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Gastrointestinal Absorption of Plutonium, Uranium and Neptunium in Fed and Fasted Adult Baboons: Application to Humans

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Abstract

Gastrointestinal (GI) absorption values of plutonium, uranium, and neptunium were determined in fed and fasted adult baboons. A dual isotope method for determining GI absorption, which does not require animal sacrifice, was validated and shown to compare well with the sacrifice method (summation of oral isotope in urine with that in tissues at sacrifice). For all three elements, mean GI absorption values were significantly higher (5- to 50-fold) in 24-hour (h)-fasted animals than in fed animals, and GI absorption values for baboons agreed well with those for humans. For plutonium, GI absorption values in baboons were almost identical to those in mice under both fed and fasted conditions (ca. 0.2% in fasted animals, 0.01% in fed animals), and the values for fed animals agreed with estimates for humans. For uranium, GI absorption values in fed (0.5%) and fasted (4%) baboons were 6–7 times higher than those in mice and agreed well with those in fed and fasted humans. For neptunium, GI absorption values in fed baboons were lower for small amounts of ^{239}Np (0.03%) than for much larger amounts of ^{237}Np (0.3%). Neptunium GI absorption values in fasted baboons (1.5%) were independent of amounts ingested and were considerably higher than those in fed animals. The GI absorption of ^{239}Np in fed animals was essentially the same in mice, baboons, and humans. In fasted animals, mice absorbed 4 times less ^{239}Np than did baboons (values for humans are not available). For one baboon that was not given its morning meal, both plutonium and neptunium GI absorption values at 0900 hours, 2 h after the usual mealtime (14-h overnight fast, "baboon without breakfast"), were the same as those in baboons fasted for 24 h. In contrast, for baboons that received a morning meal, plutonium and neptunium absorptions did not rise to the value found in 24-h-fasted baboons even 8 h after the meal. The authors conclude that GI absorption values for plutonium, uranium, and neptunium in adult baboons are good estimates of the values in humans (and better than those in mice) and that the values for the fasted condition need to be taken into account when standards are set for oral exposures of persons in environmental and workplace settings. A rational way of doing this for plutonium is discussed.

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Executive Summary

Because oral exposure is the major route of human exposures in environmental settings, gastrointestinal (GI) absorption values of radionuclides in the nuclear fuel cycle are critical to setting limits for releases of these elements to the environment from nuclear power facilities and nuclear waste sites. Plutonium and uranium are integral parts of the nuclear fuel cycle, and ^{237}Np is a fission product identified as important to evaluating human exposures from nuclear waste sites over a long period of time because of its alpha emission, long physical half-life (2×10^6 years [y]), relatively high GI absorption values, and relative mobility in the environment (Pentreath and Harvey, 1981; Cohen, 1982).

Several unique features of the results reported here should be identified. First, GI absorption values were obtained in nonhuman primates (i.e., baboons), making the results particularly relevant to humans. Second, all three elements — plutonium, neptunium, and uranium — were administered to a given animal at the same time, allowing direct interelement comparisons of GI absorption and metabolic pathways. Third, for plutonium and neptunium, multiple isotopes were used to obtain GI values for both fed and fasted conditions in the same baboon, providing a measure of the significant increase in GI absorption due to fasting in individual animals. Finally, use of a dual isotope method in combination with multiple element and multiple isotope administrations resulted in our determination of 29 separate GI absorption values in seven adult baboons, only three of which were sacrificed for this study (Expt. 1, four baboons, effects of 14- to 24-h fast; Expt. 2, three baboons, effects of 4- to 8-h fast and uranium absorption in fed baboons).

Below, the results are summarized individually for plutonium, uranium, and neptunium, and the major conclusions of our study are presented. Elements were administered in the VI oxidation state in bicarbonate medium to simulate uptake from chlorinated drinking water (Larsen and Oldham, 1978). Results can also be applied to evaluating the absorption of soluble forms of these elements in the occupational setting.

Plutonium

Effects of Feeding Regimen

Fractional GI absorption values of Pu(VI) bicarbonate for individual 24-hour (h)-fasted adult baboons were (Table 3.9)

B704	2.2×10^{-4} (0.022%)
B1048	13×10^{-4} (0.13%)
B1050	15×10^{-4} (0.15%)
B1046	59×10^{-4} (0.59%)

- The mean GI absorption value for Pu(VI) in 24-h-fasted baboons was $(22 \pm 13) \times 10^{-4}$ (mean ± standard error [SE], n = 4), or 0.22%. The mean without baboon B704 was $(29 \pm 15) \times 10^{-4}$ (n = 3), or 0.29%. (B704 was our first 24-h-fasted baboon, and the uniformly low GI absorption values obtained for simultaneously administered plutonium, uranium, and neptunium indicate that she may have inadvertantly obtained some food.)

- In fed baboons, fractional GI absorption values of Pu(VI) bicarbonate were (Table 3.9)

B704	2.5×10^{-4} (0.025%)
B1050	0.38×10^{-4} (0.0038%)
B1046	0.47×10^{-4} (0.0047%)

(For this administration, the fourth baboon, B1048, instead of being fed, underwent a 14-h overnight fast; results are shown below.)

- The mean GI absorption value for Pu(VI) in fed adult baboons was $(1.1 \pm 1.2) \times 10^{-4}$ (n = 3), or 0.011%.

- Individual increases in plutonium GI absorption due to a 24-h fast were 39-fold for B1050, 126-fold for B1046, and zero for B704. On comparison of the means, the increase due to 24-h fasting was 26-fold, from 0.011% to 0.29%.

- In one baboon (B1048) who was provided no breakfast and was administered Pu(VI) at 0900 hours, 2 h after her normal breakfast time (14-h overnight fast), the fractional GI absorption value was 29×10^{-4} (0.29%), the same as the mean in 24-h-fasted animals (Table 3.9) and about 2-fold higher than in the same baboon after a 24-h fast (0.13%).

- In baboons provided with breakfast, GI absorption values for Pu(VI) did not increase significantly over those for fed baboons by even 8 h after the morning meal in the absence of further feeding (Table 3.12).

Sacrifice vs. Dual Isotope Methods

- GI absorption values of plutonium in fed and fasted adult baboons determined by the sacrifice method (by summation of amounts excreted in urine and amounts in tissues at sacrifice) were 72 ± 5% (mean ± SE, n = 6) of those determined by the dual isotope method (from isotopic ratios after oral vs. intravenous [i.v.] administrations) (Table 3.10).

- Pathways for plutonium excretion and tissue retention were the same, independent of whether the plutonium entered the bloodstream by i.v. administration or GI absorption (Tables 3.4, 3.5, 3.7).

- After i.v. injection of Pu(VI), values for excretion and tissue retention (mean ± SE for number of baboons in parentheses) were as follows (percentage of administered dose; tissues taken at sacrifice 32 days [d] after administration) (Table 6.1):

Days 1–8 urine	8.3 ± 0.7% (4)
Liver	26.3 ± 5.0% (3)
Skeleton	37.5 ± 5.5% (3)
Other tissues	1.7 ± 0.5% (2)

Interspecies Comparisons

- Plutonium GI absorption values in fed (0.01%) and 24-h-fasted (0.2%) adult baboons (Table 3.13) were the same as those in fed and fasted adult mice (Bhattacharyya et al., 1986), and those in fed baboons were the same as in fed humans (Hunt et al., 1986, 1990).

Uranium

Effects of Feeding Regimen

- Fractional GI absorption values of U(VI) bicarbonate in individual 24-h-fasted adult baboons were (Table 4.7)

B704	1.2×10^{-2} (1.2%)
B1048	4.7×10^{-2} (4.7%)
B1050	4.1×10^{-2} (4.1%)
B1046	4.3×10^{-2} (4.3%)

- The mean GI absorption value for U(VI) in 24-h-fasted adult baboons was $(3.6 \pm 0.8) \times 10^{-2}$ (mean ± SE, n = 4), or 3.6%. The mean without baboon B704 was $(4.4 \pm 0.2) \times 10^{-2}$, or 4.4% (Table 4.8).

- Fractional GI absorption values of U(VI) bicarbonate in individual fed baboons were (Table 4.8)

B358	0.46×10^{-2} (0.46%)
B880	0.58×10^{-2} (0.58%)

(The third baboon, B230, regurgitated shortly after the uranium administration.)

- The mean GI absorption value for U(VI) in fed adult baboons was $(0.52 \pm 0.06) \times 10^{-2}$ (mean ± SE, n = 2).

- On comparison of the means, uranium GI absorption was increased 9-fold by a 24-h fast, from 0.52% to 4.4%.

Sacrifice vs. Dual Isotope Methods

- GI absorption values of uranium determined by the sacrifice method in fasted adult baboons were 79 ± 3% (mean ± SE, n = 3) of those determined by the dual isotope method (Table 4.8).

- Pathways for uranium excretion and tissue retention were the same, independent of whether the uranium entered the bloodstream by i.v. administration or GI absorption (Tables 4.3–4.5).

- After i.v. injection of U(VI), values for excretion and tissue retention (mean ± SE for number of baboons shown in

parentheses) were as follows (percentage of administered dose; tissues taken at sacrifice 32 d after administration) (Table 6.1):

Days 1–8 urine	82.7 ± 1.4% (4)
Liver	0.32 ± 0.07% (3)
Skeleton	9.6 ± 1.8% (3)
Other tissues	0.45 ± 0.05% (2)

Interspecies Comparisons

- Uranium GI absorption values in fed (0.5%) and fasted (4%) adult baboons (Table 4.9) were the same as those reported for fed and fasted humans (Larsen and Orlandini, 1984; Hursh et al., 1969) and were 6- to 7-fold higher than those in fed and fasted mice (Bhattacharyya et al., 1989).

