ears, skin, teeth and genitalia, palpation of abdominal lumps, and evaluation of breathing and chest sounds.

Injections

Radionuclide injections were made and frequent early blood samples were drawn under tranquilization with "Ketelar" (ketamine hydrochloride, Parke-Davis, Detroit, MI). One animal (C106M) received the photon-emitting isotope ^{237}Pu in addition to ^{238}Pu: ^{237}Pu uptake from an intramuscular injection site was followed for several hours, and ^{237}Pu distribution was measured every few days thereafter with external counting equipment (42). The injection and subsequent measurements, which required that the animal remain still, were conducted under tranquilization with "Sernylan" (phencyclidine hydrochloride, Bio-ceutic Lab., St. Joseph, MO) and Acepromazine (Ayerst Labs., New York, NY). Atropine sulfate (Hart-Delta Labs., Baton Rouge, LA) was administered to suppress salivation.

Intravenous injections (i.v.) were made into a superficial vein of the lower leg, and intramuscular injections (i.m.), into the calf or thigh muscle. Animal C95F was injected beneath the skin of the left calf (subcutaneous, s.c.), because the needle slipped during an i.v. injection. Injection data for the 21 adult and five adolescent monkeys in this study are presented in Table 1; the individual histories of the animals in the experiment are collected in Appendix B.

Metabolic Balance

A complete balance study was performed for each ^{238}Pu-injected monkey. All excreta were collected and the ^{238}Pu content was determined. All soft tissues, bones and periodic blood samples were analyzed for their ^{238}Pu content.

Table 1. Injection data for Macaques in the ^{238}Pu metabolic study

Animal number[a]	Days p.i.[b]	Age (y)	Weight (kg)	^{238}Pu (Bq/kg)	Injection mode[c]
Adult					
C77F	0.083	>11	4.0	43,290	i.m.
C108F	0.83	>6.3	4.0	37,000	i.m.
C109F	7	6	3.4	22,570	i.v.
C89M	7	7.8	6.9	37,000	i.v.
S114F	7	>8	11.4	12,580	i.m.
C95F	8	>10.5	4.0	74,000	s.c.
R101F	8	>10	6.2	13,320	i.v.
R12M	8	~14	11.0	11,100	i.v.
C31F	56	>6.4	4.9	11,100	i.m.
R100F	67	>11	6.8	11,840	i.v.
R6M	103	~18	7.7	12,950	i.m.
C106M[d]	106	>8	7.3	12,580	i.m.
C79F	106	>11	4.3	11,840	i.v.
C111F	173	>5.2	3.2	11,470	i.v.
C107M	173	~6.5	5.8	11,470	i.v.
R99F	370	14.5	7.4	12,210	i.v.
C105M	552	6.1	8.0	10,360	i.v.
S116F	559	~6	8.8	11,470	i.v.
C94F	587	~11	6.6	11,100	i.v.
R102F	1099	~8.7	4.7	13,320	i.v.
C80F	1100	>13	5.2	11,470	i.m.
Adolescent					
C103F	0.85	3.1	2.0	39,220	i.m.
R119F	7	3.8	4.0	12,580	i.v.
R122F	8	3.9	4.5	11,470	i.v.
R120M	8	4.0	3.9	14,060	i.v.
R121M	7	4.0	4.6	9,620	i.v.

[a] Colony accession number: C, Cynomolgus; R, Rhesus; S. Stump-tail; M, male; F, female.

[b] Serial sacrifice, except C77F (anesthesia accident) and R100F (cause of death unknown).

[c] i.m., intramuscular; i.v., intravenous; s.c., subcutaneous.

[d] Animal C106M also received 129,500 Bq of ^{237}Pu.

Collection of Biological Samples

Excreta: A few monkeys threw fecal matter on the floor; these animals were isolated to avoid mixing samples. The scattered feces were picked up daily and stored in a labeled beaker to be added to the next collection.

Excreta were collected daily for the first week after injection and twice weekly thereafter. The feces catch-screen was shifted to a clean dry pan lined with large pieces of ashless filter paper, onto which feces and dry food scraps were transferred with a stiff brush and a metal spatula. The screen was cleaned further with damp tissues, which were added to the solid material in the dry pan. The pan liner containing all the solids was rolled up and placed in a large labeled beaker. Feces picked up from the floor and the solid matter strained from the urine (as described below) were added to the feces collection.

Fluid in the urine catch-pan was poured through a kitchen sieve into a 2 liter Pyrex beaker lined with a plastic bag: the liner was used to avoid liquid losses, in case the beaker was cracked in transit between the colony room and the drying oven. Two or three urine beakers were needed for some monkeys with large fluid intakes. When the urine catch-pan contained little but air dried urine and finely divided food scraps, 500 to 1000 ml of hot water was added, the solid material in the bottom was loosened with scraping and the pan and contents were set aside to soak for a few minutes. The slurry and pan rinses were poured through the sieve into the urine collection. The wipes used for final cleaning of the urine catch-pan and the contents of the sieve were added to the feces collection. The "urine" samples collected after the first week tend to overestimate renal excretion, because they usually contained some particles of fecal matter which could not be picked up and passed through both the feces collection screen and the sieve.

On collection days, urine that dripped on the outside of the catch-pan or cage or had been "sprayed" onto the walls or floor was wiped up with damp tissues and added to the urine sample of the appropriate animals. Walls, floors and the outer surfaces of cages were monitored occasionally; residual alpha contamination was not detected, indicating that the cleanup procedures were adequate. At the end of the first week after injection, the animals were moved to clean cages, and their original cages were scrubbed with tissue wipes dampened with Radiac Wash (Atomic Products Corp., Center Moriches, NY). The small amount of Pu recovered in the cage wash was measured and added to the first day's urine sample. Pu was not detectable in later cage washes.

Plasma: Blood was drawn from the superficial leg veins into disposable syringes wetted with heparin. Blood samples taken after the first day were usually drawn without anesthesia; only physical restraint was used. Samples, usually 3 to 5 ml, were taken several

times during the first 6 to 8 hr after injection, daily for about two weeks and at succeedingly longer intervals thereafter. Plasma and red cells were separated by centrifugation in heavy-walled glass cones in a refrigerated unit at 2000 rpm for 30 min. Plasma was withdrawn through a long needle into a dry syringe, which was weighed full, and it was then expelled into washed new beakers. The emptied syringe was reweighed to obtain the weight of the plasma sample by difference. The plasma samples were covered with glass lids, dried overnight at 50°C and stored dry until further processing. The total Pu content of plasma was calculated using published relationships between blood and plasma volumes and body weight for Rhesus monkeys (43).

Autopsy: At autopsy, under Sernylan and overdose of Diabutal (sodium pentobarbital, Diamond Labs., Des Moines, Iowa) a final venous blood sample was drawn, the abdomen was opened and as much blood as could be withdrawn was removed through a catheter set in the inferior vena cava. The thoracic and abdominal organs were removed en bloc, examined, dissected cleanly, weighed and placed in Pyrex beakers of appropriate size for drying and ashing. Samples of tissues removed for histology and autoradiography were weighed to account for their loss from subsequent radiochemical analysis; they were then fixed in 80% alcohol for autoradiography or neutral formalin for histology only. The contents of the GI tract was removed and the tract tissues were rinsed. GI contents and rinses were added to the last feces collection. Bile and bladder urine were aspirated with needles and syringes and expelled into tared beakers. For i.m.-injected monkeys, the foot was removed from the injected leg, and the leg was disarticulated, processed and analyzed intact. The carcass was skinned and the entire pelt (including subcutaneous fat, ears and ischeal calluses) was placed in a tared beaker.

Bones: Bones were disarticulated; they were scraped free of muscle, ligaments and tendons and weighed. Hands, feet and tail were roughly cleaned; their fresh weights were estimated from ash weights, based on the ash fractions of those bones determined for three completely cleaned skeletons. Teeth were removed after the skull and mandible were ashed; their fresh weights were estimated from the ash fractions of extracted monkey teeth. The right humerus and 5th rib, two lumbar vertebrae (LV1 and LV3), one half of the calvaria and a sample of sternum were weighed and fixed in 80% alcohol. The contralateral bones or the remainder of the bones and LV2 were weighed and analyzed as separate samples to account for bones that were not analyzed. For i.m.-injected monkeys the skin, muscle and cleaned bones of the uninjected leg were analyzed as separate samples to account for the tissues of the injected leg that were included with the injection site. For all but the earliest injected monkeys (C77F, C79F), the remaining lumbar vertebrae (LV4 through LV7) were separated with a bone saw into body and arch; the ends and shafts of the long bones were separated; and the ribs were divided into anterior, central and posterior thirds. For animal R100F, the scapulae and pelvis were divided into the parts shown in Fig. 1, and the carefully cleaned small bones of the hands and feet were separated and analyzed in the

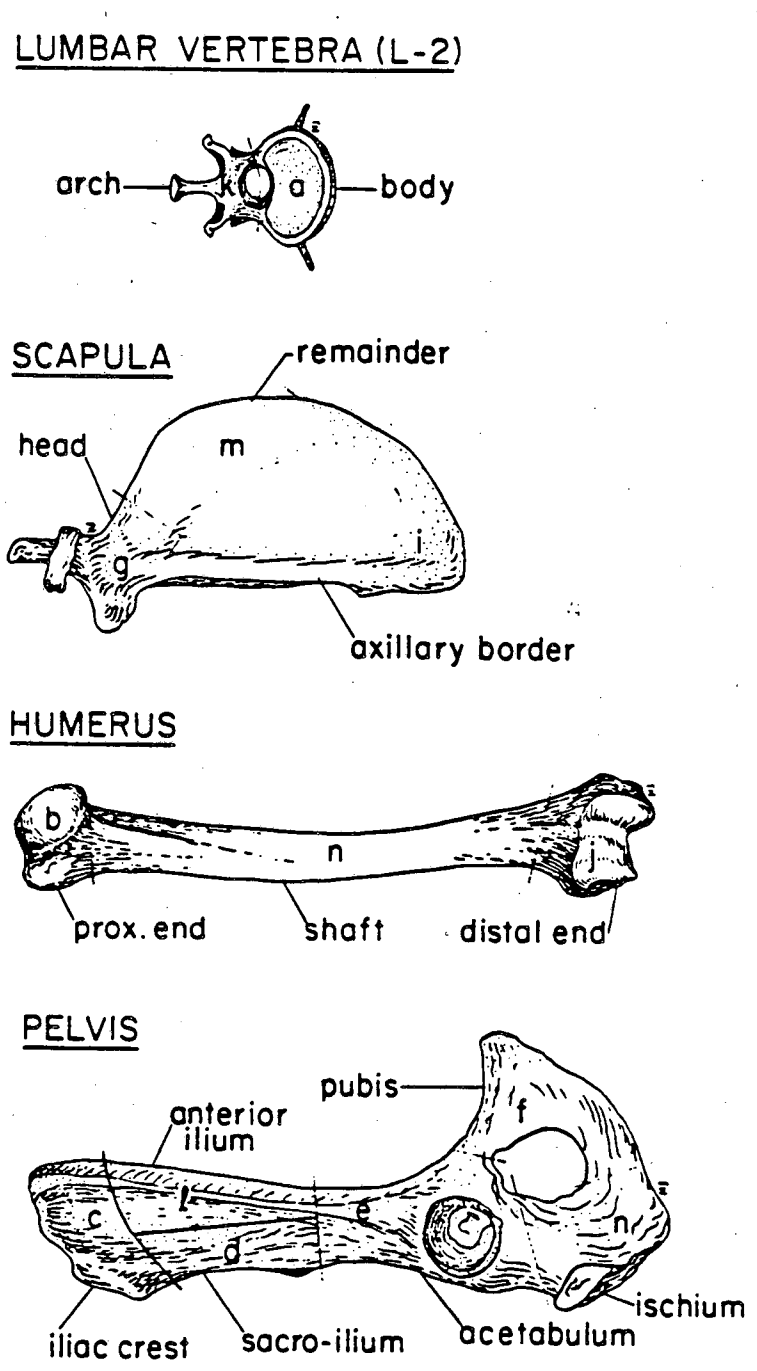

Figure 1. Division of some monkey bones into structurally distinctive parts. All long bones and lumbar vertebrae of adult Pu-injected monkeys were divided as shown for the humerus and LV2, respectively. For animal R100F, cervical (CV2-CV7) and thoracic (TV1-TV12) vertebrae were divided as shown for LV2; scapulae and pelvis were divided as shown; clavicles were divided as shown for the humerus.

following groups: carpals, metacarpals, hand phalanges, tarsals, metatarsals and foot phalanges. All soft tissue obtained in the skeletal dissection was collected in tared beakers and weighed.

Drying and ashing: Tissue, bone and excreta samples were dried at 100 to 200°C. Beakers containing dried muscle, skin or the mesentery were weighed, liquid fat was decanted and the beakers were reweighed to obtain the weight of the discarded fat. Fat samples from the first three monkeys injected with ^{238}Pu had been ashed and analyzed, and there was no detectable ^{238}Pu in them; subsequently, fat was discarded. The dried samples were ashed in a furnace at 600°C as long as was necessary to reduce them to a grey ash. The ash weights of the bones were recorded. The dry-ashed excreta and large soft tissues were further digested with concentrated HNO_3 to produce a carbon-free-salt.

The plasma samples were ashed in a small furnace reserved for low activity specimens. The dried samples, covered with glass lids, were placed in the cold furnace, and the temperature was raised over several hours to 450 to 500°C and held overnight. When cool, the ash was dissolved in 6N HNO_3 and transferred with rinsing into small volumetric flasks.

Radiochemical Analysis of ^{238}Pu

Alpha counting: Alpha counting was used to detect ^{238}Pu in plasma, small tissues and bones (e.g., hyoid, 5th rib) and aliquots of large soft tissues of low activity. Ashed samples were dissolved in 6N HNO_3. The entire solution and rinses or a suitable aliquot was placed in a tared glass planchet (2.5 to 3.0 cm diameter with a 0.3 cm rim, custom made in the LBL glass shop). The samples were dried on a warm hot plate and then strongly heated to expel volatile nitrates. After cooling, the planchets were reweighed to obtain the sample mass needed to apply the self-absorption correction (App. Fig. A-1). Alpha activity was detected with a windowless, continuous flow proportional counter with an average background of 1.5 counts/min (Model D47, Nuclear-Chicago Corp., 333 E. Howard Ave., Des Plaines, IL 60018).

Photon counting: The 17 keV L x rays of the ^{234}U daughter were used to detect ^{238}Pu in the bones, large soft tissues and excreta. Ashed samples of tissues, bones and excreta collected in the first 2 weeks were dissolved in 50 ml of 6N HNO_3 and transferred with water rinses into 60 or 125 ml plastic bottles with screw caps. The liver from animals killed at times less than 1 y post-injection was divided among three or four bottles. Bones of greater than 4 g ash weight were dissolved, transferred with rinsing into volumetric flasks, and an aliquot containing about 4 g ash was taken for counting.

Self-absorption of 17 keV photons is significant, and it is dependent on the composition of the sample. Therefore, separate self-absorption curves of appropriate solutions in 60 or 125 ml bottles were prepared for soft tissues and urine (major salt constituents,

alkali metal chlorides, App. Figs. A-2 and A-4) and for bone and feces (major salt constituent, calcium phosphate, App. Figs. A-3 and A-4). Unprocessed muscle and excreta ash contain ^{40}K, which contributed a small but measurable count in the 17 keV peak. Therefore, background blanks were prepared from KCl solutions of known composition and from dissolved, acid-digested ash of urine or feces collected during 1-, 2- or 7-day intervals from uninjected animals of the same body sizes (and presumably the same food intakes) as the Pu-injected animals. The corrections for excreta samples ranged from 0.3 to 0.6 count/min/day in unprocessed fecal samples and from 1.5 to 3.0 count/min/day in urine samples. The count rates of muscle samples were corrected by subtracting 4.7 count/min/kg of wet tissue from the measured values, based on the mean count rate in the KCl blanks of 1.8 ± 0.3 count/min/g K and the reported K content of human muscle (about 2.7 g K/kg of fresh weight, ref. 44).

The photon detector was a pair of large coaxially mounted, thin NaI(Tl) crystals (0.3 mm thick and 13 cm diameter) connected to a multichannel analyzer (Tracor Model No. 1710, 2551 West Beltline Highway, Middletown, WI 53652) and housed in a large custom-built lead shield. With the crystals set 5 cm apart and the center of the 8.3 cm tall liquid column in the upright bottle aligned with the axis of the crystals, the geometry of the system is a virtual well. In that configuration, a plastic bottle containing 125 ml of a dilute acid solution of ^{238}Pu has a counting rate of 0.324 count/min/Bq; the background in the 17 keV peak is about 26 count/min. Samples were counted long enough to obtain a total statistical error of ± 5%.

Bones, large tissues and excreta samples from animal C106M were counted after autopsy with a pair of 2.5 cm thick NaI crystals (mounted in the same shielded box) to detect the 60 and 100 KeV photons from ^{237}Pu (37). They were recounted from 22 to 26 weeks later with the thin crystals to determine their ^{238}Pu content; at that time about 25% of the photons in 17 keV peak were contributed by the ^{237}Pu. No self-absorption corrections were needed for the higher energy photons. The Pu contents of the individual bone, tissue and excreta samples, as measured by the two isotopes, all agreed well with each other (see Table 2a), confirming the adequacy of the various self-absorption corrections that were applied to the ^{238}Pu counting data and the overall validity of the methods used to detect ^{238}Pu in large biological samples.

Chemical processing of excreta: Ashed urine and feces samples collected after the first two weeks were subjected to chemical processing to remove the sodium and potassium salts, which reduce the count rate by increasing self-absorption (App. Fig. A-4), increase the background count rate by their ^{40}K content and introduce errors into the determination of the dry weight of the acid-digested ash, because their nitrates are hygroscopic. Entire ashed urine samples (1- to 2-week pools) and 1/5 to 2/5 of feces samples (1- to 2-week pools) were diluted with water in tared beakers, and 500 mg of Ca^{+2} was added to urine samples. They were heated to boiling, and oxalic acid was

added (5 g to urine and 15 g to feces). The ^{238}Pu was scavenged with calcium oxalate, which was precipitated by titration with 50% NH_4OH to pH 9 (bromthymol blue indicator). After digestion and cooling, the precipitate was collected with washing in ashless filter paper in large funnels. The filter containing the precipitate was returned to the tared beaker, dried and fired for 2 to 4 hr at 600°C. The weight of the cooled, mixed Ca salts [$CaCO_3$-CaO-$Ca_3(PO_4)_2$] plus any insoluble residue that had been carried through the process was recorded and used to correct for self-absorption (App. Fig. A-3). The solid was dissolved in 8 N HNO_3 and transferred with rinsing to a counting bottle. The procedure was found to carry ^{238}Pu quantitatively.