Neptunium

Effects of Feeding Regimen and Neptunium Mass

- Fractional GI absorption values of Np(VI) bicarbonate in individual 24-h-fasted adult baboons were (Table 5.7)

B704	^{237}Np	0.32×10^{-2} (0.32%)
B704	^{239}Np	0.95×10^{-2} (0.95%)
B1050	^{239}Np	0.85×10^{-2} (0.85%)

(The ^{237}Np administration to B704 was on the day when B704 was suspected of inadvertently obtaining some food.)

- The mean GI absorption value for Np(VI) in the above 24-h-fasted adult baboons was $(0.71 \pm 0.20) \times 10^{-2}$ (n = 3), or 0.71%. The mean without the first B704 value was $(0.90 \pm 0.05) \times 10^{-2}$ (n = 2), or 0.90%. A mean including additional administrations at NYUMC was $(1.5 \pm 0.3) \times 10^{-2}$ (n = 8), or 1.5% (Tables 5.9 and 5.10).

- In 24-h-fasted baboons, the GI absorption of neptunium was independent of the mass administered (Tables 5.9 and 5.10).

- In fed baboons, the GI absorption of high masses of neptunium was 10-fold higher than that of low masses: 0.30% for ^{237}Np (3×10^{-2} mg/kg) vs. 0.03% for ^{239}Np (9×10^{-8} mg/kg) (Tables 5.9 and 5.10).

- On comparison of the means, neptunium GI absorption was increased due to a 24-h fast by 5-fold for ^{237}Np, from 0.3% to 1.5%, and 50-fold for ^{239}Np, from 0.03% to 1.5%.

- In one baboon (B1048) who was provided no breakfast and was administered ^{237}Np(VI) at 0900, 2 h after her normal breakfast time (14-h overnight fast), the fractional GI absorption value was 1.2×10^{-2}, or 1.2%, essentially the same as in 24-h-fasted animals (Table 5.9).

- In baboons provided with breakfast, GI absorption values of ^{237}Np did not increase significantly over those for fed baboons by even 8 h after the morning meal in the absence of further feeding (Table 5.9).

Sacrifice vs. Dual Isotope Methods

- GI absorption values of neptunium determined by the sacrifice method in fasted adult baboons were 102 ± 4% (mean ± SE, n = 3) of those determined by the dual isotope method (Table 5.8).

- Pathways for neptunium excretion and tissue deposition were the same, independent of whether the neptunium entered the bloodstream by i.v. administration or GI absorption (Tables 5.3-5.5).

- After i.v. injection of Np(VI), values for excretion and tissue retention (mean ± SE for number of baboons in parentheses) were as follows (percentage of administered dose; tissues taken at sacrifice 30–32 d after administration) (Table 6.1):

Days 1–8 urine	41.0 ± 2.2% (14)
Liver	8.1% (1)
Skeleton	46.3% (1)
Other tissues	2.2% (1)

Interspecies Comparisons

- ^{239}Np GI absorption values in fed adult baboons (0.03%) were the same as those for fed adult mice (Larsen et al., 1982) and humans (Poppelwell et al., 1991). ^{239}Np values in fasted adult baboons (1.5%) were 4-fold higher than in fasted mice (Table 5.10). (No data are available on fasted humans.)

Conclusions

- GI absorption values for plutonium, uranium, and neptunium in adult baboons provide good estimates of GI absorption values in humans.

- The dual isotope method provides an excellent means of determining GI absorption values without requiring sacrifice of the animal (study subject). The method was recently applied to determining the GI absorption of ^{239}Np in fed humans (Popplewell et al., 1991).

- Plutonium, neptunium, and probably uranium consumed before the first meal of the day (in liquids such as coffee, or at work for someone who has skipped breakfast) will be absorbed at the level of the 24-h-fasted state -- 0.2% for plutonium, 1% for neptunium, and 4% for uranium.

- These elements consumed either in food or liquids or in other media after the morning meal will be absorbed at the level of the fed state — 0.01% for plutonium, 0.03% for small amounts of neptunium (e.g., 10^{-8} mg ^{239}Np/kg) and 0.3% for large amounts of neptunium (e.g., 10^{-1} mg ^{237}Np/kg), and 0.5% for uranium.

- The above results should be applied to incorporate GI absorption values of fasted animals into standards set for oral exposure of humans to plutonium, uranium, and neptunium in both environmental and workplace settings. A rational way of doing that for plutonium is discussed.

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The experiments described here resulted from a significant collaboration between the Department of Energy and the Nuclear Regulatory Commission, and credit is due to both organizations for their support and interest.

During the period when this report was prepared, one of its co-authors, Dr. Robert P. Larsen, passed away. Studying the data base after his death brought sadness, but more often it brought back memories of the many wonderful times we had together -- planning, debating, discussing, analyzing, and arguing. This work is to a great extent a product of his insights, experience, and dedication to excellence and represents the friendship that bonded us all together. We miss him.

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Abbreviations

ALI	annual limit on intake
ANL	Argonne National Laboratory
ASID	alpha spectrometric isotope dilution
DOE	Department of Energy
GI	gastrointestinal
ICRP	International Commission on Radiological Protection
i.g.	intragastric
i.v.	intravenous
Np	neptunium
NRC	Nuclear Regulatory Commission
NYUMC	New York University Medical Center
Pu	plutonium
SE	standard error
U	uranium

1 Introduction

1.1 Background

Prior to conducting this study in adult baboons, we had conducted a series of experiments in mice for the Nuclear Regulatory Commission (NRC) that identified a number of factors that might influence the gastrointestinal (GI) absorption of soluble forms of plutonium (Bhattacharyya et al., 1985):

- oxidation state (Pu[IV] vs. Pu[VI])
- species (mouse vs. rat vs. dog)
- feeding regimen (fed vs. fasted animals)
- plutonium concentration (10^{-12} M to 10^{-6} M)
- age of animal (neonate vs. adult)
- administration medium (bicarbonate vs. nitric acid vs. citrate)
- state of plutonium hydrolysis (solutions of high vs. low ultrafilterability).

Because nearly all of the above studies were conducted in mice, a major question left unanswered was the relevance to humans of the GI absorption values obtained.

With joint support from the NRC and the Department of Energy (DOE), the studies reported here were undertaken by a team of scientists from Argonne National Laboratory (ANL) in collaboration with a team from the Institute of Environmental Medicine at New York University Medical Center (NYUMC). GI absorption values for plutonium and uranium were obtained in fed and fasted adult baboons by ANL scientists (joint NRC/DOE support), and values for neptunium were determined by NYUMC scientists as a part of their DOE program. Results for all three elements are reported here to provide one document in which all results appear and to allow for direct comparisons of GI absorption values among elements.

As with the preceding studies in mice, elements were administered in the VI oxidation state in bicarbonate medium to simulate environmental exposures in chlorinated drinking water (Larsen and Oldham, 1978). The results can also be applied to evaluating the absorption of soluble forms of these elements in the occupational setting.

Annual limits on intake (ALIs) of radionuclides by workers are recommended by the International Commission on Radiological Protection (ICRP) to provide guidelines for the protection of workers where there is a potential for exposure to radionuclides in the workplace. At present, the ALIs for oral exposure to compounds of plutonium, neptunium, and uranium are recommended without consideration of the effect of fasting on their GI absorption (ICRP, 1979). This approach was adopted in 1979 because the effects of fasting had not been systematically studied prior to publication of ICRP Publication 30.

It has since become clear that the GI absorption of plutonium and other elements may be at least 10–15 times greater in 24-h-fasted animals than in fed animals (ICRP, 1986; Sullivan et al., 1979; Stather et al., 1980). However, even today, two important questions remain: (1) What is the relevance to humans of GI absorption values obtained in animals that have been fasted for 24 h, a period that is considerably longer than the customary overnight fast in humans? and (2) How reliably can we extrapolate to humans data that have been obtained in rats or mice?

In a recent study with mice, we addressed the first question and demonstrated that the GI absorption of plutonium rises 10- to 15-fold after only 2 h of fasting if the fast is initiated at the start of the mouse's active phase (Bhattacharyya et al., 1986). We concluded that persons who skipped breakfast and were orally exposed to plutonium before their first meal might absorb considerably more plutonium than their nonfasted counterparts. However, we recognized that the effect of duration of fast in mice might differ from that in humans. We therefore conducted the study reported here in a nonhuman primate, the baboon.

1.2 Overview and Objectives

Occupational and environmental exposure standards for plutonium, neptunium, and uranium are required to control exposures in the workplace and to regulate releases into the environment from nuclear power facilities and from nuclear waste disposal sites. In the study reported here, GI

absorption values for soluble forms of plutonium, neptunium, and uranium were determined in fed and 24-h-fasted adult baboons. A feeding regimen study was conducted with shorter fasting intervals to evaluate the relevance to humans of GI absorption values obtained in 24-h-fasted baboons. Where possible, values in baboons were compared with those reported for both mice and humans, providing a basis for evaluating the application of data in laboratory animals to humans.

2 Materials and Methods

2.1 Animals

Seven adult female baboons (*Papio cynocephulus*, *P. anubis*, and *P. hymadryus*), 5 to 17 years old (mean ± standard deviation, 10 ± 5 y), weighing 12–18 kg (mean ± standard deviation, 13.8 ± 1.8 kg), were used in this study (Table 2.1). Animals were chosen from a preconditioned colony based on similarities in size, weight, and age to minimize intraspecies differences and to provide reproducible whole-body counting geometries for the measurement of neptunium isotopes (^{237}Np and ^{239}Np). Female baboons were chosen over males because they allow for more precise excreta collections, are considerably smaller (by approximately half the weight), and are less aggressive (making them easier to handle).

The baboons were housed and cared for by the technical and veterinary staff at New York University's Laboratory for Experimental Medicine and Surgery in Primates in Tuxedo, New York. They were housed individually in wall-mounted, stainless steel metabolism cages (20 × 36 × 48 in.) with floor clearances of 3 ft to accommodate excreta collectors. Baboons were maintained on two daily meals of Purina High Protein Monkey Chow (Ralston-Purina, St. Louis, Missouri) at 0700 and 1600 hours, supplemented with fresh fruits at noon. Water was provided *ad libitum*. The animal facility maintained 12-h day and night cycles and strict climate conditions.

2.2 Solution Preparation

The ^{236}Pu (half-life, 2.9 y), ^{238}Pu (half-life, 88 y), ^{233}U (half-life, 1.6×10^5 y), ^{236}U (half-life, 2.3×10^7 y), and ^{237}Np (half-life, 2.1×10^6 y) used in this study were obtained from ANL. The ^{239}Np (half-life, 2.36 d) was prepared from ^{243}Am at NYUMC. Each isotope had an isotopic purity (on an activity base) of greater than 99.9%. Where necessary, this purity for plutonium was achieved with the mass separator at ANL. Purity was established by alpha spectrometric assay of material electrodeposited onto stainless steel disks.

Solutions of plutonium were prepared as described previously (Bhattacharyya et al., 1986). Briefly, the plutonium in HNO_3 stock solution was reduced to Pu(III) with HBr, oxidized to Pu(IV) with HNO_3, and oxidized electrochemically to Pu(VI). The Pu(VI) solution was made 0.01 M in $NaHCO_3$ and 1 ppm in chlorine (pH 8.3) for administration to the animals. The plutonium in the administered solutions was in the VI oxidation state (86 ± 5% Pu[VI]) and was 84 ± 5% ultrafilterable.

Table 2.1 Characteristics of adult female baboons used in gastrointestinal absorption studies

Baboon number	Age at start of study (y)	Mean study wt. (kg)[a]	Species
B704	11	12.7 ± 0.9 (8)	*P. hymadryus*
B1046	5	12.4 ± 0.9 (17)	*P. anubis*
B1048	5	13.9 ± 1.4 (8)	*P. anubis*
B1050	5	13.9 ± 0.4 (8)	*P. anubis*
B230	17	14.2 ± 0.8 (26)	*P. cynocephulus*
B358	17	17.8 ± 0.9 (12)	*P. anubis*
B880	11	12.2 ± 0.3 (11)	*P. anubis*
Mean ± SD	10 ± 5	13.9 ± 1.8	
Range	5–17	12.2–17.8	

[a]Values are mean ± standard deviation for the number of times the animal was weighed, which is shown in parentheses.

Solutions of uranium were prepared by diluting a stock solution (generally in 8 M HNO_3) with water until it was 1 M in HNO_3 and titrating dropwise with 1 M $NaHCO_3$ until the pH of the solution was 7.0–7.5. A solution that was 1 M in $NaHCO_3$ and 0.0015 M in NaOCl (100 ppm in chlorine) was added, and the resulting solution was diluted with water to achieve concentrations in the administered solutions of 0.01 M in $NaHCO_3$ and 1 ppm in chlorine (pH 8.3). The uranium in these solutions was in the VI oxidation state.

Solutions of neptunium were prepared as described (Cohen and Ralston, 1987; Ralston, 1990), by using either electrochemical or chemical oxidation to convert the neptunium to the VI oxidation state. ^{239}Np was separated from the parent ^{243}Am on a Dowex 50 X-2 cation exchange column just before use. Prior to this, the ^{239}Pu (and ^{239}Np) present in the original $^{243}Am/^{239}Np$ solution was removed by chromatography on a Dowex-1 column. Within 14 d, this ^{243}Am solution was used to yield ^{239}Np that was free of ^{239}Pu. This was important because ^{239}Np was administered to baboons that had previously received known amounts of ^{239}Pu. As with the other radioelements, the neptunium was in the VI oxidation state, and the medium of the administered solutions was 0.01 M in $NaHCO_3$ and 1 ppm in chlorine.

As an example, the isotopic compositions and chemical characteristics of the solutions of plutonium, uranium, and neptunium administered to baboon B704 are presented in Table 2.2.

2.3 Solution Administration

Solutions of plutonium, uranium, and neptunium were administered to the tranquilized baboons both intravenously and intragastrically. An intramuscular injection of 10 mg/kg of ketamine HCl (Ketaset, Bristol-Myers Co., Syracuse, New York) was used to tranquilize the animals prior to handling outside of confinement. Injections were via the saphenous or femoral vein (1–2 mL); intragastric (i.g.) administrations (10–20 mL) were made directly into the stomachs of fed or fasted baboons through a catheter introduced nasally. Animals remained tranquilized for 10–15 minutes (min) for i.v. injections and for 20-30 min for gavage administrations. Recovery from the effects of tranquilization was generally complete by 2 h after administration.

2.4 Sampling and Sacrifice Procedures

Ten-milliliter blood samples were drawn from each animal at various times after injection and gavage. Separate urine and fecal samples were collected daily from each animal with use of collectors of nylon mesh screen (to collect feces) and plastic sheet (to direct urine flow to collection bottles) positioned under the metabolism cages. Urine was collected in 1-L plastic bottles, and samples were acidified with 2 mL of concentrated HCl per 100 mL of urine to prevent adsorption of radioactivity to the walls of the bottles. Fecal samples were weighed wet, dried in a small convection oven for 1–2 d, reweighed, and pulverized in a ball-mill shaker.

Three baboons (B704, B1048, B1050) were sacrificed by exsanguination under heavy ketamine anesthesia to avoid any animal discomfort. Soft-tissue samples were removed. The eviscerated carcass was stripped of the pelt and muscle, and the skeleton was disarticulated. The liver was separated into its four lobes, and the GI tract was separated into esophogus, stomach, small intestine, and large intestine.

For the remaining four baboons (B1046, B358, B880, and B230), biopsy samples of liver and caudal vertebrae were surgically removed under ketamine tranquilization to allow determination of GI absorption values by the dual isotope method from the isotopic ratios in these tissues. Surgery was carried out by highly experienced veterinarians, with all precautions taken to minimize animal discomfort. These baboons were not sacrificed.

2.5 Sample Analyses

All tissue and excreta samples from the baboons were analyzed for isotopes of plutonium and uranium by means of alpha spectrometric isotope dilution (ASID) with ion exchange chromatography and electrodeposition.

Samples were ashed in a muffle furnace at 600 °C. The ash was dissolved in concentrated HNO_3, and the solution was diluted to a known volume with 8 M HNO_3. Known amounts of ^{242}Pu and ^{238}U (isotopic diluents) were added to an aliquot of each solution, and the solution was evaporated to incipient dryness. The material was dissolved in

Table 2.2 Isotopic composition and chemical characteristics of solutions administered to baboon B704

Date/solution	Administration mode	Feeding regimen	Radionuclide composition	Activity administered[a] (dpm)	Ultrafiltration value[a,b] (%)	Percentage of Pu in VI oxidation state[a]
7/9/82						
$^{239}Pu/^{239}Np$	i.g.	Fed	^{239}Pu	43,500 ± 610	100 ± 1	81 ± 2
			^{239}Np	5.5×10^8	100 ± 1	
			^{238}Pu	6100 ± 100	--	--
			^{237}Np	< 400	--	
7/23/82						
^{236}Pu	i.g.	Fasted	^{236}Pu	83,000 ± 1600	100 ± 4	99 ± 2
			^{238}Pu	3620 ± 110	--	
			^{239}Pu	800 ± 40	--	
^{238}Pu	i.v.	Fasted	^{238}Pu	766 ± 6	100 ± 2	99 ± 2
^{233}U	i.g.	Fasted	^{233}U	113,900 ± 560	84 ± 1	
^{236}U	i.v.	Fasted	^{236}U	569 ± 9	84 ± 2	
			^{233}U	9.3 ± 0.4	--	
^{237}Np	i.g.	Fasted	^{237}Np	53,540 ± 360	96 ± 1	
8/23/82						
^{239}Np	i.g.	Fasted	^{239}Np	3.6×10^8	98 ± 1	
			^{239}Pu	549 ± 22	--	--
			^{243}Am	68 ± 1	--	
			^{238}Pu	5 ± 1	--	--
			^{237}Np	ca. 15	--	

[a]Values are mean ± SE.

[b]Indicates the state of polymerization of the radioelement, expressed as the percentage of the element that passes through an ultrafiltration membrane as determined by the procedure of Lindenbaum and Westfall (1965).

9 M HBr and again brought to incipient dryness. (This step ensured plutonium isotopic exchange.) The plutonium and uranium were taken up in 12 M HCl containing about 100 ppm of chlorine, the solution was applied to a BioRad AG1 X-2 anion exchange column, and the column was washed with a solution of the same composition. The plutonium and neptunium were eluted with 9 M HBr. The column was washed with 8 M HCl/0.05 M NH_4I to remove iron, and the uranium was eluted with 0.05 M HCl. After elution, the plutonium and uranium fractions from the column were separately electrodeposited onto stainless steel planchets, and the planchets were analyzed alpha spectrometrically.

A typical alpha spectrum for determination of the ^{239}Pu, ^{238}Pu, and ^{236}Pu in our samples is shown in Figure 2.1. Good separation of the peaks of these isotopes was achieved. Measurement of the ^{242}Pu spike allowed determination of plutonium recovery through the analysis steps. Samples were counted in a low-background counting system (background < 10^{-4} counts per min) until adequate counting statistics were achieved for each of the radionuclides.