Autoradiographs

Detailed autoradiographs of soft tissues were prepared by dipping deparaffinized slides in warm photographic emulsion (Kodak Nuclear Track Emulsion, Type NTB, Eastman Kodak Co., 343 State St., Rochester, NY 14650).

Gross autoradiographs of bone specimens were prepared by placing machine-smoothed slices of bone embedded in plastic (Bio-Plastic, Ward's Natural Scientific Establishment, Inc., P.O. Box 1749, Monterey, CA 93940) solidly in contact with single-coated, fine-grain x-ray film (Kodak Professional Copy Film, Catalog 171 4062, Eastman Kodak Co., 343 State St., Rochester, NY 14650).

In Vivo Measurements of Animal C106M

Three techniques were used for in vivo measurements of the whole- and partial-body content of ^{237}Pu (42).

Large single NaI crystal: A NaI crystal (10 cm thick, 24 cm diameter) mounted inside a low-background iron room was used to measure whole and partial body content. Under Sernylan tranquilization the animal was placed on its left side in a curved position in a fastened cardboard animal carrying box (25 cm x 46 cm, bottom area). The box was placed on the floor of the room 1 m from the crystal face, and depending on the amount of ^{237}Pu remaining in the animal, counts were recorded for 10 to 30 min. A second measurement was made with a cylindrical lead shield (1.3 cm thick, 13 cm long) in place over the liver region. The counting standard was a known amount of nuclide in a 1 liter plastic bottle. Measurements were made just before death and after autopsy and removal of the liver to provide correlations between the last body count and the radiochemical analyses of the tissues and to determine the amount of Pu radioactivity in the "liver region" contributed by other tissues -- chiefly bone.

Multi-crystal detector: Four independently recording NaI crystals connected to a computer (model PDP-12, Digital Equipment Corp., 146 Main St., Maynard, MA 01754) were used to measure uptake kinetics of the intramuscularly injected ^{237}Pu. Detectors were

positioned over liver, trabecular bone (lower lumbar spine), compact bone (top of head), and injection site (calf muscle). This instrument was also used for serial measurements, but the results were uncertain because of errors in repositioning the detectors.

Whole-body scanner: A custom-made Anger multicrystal detector with a moving bed and a fixed overhead gamma-ray source for transmission scanning was used to detect the whole-body distribution of ^{237}Pu from 8 days to 3 months (42). The monkey under Sernylan and Acepromazine tranquilizers, was positioned prone on the center of the bed with the head to one side, arms extended and legs flexed; only gauze ropes and masking tape were used for physical restraint. An emission scan required from 30 to 45 min. The ^{241}Am source fixed above the bed was used to produce a skeletal radiograph, which allowed body regions to be identified repeatedly without precise repositioning on the bed. A computer summed the counting data over "regions of interest" as well as over the whole body. The small size of the monkey, the tendency to flexion of the legs, and the small amount of ^{237}Pu injected limited the definable "regions of interest" to the following: head, limbs, "liver," remainder of torso (excluding liver), and injection site. Measurements were made on the day the animal was killed both before and after removal of the liver to obtain a measure of the contribution to the "liver region" from overlying bone.

RESULTS

Material recovery in these complete balance studies ranged from 87 to 113% of the injected Pu, with a mean and standard deviation (S.D., ref. 45) of 101 ± 7.2 % ID. The monomeric state of the injected ^{238}Pu was confirmed by a common early tissue distribution independent of mode of injection, slow plasma clearance after i.v. injection, consistently low ^{238}Pu concentrations in spleen and lymph nodes, rapid absorption from an i.m. site and absence of alpha track stars in autoradiographs of livers from animals killed 1 to 8 d after injection.

Data summaries for the individual animals appear in Appendix B. The gross distribution and total excretion of ^{238}Pu in all the animals in the study are collected in Tables 2a (adults) and 2b (adolescents). The Pu content and concentration in gonadal tissues of individual monkeys are shown in Tables 3a (ovary) and 3b (testis). Data for the Pu content of soft tissues are expressed throughout as percent injected dosage (% ID) and for Pu concentration as percent injected dosage/g wet tissue (% ID/g). Data for the Pu content of bones and teeth are expressed as % ID and for Pu concentration as % ID/g ash.

Absorption

Absorption of ^{238}Pu citrate from an intramuscular injection was 95% complete in 10 d (Table 2a). The tissue distributions of this Pu(IV) citrate preparation at 7 to 8 d after injection were indistinguishable after three modes of parenteral administration

Table 2a. Summary of distribution and excretion of ^{238}Pu, injected as Pu(IV) citrate, in adult Macaques

Days p.i.	Monkey number[b]	^{238}Pu content (% injected activity)[a]								
		Bones (no tail)	Teeth	Liver	Kidneys	Spleen	Other tissues[c]	Urine	Feces	Inj. site
0.83	C108F	20	.16	41	1.89	.23	35	.31	2.05	32
7	C109F	28	.19	60	.53	.36	4.15	2.54	2.87	---
7	C89M	31	.15	62	.68	.15	2.74	2.48	.61	---
7	S114F	26	.10	66	.81	.27	4.13	1.43	1.01	8.87
8	C95F	31	.064	47	.98	.18	12	3.04	4.34	---
8	R101F	40	.12	50	.52	.11	3.66	2.53	1.29	---
8	R12M	15	.057	76	.24	.13	3.66	2.22	2.22	---
56	C31F	18	.18	34	.094	.27	1.73	3.04	43	1.17
67	R100F	31	.18	36	.15	.14	1.47	3.63	26	---
103	R6M	27	.12	20	.10	.13	1.95	3.54	46	.65
106 (^{238}Pu)	C106M	21	.14	42	.18	.074	3.10	3.57	30	2.63
106 (^{237}Pu)	C106M	21	.14	42	.16	.071	2.75	3.29	31	2.40
106	C79F	20	.32	25	.17	.26	3.03	6.23	46	---
173	C111F	23	.16	40	.20	.42	1.61	3.49	30	---
173	C107M	20	.14	42	---	.26	1.62	4.03	29	---
370	R99F	21	.17	4.16	.043	.044	1.28	7.62	66	---
552	C105M	14	.15	42	.15	.10	.99	8.38	33	---
559	S116F	13	.26	14	.018	.35	.82	6.56	66	---
587	C94F	7.27	.15	2.81	.043	.039	.58	24.3	64	---
1099	R102F	18	.24	.77	.005	.013	.60	21.0	59	---
1100	C80F	9.38	.16	.47	.036	.001	.43	5.71	84	~0

a Data are normalized to 100% material recovery and are expressed as % of injected activity (%·ID) for i.v. and s.c. injections or as % of absorbed activity for i.m. injections.

b Discrepancies are due to rounding and omission of tail.

c Species and sex designations defined in f.n. a of Table 1.

Includes blood.

Table 2b. Summary of distribution and excretion of ^{238}Pu, injected as ^{238}Pu(IV) citrate, in adolescent Macaques

		^{238}Pu content (% injected activity)[a]								
Days p.i.	Monkey number[b]	Bones (no tail)	Teeth	Liver	Kidneys	Spleen	Other tissues[c]	Urine	Feces	Inj. site
0.85	C103F	32	.29	49	1.22	.15	15	0.60	1.73	16
7	R119F	39	.22	55	.38	.16	2.36	1.94	.91	---
8	R122F	33	.17	61	.27	.10	1.89	1.99	1.32	---
8	R120M	25	.33	69	.46	---	1.74	1.68	2.51	---
7	R121M	40	.25	53	.27	.17	2.49	1.77	1.05	---

[a] Data are normalized to 100% material recovery and are expressed as % of injected activity (% ID) for i.v. and s.c. injections or as % of absorbed activity for i.m. injections. Discrepancies are due to rounding and omission of tail.

[c] Includes blood.

Table 3a. ^{238}Pu, injected as ^{238}Pu(IV) citrate, in ovary of Macaques

Days p.i.	Animal no.	^{238}Pu activity	
		Content (% ID)	Concentration (% ID/g)
Adult			
0.83	C108F	.047	.084
7	C109F	.0069	.0153
7	S114F	.003	.0047
8	C95F	.0043	.0068
8	R101F	.0083	.0081
56	C31F	.0008	.0053
67	R100F	.0034	.0079
106	C79F	.01	.044
173	C111F	.0021	.0055
370	R99F	.0004	.002
559	S116F	.0017	.0035
587	C94F	.0011	.0022
1099	R102F	.007	.0011
1100	C80F	.0014	.0021
Adolescent			
0.85	C103F	.014	.059
7	R119F	.0048	.0068
8	R122F	.0031	.0141

Table 3b. ^{238}Pu, injected as ^{238}Pu(IV) citrate, in testis of Macaques

Days p.i.	Animal no.	^{238}Pu activity	
		Content (% ID)	Concentration (% ID/g)
Adult			
7	C89M	.035	.0013
8	R12M	.058	.0013
103	R6M	.068	.0014
106	C106M	.091	.0016
173	C107M	.024	.00056
552	C105M	.019	.00038
Adolescent			
7	R121M	.04	.0031

(i.v., i.m., s.c.) in adult monkeys of both sexes (Table 4), and the data have been combined for comparison with the four adolescent monkeys killed at the same time post-injection (Table 5).

Influence of Age on Pu Distribution

As might be expected, because of the greater amount of active bone surface in the immature skeleton and the presence of developing unerupted wisdom teeth (third molar), Pu deposition in the skeleton and teeth was greater in the adolescents than in the adults (46). The larger deposition of Pu in the adolescent teeth was significant ($p = 0.01$, ref. 45). Liver deposition was the same for the two groups of monkeys; the greater amount of Pu in the mineralized tissues of the adolescents was offset by both lower soft tissue Pu contents and reduced excretion. In general, there was less variation in the Pu content of specific tissues of the younger monkeys than the adults, as is shown by the smaller fractional S.D.'s. All of the adolescents were injected i.v., they were nearly the same age and were born in captivity in the same colony, which would tend to reduce three major sources of individual variation.

Plasma

The general features of the kinetics of i.v. injected Pu(IV) citrate in the plasma of 13 adult monkeys are shown in Fig. 2. From 0 to 24 h the plasma Pu curve was defined by 13 monkeys injected i.v.; by 24 h after the injection, the plasma Pu levels of the six i.m.-injected monkeys were the same as those injected i.v., and all later blood data were combined. The composite plasma Pu curve, drawn by eye through the mean values of all animals contributing data at each time point, has four major phases. The earliest phase, from the time of injection to about 30 min (not discernable because of the small scale of the Figure), is presumed to be the net result of: (i) intravascular mixing and binding of Pu to plasma transferrin (TF, ref. 8) in competition with escape of a variable fraction of the Pu citrate complex into extracellular fluid (ECF), (ii) deposition of the Pu citrate complex in bone and liver, and iii) excretion of filterable complexes by the kidneys and into the lumen of the GI tract. The amount of Pu circulating 10 to 30 min after injection ranged from 49 to 99 % ID (mean, 77 ± 17 % ID); the amount of Pu in the circulation at that time appears to depend mainly on the rapidity of protein binding, which temporarily traps the Pu in the vascular compartment.

During the second phase, from a few minutes to 8 d after injection, most of the Pu left the plasma and was deposited in the target organs: At 7 to 8 d a small fraction, about 10% of the injected Pu, was still present in soft tissues other than liver or had been excreted, and only 0.38 ± 0.27 % ID remained in the plasma compartment.

In the third phase, from 8 to about 28 d after injection, the plasma level declined to 0.1 ± 0.08 % ID. This phase appears to be

Table 4. Comparison of ^{238}Pu distribution at 7 or 8 d in male and female Macaques after intravenous or other mode of parenteral injection.[a]

Injection mode	Intravenous	Parenteral (extravascular)
Number of monkeys	4	2[b]
Mean age (y)	>9.4	>9.2
	^{238}Pu content (% ID ± S.D.)	
Liver	62 ± 10	57 ± 14
Skeleton	29 ± 10	28 ± 3.5
Spleen	.19 ± .12	.22 ± .06
Urine	2.44 ± .15	2.24 ± 1.1

Sex of monkeys	Female	Male
Number of monkeys	4	2
Mean age (y)	>8.6	10
	^{238}Pu content (% ID ± S.D.)	
Liver	56 ± 8.9	69 ± 9.8
Skeleton	31 ± 6.3	23 ± 11
Spleen	.23 ± .11	.14 ± .014
Urine	2.38 ± .68	2.35 ± .18

[a] Data are normalized to 100% material recovery and are expressed as mean ± standard deviation (45).

[b] Monkey (S114F) injected intramuscularly; (C95F) injected subcutaneously.

Table 5. Distribution of ^{238}Pu, injected as ^{238}Pu(IV) citrate, in adolescent Macaques 7 or 8 d after administration and in adults at 7 or 8 and 711 ± 310 d

Tissue	^{238}Pu content (% injected activity)[a]		
	Adolescent 7.5 ± 0.5 d (4)	Adult 7.5 ± 0.5 d (6)	Adult 711 ± 310 d (6)
Skeleton	34 ± 6.9	28 ± 8.1	14 ± 5.3
Teeth	.24 ± .07[b]	.11 ± .05	.19 ± .05
Liver	59 ± 7.1	60 ± 11	11 ± 16
Kidneys	.34 ± .09	.63 ± .26	.05 ± .05
Spleen	.14 ± .04	.20 ± .10	.09 ± .13
Other soft tissue	2.1 ± .36	5.0 ± 3.3	.78 ± .31
Urine	1.8 ± .14	2.4 ± 5.3	12 ± 8.2
Feces[c]	1.4 ± .73	2.1 ± 1.4	62 ± 16

[a] Data are normalized to 100% material recovery and are expressed as mean ± standard deviation (45). Value in parentheses is number of animals.

[b] Underlined mean is significantly different from adult mean at 7 to 8 d, as judged by the t-test ($p < .01$) (45).

[c] Feces includes G.I. contents.

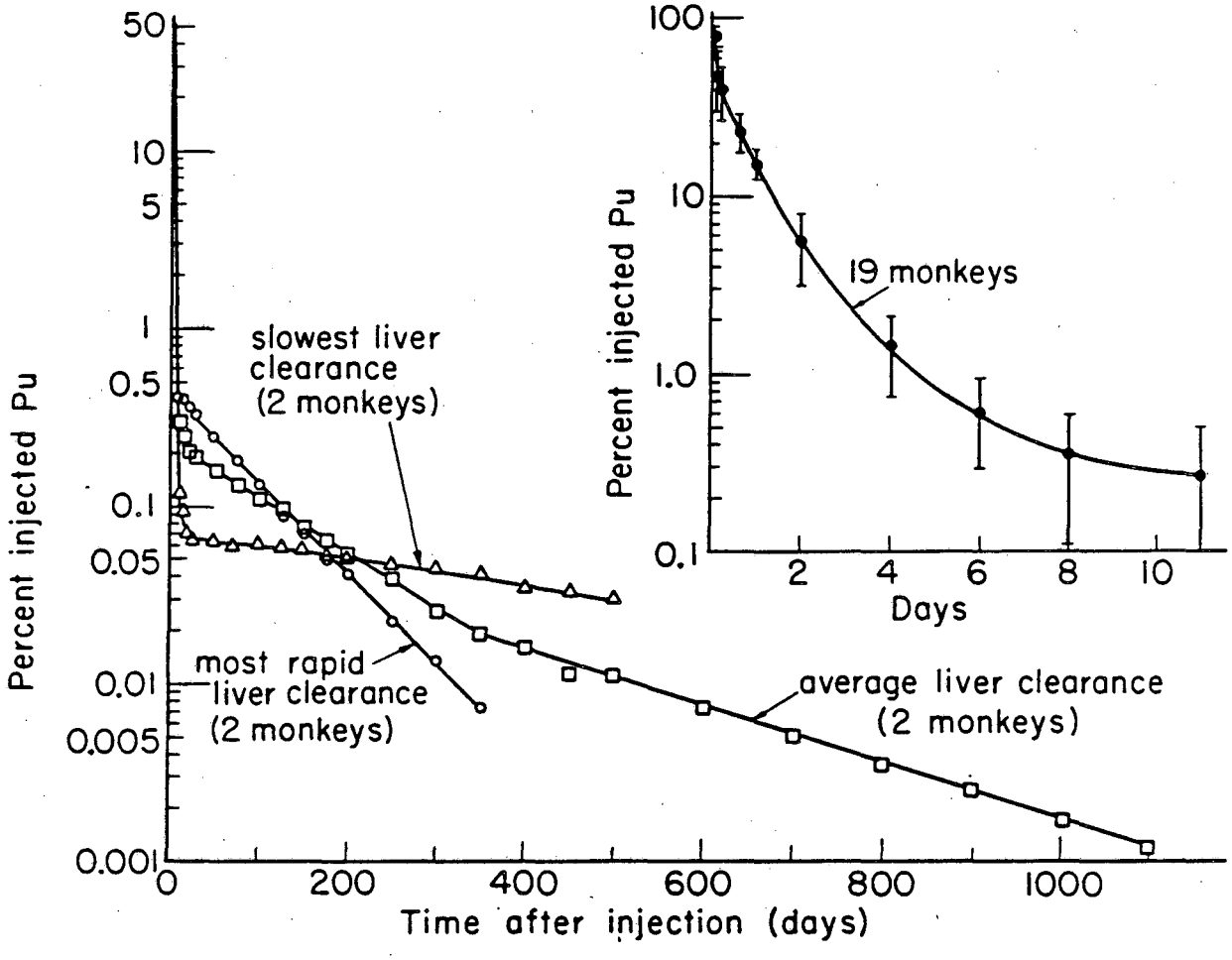

Figure 2. Clearance of Pu, injected intravenously as $^{238}Pu(IV)$ citrate, from plasma of adult Macaques (curves drawn by eye).

dominated by deposition or excretion of Pu recirculated from soft tissues other than liver. The late phase of Pu in monkey plasma, after 28 d, tended to be idiosyncratic: for some monkeys the plasma Pu level continued to decline; at the other extreme, the plasma Pu of some of the monkeys tended to plateau and remained two to five times greater than the average for the group. The late phase probably represents mainly recirculation of Pu from the skeleton, which was common to all of the animals, but in those monkeys with prolonged elevation of plasma Pu, a variable fraction of the initial liver deposit was apparently also recirculated. Rapid transfer of Pu from the liver to fecal excretion was correlated with steeper than average declines in the plasma Pu and whole-body Pu curves (Fig. 3), while prolonged retention of Pu in the liver and lower than average fecal excretion were associated with elevated plasma Pu and prolonged Pu retention in the body.