Before use, this method was validated by analysis of a urine specimen to which known amounts of ^{236}Pu, ^{239}Pu, ^{233}U, ^{236}U, and ^{237}Np had been added. Results showed excellent agreement between prepared and measured values, with measured values at 98–110% of the amounts added (Table 2.3).

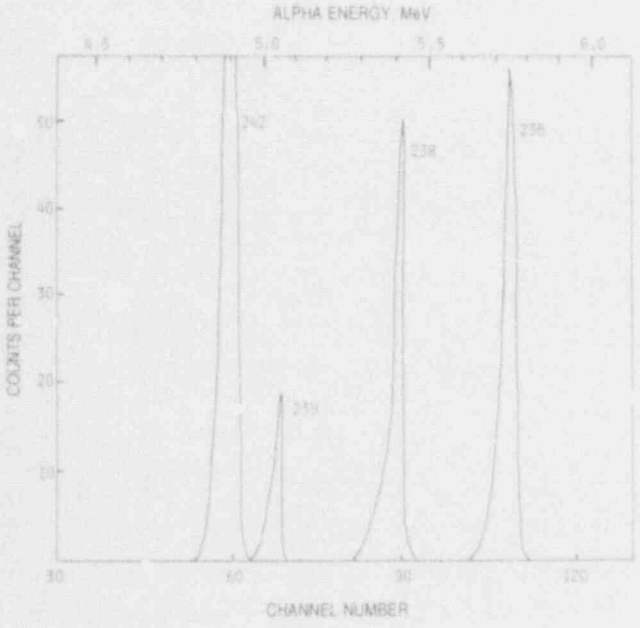

Figure 2.1 Alpha spectrum from the determination of ^{239}Pu, ^{238}Pu, and ^{236}Pu

For samples containing ^{239}Np and higher activities of ^{237}Np, three photon measurement systems were used to determine activity (Cohen and Ralston, 1987; Ralston, 1990): (1) a Ge(Li) detector for measuring large volume (1-L) urine samples in Marinelli beakers; (2) a 4 in. × 4 in. NaI(T1) detector for blood and pulverized dried fecal samples; and (3) a 3 in. × 2 in. NaI(T1) detector for 100-mL aliquots of urine and ashed tissue samples. Samples containing low activities of ^{237}Np were analyzed by ASID as described above for plutonium and uranium.

2.6 Dual Isotope Method of Determining GI Absorption Values

The GI absorption of an element can be determined by simultaneously administering two isotopes of that element to the same animal, one isotope intravenously and one orally. This method has been used to determine the GI absorption of calcium (DeGrazia et al., 1965), iron (Inamoto, 1970), and neptunium (Popplewell et al., 1980) in humans. Blood and urine samples and tissue biopsy specimens can be obtained at various times after the isotope administrations. From the known amount of the i.v. isotope injected into blood (A_i) and the oral/i.v. isotopic ratio in blood (or urine or tissue biopsy specimens), the amount of the ingested isotope that was absorbed from the GI tract to blood (A_o) can be calculated as follows:

$$A_o = A_i \times \frac{s_o}{s_i}$$

where A_o = amount of oral isotope reaching blood from GI tract

A_i = amount of i.v. isotope injected into blood

s_o = activity of oral isotope in sample s

s_i = activity of i.v. isotope in sample s

Table 2.3 Determination of actinides in a test urine sample

Isotopes		Concentration (pCi/L)	
Measured	Diluent	Prepared	Measured[a]
^{236}Pu	^{242}Pu	1.12	1.10, 1.09 (0.007)
^{238}Pu		3.28	3.27, 3.28 (0.007)
^{239}Pu		0.093	0.105, 0.099 (0.004)
^{233}U	^{238}U	1.91	1.90, 1.96 (0.04)
^{236}U		1.97	1.96, 2.02 (0.04)
^{237}Np	^{239}Np	0.387	0.383, 0.404 (0.015)

[a]Value in parentheses is the standard deviation for the two measured values.

The *fraction* absorbed to blood (the GI absorption value, f_1) is the amount reaching the blood (A_o) divided by the known dose of oral isotope ingested (D_o):

$$f_1 = \frac{A_o}{D_o}$$

Substituting for A_o from above, it can be seen that:

$$f_1 = \frac{A_o}{D_o} = \frac{A_i}{D_o} \times \frac{s_o}{s_i} = \frac{s_o}{D_o} \times \frac{A_i}{s_i} = \frac{R_{so}}{R_{si}}$$

where

$$R_{si} = \frac{s_i}{A_i} = \text{fractional retention of i.v. isotope in sample s}$$

$$R_{so} = \frac{s_o}{D_o} = \text{fractional retention of oral isotope in sample s}$$

Consequently, the fractional GI absorption value, f_1, can be calculated directly as the fractional retention of the oral isotope in a given sample (R_{so}) divided by the fractional retention of the i.v. isotope in that same sample (R_{si}). For this method to apply, the i.v. isotope must be metabolically equivalent to the absorbed portion of the oral isotope.

2.7 Experiment 1 Protocol

Experiment 1 was conducted to determine the GI absorption of plutonium and neptunium in fed and fasted baboons and of uranium in fasted baboons. On day 0 of the protocol (Fig. 2.2), each of four adult baboons was administered a known amount of ^{239}Pu(VI) (mean dose, 4.3 kBq) through a stomach tube at 0900–1000, 2 h after the morning feeding of baboons B704, B1050, and B1046, and after a 14-h overnight fast (from 2000 to 1000 hours) of baboon B1048. Blood was taken at 4 h (B704) or 8 h (B1050, B1046, B1048) after ^{239}Pu administration. On day 14 of the protocol (Fig. 2.2), each of the same four baboons was administered known amounts of ^{236}Pu(VI) (mean dose, 3.4 kBq) and ^{233}U(VI) (mean dose, 4.6 kBq) through a stomach tube at 0900–1000, after a 24-h fast. Immediately after the i.g. administrations on day 14, each baboon received an i.v. injection of ^{238}Pu(VI) (mean dose, 12.6 Bq) and ^{236}U(VI) (mean dose, 14.9 Bq). Blood samples were taken 8 h after these administrations.

Starting on day 0, each animal was housed in a stainless steel metabolism cage, and urine and feces were collected daily. In addition, for each baboon except B704, one urine sample was obtained by catheterization 4 d after the plutonium and uranium administrations. On day 46 of the experiment, 32 d after the dual isotope administrations on day 14, three baboons (B704,

Day 0	Fed	^{239}Pu i.g. + ^{239}Np i.g.
14	Fasted	^{236}Pu i.g. + ^{238}Pu i.v., ^{233}U i.g. + ^{236}U i.v., ^{237}Np i.g.
45	Fasted	^{239}Np i.g.
46	Sacrifice	

Figure 2.2 Experiment 1 design: GI absorption of plutonium and neptunium in fed and fasted adult baboons and of uranium in fasted adult baboons

B1050, B1948) were sacrificed, and one baboon (B1046) had biopsies taken of the liver and caudal vertebrae. All excreta and all tissues taken at sacrifice were ashed and analyzed for isotopes of uranium and plutonium by means of ASID. This experiment provided GI absorption values of plutonium in fed (^{239}Pu) and fasted (^{236}Pu) adult baboons and of uranium in fasted (^{236}U) adult baboons. GI absorption values were obtained by the dual isotope method from isotopic ratios in samples of blood, urine, liver, and bone. For the baboons that were sacrificed, values were also obtained by summation of the amounts of isotope in urine and tissues. As part of this collaborative study with NYUMC, the baboons were also administered known amounts of ^{239}Np (day 0 and day 45; 5.9 ± 1.6 MBq) and ^{237}Np (day 14; 5.1 ± 1.9 kBq) through a stomach tube (Cohen and Ralston, 1987; Ralston, 1990).

2.8 Experiment 2 Protocol

This experiment was conducted to determine the GI absorption of uranium in fed adult baboons and the GI absorption of plutonium and neptunium at various times after a morning meal. On day 0 of the protocol (Fig. 2.3), three adult baboons (B358, B880, B230) were given a breakfast of one banana (peeled, 100 g) and three large pecan oatmeal cookies (80 g, Archway Co.) at 0700. The animals all ate their meals immediately. At 1100, 4 h after the meal, each was administered ^{236}Pu(VI) orally (mean dose, 7.5 kBq) and ^{238}Pu(VI) intravenously (mean dose, 11 Bq). A blood sample

Day 0	4-h Fast	^{236}Pu i.g. + ^{238}Pu i.v., ^{237}Np i.g.
21	6-h Fast	^{239}Pu i.g. + ^{238}Pu i.v., ^{237}Np i.g.
42	8-h Fast	^{239}Pu i.g. + ^{238}Pu i.v., ^{237}Np i.g.
56	Fed	^{233}U i.g. + ^{236}U i.v.
70	Biopsy	

Figure 2.3 Experiment 2 design: GI absorption of uranium in fed adult baboons and effects of duration of fast on GI absorption of plutonium and neptunium in adult baboons

was taken from each animal 8 h after the administrations. Urine samples were collected daily, and a separate urine specimen was collected by catheterization on day 4.

On day 21, when blood and urine concentrations of ^{236}Pu and ^{238}Pu had decreased to very low levels, the same three baboons were again given the same breakfast at 0700. At 1300, 6 h after the meal, each baboon was again administered two isotopes of plutonium, this time ^{239}Pu(VI) orally (mean dose, 5.4 kBq) and ^{238}Pu(VI) intravenously (mean dose, 11 Bq). Blood samples were taken just prior to the administrations and 8 h after. Urine samples were collected during the 24-h period prior to the administrations and daily thereafter. A separate specimen was obtained by catheterization on day 28, 2 d after the second set of plutonium administrations.

On day 42, the same three baboons were again given the same breakfast at 0700. At 1500, 8 h after the meal, each baboon was administered two plutonium isotopes in the same amounts as before, ^{239}Pu(VI) orally and ^{238}Pu(VI) intravenously. Blood and urine samples were collected as for the second set of plutonium administrations. As part of this collaborative study with NYUMC, the baboons were also administered known amounts of ^{237}Np (10 ± 1 kBq) through a stomach tube on days 0, 21, and 42 (Fig. 2.3) (Ralston, 1990).

On day 56, the same three baboons were given two isotopes of uranium, ^{233}U orally (13 kBq) and ^{236}U intravenously (16 Bq). Administration was at 0900, 2 h after their morning feeding. Urine samples were collected daily during the day 56–66 interval, and urine specimens were obtained by catheterization on day 60, 4 d after the uranium administrations. On day 70, samples of caudal vertebrae were removed from each baboon at biopsy. No animal was sacrificed. Only samples of caudal vertebrae could be analyzed from this study because of programmatic restrictions. These samples were ashed and analyzed for plutonium, uranium, and neptunium.

3 Results: Plutonium

3.1 Gastrointestinal Absorption of Plutonium: Sacrifice Method

One method for determining the GI absorption of plutonium is to administer an isotope orally and to sum the amounts retained in tissues obtained at sacrifice with the amount excreted in urine. Table 3.1 presents detailed results for this method applied to determining the GI absorption of ^{236}Pu in baboon B704 on day 14 of experiment 1. As can be seen, the liver and skeleton at sacrifice 32 d after administration contained most of the retained plutonium, with a liver/skeleton ratio of approximately 1:1. The plutonium concentration in muscle was low, but muscle mass was high, resulting in the remaining organs containing plutonium in the order muscle > spleen > kidneys ≈ lungs. The first 24-h urine sample contained 13.8% of the absorbed plutonium, where absorbed plutonium = sum of plutonium in tissues + urine. After day 15, plutonium levels in urine were high due to contamination by ^{236}Pu in feces from the oral dose. The plutonium fractional GI absorption value for B704 after a 24-h fast was 1.60×10^{-4} (0.016%) as determined by this method. The sacrifice method does not take into account any ^{236}Pu that was absorbed and then excreted in feces because of the inability to distinguish between unabsorbed ^{236}Pu from the administered dose and ^{236}Pu absorbed and then excreted in feces.

Table 3.1 Gastrointestinal absorption of plutonium in fasted baboon B704: sacrifice method[a]

Sample	Sample wt.[b] (g)	^{236}Pu content[c]		Percentage of retained plutonium
		dpm	10^4 × fraction of dose	
Skeleton	476	4.92 ± 0.24	0.60 ± 0.03	43.5
Liver	264	5.55 ± 0.22	0.67 ± 0.03	48.6
Muscle	3990	0.758 ± 0.160	0.0913 ± 0.0193	6.6
Spleen	--[d]	0.082 ± 0.011	0.0099 ± 0.0013	0.7
Left kidney	18.4	0.017 ± 0.004	0.0042 ± 0.0011	0.3
Right kidney	18.8	0.018 ± 0.005		
Lungs	68.3	0.028 ± 0.006	0.0034 ± 0.0007	0.3
Total retained ^{236}Pu			1.38 ± 0.04	100
Day-15 urine	1567	1.86 ± 0.09	0.22 ± 0.01	13.8[e]
Total absorbed ^{236}Pu			1.60 ± 0.04	

[a]Baboon B704 was administered 83,000 dpm ^{236}Pu (1.38 kBq) by i.g. intubation at 0900 on day 14 of experiment 1 after a 24-h fast. Samples other than urine were obtained at sacrifice of the baboon on day 46, 32 d after ^{236}Pu administration. The day-15 urine sample was a 24-h collection obtained one day after ^{236}Pu administration, before the appearance of high levels of ^{236}Pu in feces.

[b]Ash weight for skeleton, wet weight for other samples. Weights are for whole organ (tissues) and 24-h collection (urine).

[c]Values are mean ± SE. Fraction of dose = fraction of intragastrically administered ^{236}Pu retained per sample. SE values show the uncertainty associated with α-counting ^{236}Pu in the sample. Total retained ^{236}Pu = sum of samples; the total absorbed ^{236}Pu = samples + urine.

[d]Not weighed.

[e]Percentage of absorbed (not retained) ^{236}Pu.

In Experiment 1, three baboons were sacrificed: B704, B1048, and B1050. Plutonium GI absorption values determined by the sacrifice method for these baboons after a 14-h or 24-h fast are presented in Table 3.2. There was a 16-fold range in fractional GI absorption values, from 1.6×10^{-4} for B704 (0.016%) to 26×10^{-4} for B1048 (0.26%). The mean value for the fasted animals was $(12 \pm 5) \times 10^{-4}$ (mean ± SE, n = 4), or 0.12%. GI absorption values for fed animals are presented in Table 3.3. The two values had a 5-fold range and a mean of $(0.91 \pm 0.6) \times 10^{-4}$ (mean ± SE, n = 2), or 0.009%.

On comparison of mean values, fasting caused a 13-fold increase in the GI absorption of plutonium in the adult baboon. On comparison of values for individual baboons, B704 showed essentially no increase due to fasting, while B1050 showed a 33-fold increase. (Because GI absorption values for ^{239}Pu, ^{233}U, and ^{237}Np were all low for administrations on day 14 to fasted baboon B704, we suspect that B704, the first 24-h-fasted animal in our study, may have inadvertantly obtained some food.)

Table 3.2 Gastrointestinal absorption of plutonium in fasted adult baboons: sacrifice method[a]

	Plutonium content (10^4 × fraction of dose)			
	^{236}Pu			^{239}Pu
Sample	B704	B1048	B1050	B1048
Skeleton	0.60	2.97	5.64	14.43
Liver	0.67	4.35	3.40	8.40
Other tissues[b]	0.11	0.48[c]	0.39	2.49[c]
Total retained Pu	1.38	7.80	9.43	25.32
Day-15 urine	0.22	0.30	0.93[d]	0.57[e]
Total absorbed Pu	1.60	8.10	10.36	25.89

[a]Baboons were administered ^{236}Pu (1.4-6.7 kBq) by i.g. intubation at 0900 on day 14 of experiment 1 after a 24-h fast. Baboon B1048 was also administered ^{239}Pu (6.7 kBq) intragastrically at 0900 on day 0 after a 14-h overnight fast (no breakfast). See Table 3.1, footnote a, for notes on sample collection.

[b]For B704, "other tissues" = kidneys, muscle, lungs, and spleen, analyzed separately and summed. For B1050, "other tissues" = kidneys, muscle, and lungs analyzed separately and summed with a soft tissue composite containing aorta, trachea, spleen, heart, pancreas, uterus, ovaries and tubes, eyes, thyroid, and adrenals.

[c]For B1048, "other tissues" were not analyzed; values were calculated based on the mean fraction of total retained Pu in "other tissues" for the other two baboons.

[d]For B1050, day-15 urine was contaminated with ^{236}Pu in feces from i.g. administration on day 14. The value given was calculated based on the mean fraction of total retained Pu excreted in the urine of other two baboons.

[e]This urine was collected on day 1 (not day 15), 24 h after ^{239}Pu administration.

Table 3.3 Gastrointestinal absorption of plutonium in fed adult baboons: sacrifice method[a]

Sample	^{239}Pu Content (10^4 × fraction of dose)	
	B704	B1050
Skeleton	0.80	0.181
Liver	0.52	0.087
Other tissues[b]	0.11	0.038
Total retained Pu	1.43	0.306
Day-1 urine	0.04	0.004
Total absorbed Pu	1.47	0.310

[a]Baboons were administered ^{239}Pu (B704, 0.73 kBq; B1050, 9.1 kBq) by i.g. intubation at 0900 on day 0 of experiment 1, 2 h after their morning feeding. Day-1 urine was a 24-h collection obtained one day after ^{239}Pu administration. Skeleton, liver, and other tissues were obtained at sacrifice 46 d after ^{239}Pu administration.

[b]"Other tissues" were as described in Table 3.2, footnote b.

3.2 Plutonium Metabolism after Oral vs. Intravenous Administration

For the dual isotope method to apply, the intravenous isotope must be metabolically equivalent to the absorbed portion of the oral isotope. Table 3.4 gives an accounting of the oral ^{236}Pu vs. i.v. ^{238}Pu in baboon B704. After both administration modes, 8–10% of the absorbed plutonium was excreted in urine in the first 24 h (day-15 urine). In addition, by both modes, the ratio of plutonium in liver vs. skeleton was 1:1. These results indicate that the major plutonium metabolic pathways were the same, independent of whether the plutonium entered the bloodstream by i.v. injection or via the GI tract.

Upon summing the amounts of ^{238}Pu in urine, liver, and skeleton, we were surprised to find that 29% of the i.v. dose was not accounted for ("Other," Table 3.4). While about 6% of the i.v. dose was present in tissues other than liver and skeleton, we postulate that the remaining 23% might have been excreted in feces. (Twenty-three percent of the i.v. ^{238}Pu dose [175 dpm] could not be clearly quantitated in feces because ^{238}Pu was also present in feces as a small fraction of the oral ^{236}Pu [Table 2.2].) Assuming that a similar fraction of the ^{236}Pu absorbed through the GI tract was present in the "other" fraction, the total fractional absorption of ^{236}Pu by baboon B704 was 2.12×10^{-4} (0.021%).