Soft Tissues

The initial distribution of Pu in soft tissues of six adult monkeys killed at 7.5 ± 0.5 d (three each at 7 and 8 d, see Table 2a), and the initial partitioning of the Pu in the body between liver and non-liver tissues (mainly bone) agree well with results obtained for similar Pu(IV) preparations and for Am(III) in mature animals other than rats (32,47-52). Autoradiographs showed that, initially, Pu was prominent in hepatic cells, non-skeletal mineralized structures, medial layers of arteries and arterioles, renal tubular structures, and occasionally, in involuting ovarian follicles and corpora lutea of menstruation. Low and declining concentrations of Pu were present in the reticulum of all tissues examined autoradiographically. Within 3 y, as shown in Table 2a and Fig. 4, Pu in the soft tissues other than liver was reduced at the least to 50% and at the most to 10% of the Pu content at one week. Clearance of Pu from the liver, as inferred from the plasma and excretion data occurred by both biliary excretion and recirculation.

Non-liver soft tissues: The amounts of Pu present at 7.5 ± 0.5 d in the soft tissues of adult monkeys were small: 1.9 % ID in the muscle and pelt and 3.1 % ID in the large organs. The Pu they contained was probably either in ECF or associated with tissue constituents, because at that time only a small fraction of the Pu in the soft tissues could be accounted for by Pu in the plasma (0.38/5.0 = 0.08, see Fig. 2). Within 3 y, as shown in Table 2a and Fig. 4, the Pu in the major soft tissues other than liver was reduced significantly, to about 10% of the amount present at one week, suggesting that most of the Pu initially associated with the constituents of those tissues was labile.

Deposition and retention of Pu in the kidneys was reasonably well described by a two-exponential curve (Fig. 4) fitted by least squares [2.3 $\log_{10}$ (% ID) vs. days p.i., r is the correlation coefficient,

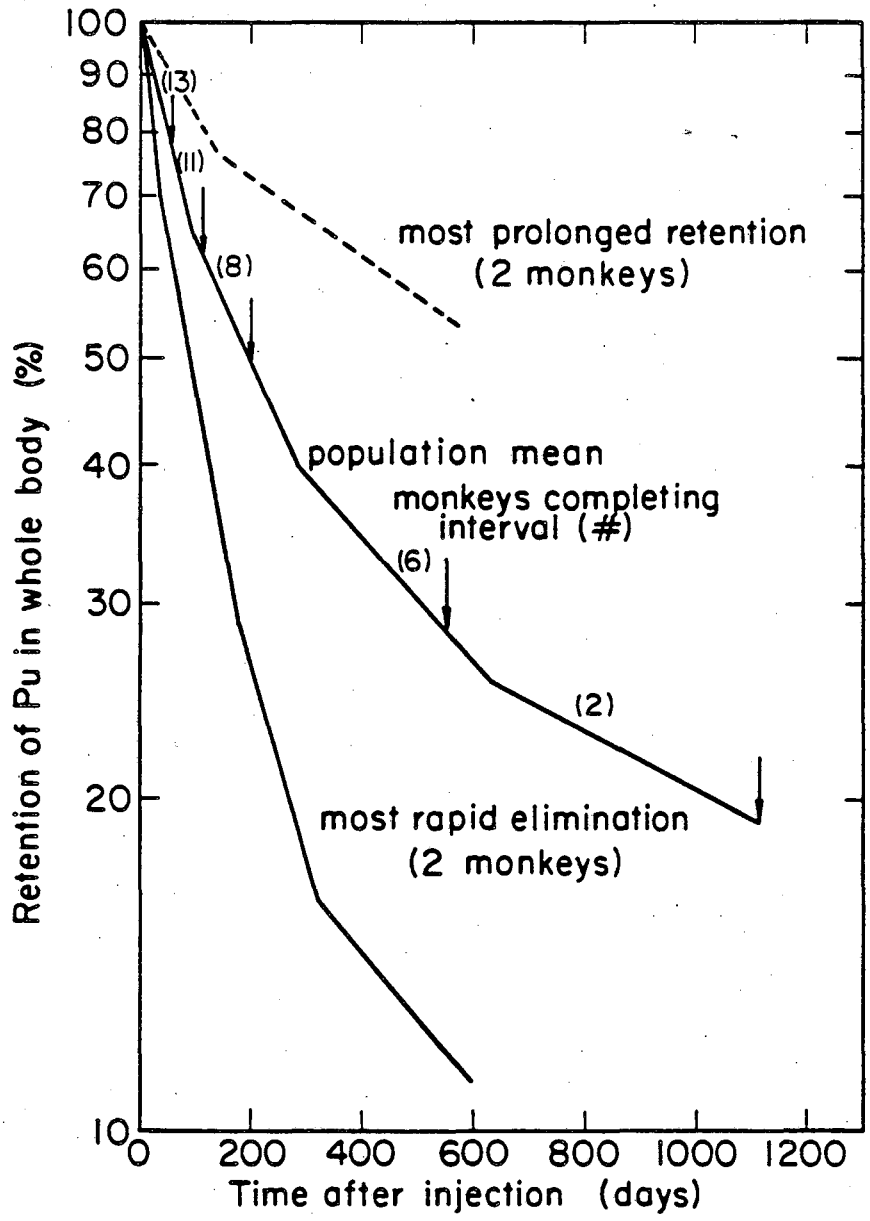

Figure 3. Retention of Pu, injected as ^{238}Pu(IV) citrate, in the whole body of adult Macaques (curves drawn by eye).

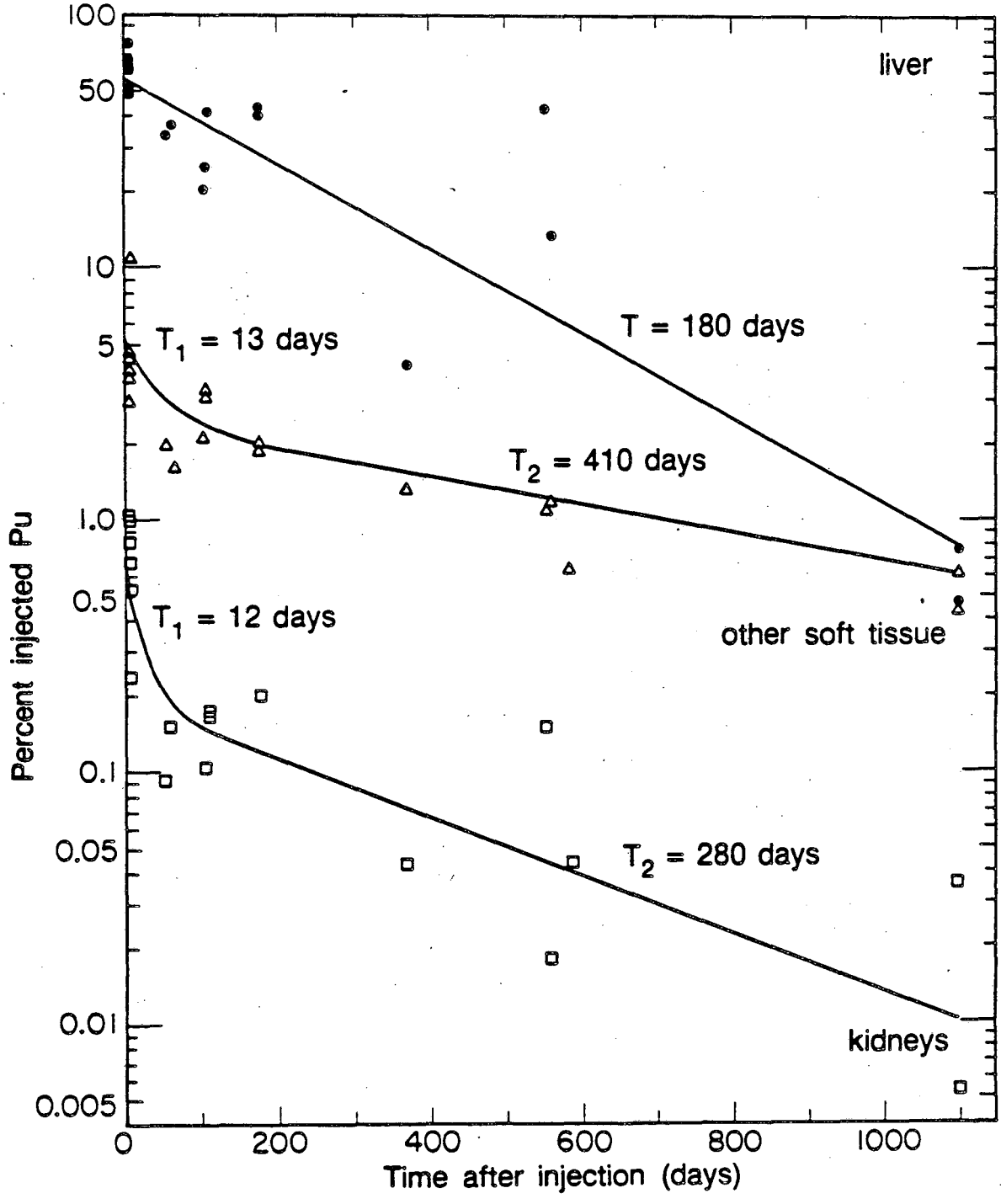

Figure 4. Retention of Pu, injected as $^{238}Pu(IV)$ citrate, in liver, kidneys and soft tissue remainder (mainly muscle, pelt, GI tract tissue, thoracic organs, brain) of adult Macaques (curves fitted as described in the text).

ref. 53][1] from 7 to 67 d ($r = -0.84$) and from 103 to 1100 d ($r = -0.78$): The equation is,

$$\text{Pu content of kidney, \% ID}(t) = 0.51e^{-0.058t} + 0.19e^{-0.0025t}.$$

[In this and all other retention equations time is in days p.i.] The retention curve of Pu in kidney is roughly parallel to the two later phases of the plasma Pu curve (Fig. 2), indicating that little of the Pu that passed through this excretory organ was retained long in its specific structures.

The Pu content of all soft tissues except liver could be described by a two-component exponential curve, fitted from 7 to 67 d ($r = -0.76$) and 103 to 1100 d ($r = -0.92$), for which the equation is,

$$\text{Pu content of non-liver soft tissue, \% ID}(t) = 3.3e^{-0.036t} + 2.7e^{-0.00155t}.$$

The shapes of the curves of Pu in the kidneys and in major soft tissues other than liver generally reflected the plasma Pu curve, providing additional evidence that most of the Pu in non-liver soft tissues was transient. At long times after intake to plasma, most of the Pu in soft tissues other than liver was probably derived from contemporaneous recirculation by the liver and skeleton. However, the smaller, but variable and statistically insignificant, reduction in the Pu content of the spleen suggests the potential for more prolonged storage of some Pu in RE cells in many tissues.

Endocrines: The amounts of Pu initially deposited in the endocrine glands of the adult monkeys were small, ranging from 5×10^{-4} % ID in the pituitary (mean weight, 0.08 g) to 1.2×10^{-2} % ID in the pancreas (mean sample weight, 8 g). Net Pu loss from these tissues was slower than from the major soft tissues and ranged from 0.0005 d^{-1} ($T_{1/2} \sim 1350$ d) in the adrenal to 0.0011 d^{-1} ($T_{1/2} \sim 625$ d) in thyroid, pancreas and pituitary.

Ovary: Deposition and retention in gonadal tissue are important components of the calculations of the new ICRP system for limiting intake of radionuclides (6). Menarche occurs in Macaques at 1.5 to 2.5 y, and normal cycles are well established by 4 y of age (26). The Pu deposition and concentration at 7.5 ± 0.5 d after injection in ovary of four skeletally mature and two late adolescent female monkeys were not significantly different (Table 3a): Pu content and concentration for the adults and adolescents were, respectively, 0.0056 ± 0.0024 and 0.0040 ± 0.0012 % ID, and 0.0087 ± 0.0029 and 0.0104 ± 0.0052 % ID/g wet. The data for all six females killed at 7.5 ± 0.5 d were combined: Pu content, 0.0051 ± 0.0021 % ID; Pu

---

[1]The retention curves shown in the preliminary summaries (30,31) were drawn by eye, so there are some small discrepancies between the parameters given here and those presented earlier.

concentration, 0.0093 ± 0.0043 % ID/g wet.

The Pu content and concentration in ovary of these sexually mature, and presumably fertile, primates declined notably with time, contrary to the ICRP assumption of infinite retention of actinides in ovary. By 836 ± 301 d (four monkeys killed 552 to 1100 d) Pu in ovary was about 24% of the amount present at 7.5 ± 0.5 d: 0.0012 ± 0.00043 % ID and 0.0022 ± 0.001 % ID/g wet. Even though the groups were small and individual variation was large, the differences were significant ($p < 0.01$).

Linear regression of $\log_{10}$ Pu content or concentration in ovary on time after injection for 15 female monkeys killed from 7 to 1100 d yielded the following equations:

$$\text{Pu content of ovary, \% ID}(t) = 0.0036e^{-0.0016t} \qquad (r = -0.60)$$

$$\text{Pu concentration in ovary, \% ID/g}(t) = 0.0091e^{-0.0018t} \qquad (r = -0.74).$$

Testis: Adult and late adolescent male monkeys are difficult to obtain and keep in the laboratory, so there are fewer data for males. The Pu analysis of testes of adolescent male R120M was lost in a contamination incident: The testes of the other adolescent (R121M) were small, and they had not descended, so that animal was considered too immature to be combined with the other males.

The six adult males was too small a population to examine the testis data by methods other than linear regression (Table 3b). Semi-log plots of the Pu content and concentration in testis with time after injection were approximately straight lines, and least squares fitting yielded the following equations:

$$\text{Pu content of testis, \% ID}(t) = 0.058e^{-0.002t} \qquad (r = -0.65)$$

$$\text{Pu concentration in testis, \% ID/g}(t) = 0.0014e^{-0.0025t} \qquad (r = -0.86).$$

Liver: Initially, as defined by the six adult monkeys killed at 7.5 ± 0.5 d, 60 ± 11 % ID of Pu was taken up in the liver. Clearance of Pu from the liver was highly individualistic, and as inferred from plasma and excretion data, it occurred by both biliary excretion and recirculation. The clearance of Pu from the livers of some of the animals was accompanied within a few months after injection by the appearance in feces of an amount of Pu about the same as the average initial liver deposit (presumably via biliary excretion); there was no indication from their plasma Pu levels of significant recirculation of Pu from the liver. The behavior of Pu in the livers of those monkeys resembled injected Am and Cm in the baboon (49,50). More prolonged retention of Pu in the livers of some monkeys was accompanied by reduced fecal Pu excretion and elevated plasma Pu, both strong indications that a significant fraction of the initial liver Pu burden

was being recirculated. Variable partitioning of the initial liver Pu burden between biliary excretion and recirculation was previously observed in Am-injected Cynomolgus monkeys (9). The overall trend for 14 adult monkeys killed from 7 to 1100 d after injection was a decline in the Pu content of the liver that could be described by a single fitted exponential with a half-time of 180 d,

$$\text{Pu content of liver, \% ID}(t) = 56.6e^{-0.0039t} \qquad (r = -0.907).$$

For those monkeys with inefficient fecal excretion of liver Pu (notably C105M and S116F) the skeletal Pu at death (14 and 13%, respectively) was about one-half of that for the group of six killed at 7.5 ± 0.5 d (28.5 ± 8.1 % ID), and it was also less than the lowest individual initial skeletal value (R12M, 15.3 % ID). Furthermore, the total Pu excretion by the six longest-term monkeys (74 ± 18 % ID in 711 ± 310 d) was greater than the amount present in liver plus all other soft tissues at 7.5 ± 0.5 d (about 66 % ID). All of those findings suggest that the Pu in the livers of animals C105M and S116F at death represented both slow clearance of the initial liver deposit and Pu accumulated from circulatory feedback. A subsequent report in this series will examine in detail the kinetics of Pu in plasma and fecal Pu excretion of individual monkeys and provide estimates of (i) the fractions of the initial liver Pu deposit that are recirculated or excreted, (ii) the fraction of the initial skeletal Pu deposit that is recirculated and (iii) the rates of those processes.

Skeleton

Initial deposition of Pu, injected as ^{238}Pu(IV) citrate, in the adult monkey skeleton ranged from 15.3 to 40.1 % ID with a mean of 28.4 ± 8.1 % ID for six animals killed 7.5 ± 0.5 d after injection. That deposited fraction is smaller than has been reported for young adult beagles (50 % ID, 4 to 7 d after Pu injection in dogs 540 d old, ref. 51), but it agrees with the deposition in older beagles (about 24 % ID, one week after Pu injection in 5 y old dogs, ref. 52).

The general trend of skeletal Pu in adult monkeys from 7 to 1100 d after injection could be described by a single fitted exponential term.

$$\text{Pu content of skeleton, \% ID}(t) = 25e^{-0.00079t} \qquad (r = -0.68).$$

The significance of the downward trend of skeletal Pu in monkeys, a species that experiences skeletal remodelling in adulthood and possesses a significant excretory outlet for Pu, was verified by using the t-test to compare the initial mean skeletal Pu with the mean for the six monkeys killed from 370 to 1100 d after injection (13.8 ± 5.3 % ID); $p < 0.01$ (45).

Variable Pu recirculation and secondary deposition in bone superimposed on individual variation of initial skeletal Pu deposition created so much scatter in the data that the real shape of the

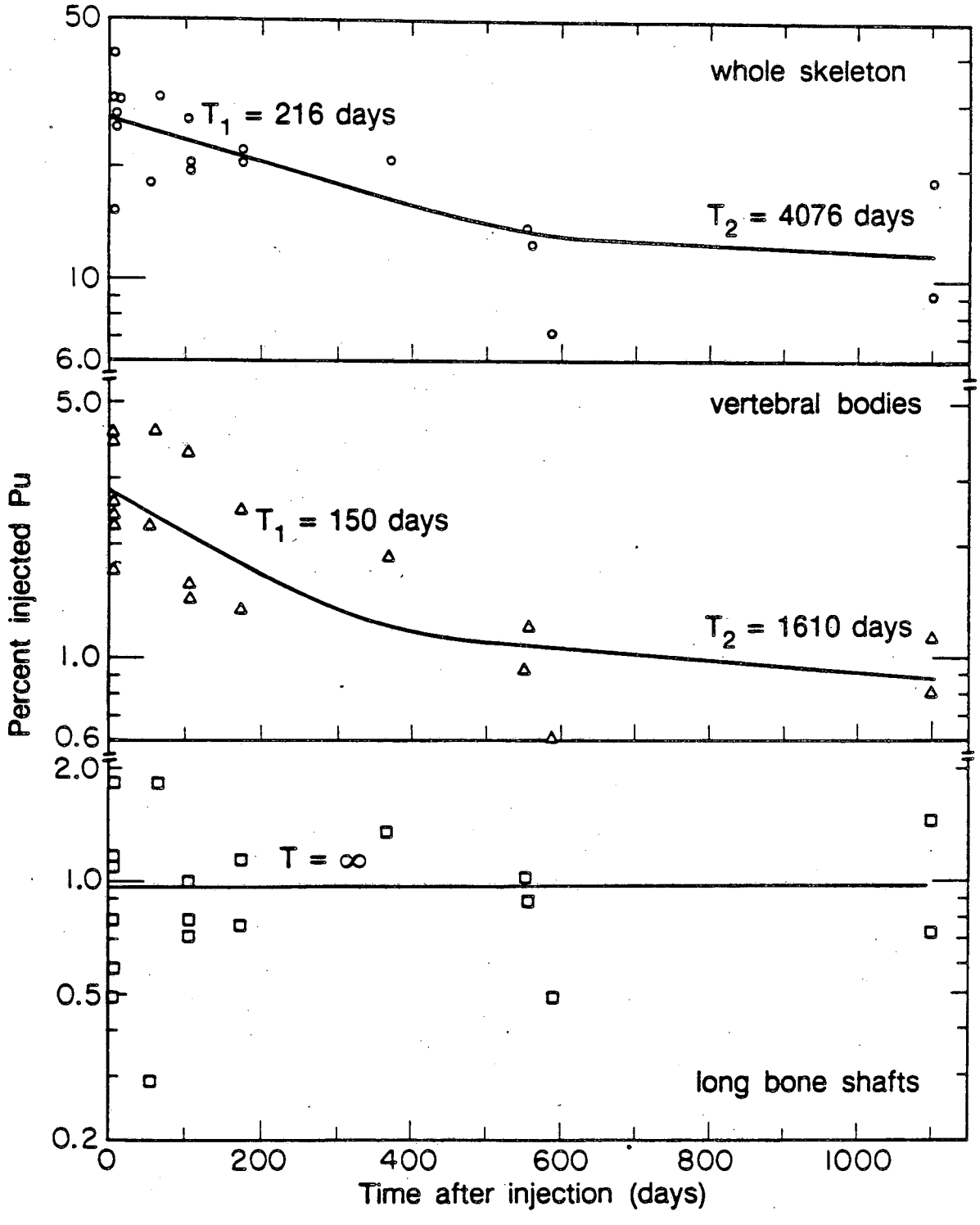

Figure 5. Retention of Pu, injected as ^{238}Pu(IV) citrate, in whole skeleton, four lumbar vertebral bodies (LV4-LV7) and shafts of six long bones (humerii, radii, ulnae, femora, tibiae, fibulae) of adult Macaques (curves fitted as described in the text).

skeletal Pu curve was obscured (see Fig. 5). A downward trending two-component curve was selected as the best simple description of the processes contributing at any time to net skeletal Pu. Evidence for different deposited fractions and loss rates of Pu for compact bone and for cancellous bone in red marrow are discussed in the next section. A two-component exponential curve was fitted by least squares over the two intervals that gave the best agreement with mean skeletal Pu at 7.5 ± 0.5 d and at 711 ± 310 d (mean time of death for the six monkeys observed from 370 to 1100 d). The selected intervals and regression coefficients were: 7 to 173 d ($r = -0.37$) and 370 to 1100 d ($r = -0.15$), and the equation of the fitted curve shown in Fig. 5 is

$$\text{Pu content of skeleton, \% ID}(t) = 12.4e^{-0.0034t} + 14.8e^{-0.00017t}.$$

Intraskeletal distribution: Analytical results for the highly subdivided skeleton of monkey R100F are presented in Tables 6a-6c. That level of detail was available for only one Pu-injected monkey, because the skeletons of the other Pu-injected animals had already been analyzed before results from the well-divided whole skeleton of a ^{241}Am-contaminated individual indicated that a more detailed intraskeletal distribution aided interpretation of the radiochemical data (15). However, for all the animals in this study lumbar vertebrae were separated into bodies and arches and the bony sternum was dissected from the costal cartilages providing anatomically defined specimens of cancellous bone in red marrow, and the six major long bones were divided into ends and shafts yielding well defined specimens of cancellous bone in fatty marrow and compact bone, respectively.

It has been amply demonstrated autoradiographically that the initial deposition of Pu in the mammalian skeleton is on bone surfaces, and that it is highly skewed in favor of cancellous surfaces in red marrow (8-12,30,54-58). Quantitative autoradiography is technically difficult, and the results are not readily generalizable, so other ways are needed to describe and quantitate the early association of Pu with the surface in various bones.

The ash fraction (ash weight/wet weight) of many, but not all, bones and bone parts is a reasonable estimate of the total volume, but not the organization, of their mineralized tissue. Bone parts with large ash fractions tend to have small surface volume ratios (S/V), small total surfaces and small marrow spaces: bones of this type (compact bone) include both densely mineralized structures with little marrow space, such as the bones of the head, and the thick tubular bones with large central cavities, which in man and monkeys contain only fatty marrow in adult life. Bone parts with small ash fractions tend to have large S/V ratios, large total surfaces and large marrow spaces: this bone type (cancellous bone) can be further divided into two subgroups -- bones that contain mostly red marrow, such as vertebral bodies and sternum, and those that contain fatty marrow in adult life, such as most of the long bone ends.

Table 6a. Measured ^{238}Pu content and concentration in bone specimens of an individual monkey (R100F).

Nuclide: 238-Pu Days from injection to death: 67.000 Animal No: R100F

	Weight (g)			Radioactivity	
	Wet	Ashed	%ash	%ID	%ID/g ash
Parietal & temporal (part) bones	18.60	10.70	57.5	.215	.0201
Frontal, maxillary, occipital & temporal (part) bones	94.20	32.30	34.3	1.426	.0441
Mandible	29.10	13.20	45.4	.498	.0377
Axil. border	9.66	3.84	39.8	.377	.0982
Head	11.16	4.30	38.5	.526	.1223
Remainder	8.80	4.46	50.7	.147	.0330
Sternal end	2.04	.46	22.5	.167	.3630
Acrom. end	1.38	.34	24.6	.085	.2500
C. shaft	3.30	1.58	47.9	.055	.0348
Ribs	45.50	15.90	34.9	1.640	.1031
5th ribs	4.50	1.66	36.9	.150	.0904
Sternum	9.39	1.32	14.1	.814	.6167
Costal cartilages	11.80	1.18	10.0	.034	.0288
Atlas	2.09	.85	40.7	.033	.0386
CV2-CV7 arches	9.57	3.74	39.1	.242	.0647
CV2-CV7 bodies	3.86	1.18	30.6	.342	.2898
TV arches	24.83	9.45	38.1	1.170	.1238
TV bodies	24.46	4.94	20.2	3.070	.6215
Second lumbar vertebra	11.40	3.07	26.9	.887	.2889
LV 1-3 arches	13.03	5.18	39.8	.445	.0859
LV 4-7 arches	15.10	6.40	42.4	.407	.0636
LV 1-3 bodies	21.30	4.71	22.1	2.570	.5456
LV 4-7 bodies	35.85	8.22	22.9	3.980	.4842
Sacrum	19.50	4.98	25.5	1.377	.2765
Iliac crest	7.96	2.18	27.4	.530	.2431
Sacro-ilium	12.76	5.20	40.8	.788	.1515
Anterior ilium	6.76	3.18	47.0	.147	.0462
Acetabulum	23.36	9.06	38.8	1.200	.1325
Ischium	16.52	4.44	26.9	.464	.1045
Pubis	8.24	2.48	30.1	.285	.1149
H. shaft	33.30	16.86	50.6	.370	.0219
H. prox. end	15.10	4.32	28.6	1.097	.2539
H. dist. end	15.10	6.26	41.5	.416	.0665
U.shaft	18.50	9.30	50.3	.186	.0200
U. prox. end	10.74	4.43	41.2	.271	.0612
U. dist. end	2.31	.65	28.1	.027	.0415
R. shaft	17.20	8.77	51.0	.140	.0160
R. prox. end	2.43	.82	33.7	.122	.1488
R. dist. end	4.68	1.32	28.2	.062	.0470
Fe shaft	44.70	23.00	51.5	.464	.0202
Fe prox. end	24.90	9.95	40.0	1.576	.1584
Fe dist. end	21.90	6.68	30.5	1.040	.1557
T. shaft	40.90	17.27	42.2	.626	.0362
T. prox. end	15.62	3.59	23.0	.702	.1955
T. dist. end	8.66	2.63	30.4	.138	.0525
Fi. shaft	8.30	4.35	52.4	.052	.0120
Fi. ends	4.33	1.25	28.9	.105	.0840
Patellae & fabellae	6.25	1.96	31.4	.175	.0893
Carpals	8.80	2.68	30.5	.090	.0337
Metacarpals	12.30	4.58	37.2	.126	.0275
H. phalanges	11.70	3.52	30.1	.077	.0220
Tarsals	32.48	10.94	33.7	.266	.0243
Metatarsals	18.42	7.38	40.1	.154	.0209
F. phalanges	17.62	4.34	24.6	.082	.0190
Tail	26.20	4.75	18.1	.270	.0568
Upper	12.60	7.56	60.0	.129	.0171
Lower	8.60	5.17	60.1	.047	.0090
Hyoid bone	-	.14	-	.018	.1286
Bonedust	-	.21	-	.024	.1143

Table 6b. ^{238}Pu content and concentration in whole monkey bones and groups of similar bones and bone parts, calculated by summing measured bone samples shown in Table 6a for animal R100F.

Nuclide: 238-Pu Days from injection to death: 67.000 Animal No: R100F

	Weight (g)			Radioactivity	
	Wet	Ashed	%ash	%ID	%ID/g ash
Skull*	112.80	43.00	38.1	1.641	.0382
Parietal & temporal (part) bones	18.60	10.70	57.5	.215	.0201
Frontal, maxillary, occipital & temporal (part) bones	94.20	32.30	34.3	1.426	.0441
Mandible*	29.10	13.20	45.4	.498	.0377
Scapulae*	29.62	12.60	42.5	1.050	.0833
Axil. border	9.66	3.84	39.8	.377	.0982
Head	11.16	4.30	38.5	.526	.1223
Remainder	8.80	4.46	50.7	.147	.0330
Clavicles*	6.72	2.38	35.4	.307	.1290
Sternal end	2.04	.46	22.5	.167	.3630
Acrom. end	1.38	.34	24.6	.085	.2500
C. shaft	3.30	1.58	47.9	.055	.0348
Ribs*	45.50	15.90	34.9	1.640	.1031
5th ribs	4.50	1.66	36.9	.150	.0904
Sternum & costal cartilages*	21.19	2.50	11.8	.848	.3392
Sternum	9.39	1.32	14.1	.814	.6167
Costal cartilages	11.80	1.18	10.0	.034	.0288
Cervical & thoracic vertebrae*	64.81	20.16	31.1	4.857	.2409
Cervical vertebrae	15.52	5.77	37.2	.617	.1069
Atlas	2.09	.85	40.7	.033	.0386
CV2-CV7 arches	9.57	3.74	39.1	.242	.0647
CV2-CV7 bodies	3.86	1.18	30.6	.342	.2898
Thoracic vertebrae	49.29	14.39	29.2	4.240	.2946
TV arches	24.83	9.45	38.1	1.170	.1238
TV bodies	24.46	4.94	20.2	3.070	.6215
Lumbar & sacral vertebrae*	104.78	29.49	28.1	8.779	.2977
Second lumbar vertebra	11.40	3.07	26.9	.887	.2889
Lumbar vertebrae	85.28	24.51	28.7	7.402	.3020
Lumbar vertebral arches	28.13	11.58	41.2	.852	.0736
LV 1-3 arches	13.03	5.18	39.8	.445	.0859
LV 4-7 arches	15.10	6.40	42.4	.407	.0636
Lumbar vertebral bodies	57.15	12.93	22.6	6.550	.5066
LV 1-3 bodies	21.30	4.71	22.1	2.570	.5456
LV 4-7 bodies	35.85	8.22	22.9	3.980	.4842
Sacrum	19.50	4.98	25.5	1.377	.2765
Pelvis*	75.60	26.54	35.1	3.414	.1286
Iliac crest	7.96	2.18	27.4	.530	.2431
Sacro-ilium	12.76	5.20	40.8	.788	.1515
Anterior ilium	6.76	3.18	47.0	.147	.0462
Acetabulum	23.36	9.06	38.8	1.200	.1325
Ischium	16.52	4.44	26.9	.464	.1045
Pubis	8.24	2.48	30.1	.285	.1149
Humerii*	63.50	27.44	43.2	1.883	.0686
H. shaft	33.30	16.86	50.6	.370	.0219
H. ends	30.20	10.58	35.0	1.513	.1430
H. prox. end	15.10	4.32	28.6	1.097	.2539
H. dist. end	15.10	6.26	41.5	.416	.0665
Long bones (except Hum.&Calv.)*	225.17	94.01	41.8	5.511	.0586
LB - H shafts	129.60	62.69	48.4	1.468	.0234
LB - H ends	95.57	31.32	32.8	4.043	.1291

Table 6b continued

Ulnae & radii	55.86	25.29	45.3	.8ØØ8	.Ø319
U&R shafts	35.7Ø	18.Ø7	5Ø.6	.326	.Ø18Ø
U&R ends	2Ø.16	7.22	35.8	.482	.Ø668
Ulnae	31.55	14.38	45.6	.484	.Ø337
U.shaft	18.5Ø	9.3Ø	5Ø.3	.186	.Ø2ØØ
U. ends	13.Ø5	5.Ø8	38.9	.298	.Ø587
U. prox. end	1Ø.74	4.43	41.2	.271	.Ø612
U. dist. end	2.31	.65	28.1	.Ø27	.Ø415
Radii	24.31	1Ø.91	44.9	.324	.Ø297
R. shaft	17.2Ø	8.77	51.Ø	.14Ø	.Ø16Ø
R. ends	7.11	2.14	3Ø.1	.184	.Ø86Ø
R. prox. end	2.43	.82	33.7	.122	.1488
R. dist. end	4.68	1.32	28.2	.Ø62	.Ø47Ø
Femora	91.5Ø	39.63	43.3	3.ØØØ	.Ø777
Fe shaft	44.7Ø	23.ØØ	51.5	.464	.Ø2Ø2
Fe ends	46.8Ø	16.63	35.5	2.616	.1573
Fe prox. end	24.9Ø	9.95	4Ø.Ø	1.576	.1584
Fe dist. end	21.9Ø	6.68	3Ø.5	1.Ø4Ø	.1557
Tibiae & Fibulae	77.81	29.Ø9	37.4	1.623	.Ø558
T&Fi shafts	49.2Ø	21.62	43.9	.678	.Ø314
T&Fi ends	28.61	7.47	26.1	.945	.1265
Tibiae	65.18	23.49	36.Ø	1.466	.Ø624
T. shaft	4Ø.9Ø	17.27	42.2	.626	.Ø362
T. ends	24.28	6.22	25.6	.84Ø	.135Ø
T. prox. end	15.62	3.59	23.Ø	.7Ø2	.1955
T. dist. end	8.66	2.63	3Ø.4	.138	.Ø525
Fibulae	12.63	5.6Ø	44.3	.157	.Ø28Ø
Fi. shaft	8.3Ø	4.35	52.4	.Ø52	.Ø12Ø
Fi. ends	4.33	1.25	28.9	.1Ø5	.Ø84Ø
Patellae & fabellae*	6.25	1.96	31.4	.175	.Ø893
Hands and feet*	1Ø1.32	33.44	33.Ø	.796	.Ø238
Hands	32.8Ø	1Ø.78	32.9	.294	.Ø272
Carpals	8.8Ø	2.68	3Ø.5	.Ø9Ø	.Ø337
Metacarpals	12.3Ø	4.58	37.2	.126	.Ø275
H. phalanges	11.7Ø	3.52	3Ø.1	.Ø77	.Ø22Ø
Feet	68.52	22.66	33.1	.5Ø2	.Ø222
Tarsals	32.48	1Ø.94	33.7	.266	.Ø243
Metatarsals	18.42	7.38	4Ø.1	.154	.Ø2Ø9
F. phalanges	17.62	4.34	24.6	.Ø82	.Ø19Ø
Tail	26.2Ø	4.75	18.1	.27Ø	.Ø568
Teeth	21.2Ø	12.73	6Ø.Ø	.176	.Ø138
Upper	12.6Ø	7.56	6Ø.Ø	.129	.Ø171
Lower	8.6Ø	5.17	6Ø.1	.Ø47	.ØØ9Ø
Hyoid bone	-	.14	-	.Ø18	.1286
Bonedust	-	.21	-	.Ø24	.1143

*The asterisked bones or groups of bones make up the total skeleton and contain within them the listed components

Table 6c. Summary of ^{238}Pu in the major sections of a monkey skeleton (animal R100F).