Table 3.5 presents a detailed distribution of the oral and i.v. isotopes in the skeleton. The oral/i.v. isotopic ratio is nearly the same for each of the 24 skeletal parts, again demonstrating the equivalent handling of the i.v. and oral plutonium by the body.

In contrast to the tissue distribution data, the urinary excretion of the oral isotope differed considerably from that of the i.v. isotope (Fig. 3.1). While 8% of the i.v. ^{238}Pu appeared in urine during the first 24 h, very little appeared in urine after that. For the oral ^{236}Pu, urinary plutonium increased until 3 d after administration and then decreased to low levels by 8 d. Although the shape of the urinary ^{238}Pu peak looked regular and might have indicated a difference between

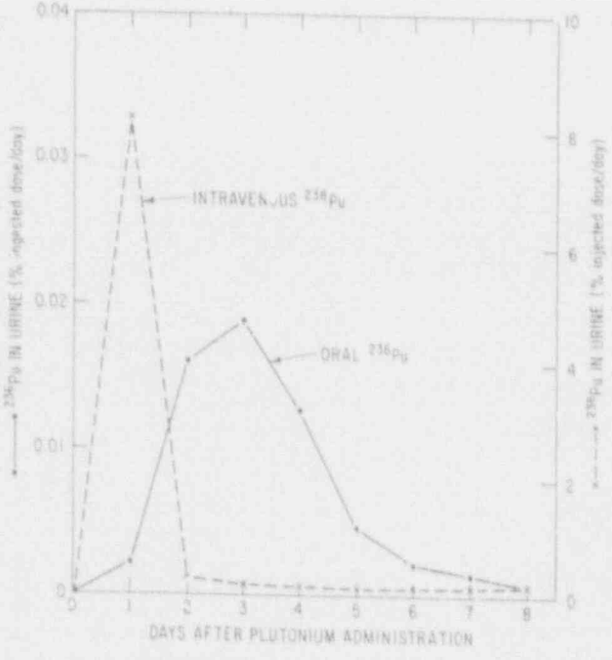

Figure 3.1 Plutonium content of urine during days 1–8 after oral or intravenous plutonium administration to baboon B704

Table 3.4 Comparison of metabolism of plutonium in adult baboon B704: oral vs. intravenous administration[a]

Sample	No. of samples analyzed	Plutonium content (fraction of administered dose)	
		Oral ^{236}Pu (10^4 × fraction)	i.v. ^{238}Pu
Urine			
Day 15	1	0.22 (10%)	0.082 (8%)
Days 16-46, cumulative	13	6.17[b] (--)	0.029 (3%)
Total		0.22	0.111
Tissues on day 46			
Liver	4	0.67 (32%)	0.298 (30%)
Skeleton	25	0.60 (28%)	0.296 (30%)
Other[c]	--	0.63 (30%)	0.295 (29%)
Total		1.90	0.889
Total absorbed (urine + tissues)		2.12 (100%)	1.000 (100%)

[a]Baboon B704 was administered ^{236}Pu (1.38 kBq) by i.g. intubation and ^{238}Pu (13 Bq) by i.v. administration at 0900 on day 14 of experiment 1. B704 was sacrificed on day 46.

[b]Not included in calculation of total absorbed ^{236}Pu due to contamination of urine by ^{236}Pu in feces from i.g. dose.

[c]Values for "other" were calculated. For the i.g. ^{236}Pu, "other" was calculated by analogy to the i.v. ^{238}Pu, making the total absorbed ^{236}Pu in this table (2.12×10^{-4}) somewhat higher than the value in Table 3.1 (1.60×10^{-4}). For the i.v. ^{238}Pu, "other" is the amount of the i.v. dose not accounted for by ^{238}Pu in urine, liver, and skeleton. A small portion represents ^{238}Pu in tissues other than liver and skeleton (Table 3.2). The remaining may represent ^{238}Pu excreted in feces. (Excretion of i.v. ^{238}Pu in feces could not be directly measured because of ^{238}Pu in feces from the presence of that isotope in the ^{236}Pu preparation [Table 2.2]).

excretion pathways for oral vs. i.v. plutonium, we postulated that the urine, which was collected in a metabolism cage, was contaminated by ^{238}Pu in feces. To test this hypothesis, we collected a urine sample from baboon B1048 by catheterization 4 d after $^{236}Pu/^{238}Pu$ administration and compared the oral/i.v. isotopic ratio for the catheter sample with the ratio for the urine collected in the cage on that same day.

Figure 3.2 shows the amounts of oral ^{236}Pu and i.v. ^{238}Pu in urine during the first 8 d after administration to baboon B1048. Clearly, the peak of ^{236}Pu in urine was not as regular as for B704 (Fig. 3.1). In addition, for plutonium, there was an overabundance of oral ^{236}Pu (presumably from feces) in the cage-collected urine sample compared with the catheter urine sample (Table 3.6).

The results also demonstrated that contamination of urine by oral isotopes in feces was critical for plutonium, but not uranium. Contamination of urine by feces was low enough to not significantly disturb the oral/i.v. isotopic ratio for uranium (Table 3.6). This is because the oral uranium was more abundant in urine (it was absorbed through the GI tract to a greater extent than was the plutonium, and most of the absorbed uranium was excreted in urine).

Table 3.5 Comparison of distribution of plutonium in bones of baboon B704: oral vs. intravenous administration

Bone	Ash wt. (g)	Plutonium content[a] ^{236}Pu (oral) Ash (dpm/g)	^{236}Pu (oral) 10^5 × fraction retained [A]	^{238}Pu (i.v.) Ash (dpm/g)	^{238}Pu (i.v.) 10^2 × fraction retained [B]	Oral/i.v. ratio [A/B]
Skull (without calvarium)[b]	78.14	0.0088	0.828	0.398	4.06	0.20
Calvarium	21.52	0.0120	0.310	0.561	1.57	0.20
Total skull[b]	99.66		1.138		5.63	0.20
Cervical vertebrae	9.50	0.0113	0.130	0.466	0.58	0.22
Thoracic vertebrae	21.61	0.0219	0.466	1.014	2.73	0.17
Lumbar vertebrae	30.06	0.0205	0.742	1.029	4.04	0.18
Caudal vertebrae (tail)	13.33	0.0041	0.066	0.224	0.39	0.17
Pelvis + sacral vertebrae	53.41	0.0105	0.674	0.672	4.68	0.14
Rib 5	2.51	0.0138	0.040	0.608	0.20	0.20
Rib 7	2.84	0.0204	0.070	0.643	0.24	0.29
Rib 9	2.82	0.0126	0.044	0.647	0.24	0.18
Ribs (all other)	19.24	0.0199	0.460	0.638	1.60	0.29
Scapulae	21.20	0.0120	0.266	0.545	1.52	0.18
Clavicles	2.27	0.0123	0.034	0.608	0.18	0.19
Sternum	2.26	0.0403	0.104	1.769	0.50	0.21
Total axial	181.05		3.096		16.90	0.18
Femora	46.21	0.0090	0.514	0.409	2.70	0.19
Patellae	1.84	0.0090	0.020	0.238	0.06	0.33
Tibiae — large end	7.83	0.0087	0.140	0.501	0.50	0.28
Tibiae — shaft	18.74	0.0018	0.046	0.096	0.22	0.21
Tibiae — small end	3.51	ND[c]	ND	0.135	0.06	--
Fibulae	5.67	0.0024	0.024	0.123	0.10	0.24
Hands and feet	35.28	0.0046	0.192	0.108	0.50	0.38
Humeri	40.17	0.0122	0.590	0.443	2.35	0.25
Radii	18.85	0.0036	0.086	0.103	0.25	0.33
Ulnae	18.34	0.0053	0.118	0.122	0.29	0.39
Total appendicular	196.44		1.730		7.03	0.25
Total skeleton[b]	477.15		5.964		29.56	0.20

[a]The relative standard deviation of the mean for the values presented averaged 23% (range 10–50%) for the ^{236}Pu content and 4% (range 1-14%) for the ^{238}Pu content. "dpm/g" shows concentration; "fraction retained" shows amount per sample.

[b]Not including teeth.

[c]ND = not detectable.

Table 3.6 Evidence for plutonium, but not uranium, contamination of cage-collected urine samples by the oral isotope in feces[a]

Sample	Oral/i.v. isotopic ratio	
	$^{236}Pu/^{238}Pu$ (dpm/dpm)	$^{233}U/^{236}U$ (dpm/dpm)
Day-18 urine		
Cage-collected, 24 h	25	108
Catheterized	0.80	89

[a]Data are for baboon B1048. Day-18 cage-collected urine was a 24-h collection obtained 2 d after administration of ^{236}Pu (6.7 kBq) and ^{233}U (6.7 kBq) by i.g. intubation and ^{238}Pu (16 kBq) and ^{236}U (16 Bq) by i.v. administration (Fig. 2.2). On day 18, a urine sample was also obtained directly from the bladder by catheterization to avoid contamination by the oral isotope in feces.