Nuclide: 238-Pu Days from injection to death: 67.000 Animal No: R100F

	Weight (g)			Radioactivity	
	Wet	Ashed	%ash	%ID	%ID/g ash
Head	141.90	56.34	39.7	2.163	.0384
Thorax	103.58	33.38	32.2	3.852	.1154
Spine	171.10	49.48	28.9	13.376	.2703
Pelvis	75.80	26.50	35.0	3.410	.1287
Upper limbs	152.02	63.57	41.8	2.992	.0471
Lower limbs	242.78	93.06	38.3	5.336	.0574
Tail	26.20	4.75	18.1	.270	.0568
Teeth	21.20	12.73	60.0	.175	.0137
Grand total	932.59	322.54	34.6	31.155	.0966

The early distribution of Pu in the monkey skeleton was well correlated both with total bone surface and the presence of red marrow (shown for R100F in Table 6a-c). The monkey bones with the greatest Pu concentrations (0.25 to 0.62 % ID/g ash) were sternum, vertebral bodies, sacrum, iliac crest, proximal humerus and clavicle ends -- structures composed mainly of cancellous bone with S/V ratios greater than 100 cm^2/cm^3, with ash fractions ranging from 14% in sternum to 30% in cervical vertebral bodies) and containing red marrow (29,59,60).

The bones of lowest Pu concentration (0.012 to 0.047 % ID/g ash) were those of the head, the teeth, the hand and foot bones and the shafts of the long bones -- structures composed mainly of compact bone with small S/V ratios, ash fractions ranging from 33% in hand and foot bones to 58% in the temporal and parietal bone of the skull, and small spaces containing mixed marrow (skull bones) or a single large fat-filled marrow cavity (tubular bones) (29,60,61).

The ribs, ends of long bones (except proximal humerus and femur), vertebral arches, scapulae and pelvis had Pu concentrations in the mid-range, from 0.06 to 0.20 % ID/g ash. Monkey ribs have an ash fraction of about 35% and a low-to-medium gross S/V ratio (see ref. 62 for man); they contain mainly red marrow. The ends of monkey long bones have ash fractions ranging from 23 to 41% and medium-to-large S/V ratios (ref. 29, monkeys; ref. 60, dog; ref. 59, man); except for the proximal ends of the humeri and femora, fatty marrow is present in adult life. For monkey R100F, the regions of the scapula and pelvis designated in Fig. 1 had ash fractions ranging from 30 to 51%; the gross S/V ratios of those parts have not been measured, but they are probably medium to small. Except for the head of the scapula and the iliac crest and sacro-iliac regions of the pelvis, which contain red marrow, the small amount of marrow space in the monkey scapulae and pelvis appears to contain mainly fatty marrow. The vertebral arches of Macaques are about 40% ash; they are mainly compact bone and can be expected to have a correspondingly small gross S/V ratio; their large spherical cavities are filled with fatty marrow.

For purposes of radiation protection, the ICRP presently assumes that Pu and other surface-seeking radionuclides are uniformly deposited on the surfaces of adult human bones (6). The degree of divergence from uniform initial Pu deposition on surfaces of monkey bones can be demonstrated by comparing the measured initial Pu concentrations in fine cancellous bone in red marrow (e.g., vertebral bodies and sternum) with the concentrations in compact bone (e.g., long bone shafts). We calculate from measured S/V ratios and the ash contents and densities of cancellous and compact bone of monkeys that the concentration ratio (compact/cancellous) should be about 0.13 for a uniform deposit of Pu on bone surfaces (28,29,58,59,61). At 7.5 ± 0.5 d after injection, the Pu concentrations (% ID/g ash) in adult monkey bones were as follows: lumbar vertebral bodies, 0.78 ± 0.40; sternum, 0.73 ± 0.42; long bone shafts, 0.022 ± 0.015. The corresponding initial concentration ratios [compact bone (% ID/g

ash)/cancellous bone (% ID/g ash)], 0.026 ± 0.011 for the lumbar vertebral bodies and 0.031 ± 0.017 for the sternum, were one-fourth to one-fifth of that expected for an uniform surface deposit, and the implication is that the initial concentration of Pu on surfaces of trabeculae in red marrow is at least 4.5 times that on compact bone surfaces. That estimate agrees with the ratios of Pu surface concentrations (ranging from 3.6 to 4.6) obtained from quantitative autoradiography of dog bones (63-65), but it is less than the ratio of 8.3 that can be obtained from quantitative autoradiography of the initial Pu labelling of trabecular and long bone shaft surfaces of a human Pu injection case (58). Concentration ratios based on these radiochemical measurements are expected to be less than those obtained from counting the alpha tracks only on microscopically identifiable trabecular and cortical bone surfaces, because the cancellous bone specimens contained some cortical bone (outer shells and incomplete separation of vertebral bodies from arches), and the specimens of compact bone (long bone shafts) were not freed of all trabeculae.

Thus, gross initial concentration ratios (cancellous/compact) based on measurement of injected radioactivity/g ash in standardized samples of bone agree reasonable well with those obtained by quantitative autoradiography, and can be used in their stead for calculating initial deposited Pu fractions in rapidly and slowly renewing bone compartments for purposes of metabolic modelling.

Pu retention in skeletal parts: Net Pu retention in several bones and groups of structurally similar bones and bone parts was examined over the study interval.

The t-test was used to compare the mean Pu content of selected bone specimens of six adult monkeys killed at 7.5 ± 0.5 d (initial deposition) with the mean for six monkeys killed between 370 and 1100 d after injection (mean time of death 711 ± 310 d). The results are presented in Table 7. Bones that lost a larger fraction of their initial Pu content than the whole skeleton were sternum, sacrum and lumbar vertebral bodies. Those that lost about the same fraction of their initial Pu as the whole skeleton were ribs, pelvis, skull, scapulae and mandible. The ends of the long bones lost a smaller fraction of their initial Pu content than the whole skeleton, and there was no demonstrable loss (or perhaps a small gain) from the feet and hands (not shown) and long bone shafts. The Pu content of the whole skeleton and all of the selected bone specimens except long bone ends (excluding proximal humeri and femora), feet, hands and long bone shafts was significantly less ($p < 0.05$) at 1 to 3 y than it was initially.

The Pu retention in the selected skeletal parts was also examined by linear regression. Semi-log plots were prepared for the 13 sets of bone data. Fig. 5 shows those for whole skeleton (excluding teeth and tail), the bodies of four lumbar vetebrae (LV4-LV7, which are mainly cancellous bone in red marrow) and the long bone shafts (which are mainly compact bone). The parameters of regression lines were

Table 7. ^{238}Pu content of selected skeletal parts of adult monkeys, initially (7.5 ± 0.5 d), and several years (711 ± 310 d) after injection of ^{238}Pu(IV) citrate

Skeletal part	Pu content (% ID ± S.D.) at days after injection[a] 7.5 ± 0.5 d	711 ± 310 d[c]	Fraction of Pu retained[b]
Sternum	.68 ± .15	.22 ± .11	.32
Sacrum	1.6 ± .81	.51 ± .21	.32
Four vert. bodies (LV4-LV7)	2.8 ± .90	1.1 ± .43	.39
Ribs	1.9 ± .41	.87 ± .38	.46
Pelvis	3.1 ± 1.44	1.5 ± .73	.47
Skull[d]	3.5 ± 1.4	1.7 ± .69	.48
Skeleton[e]	28.4 ± 8.1	13.9 ± 5.4	.49
Scapulae	1.1 ± .29	.61 ± .22	.54
Mandible[d]	.82 ± .33	.45 ± .06	.55
Prox. hum. & fem.	1.6 ± .54	.95 ± .46	.58
Other long bone ends[f]	1.1 ± .65	.78 ± .38	.74
Feet	.49 ± .27	.40 ± .23	.82
Long bone shafts[g]	.99 ± .49	.99 ± .37	1.0

[a] Six animals killed in each designated interval.
[b] Fraction of Pu retained = [Pu (% ID) at 711 ± 310 d]/[Pu (% ID) at 7.5 ± 0.5 d].
[c] Means at 7.5 ± 0.5 and at 711 ± 310 d were compared using the t-test (45); single underline ($0.02 < p < 0.05$; double underline, $p < 0.01$.
[d] Teeth excluded.
[e] Skeleton does not include teeth or tail.
[f] Proximal and distal ends of radii, ulnae, tibiae and fibulae and distal ends of humeri and femora.
[g] Shafts of humeri, radii, ulnae, femora, tibiae, fibulae.

calculated by least squares fitting of 2.3 $\log_{10}$ (% ID) of skeletal part vs. days after Pu injection, for the following intervals: (i) 7 to 173 d and 173 to 1100 d or 370 to 1100 d, (ii) 7 to 1100 d (all data). The appropriate regression lines (or line) were selected for each bone data set based on the agreement between the measured values at 7.5 ± 0.5 d and at 711 ± 310 d (see Table 7) and the values calculated from the equations of the fitted curves. The parameters of the selected exponential functions are collected in Table 8. Because of the small size of the data set and the individual variations in initial Pu deposition and in Pu recirculation, more rigorous or sophisticated curve fitting procedures did not seem to be warranted.

The temporal pattern of Pu retention in each bone specimen generally agreed with the behavior expected from its structure:

• Sternum, vertebral bodies and sacrum have large complements of cancellous bone in red marrow and thin cortical shells. They lost 29 to 51% of their initial Pu content rapidly ($T_{\frac{1}{2}}$ of fast component, 84 to 144 d), and they continued to lose Pu faster than the whole skeleton ($T_{\frac{1}{2}}$ of slower component, 729 to 1612 d).

• Pelvis, scapulae, ribs and the proximal ends of the humeri and femora contain some cancellous bone in red marrow but have thick cortical shells (ribs, long bone ends) or a significant complement of compact bone (pelvis, scapulae). They lost 31 to 56% of their initial Pu content somewhat faster or at about the same rate as the whole skeleton ($T_{\frac{1}{2}}$ of fast component, 110 to 364 d). The ribs and scapulae experienced no further net Pu loss, while the pelvis and humeri and femora proximal ends continued to lose Pu at the same rate as the skeleton ($T_{\frac{1}{2}}$ of slower component, 4076 d).

• Skull and mandible are mainly compact bone, but they contain small amounts of coarse trabeculae, and some skull bones contain red marrow; the long bone ends (except humerii and femora) contain trabecular bone with a wide range of S/V ratios; they have thick cortical shells and fatty marrow. The Pu content of those bones was best represented by one exponential term, fitted from 7 to 1100 days after injection. Net Pu loss from those bones occurred at a rate about twice as fast as the slower component of the whole skeleton ($T_{\frac{1}{2}}$, 990 to 2038 d).

The bones of the hands and feet are comprised of compact bone and coarse trabecular bone in fatty marrow; the long bone shafts are nearly all compact bone. There was no net loss of Pu from those bones, and their Pu content was best described from 7 to 1100 d after injection by the grand mean ± S.D. of all the measured values. Linear regression calculated for all data points yielded positive slopes for these bones, but the grand mean agreed better with the means calculated at 7.5 ± 0.5 d and 711 ± 310 d.

The differential rates of Pu loss from compact and cancellous bone structures are shown most clearly in Fig. 6 by the five-fold

Table 8. Retention of ^{238}Pu, injected as ^{238}Pu(IV) citrate, in representative parts of the adult monkey skeleton expressed as the parameters (coefficients, A_i, % ID; rate constants, λ_i, d^{-1}) of an exponential equation of the form:

$$R(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t}$$

Skeletal part	A_1 (% ID)	λ_1 (d^{-1})	A_2 (% ID)	λ_2 (d^{-1})	$A_1/(A_1+A_2)$
Sternum[a]	.35	.0078	.35	.00084	.50
Sacrum[b]	.41	.0082	.98	.00098	.29
Four vert. bodies[a] (LV4-LV7)	1.43	.0048	1.36	.00043	.51
Pelvis[a]	1.13	.0062	1.52	.00021	.43
Ribs[a]	1.04	.0036	.83	~0	.56
Skeleton[a,e]	12.4	.0032	14.7	.00017	.46
Prox. hum. & fem.[b]	.47	.0029	1.05	.00016	.31
Scapulae[a]	.50	.0019	.58	~0	.46
Skull[c,e]	---	---	2.86	.0007	---
Mandible[c,e]	---	---	.76	.0006	---
Other long bone ends[c]	---	---	1.0	.00034	___
Feet[d]	---	---	.44	~0	---
Long bone shafts[d]	---	---	.97	~0	---

[a] Two exponential components fitted independently by least squares over the intervals 7 to 173 d and 370 to 1100 d.

[b] Two exponential components fitted independently by least squares over the intervals 7 to 173 d and 173 to 1100 d.

[c] One exponential component fit by least squares to all data points, 7 to 1100 d. See also f.n. f, Table 7.

[d] Arithmetic mean of all data points, 7 to 1100 d. See also f.n. g, Table 7.

[e] Skull, mandible and skeleton exclude teeth; skeleton also excludes tail.

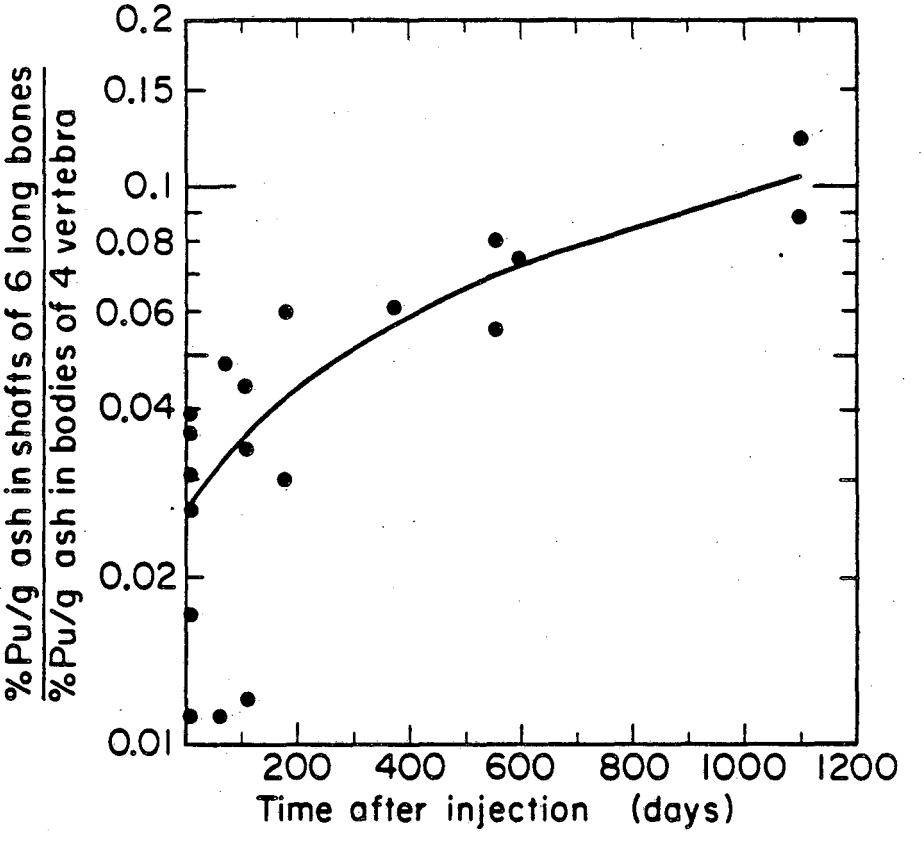

Figure 6. Change with time after injection of ^{238}Pu(IV) citrate of ratio of Pu concentrations in compact bone (% injected Pu/g ash, six paired long bone shafts) to cancellous bone (% injected Pu/g ash, four lumbar vertebral bodies, LV4-LV7).

increase in the concentration ratio (compact/cancellous) between 7.5 ± 0.5 and 1100 d.

DISCUSSION

Although the greatest potential hazards from Pu absorbed into the body are damage or neoplasia in skeletal tissues (8), the new ICRP protection system requires that other tissues also be taken into account in assessing total risk and setting limits (6). It is, therefore, desirable to define Pu distribution and retention in gonads and in liver and other organs with significant 50-y committed dose equivalents, because conservative default values must be applied in the absence of data (66). This study supplies detailed data for the deposition and retention of Pu in 22 distinct soft tissues, four endocrine glands, the male and female gonads and eight reproductive accessory structures of adult monkeys.

Extraskeletal Pu distribution in the monkeys was qualitatively similar to other animals studied (7,8,32,39,47,51). Initially, Pu was prominent in hepatic cells, and to a lesser degree, in renal tubular structures, nonskeletal mineralized structures (e.g., tracheal cartilages, renal stones) and the medial layers of arteries and arterioles; it was consistently present at low concentrations in the reticulum of all tissues. With time, the reticular component of Pu diminished to occasional single, rarely multiple, alpha tracks emanating from brown pigment, presumed to be hemosiderin, contained by phagocytes (RE cells).

Considerable care will be needed in using the monkey data to develop human models, as is demonstrated by the following example. For the adult monkey at 1 d, the Pu in soft tissues other than liver and kidneys was about 35 % ID (animal C108F), and that was close to the value of 24 % ID obtained by extrapolation of available human data (16). The half-times of the slow (second) components of the two-component exponential equations used to describe the soft tissue data for monkeys and man were also close, 448 and 495 d, respectively. In two important respects the patterns of Pu loss from the bulk of soft tissue differed between the two species: (i) the early rate of Pu loss, from 1 to about 21 d after intake to plasma, was somewhat faster in the monkey than in the Pu-injected people; the half-times, which are poorly defined, were roughly 3 and 7 d, respectively. (ii) The most striking difference was the magnitude of the slowly clearing soft tissue compartment; about 88% of the Pu present in the monkey soft tissues at 1 d was lost at the rapid rate, while about two-thirds of the Pu in the human soft tissues at 1 d was lost at the slower rate.

Within days after intake to plasma, only a small fraction of the Pu in monkey soft tissues can be accounted for by trapped plasma or ECF or by contemporaneous circulatory feedback. The data suggest that larger amounts of connective tissue, specialized RE cells and/or foci of extraskeletal mineralization -- all entities that can sequester or bind Pu -- are present in older people than in adult monkeys or young

adult dogs (39,47,51).