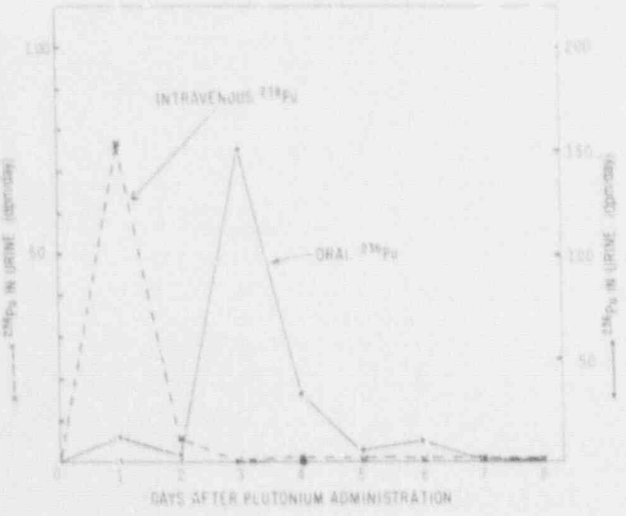

Figure 3.2 Plutonium content of urine during days 1–8 after oral or intravenous plutonium administration to baboon B1048

In conclusion, differences in the temporal patterns of plutonium in urine for the oral vs. i.v. isotopes clearly reflected contamination of urine by feces and not differences in excretion pathways for the oral vs. i.v. isotopes.

3.3 Gastrointestinal Absorption of Plutonium: Dual Isotope Method

Table 3.7 presents fractional GI absorption values for $^{236}Pu(VI)$ in baboon B704, calculated by the dual isotope method from the ratio of R_{so}/R_{si} in various samples. Although there was close to a 2-fold range from the low to the high value depending on the tissue sample analyzed, the calculated GI absorption value was largely consistent from sample to sample, independent of whether the sample contained a large fraction of the retained dose (e.g., liver) or a small fraction (e.g., rib 5), again indicating that the oral and i.v. isotopes were behaving metabolically the same. The mean calculated fractional GI absorption value, 2.0×10^{-4} (0.020%), is only 25% higher than the value obtained by the sacrifice method, 1.6×10^{-4} (0.016%) (Table 3.1). The clear advantages of the dual isotope method are (1) it does not require sacrifice of the animal and thus can be used to determine GI absorption values in humans; (2) it requires much less sample analysis time; and (3) the same animal can provide multiple GI absorption values by readministration of a dual set of isotopes after the original isotopes have cleared from blood and urine.

Table 3.7 Gastrointestinal absorption of plutonium in fasted baboon B704: dual isotope method

Sample	Plutonium content[a] (fraction of dose)		$10^4 \times$ calculated fractional GI absorption[b]
	^{236}Pu ($10^5 \times R_{so}$)	^{238}Pu ($10^2 \times R_{si}$)	
Blood, 8 h	5.6[c]	25[c]	2.2
Urine, day 15[d]	2.2	8.2	2.7
Liver	6.7	30	2.2
Total skeleton	6.0	30	2.0
Caudal vertebrae	0.066	0.39	1.7
Skull	0.83	4.06	2.0
Pelvis + sacral vertebrae	0.67	4.68	1.5
Rib 5	0.040	0.20	2.0
Mean ± SE (n)			2.0 ± 0.1 (8)

[a]Values are the fraction of administered plutonium retained by the sample (^{236}Pu administered orally, ^{238}Pu administered intravenously). Samples other than blood and urine were obtained at sacrifice of the baboon 32 d after administration of ^{236}Pu (1.4 kBq) and ^{238}Pu (18 Bq) (day 46 of experiment 1).

[b]Sample calculation for 8-h blood:

$$f_1 = \frac{R_{so}}{R_{si}} = \frac{5.6 \times 10^{-5}}{25 \times 10^{-2}} = 2.2 \times 10^{-4}$$

where R_{so} = fractional retention of i.g. dose in sample
R_{si} = fractional retention of i.v. dose in sample

[c]Value is for total blood in the animal at 8 h (assuming blood equals 7% of body weight), indicating that, for example, 25% of the i.v. plutonium was present in the blood at 8 h after administration.

[d]Day-15 urine sample was a 24-h collection obtained one day after the administration of ^{236}Pu and ^{238}Pu (on day 14 of experiment 1). Only day-15 urine was used to calculate f_1 for plutonium because contamination of urine by ^{236}Pu in feces was unlikely on that day; the orally administered actinides were assumed to be present in feces after (but not on) day 15 (Fig. 3.1, Table 3.6).

Table 3.8 gives the values of R_{so} (fractional retention of ^{239}Pu and ^{236}Pu) and R_{si} (fractional retention of ^{238}Pu) that were used to calculate GI absorption values for baboons B704, B1048, B1050, and B1046 by the dual isotope method. ^{239}Pu was administered orally to fed animals (except for B1048) and ^{236}Pu was administered orally to 24-h-fasted animals. Table 3.9 provides the fractional GI absorption values calculated from the fractional retention values, R_{so} and R_{si}, in Table 3.8. The tissues selected to provide GI absorption values in Table 3.9 (blood, urine, caudal vertebrae, liver biopsy specimen) are those that could be obtained without sacrifice of the animal and thus might be used by other investigators.

GI absorption values calculated from ratios for individual samples of blood, urine, bone, and liver in general agreed well with one another and almost always were close to the mean value for all samples. Calculated GI absorption values for plutonium ranged from 2.2×10^{-4} for B704 to 59×10^{-4} for B1046 for the fasted animals and from

Table 3.8 Plutonium content of samples used to determine GI absorption by the dual isotope method

	Plutonium content (fraction of dose)											
	B704			B1048			B1050			B1046		
Sample[a]	^{239}Pu ($10^5 \times R_{so}$)	^{236}Pu ($10^5 \times R_{so}$)	^{238}Pu ($10^2 \times R_{si}$)	^{239}Pu ($10^5 \times R_{so}$)	^{236}Pu ($10^5 \times R_{so}$)	^{238}Pu ($10^2 \times R_{si}$)	^{239}Pu ($10^5 \times R_{so}$)	^{236}Pu ($10^5 \times R_{so}$)	^{238}Pu ($10^2 \times R_{si}$)	^{239}Pu ($10^5 \times R_{so}$)	^{236}Pu ($10^5 \times R_{so}$)	^{238}Pu ($10^2 \times R_{si}$)
Blood, 8 h[b]	3.02[c]	5.97	26.7	53.6	25.5	21.5	0.61	23.2	43.3	ND[d]	126	26.7
Urine, day 1[e]	0.43	2.24	8.22	--	--	--	--	--	--	--	--	--
day-4 cath.[f]	--	--	--	--	1.69	1.09	--	0.75	0.41	--	9.22	1.09
Caudal vertebrae[g]	0.18	0.066	0.39	1.19	0.50	0.72	0.015	0.28	0.28	ND	0.20	0.064
Liver, biopsy[h]	--	--	--	1.78	0.54	0.40	0.010	0.47	0.22	0.036	5.59	0.76
Total liver	5.17	6.70	29.8	--	--	--	--	--	--	--	--	--

[a]Samples other than blood and urine were obtained either by sacrifice (B704, B1048, B1050) or by biopsy (B1046) on day 46 of experiment 1, 46 d after ^{239}Pu administration and 32 d after ^{236}Pu/^{238}Pu administration.

[b]Blood was obtained 8 h after isotope administration on day 9 (for ^{239}Pu) and day 14 (for ^{236}Pu and ^{238}Pu). Values are for whole blood assuming blood = 7% of body weight).

[c]Blood sample taken at 4 h (rather than 8 h) after ^{239}Pu administration.

[d]ND = not detectable.

[e]Urine was collected during the first 24 h after isotope administration; i.e., on day 1 for ^{239}Pu and day 15 for ^{236}Pu and ^{238}Pu.

[f]Sample obtained from the bladder by catheterization 4 d after isotope administration (day 18 of experiment 1). Values are calculated to correspond to 24-h urine collection based on fraction of 24-h urine weight obtained by catheterization. Catheterized and 24-h urine weights were 4.8 g and 1900 g for B1048; 9.9 g and 1223 g for B1050; 26 g and 888 g for B1046.

[g]Caudal vertebrae 1-17 for B704; 1-14 for B1048; 1 & 2, 11-13, and part of 14 for B1050; and 9-16 and part of 17 for B1046.

[h]Values are Pu contents of biopsy sample. Liver biopsy and total liver weights were 2.7 g and 218 g for B1048; 3.2 g and 205 g for B1050; 4.2 g and unknown for B1046 (which was not sacrificed, so the liver weight is unknown).

Table 3.9 Gastrointestinal absorption of plutonium in fed and fasted adult baboons: dual isotope method[a]

	10^4 × calculated fractional GI absorption[b]				
Sample	**B704**	**B1048**	**B1050**	**B1046**	**B1048[c]**
Fasted animals[d]					
Blood, 8 h	2.2	12	5	47	25
Urine, 4 d cath.	2.7	16	18	85	--
Bone, caudal vert.	1.7	10	16	31	17
Liver, biopsy	2.2	14	21	74	45
Mean ± SE (n)	2.2 ± 0.2 (4)	13 ± 1 (4)	15 ± 3 (4)	59 ± 11 (4)	29 ± 7 (4)
Fed animals[e]					
Blood, 8 h	1.1	--	0.14	ND[f]	--
Bone, caudal vert.	4.6	--	0.54	ND	--
Liver, biopsy	1.7	--	0.46	0.47	--
Mean ± SE (n)	2.5 ± 0.9 (3)	--	0.38 ± 0.10 (3)	0.47 (1)	--

[a]On day 0 of experiment 1, fed baboons were administered ^{239}Pu (0.73-9.1 kBq) by i.g. intubation at 0900. On day 14, fasted baboons were administered ^{236}Pu (1.4-6.7 kBq) by i.g. intubation at 0900 and ^{238}Pu (10-16 Bq) by i.v. injection immediately afterwards. For fasted animals, administrations were after a 24-h fast except where indicated; for fed animals, administrations were 2 h after a morning meal.

[b]Values calculated by dual isotope method (see text and Table 3.7, footnote b).

[c]Values based on ^{239}Pu/^{238}Pu ratios (R_{so}/R_{si}, Table 3.8) of indicated samples. B1048 was administered ^{239}Pu on day 0 after a 14-h overnight fast to simulate a baboon "without breakfast."