The ICRP recommends deposited fractions for Pu in human testis and ovary, expressed as percent of intake to plasma, of 3.5×10^{-2} and 1.1×10^{-2} %, respectively (6). The Pu content of adult monkey testis and ovary, was 5.8×10^{-2} and 5.1×10^{-3} % ID, respectively (Tables 3a and 3b). The monkey testis and ovary initially accumulated 1.7 and 0.46 times, respectively, the recommended deposited fractions for Pu in the human gonads. The level of agreement, within a factor of two, between the measured values for Pu deposition in monkey gonads and the nominal values ICRP has assumed for people provides support for the ICRP recommendations. However, the initial Pu concentrations in the monkey gonads (%/g) are 1.4 and 9.3 times, respectively, those assumed by ICRP for human testis and ovary. The proportional weights of the mature fertile gonads of the two species differ substantially: 0.5 g/kg and 5.8 g/kg for human and monkey testis, respectively, and 0.2 g/kg and 0.1 g/kg for human and monkey ovary, respectively. One source of confusion is the variable presence of corporea lutea of menstruation and atrectic follicles, which add mass and Pu-binding capacity but contain no germinal tissue. The rather large differences in the gonad proportion of the body weight of fertile young adult to middle aged members of these two closely related species indicates the need for new work in quantitative microanatomy to describe the amounts and organization of testicular and ovarian germinal and connective tissue constituents and the changes in their amounts and proportions that accompany advancing age.

This study focusses attention once again on the interspecies variation in the kinetics of the actinides (and probably other multicharged cations as well) in the mammalian liver. In both dogs and monkeys, there appears to be more, and more rapid, recirculation of liver Am than liver Pu at administered dosages that probably do not produce large amounts of early radiation damage (9,51,67). The major difference between the metabolism of actinides by dog and monkey livers appears to be the rate of release of hepatic actinide to bile -- slow in the dog and fast in the monkey. The available data suggest that while the excretory outlet for Pu from human liver is not fast, the true half time is less than the 40 y recommended by ICRP (6,7). The data from these two animals suggest that while net retention of Pu in human liver may be long, there is much dosimetrically important recirculation of Pu between liver and bone. When these studies are complete, there will be four large data sets for two nuclides (Am and Pu) in two large, long-lived species (dogs and monkeys), which should allow preparation and testing of a more physiologically descriptive model for tri- and tetravalent actinide elements in mammalian liver.

The new ICRP system for limiting radionuclide intakes by workers requires calculation of the average radiation dose to the endosteal cells of bone (the 10 μm thick layer of surface) rather than the whole skeleton as was done formerly (6,4). The recommended mass of endosteal cells was based on measurements of S/V ratios in some

representative specimens of cancellous and compact bone and estimates of the masses of those constituents of each bone or group of similar bones (59,61,62). Bone-surface-seeking nuclides are assumed to be initially deposited uniformly on all bone surfaces and to remain there until removed at an uniform rate for the whole skeleton. It was acknowledged that the skeleton is a complex organ composed of mineralized and connective tissue and active (red) and fatty marrow in proportions and geometric arrangements unique to each bone or group of similar bones. Radiation dose rates and 50-y committed doses were not calculated separately for the endosteal surfaces of cancellous and compact bone, because the needed data were lacking for intraskeletal distributions of bone-seeking nuclides and the temporal changes of their amounts and locations in the normal adult human skeleton.

Jee and co-workers have established the following in the dog: (i) the broad range of S/V ratios among trabeculae in different skeletal sites, (ii) the equally broad range of directly related structural remodelling (turnover) rates, and (iii) the high degree of association of Pu deposition on the surfaces of the finest and most rapidly remodelled trabeculae in red marrow sites (11,12,56,60,63,64). Those findings have been confirmed for the monkey by measurement of S/V ratios in a small selection of trabecular and compact monkey bone samples (29,59) and of Pu content and concentration in the parts of well subdivided skeletons of serially sacrificed monkeys in this study. The monkey has an efficient outlet for Pu, by way of the liver and biliary excretion, which suppresses circulatory feedback enough to permit demonstration by radiochemical evidence alone of the greater turnover of Pu in cancellous structures in red marrow than in other skeletal parts. As predicted by anatomical and radiochemical evidence in the dog (11,12,39,47,51,56,60,63,64), both the amount of Pu lost and the rate of loss of Pu from the skeletal parts of the monkey was in the order: fine cancellous bone in red marrow > fine to coarse trabeculae in fatty marrow > compact bone.

The autoradiographic and radiochemical data from both dogs and monkeys concerning the initial Pu distribution in the skeleton (skewed to cancellous bone in red marrow), the patterns of Pu loss from different bone structures (more rapid from cancellous bone in red marrow), and the influence of circulatory feedback on late Pu distribution (continuous slow accumulation in compact bone), agree with recent findings on Pu distribution in the adult human skeleton. The early preferential deposition of Pu on cancellous bone surfaces in red marrow, was observed in the exhumed bones of a young woman who died of Cushing's disease 17 months after a Pu injection (13,14,58), while the Pu distribution was much more uniform in the skeletal remains of a man who died of natural causes 20.7 y after a Pu injection (58).

The detailed data for intraskeletal Pu distribution, provided by this study for monkeys during the first 3 y after intake to plasma, should materially assist development of a more realistic location-specific time-dependent dosimetric model for Pu and other

actinides in bone. An assumed linear dose-effect relationship presently supplies the estimate of bone cancer risk that underlies calculation of risk or radiation dose per unit of intake for bone-seeking radionulcides (6). While that practice may be appropriate for radiation protection purposes, it is a fact that we still do not know how to calculate the quantity, location or rate of delivery of the radiation dose that is biologically relevant to bone cancer induction in man or any experimental animal. The availability of a new bone dosimetry model, that incorporates the peculiar initial distribution of the actinides (especially Pu), the differential rates of release of nuclides from various skeletal parts and the contribution of circulatory feedback to bone surface dose should advance our efforts to define the appropriate cancerogenic bone dose.

REFERENCES

1. American Physical Society Study Group on Nuclear Fuel Cycles and Waste Management. Rev. Mod. Phys. 50, No. 1, pt. 2, Jan. 1978.

2. T.H. Pigford and K.P. Ang, The plutonium fuel cycles. Health Phys. 29, 451-468 (1975).

3. National Academy of Sciences - National Research Council Committee on Radioactive Waste Management, Panel on Hanford Wastes, Radioactive Wastes on the Hanford Reservation: A Technical Review. National Academy of Sciences, Washington, D.C. (1978).

4. International Commission on Radiological Protection, Report of Committee II on Permissible Dose for Internal Radiation. Health Phys. 3, 1-380 (1960).

5. W.H. Langham, S.H. Bassett, P.S. Harris and R.E. Carter, Distribution and Excretion of Plutonium Administered Intravenously to Man, Los Alamos Scientific Laboratory. LA-1151 (1950). Reproduced in Health Phys. 38, 1031-1060 (1980).

6. International Commission on Radiological Protection, Limits for Intakes of Radionuclides by Workers, ICRP Pub. 30, Part 1. Ann. ICRP 2 (No. 3/4), 1-116 (1979).

7. International Commission on Radiological Protection, The Metabolism of Compounds of Plutonium and Other Actinides, report of a Task Group of Committee 2. ICRP Pub. 19, Pergamon Press, Oxford (1972).

8. J. Vaughan, B. Bleaney and D.M. Taylor, Distribution, excretion and effects of plutonium as a bone-seeker. In Handbook of Experimental Pharmacology, v. 36, Uranium, Plutonium, Transplutonic Elements (H.C. Hodge, J.N. Stannard and J.B. Hursh, eds.) pp. 349-502. Springer-Verlag, Berlin (1973).

9. P.W. Durbin, Metabolism and biological effects of the transplutonium elements. Ibid, pp. 739-896.

10. P.W. Durbin and N. Jeung, Reassessment of plutonium in the human body based on experiments with non-human primates. In Health Effects of Plutonium and Radium (W.S.S. Jee, ed.) Proc. of a Workshop, Sun Valley, Idaho, Oct. 6-9, 1975, pp. 297-314. The JW Press, Dept. of Anatomy, Univ. of Utah, Salt Lake City (1975).

11. W.S.S. Jee, The relationship of trabecular bone surface areas, bone turnover rates, and initial uptake of Pu and Ra to sites of occurrence of osteosacoma in beagles. Radiobiology Laboratory Annual Report, Univ. of Utah, College of Medicine, Salt Lake City, UT 84112. COO-119-253, pp. 220-223 (1978).

12. T.J. Wronski, J.M. Smith and W.S.S. Jee, The microdistribution and retention of injected ^{239}Pu on trabecular bone surfaces of the beagle: Implications for the induction of osteosacroma. Radiat. Res. 83, 74-89 (1980).

13. R.P. Larsen, R.D. Oldham, C.G. Cacic, J.E. Farnham and J.R. Schneider, Distribution of injected plutonium in the skeleton and certain soft tissues. Radiological and Environmental Research Division Annual Report, Argonne National Laboratory, 9700 S. Cass Ave., Argonne, IL 60439. ANL-78-65, Part II, pp. 145-153 (1978).

14. R.P. Larsen, R.D. Oldham and S.M. Martin, Distribution of plutonium amongst and within selected bones from an injection case. Radiological and Environmental Research Division Annual Report, Argonne National Laboratory, 9700 S. Cass Ave., Argonne, IL 6039. ANL-79-65, Part II, pp. 115-119 (1979).

15. B.D. Breitenstein, C.E. Newton, H.T. Norris, K.R. Heid, B. Robinson, E.H. Palmer, G.A. Rieksts, H.B. Spitz, J.F. McInroy, H.A. Boyd, B.C. Eutsler, D. Romero, P.W. Durbin and C.T. Schmidt, The U.S. Transuranium Registry Report on the ^{241}Am content of a whole body, Parts I - V. Health Phys. In press.

16. P.W. Durbin, Plutonium in man: a new look at the old data. In Radiobiology of Plutonium (B.J. Stover and W.S.S. Jee, eds.) pp. 469-530. The JW Press, Dept. of Anatomy, Univ. of Utah, Salt Lake City (1972).

17. E.E. Campbell, M.F. Milligan, W.D. Moss, H.F. Schulte and J.F. McInroy, Plutonium in Autopsy Tissue, Los Alamos Scientific Laboratory, Los Alamos, NM 87544. LA-4875 (1973).

18. L.H. Hempelmann, C.R. Richmond and G.L. Voelz, A Twenty-Seven Year Study of Selected Los Alamos Plutonium Workers, Los Alamos Scientific Laboratory, Los Alamos, NM 87544. LA-5148-MS (1973).

19. I.C. Nelson, K.R. Heid, P.A. Fuqua and T.D. Mahoney, Plutonium in autopsy tissue samples. Health Phys. 22, 925-930 (1972).

20. C.R. Lagerquist, S.E. Hammond and D.B. Hylton, Distribution of plutonium and americium in the body 5 years after an exposure via contaminated puncture wound. Health Phys. 22, 921-924 (1972).

21. B.G. Bennett, Environmental pathways of transuranic elements. In Plutonium and Other Transuranium Elements: Sources, Environmental Distribution and Biomedical Effects. U.S. Atomic Energy Commission Report WASH-1359, pp. 131-152 (1974). National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161.

22. J.F. McInroy, E.E. Campbell, W.D. Moss, G.L. Tietjen, B.C. Eutsler and H.A. Boyd, Plutonium in autopsy tissue: a revision and updating of data reported in LA-4875. Health Phys. 37, 1-136 (1979).

23. T. Fox, G.L. Tietjen and J.F. McInroy, Statistical analysis of a Los Alamos Scientific Laboratory study of plutonium in U.S. autopsy tissue. Health Phys. 39, 877-892 (1980).

24. H. Mussalo, T. Jaakkola and J.K. Miettinen. Distribution of fallout plutonium in southern Finns. Health Phys. 39, 245-255 (1980).

25. K. Bunzl and W. Kracke, Fallout $^{239/240}$Pu and ^{238}Pu in human tissues from the Federal Republic of Germany. Health Phys. 44, 441-450 (1983).

26. J.R. Napier and P.H. Napier, A Handbook of Living Primates. Academic Press, London (1967).

27. I.S. Bernstein, Birth of two second generation hybrid Macaques. J. Human Evolution 3, 205-206 (1974).

28. J.K. Gong, J.S. Arnold and S.H. Cohn, Composition of trabecular and cortical bone. Anat. Rec. 149, 325-332 (1964).

29. J.M. Smith, P.W. Durbin, N. Jeung, G. Van Wagenen and W.S.S. Jee, Measurement of some characteristics of trabecular bone of humerus, lumbar vertebrae, calvarium, and of cortical bone of humerus of adult Rhesus monkey (Macaca mulatta), Radiobiology Division Annual Report, Univ. of Utah, College of Medicine, Salt Lake City, UT 84112. COO-119-254, pp. 33-54 (1979).

30. P.W. Durbin, N. Jeung and C.T. Schmidt, Distribution and retention of ^{238}Pu in Macaque monkeys. In Proceedings of the Seventh International Congress of Radiation Research (J.J. Broerse et al., eds.) Sessions E, Dosimetry, Radionuclides and Technology, paper No. E5-03. Martinus Nijhoff Publishers, Amsterdam (1983).

31. P.W. Durbin, N. Jeung and C.T. Schmidt, Distribution and retention of ^{238}Pu in Macaque monkeys. Biology and Medicine Division Annual Report, Lawrence Berkeley Laboratory, Berkeley, CA 94720. LBL-16840, pp. 40-42 (1984).

32. P.W. Durbin, Plutonium in mammals: influence of plutonium chemistry, route of administration, and physiological status of the animal on initial distribution and long-term metabolism. Health Phys. 29, 495-510 (1975).

33. P.W. Durbin and N. Jeung, Early behavior of ^{238}Pu in the monkey (Macaca mulatta, Macaca fasicularis). Radiat. Res. 62, 576 (1975), abstract.

34. P.W. Durbin, M.W. Parrott, M.H. Williams, M.E. Johnston, C.W. Asling and J.G. Hamilton, Metabolic studies with strontium-90 in the Rhesus monkey (preliminary report). In The Shorter-term Biological Hazards of a Fallout Field (G.M. Dunning and J.A. Hilcken, eds.) proc. of a conference, Dec. 1956, Washington, D.C. sponsored by U.S. AEC and DOD, pp. 173-183 (1956). Superintendent of Documents. U.S. Government Printing Office, Washington, DC.

35. P.W. Durbin, M.H. Williams and N. Jeung, Long-term retention and intraskeletal distribution of ^{90}Sr in Rhesus monkeys (Macaca mulatta). Health Phys. 25, 335 (1973), abstract.

36. P.W. Durbin, N. Jeung, M.H. Williams and M.W. Parrott, Long-term metabolism of ^{90}Sr in Rhesus monkeys (Macaca mulatta). In Proceedings of the Third International Congress of the International Radiation Protection Association, Washington, D.C., Sept. 9-14, 1973, pp. 1412-1417. CONF-730907 (1974).

37. C.M. Lederer and V.S. Shirley (eds.) Table of Isotopes, 7 ed., John Wiley, New York (1978).

38. K.L. Swinth and P.N. Dean, Intercalibration for low-energy photon measurements. Health Phys. 25, 599-603 (1973).

39. B.J. Stover, D.R. Atherton, F.W. Bruenger and D.S. Buster, Further studies of the metabolism of ^{239}Pu in adult beagles. Health Phys. 8, 589-598 (1962).

40. G. Van Wagenen and C.W. Asling, Roentgenographic estimation of bone age in the Rhesus monkey (Macaca mulatta). Am J. Anat. 103, 163-186 (1958).

41. V.O. Hurme and G. Van Wagenen, Basic data on the emergence of permanent teeth in the Rhesus monkey (Macaca mulatta). Proc. Am. Phil. Soc. 105, 105-140 (1961).

42. C.T. Schmidt and P.W. Durbin, In vivo measurement of the distribution kinetics of ^{241}Am in monkeys with a fixed-position 4-detector counter and a whole-body scanner. Health Phys. 31, 543 (1976). Abstract.

43. M.I. Gregersen, H. Sear, R.A. Rawson, S. Chien and G.L. Saiger, Cell volume, plasma volume, total blood volume and F_{cells} factor in the Rhesus monkey. Am. J. Physiol. 196, 184-187 (1959).

44. E.M. Widdowson and J.W.T. Dickerson, Chemical composition of the body. In Mineral Metabolism (C.L. Comar and F. Bronner, eds.) vol. II, part A., pp. 2-248. Academic Press, New York (1964).

45. R.A. Fisher, Statistical Methods for Research Workers. Hafner Publishing Co., New York (1954).

46. F.W. Bruenger, J.M. Smith, D.R. Atherton, S.C. Miller, W.S.S. Jee and W. Stevens, Radiation dose rates to the proximal humerus of growing beagles injected with ^{239}Pu. Radiat. Res. 97, 302-317 (1984).

47. R.D. Lloyd, D.R. Atherton, S.S. McFarland, C.W. Mays, W. Stevens, J.L. Williams and G.N. Taylor, Studies of injected ^{237}Pu(IV) citrate in beagles. Health Phys. 30, 47-52 (1976).

48. J.A. Mewhinney, Radiation dose patterns in immature and aged beagle dogs following inhalation of $^{241}AmO_2$. Inhalation Toxicology Research Institute Annual Report, Lovelace Biomedical and Environmental Research Inst., P.O. Box 5890, Albuquerque, NM 87185. LMF-113, pp. 102-106 (1984).

49. R.A. Guilmette, N. Cohen and M.E. Wrenn, Distribution and retention of ^{241}Am in the baboon. Radiat. Res. 81, 173-183 (1981).

50. T. Lo Sasso, N. Cohen and M.E. Wrenn, Distribution and retention of $^{243,244}Cm$ in the adult baboon. Radiat. Res. 85, 173-183 (1981).

51. B.J. Stover, D.R. Atherton and D.S. Buster, Retention of ^{239}Pu(IV) in the beagle. In Radiobiology of Plutonium (B.J. Stover and W.S.S. Jee, eds.) pp. 149-170. The J.W. Press, Department of Anatomy, University of Utah, Salt Lake City (1972).

52. F.W. Bruenger, W. Stevens, D.R. Atherton, W.S.S. Jee and J.M. Smith, Skeletal retention of ^{239}Pu and ^{226}Ra in beagles injected at ages ranging from 2 days to 5 years. Radiobiology Laboratory Annual Report, Univ. of Utah College of Medicine, Salt Lake City, UT 84112. COO-119-257, pp. 12-15 (1982).

53. M.J. Moroney, Facts from Figures. Penguin Books Ltd., Harmondsworth, Middlesex (1951).

54. J.G. Hamilton, The metabolism of the fission products and the heaviest elements. Radiology 49, 325-343 (1947).

55. J.S. Arnold and W.S.S. Jee, Bone growth and osteoclastic activity as indicated by radioautographic distribution of plutonium. Am. J. Anat. 101,367-417 (1957).

56. J.S. Arnold and W.S.S. Jee, Autoradiography in the localization and radiation dosage of Ra-226 and Pu-239 in the bones of dogs. Lab. Invest. 8, 194-204 (1959).

57. N.D. Priest and S. Jackson, Plutonium in bone: a high resolution autoradiographic study using plutonium-241. Int. J. Radiat. Biol. 32, 325-350 (1977).

58. R.A. Schlenkere and B.G. Oltman, Plutonium microdistribution in human bone. In Actinides in Man and Animals (M.E. Wrenn, editor) pp. 199-206. The RD Press, Univ. of Utah, Salt Lake City (1981).

59. A.H. Beddoe, A quantitative study of the structure of trabecular bone in man, Rhesus monkey, beagle and miniature pig. Calcif. Tiss. Res. 25, 273-281 (1978).

60. D. Kimmel, C. Smith and W.S.S. Jee, Comparison of bone turnover in various regions of trabecular bone in the young adult beagle. Radiobiology Division Annual Report, Univ. of Utah College of Medicine, Salt Lake City, UT 84112. COO-119-256, pp. 74-89 (1980).

61. A.H. Beddoe, Measurements of the microscopic structure of cortical bone. Phys. Med. Biol. 22, 298-308 (1977).

62. E. Lloyd and D. Hodges, Quantitative characterization of bone: A computer analysis of microradiographs. Clin. Orthop Rel. Res. 78, 230-250 (1970).

63. J.A. Twente, E.G. Butler and W.S.S. Jee, The localized distribution of ^{239}Pu in the lumbar vertebral centra of 5-level dogs. Radiobiology Laboratory Annual Report, Univ. of Utah College of Medicine, Salt Lake City, UT 84112. COO-119-220, pp. 168-196 (1960).

64. N.L. Dockum, R.S. Mical, R. Tegge, M. Lowe, C.W. Mays and W.S.S. Jee, Quantitative autoradiographic dose determinations of ^{239}Pu in bones. Radiobiology Laboratory Annual Report, Univ. of Utah College of Medicine, Salt Lake City, UT 84112. COO-119-229, pp. 127-132 (1964).

65. R.D. Lloyd, W.S.S. Jee, D.R. Atherton, G.N. Taylor and C.W. Mays, Americium-241 in beagles: Biological effects and skeletal distribution. In Radiobiology of Plutonium (B.J. Stover and W.S.S. Jee, eds.)
pp. 141-148. The J.W. Press, Dept. of Anatomy, Univ. of Utah, Salt Lake City (1972).

66. International Commission on Radiological Protection, Limits for Intakes of Radionuclides by Workers, ICRP Pub. 30, Suppl. to Part 1. Ann. ICRP 3 (No. 1/4), 1-552 (1979).

67. R.D. Lloyd, C.W. Mays, G.N. Taylor, and D.R. Atherton, Americium-241 studies in beagles. Health Phys. 18, 149-156 (1970).

Appendix A. Experimentally determined curves used to correct observed ^{238}Pu emission rates for self-absorption in samples

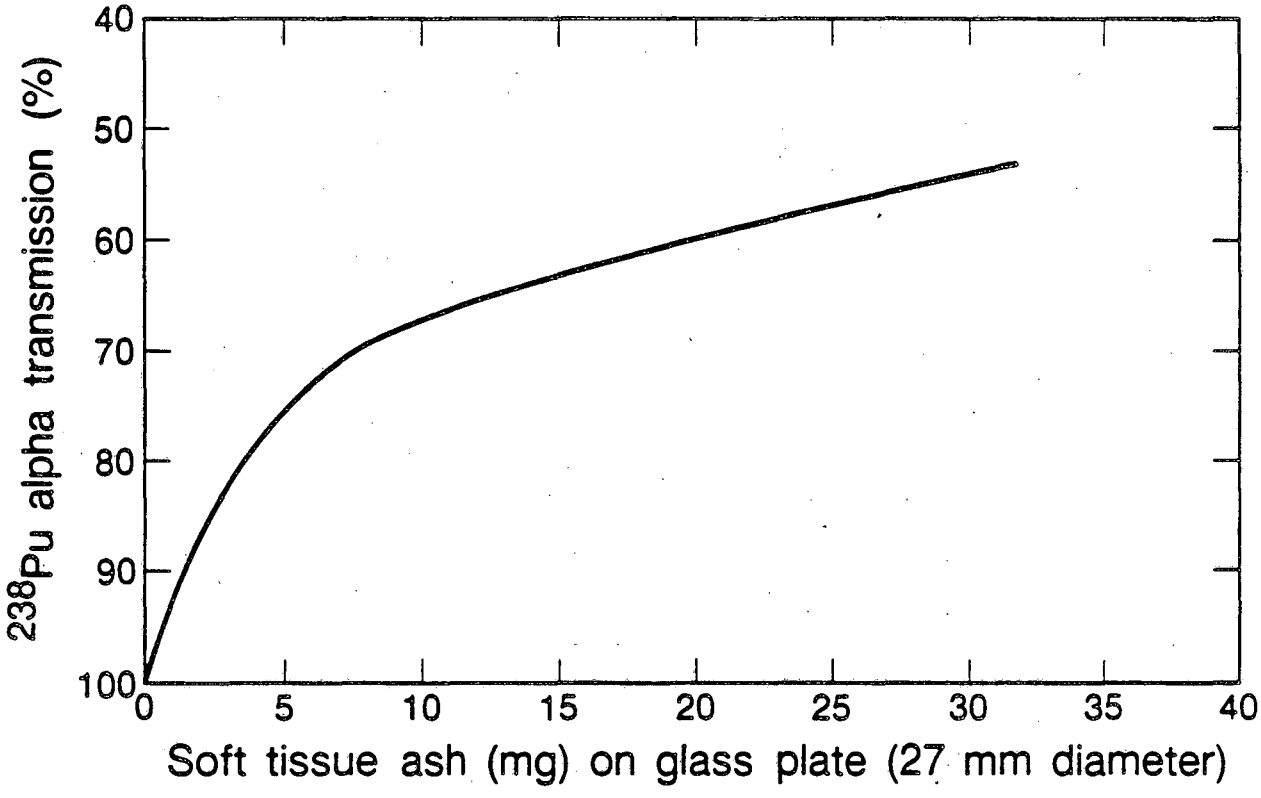

Figure A-1. Self-absorption curve for alpha counting of ^{238}Pu in plasma and aliquots of soft tissues, based on weight of dry ash on glass planchets. Aliquots of ash dissolved in 6 N HNO_3 were evenly spread and evaporated on tared glass planchets, which were reweighed. Curve shown is for planchets 27 mm in diameter. Curve was obtained by adding known amounts of ^{238}Pu to tissue and blood ash samples weighing 5 to 250 mg.

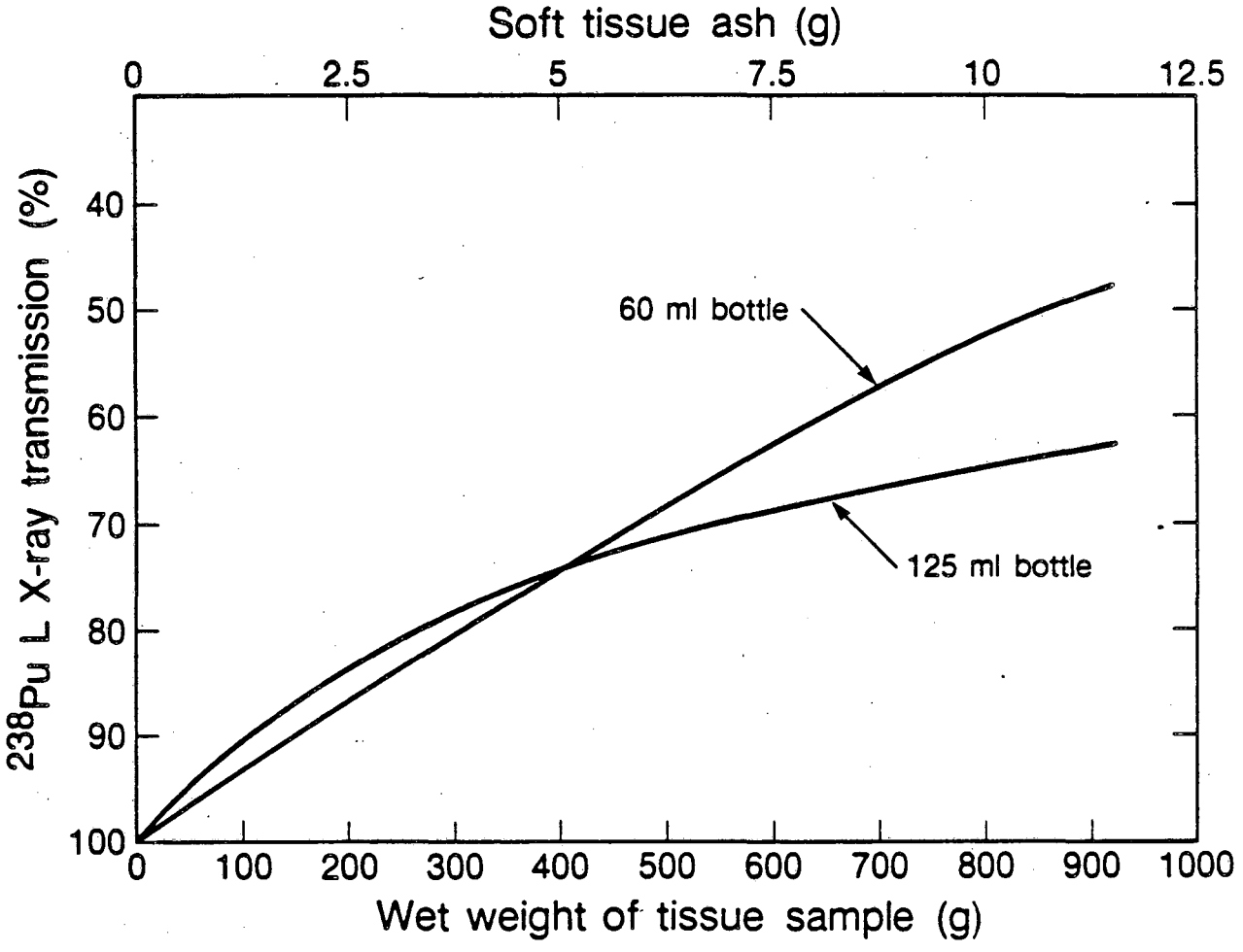

Figure A-2. Self-absorption curves for photon counting of ^{238}Pu in large soft tissues, based on fresh weight of tissue sample. Tissue samples were weighed at autopsy. Curves were obtained by adding known amounts of ^{238}Pu to serial dilutions of a suitably compounded mixture of the mineral constituents of soft tissue ash (44) representing fresh soft tissue samples ranging in weight from 15 g (0.19 g salts) to 1000 g (12.5 g salts).

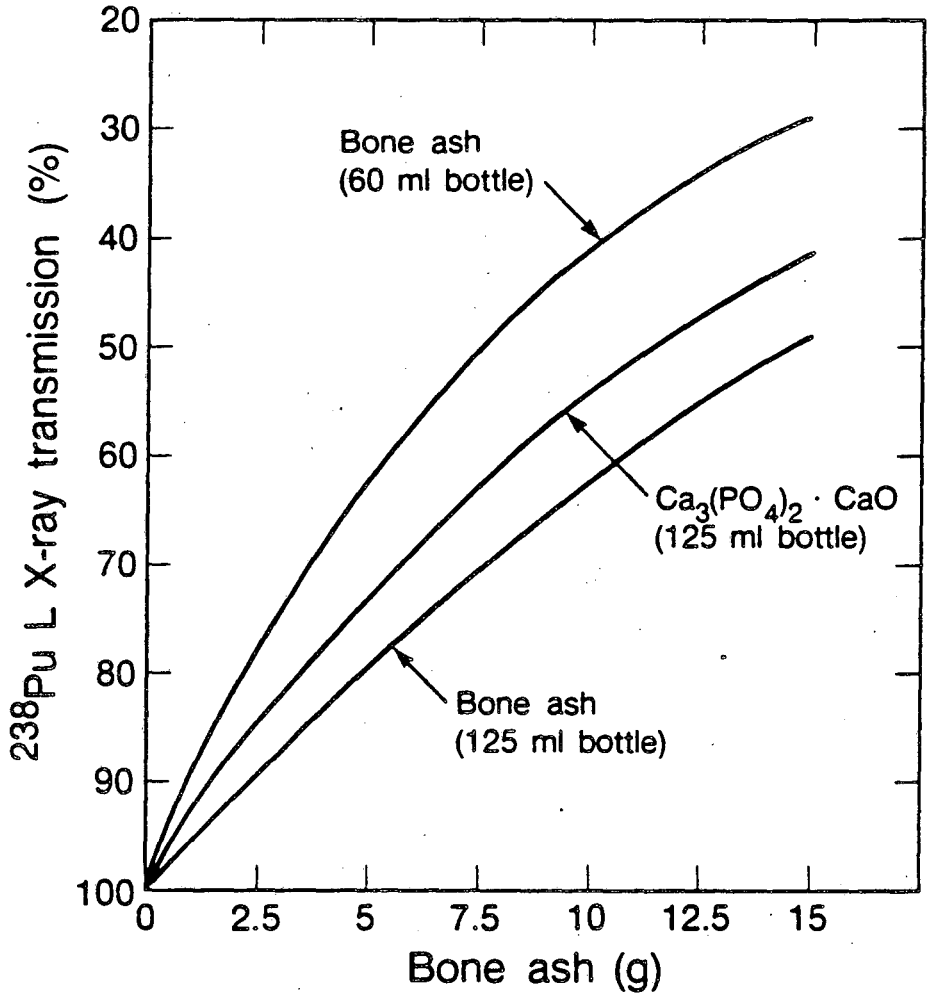

Figure A-3. Self-absorption curves for photon counting of ^{238}Pu in (i) bones, based on ash weight of samples; curves were prepared by adding known amounts of ^{238}Pu to samples of ashed bone weighing 0.1 to 20 g dissolved in the standard volumes of dilute acid: (ii) excreta samples processed by alkaline calcium oxalate scavenging, based on weight of the mixed $Ca_3(PO_4)_2 \cdot CaO \cdot CaCO_3$ product; ashed excreta were treated with oxalic acid and ammonia to precipitate a mixture of $Ca_3(PO_4)_2$ and CaC_2O_4 which was fired at 600 °C in a tared beaker; curves, which corrected both for self-absorption and recovery, were prepared by adding known amounts of ^{238}Pu to dry urine or feces ash or $Ca_3(PO_4)_2$ samples that weighed from 0.5 to 20 g before processing.

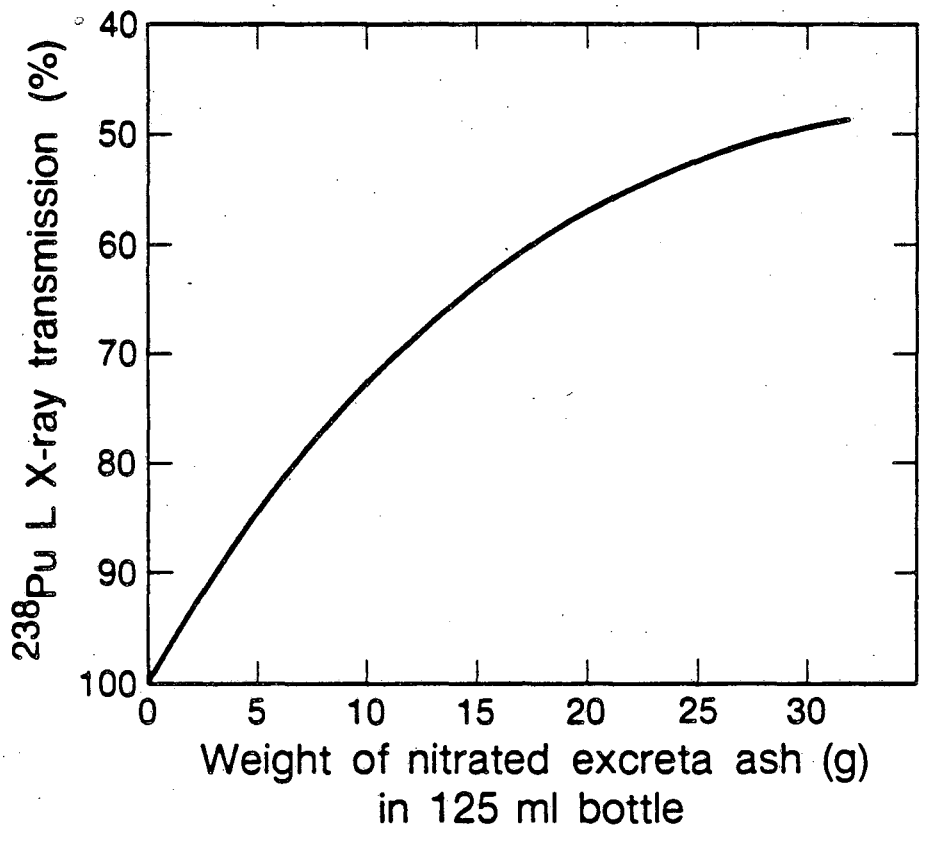

Figure A-4. Self-absorption curve for photon counting of ^{238}Pu in unprocessed excreta, based on weight of dry nitrated ash. Samples were dry ashed, digested in HNO_3 (conc) in tared beakers, dried and reweighed. Curves were prepared by adding known amounts of ^{238}Pu to redissolved samples of dried, digested excreta ash weighing from 0.25 to 32.5 g.

Appendix B. Descriptions of individual monkeys at ^{238}Pu injection and at death and summaries of their ^{238}Pu distribution

Summary

Nuclide: 238-Pu Days from injection to death: Ø.ØØ83 Animal no: C77F

Injection data:

Date	1Ø/Ø9/73
Age (yr)	>11
Weight (kg)	4.ØØØØ
Amount (uCi)	4.65ØØ
Dosage (uCi/kg)	1.17ØØ
Injection mode	i.m.
Unabsorbed from i.m. site(%ID)	3Ø.9ØØØ

Termination data:

Date	1Ø/Ø9/73
Age (yr)	>11
Weight (kg)	4.ØØØØ
Material recovery(%ID)	99.9ØØØ
Cause of death	accident

Sample	% Injected activity
Liver	7.31
Kidneys	3.37
Spleen	.ØØØØØØØØ
Muscle	34.9
Pelt	14.5
Gonads	.ØØØØØØØØ
Soft tissue balance	25.5
Bones	13.3
Teeth	.21Ø
Tail	.44Ø
Urine	.42Ø
Feces	.Ø22Ø

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: Ø.83Ø Animal no: C1Ø8F

Injection data:

Date	8/22/77
Age (yr)	>6.3
Weight (kg)	4.ØØØØ
Amount (uCi)	4.ØØØØ
Dosage (uCi/kg)	1.ØØØØ
Injection mode	i.m.
Unabsorbed from i.m. site(%ID)	32.5ØØØ

Termination data:

Date	8/23/77
Age (yr)	>6.3
Weight (kg)	4.ØØØØ
Material recovery(%ID)	99.9ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	4Ø.6
Kidneys	1.89
Spleen	.23Ø
Muscle	11.7
Pelt	6.34
Gonads	.Ø47Ø
Soft tissue balance	17.3
Bones	19.5
Teeth	.16Ø
Tail	.4ØØ
Urine	.31Ø
Feces	2.Ø5

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 7.ØØØ Animal no: C1Ø9F

Injection data:

Date	7/27/77
Age (yr)	6
Weight (kg)	3.4ØØØ
Amount (uCi)	2.Ø9ØØ
Dosage (uCi/kg)	.6iØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	8/Ø3/77
Age (yr)	6
Weight (kg)	3.4ØØØ
Material recovery(%ID)	87.6ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	6Ø.5
Kidneys	.53Ø
Spleen	.36Ø
Muscle	1.56
Pelt	.91Ø
Gonads	.ØØ69Ø
Soft tissue balance	1.68
Bones	28.Ø
Teeth	.19Ø
Tail	.72Ø
Urine	2.54
Feces	2.87

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 7.ØØØ Animal no: S114F

Injection data:

Date	1/13/77
Age (yr)	>8
Weight (kg)	11.4ØØØ
Amount (uCi)	3.88ØØ
Dosage (uCi/kg)	.34ØØ
Injection mode	i.m.
Unabsorbed from i.m. site(%ID)	8.87ØØ

Termination data:

Date	1/2Ø/77
Age (yr)	>8
Weight (kg)	11.4ØØØ
Material recovery(%ID)	1Ø5.5ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	66.3
Kidneys	.81Ø
Spleen	.27Ø
Muscle	1.83
Pelt	.83Ø
Gonads	.ØØ3ØØ
Soft tissue balance	1.47
Bones	25.9
Teeth	.Ø95Ø
Tail	.Ø46Ø
Urine	1.43
Feces	1.Ø1

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 7.ØØØ Animal no: C89M

Injection data:

Date	1/Ø9/75
Age (yr)	7.8
Weight (kg)	6.9ØØØ
Amount (uCi)	7.ØØØØ
Dosage (uCi/kg)	1.ØØØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	1/16/75
Age (yr)	7.8
Weight (kg)	6.2ØØØ
Material recovery(%ID)	1Ø9.ØØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	62.1
Kidneys	.68Ø
Spleen	.15Ø
Muscle	.99Ø
Pelt	.55Ø
Gonads	.Ø35Ø
Soft tissue balance	1.2Ø
Bones	3Ø.8
Teeth	.15Ø
Tail	.19Ø
Urine	2.48
Feces	.61Ø

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 8.ØØØ Animal no: C95F

Injection data:

Date	2/Ø5/74
Age (yr)	>1Ø.5
Weight (kg)	4.ØØØØ
Amount (uCi)	8.ØØØØ
Dosage (uCi/kg)	2.ØØØØ
Injection mode	sub.cut.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	2/13/74
Age (yr)	>1Ø.5
Weight (kg)	3.52ØØ
Material recovery(%ID)	99.ØØØØ
Cause of death	serial sacrifice

Sample	% Injected activity
Liver	47.1
Kidneys	.98Ø
Spleen	.18Ø
Muscle	4.3Ø
Pelt	3.49
Gonads	.ØØ43Ø
Soft tissue balance	3.92
Bones	3Ø.8
Teeth	.Ø64Ø
Tail	.18Ø
Urine	3.Ø4
Feces	4.34

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 8.ØØØ Animal no: R1Ø1F

Injection data:

Date	4/Ø6/76
Age (yr)	>1Ø
Weight (kg)	6.24ØØ
Amount (uCi)	2.25ØØ
Dosage (uCi/kg)	.36ØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	4/14/76
Age (yr)	>1Ø
Weight (kg)	6.24ØØ
Material recovery(%ID)	111.ØØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	5Ø.4
Kidneys	.52Ø
Spleen	.11Ø
Muscle	1.16
Pelt	.82Ø
Gonads	.ØØ83Ø
Soft tissue balance	1.68
Bones	4Ø.1
Teeth	.12Ø
Tail	.43Ø
Urine	2.53
Feces	1.29

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Nuclide: 238-Pu Days from injection to death: 8.ØØØ Animal no: RG12M

Injection data:

Date	7/27/76
Age (yr)	~14
Weight (kg)	11.ØØØØ
Amount (uCi)	3.3ØØØ
Dosage (uCi/kg)	.3ØØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	8/Ø4/76
Age (yr)	~14
Weight (kg)	11.ØØØØ
Material recovery(%ID)	1Ø9.8ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	76.Ø
Kidneys	.24Ø
Spleen	.13Ø
Muscle	1.44
Pelt	.68Ø
Gonads	.Ø58Ø
Soft tissue balance	1.54
Bones	15.3
Teeth	.Ø57Ø
Tail	.12Ø
Urine	2.22
Feces	2.22

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 56.000 Animal no: C31F

Injection data:

Date	3/06/75
Age (yr)	>6.4
Weight (kg)	4.8800
Amount (uCi)	1.4600
Dosage (uCi/kg)	.3000
Injection mode	i.m.
Unabsorbed from i.m. site(%ID)	1.1700

Termination data:

Date	5/01/75
Age (yr)	>6.6
Weight (kg)	4.5400
Material recovery(%ID)	95.4000
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	33.5
Kidneys	.0940
Spleen	.270
Muscle	.750
Pelt	.310
Gonads	.000800
Soft tissue balance	.670
Bones	18.5
Teeth	.180
Tail	.120
Urine	3.04
Feces	42.6

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 100% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 67.ØØØ Animal no: R1ØØF

Injection data:

Date	2/Ø8/79
Age (yr)	>11
Weight (kg)	6.8ØØØ
Amount (uCi)	2.18ØØ
Dosage (uCi/kg)	.32ØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	4/16/79
Age (yr)	>11
Weight (kg)	4.8ØØØ
Material recovery(%ID)	98.6ØØØ
Cause of death	Unknown

Sample	% Injected activity
Liver	36.5
Kidneys	.15Ø
Spleen	.14Ø
Muscle	.68Ø
Pelt	.21Ø
Gonads	.ØØ34Ø
Soft tissue balance	.58Ø
Bones	31.1
Teeth	.18Ø
Tail	.27Ø
Urine	3.63
Feces	26.5

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 103.000 Animal no: RG6M

Injection data:

Date	2/15/79
Age (yr)	~18
Weight (kg)	7.7100
Amount (uCi)	2.6800
Dosage (uCi/kg)	.3500
Injection mode	i.m.
Unabsorbed from i.m. site(%ID)	.6500

Termination data:

Date	5/29/79
Age (yr)	~18
Weight (kg)	8.4000
Material recovery(%ID)	100.1000
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	20.2
Kidneys	.100
Spleen	.130
Muscle	.740
Pelt	.370
Gonads	.0680
Soft tissue balance	.840
Bones	27.1
Teeth	.120
Tail	.360
Urine	3.54
Feces	46.5

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 100% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 106.000 Animal no: C106M

Injection data:

Date	11/16/76
Age (yr)	>8
Weight (kg)	7.3000
Amount (uCi)	2.5000
Dosage (uCi/kg)	.3400
Injection mode	i.m.
Unabsorbed from i.m. site(%ID)	2.6300

Termination data:

Date	3/02/77
Age (yr)	~9
Weight (kg)	7.5000
Material recovery(%ID)	97.2000
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	42.0
Kidneys	.170
Spleen	.0730
Muscle	1.37
Pelt	.530
Gonads	.0910
Soft tissue balance	1.10
Bones	20.6
Teeth	.140
Tail	.330
Urine	3.41
Feces	30.3

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 100% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 106.000 Animal no: C79F

Injection data:

Date	10/09/73
Age (yr)	>11
Weight (kg)	4.3000
Amount (uCi)	1.3800
Dosage (uCi/kg)	.3200
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	-

Termination data:

Date	1/23/74
Age (yr)	>11
Weight (kg)	2.9500
Material recovery(%ID)	102.2000
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	25.1
Kidneys	.1700
Spleen	.2600
Muscle	1.25
Pelt	.7200
Gonads	.0100
Soft tissue balance	1.06
Bones	19.7
Teeth	.3200
Tail	.3100
Urine	6.23
Feces	45.8

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 100% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 173.000 Animal no: C111F

Injection data:

Date	2/08/79
Age (yr)	>5.2
Weight (kg)	3.2300
Amount (uCi)	1.0000
Dosage (uCi/kg)	.3100
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.0000

Termination data:

Date	7/31/79
Age (yr)	>5.8
Weight (kg)	3.3000
Material recovery(%ID)	98.8000
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	40.2
Kidneys	.200
Spleen	.420
Muscle	.640
Pelt	.290
Gonads	.00210
Soft tissue balance	.680
Bones	22.9
Teeth	.160
Tail	.380
Urine	3.49
Feces	30.1

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 100% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 173.ØØØ Animal no: C1Ø7M

Injection data:

Date	2/15/79
Age (yr)	~6.5
Weight (kg)	5.84ØØ
Amount (uCi)	1.79ØØ
Dosage (uCi/kg)	.31ØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	8/Ø7/79
Age (yr)	~7
Weight (kg)	6.81ØØ
Material recovery(%ID)	98.6ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	42.4
Kidneys	1.26
Spleen	.26Ø
Muscle	.57Ø
Pelt	.49Ø
Gonads	.Ø24Ø
Soft tissue balance	.56Ø
Bones	2Ø.3
Teeth	.14Ø
Tail	.39Ø
Urine	4.Ø3
Feces	29.4

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 370.000 Animal no: R99F

Injection data:

Date	5/03/78
Age (yr)	14.5
Weight (kg)	7.4000
Amount (uCi)	2.4200
Dosage (uCi/kg)	.3300
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.0000

Termination data:

Date	5/08/79
Age (yr)	15.5
Weight (kg)	5.8000
Material recovery(%ID)	108.6000
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	4.16
Kidneys	.0430
Spleen	.0440
Muscle	.470
Pelt	.330
Gonads	.0004000
Soft tissue balance	.480
Bones	21.2
Teeth	.170
Tail	.120
Urine	7.62
Feces	65.9

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 100% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 552.ØØØ Animal no: C1Ø5M

Injection data:

Date	7/27/77
Age (yr)	6.1
Weight (kg)	8.ØØØØ
Amount (uCi)	2.24ØØ
Dosage (uCi/kg)	.28ØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	1/3Ø/79
Age (yr)	7.6
Weight (kg)	7.6ØØØ
Material recovery(%ID)	96.5ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	42.5
Kidneys	.15Ø
Spleen	.1ØØ
Muscle	.25Ø
Pelt	.26Ø
Gonads	.Ø19Ø
Soft tissue balance	.48Ø
Bones	13.9
Teeth	.15Ø
Tail	.28Ø
Urine	8.38
Feces	33.4

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 587.ØØØ Animal no: C94F

Injection data:

Date	7/27/76
Age (yr)	~11
Weight (kg)	6.6ØØØ
Amount (uCi)	1.97ØØ
Dosage (uCi/kg)	.3ØØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	3/Ø6/78
Age (yr)	~13
Weight (kg)	7.4ØØØ
Material recovery(%ID)	1Ø4.6ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	2.81
Kidneys	.Ø43Ø
Spleen	.Ø39Ø
Muscle	.16Ø
Pelt	.11Ø
Gonads	.ØØ11Ø
Soft tissue balance	.31Ø
Bones	7.27
Teeth	.15Ø
Tail	.11Ø
Urine	24.3
Feces	64.5

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 559.ØØØ Animal no: S116F

Injection data:

Date	7/27/77
Age (yr)	~6
Weight (kg)	8.8ØØØ
Amount (uCi)	2.75ØØ
Dosage (uCi/kg)	.31ØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	2/Ø6/79
Age (yr)	~7.5
Weight (kg)	8.5ØØØ
Material recovery(%ID)	86.9ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	13.7
Kidneys	.Ø18Ø
Spleen	.35Ø
Muscle	.22Ø
Pelt	.15Ø
Gonads	.ØØ17Ø
Soft tissue balance	.45Ø
Bones	12.7
Teeth	.26Ø
Tail	.Ø3ØØ
Urine	6.56
Feces	65.6

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 1100.000 Animal no: C80F

Injection data:

Date	3/06/75
Age (yr)	>13
Weight (kg)	5.2200
Amount (uCi)	1.6300
Dosage (uCi/kg)	.3100
Injection mode	i.m.
Unabsorbed from i.m. site(%ID)	.0000

Termination data:

Date	3/10/78
Age (yr)	>16
Weight (kg)	4.3700
Material recovery(%ID)	94.1000
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	.470
Kidneys	.0360
Spleen	.000930
Muscle	.150
Pelt	.0620
Gonads	.00140
Soft tissue balance	.220
Bones	9.38
Teeth	.160
Tail	.110
Urine	5.71
Feces	83.6

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 100% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 1099.000 Animal no: R102F

Injection data:

Date	4/06/76
Age (yr)	~8.7
Weight (kg)	4.7000
Amount (uCi)	1.7100
Dosage (uCi/kg)	.3600
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.0000

Termination data:

Date	4/10/79
Age (yr)	~11.7
Weight (kg)	5.7000
Material recovery(%ID)	112.9000
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	.770
Kidneys	.00540
Spleen	.0130
Muscle	.220
Pelt	.0550
Gonads	.000700
Soft tissue balance	.320
Bones	18.5
Teeth	.240
Tail	.240
Urine	21.0
Feces	58.7

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 100% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 7.ØØØ Animal no: R119F

Injection data:

Date	5/Ø3/78
Age (yr)	3.8
Weight (kg)	4.ØØØØ
Amount (uCi)	1.34ØØ
Dosage (uCi/kg)	.34ØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	5/1Ø/78
Age (yr)	3.8
Weight (kg)	4.ØØØØ
Material recovery(%ID)	1Ø1.62ØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	54.8
Kidneys	.38Ø
Spleen	.16Ø
Muscle	1.Ø6
Pelt	.44Ø
Gonads	.ØØ48Ø
Soft tissue balance	.86Ø
Bones	38.6
Teeth	.22Ø
Tail	.53Ø
Urine	1.94
Feces	.91Ø

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 8.ØØØ Animal no: R122F

Injection data:

Date	11/29/78
Age (yr)	3.9
Weight (kg)	4.5ØØØ
Amount (uCi)	1.38ØØ
Dosage (uCi/kg)	.31ØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	12/Ø7/78
Age (yr)	3.9
Weight (kg)	4.5ØØØ
Material recovery(%ID)	114.5ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	6Ø.7
Kidneys	.27Ø
Spleen	.1ØØ
Muscle	.57Ø
Pelt	.52Ø
Gonads	.ØØ31Ø
Soft tissue balance	.8ØØ
Bones	33.1
Teeth	.17Ø
Tail	.56Ø
Urine	1.99
Feces	1.32

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 8.ØØØ Animal no: R12ØM

Injection data:

Date	1Ø/Ø3/78
Age (yr)	4
Weight (kg)	3.9ØØØ
Amount (uCi)	1.5ØØØ
Dosage (uCi/kg)	.38ØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	1Ø/11/78
Age (yr)	4
Weight (kg)	3.9ØØØ
Material recovery(%ID)	1Ø4.2ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	69.Ø
Kidneys	.46Ø
Spleen	.ØØØØØØØØ
Muscle	.52Ø
Pelt	.58Ø
Gonads	.ØØØØØØØØ
Soft tissue balance	.64Ø
Bones	24.8
Teeth	.33Ø
Tail	.3ØØ
Urine	1.68
Feces	2.51

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: Ø.85Ø Animal no: C1Ø3F

Injection data:

Date	6/1Ø/76
Age (yr)	3.1
Weight (kg)	2.ØØØØ
Amount (uCi)	2.13ØØ
Dosage (uCi/kg)	1.Ø6ØØ
Injection mode	i.m.
Unabsorbed from i.m. site(%ID)	16.1ØØØ

Termination data:

Date	6/11/76
Age (yr)	3.1
Weight (kg)	2.ØØØØ
Material recovery(%ID)	1Ø4.9ØØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	48.6
Kidneys	1.22
Spleen	.15Ø
Muscle	4.37
Pelt	3.37
Gonads	.Ø14Ø
Soft tissue balance	7.56
Bones	31.6
Teeth	.29Ø
Tail	.48Ø
Urine	.6ØØ
Feces	1.73

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

Summary

Nuclide: 238-Pu Days from injection to death: 7.ØØØ Animal no: R121M

Injection data:

Date	11/29/78
Age (yr)	4
Weight (kg)	4.55ØØ
Amount (uCi)	1.2ØØØ
Dosage (uCi/kg)	.26ØØ
Injection mode	i.v.
Unabsorbed from i.m. site(%ID)	.ØØØØ

Termination data:

Date	12/Ø6/78
Age (yr)	4
Weight (kg)	4.55ØØ
Material recovery(%ID)	117.Ø2ØØ
Cause of death	Serial sacrifice

Sample	% Injected activity
Liver	53.3
Kidneys	.27Ø
Spleen	.17Ø
Muscle	.66Ø
Pelt	.44Ø
Gonads	.Ø4ØØ
Soft tissue balance	1.39
Bones	4Ø.Ø
Teeth	.25Ø
Tail	.72Ø
Urine	1.77
Feces	1.Ø5

* Data are corrected for unabsorbed activity (i.m. injections) and are normalized to 1ØØ% material recovery

TECHNICAL INFORMATION DEPARTMENT
LAWRENCE BERKELEY LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA 94720