[d]Values calculated from ^{236}Pu/^{238}Pu ratios (R_{so}/R_{si}, Table 3.8) of the indicated samples except for second B1048 value, which used ^{239}Pu/^{238}Pu ratios (see note c). For B704, urine was a 24-h collection on day 1 (not a 4-d catheterization).

[e]Values calculated from ^{239}Pu/^{238}Pu ratios (R_{so}/R_{si}, Table 3.8) of indicated samples.

[f]ND = not detectable.

0.38×10^{-4} for B1050 to 2.5×10^{-4} for B704 for the fed animals. Effects of fasting were 40-fold for B1050, 125-fold for B1046, and non-existent for B704, again indicating that B704 may have inadvertantly obtained some food.

3.4 Comparison of Sacrifice vs. Dual Isotope Methods

Plutonium GI absorption values obtained by the dual isotope method agreed reasonably well with those obtained by the sacrifice method (Table 3.10). On the average, sacrifice method values were 72% of the dual isotope method values. Note that baboon B1046, whose GI absorption values were not shown in earlier tables because she was not sacrificed, had the highest GI absorption value in the 24-h-fasted state (59×10^{-4}, 0.59%) (Tables 3.9 and 3.10), bringing up the mean GI absorption value for the fasted animals from $(15 \pm 6) \times 10^{-4}$ with n = 4 to $(24 \pm 11) \times 10^{-4}$ with n = 5 (Table 3.10). As mentioned earlier, the sacrifice method values may be lower than the dual isotope method values because the former do not account for plutonium excreted into feces after GI absorption. Results demonstrate that the dual isotope method can be used as a reliable means of determining the GI absorption of plutonium in adult baboons.

Table 3.10 Plutonium GI absorption in fed and fasted adult baboons: comparison of sacrifice and dual isotope methods

Feeding regimen	10^4 × fractional GI absorption[a]		
	Sacrifice [A]	Dual isotope [B]	A/B
Fasted[b]			
B704	1.6	2.2	0.73
B1048	8.1	13	0.62
B1050	10	15	0.66
B1046	--	59	--
B1048[c]	26	29	0.90
Mean ± SE (n)	12 ± 5 (4)	24 ± 11 (5) 15 ± 6 (4)[d]	
Fed			
B704	1.5	2.5	0.56
B1050	0.31	0.38	0.82
B1046	--	0.47	--
Mean ± SE (n)	0.91 ± 0.6 (2)	1.1 ± 1.2 (3) 1.4 ± 1.1 (2)[d]	

[a]Values for sacrifice method are from Tables 3.2 and 3.3; values for dual isotope method are from Table 3.9.

[b]Animals were fasted for 24 h before plutonium administration, except where indicated.

[c]Fast was a 14-h overnight to simulate a baboon "without breakfast."

[d]Mean for dual isotope method excluding B1046, which was not sacrificed. This mean is therefore directly comparable to the sacrifice method mean.

3.5 Effects of Feeding Regimen and Animal Species on the Gastrointestinal Absorption of Plutonium

3.5.1 Feeding Regimen

In Experiment 1, we showed by two methods that the GI absorption of plutonium was about 20 × 10^{-4} (0.2%) in 24-h-fasted adult baboons and about 1 × 10^{-4} (0.01%) in fed animals given plutonium 2 h after the morning feeding (Tables 3.2, 3.3, 3.9, 3.10). We also showed that one baboon given plutonium with no morning feeding (14-h overnight fast, baboon "without breakfast") absorbed plutonium to the same extent as the 24-h-fasted animals (29 × 10^{-4}, B1048) (Table 3.10).

In Experiment 2, we asked whether the GI absorption of plutonium was increased significantly by 4–8 h after a morning meal in the absence of additional food intake. GI absorption values were determined by the dual isotope method from analyses of isotopic ratios in caudal vertebrae of animals given ^{238}Pu intravenously and either ^{236}Pu or ^{239}Pu by i.g. intubation at various times after a morning meal. Plutonium contents of the caudal vertebrae and calculated GI absorption values are shown in Table 3.11. Four hours after the morning meal, individual GI absorption values were

Table 3.11 Plutonium content of caudal vertebrae and calculated GI absorption values for adult baboons administered plutonium at 4, 6, and 8 h after a breakfast meal[a]

Animal	Isotope	Conditions	Caudal vertebrae Pu content[b] dpm/sample	Caudal vertebrae Pu content[b] Fraction of dose/sample	10^4 × calculated fractional GI absorption value (R_{so}/R_{si})
B230	^{238}Pu (i.v.)	--	0.988 ± 0.045 (2)	5.11×10^{-4} (R_{si})	--
	^{236}Pu (i.g.)	4-h fast	0.074 ± 0.005 (2)	7.20×10^{-8} (R_{so})	1.4
	^{239}Pu (i.g)	6+8-h fast	0.128 ± 0.008 (2)	1.96×10^{-7} (R_{so})	3.8
B358	^{238}Pu (i.v.)	--	2.02 ± 0.05 (2)	3.01×10^{-3} (R_{si})	--
	^{236}Pu (i.g.)	4-h fast	0.067 ± 0.011 (2)	1.47×10^{-7} (R_{so})	0.49
B880	^{238}Pu (i.v.)	--	3.76 ± 0.06 (2)	1.82×10^{-3} (R_{si})	--
	^{236}Pu (i.g.)	4-h fast	0.534 ± 0.018 (2)	7.41×10^{-7} (R_{so})	4.1
	^{239}Pu (i.g)	6+8-h fast	0.228 ± 0.014 (2)	3.48×10^{-7} (R_{so})	1.9

[a]In experiment 2, baboons received dual isotope administrations on three separate days: ^{236}Pu (i.g.) + ^{238}Pu (i.g.) at 4 h after breakfast on day 0, ^{239}Pu (i.g.) + ^{238}Pu (i.v.) at 6 h after [illegible] on day 21, and the latter isotope pair again at 8 h after breakfast on day 42. (B358 received the isotopes on [illegible] only).

[b]Caudal vertebrae #1-16 were removed on day 70. The baboons were not sacrificed. The dpm values are mean ± standard deviation for two separate aliquots of the caudal vertebrae digest.

1.4×10^{-4} and 4.1×10^{-4}, similar to those in the fed animal. Similarly, GI absorption values that were means from administrations at 6 h and 8 h after the morning meal ranged from 0.49×10^{-4} to 3.8×10^{-4}, indicating that even by 8 h after a breakfast of oatmeal cookies and a banana, the GI absorption of plutonium had still not significantly increased beyond that of the animal given plutonium 2 h after the morning feeding (Table 3.10).

A summary of effects of various feeding regimens on the GI absorption of plutonium in adult baboons and mice is shown in Table 3.12. When both baboons and mice were without food for the first 2 h of the active phase of their daily activity cycle (animals with no breakfast), the GI absorption of plutonium was the same as that of 24-h-fasted animals (Table 3.12). If the baboons and mice consumed food (banana and oatmeal cookies for baboons, mouse chow for mice) at the start of their active phase, the GI absorption of plutonium was similar to that of fed animals 2 h after the meal, and absorption did not rise to the value of 24-h-fasted animals even 8 h after the meal (Table 3.12).

3.5.2 Animal Species

Plutonium GI absorption values in fed animals were similar for mice, baboons, and humans (Table 3.13). In fasted animals, values for humans were not available, but those for mice and baboons agreed well with one another.

Table 3.12 GI absorption of plutonium in adult baboons and mice before and at various times after a breakfast meal

Condition at administration	Duration of fast[a] (h)	Percentage absorbed[b]	
		Baboons	Mice
24-h fasted	24	0.22 ± 0.13 (4)	0.19 ± 0.02 (12)
No breakfast + 2 h	14	0.28 (1)	0.17 ± 0.05 (5)
Breakfast + 2 h	2	0.012 ± 0.011 (3)	0.024 ± 0.005 (5)
Breakfast + 4 h	4	0.020 ± 0.011 (3)	0.017 ± 0.001 (5)
Breakfast + 6 h	6	0.020 ± 0.010 (2)	nd[c]
Breakfast + 8 h	8		0.090 ± 0.030 (7)

[a]Duration of fast = number of hours of fasting prior to plutonium administration. All animals were re-fed 24 h after the plutonium was administered.

[b]Values are mean ± SE, with the number of animals shown in parentheses. The value for a baboon with no breakfast was obtained by administering plutonium at 1000 after a 14-h overnight fast. Mice with "no breakfast" were fasted from the start of their active phase and administered plutonium 2 h later. Baboons with breakfast were fed as described in the text and were administered plutonium 2, 4, 6, or 8 h later. Mice with breakfast were allowed to eat for the first 4 h of their active phase before food was removed; they were administered plutonium 2, 4, and 8 h after the removal of their food. Data for mice are from Bhattacharyya et al. (1986).

[c]nd = not determined.

Table 3.13 GI absorption of plutonium: an interspecies comparison

Feeding regimen	Percentage absorbed		
	Mice[a]	Baboons	Humans[b]
Fed			
Mean	0.014	0.011	0.008
SE	0.002	0.012	0.003
n	12	3	8
Fasted[c]			
Mean	0.19	0.22	..
SE	0.02	0.13	..
n	12	4	..

[a]Data are from Bhattacharyya et al. (1986).

[b]This value is for plutonium biologically incorporated into winkles (Hunt et al., 1986, 1990) rather than in drinking water and may not be strictly comparable to the others.

[c]Animals were fasted for 24 h.

4 Results: Uranium

4.1 Gastrointestinal Absorption of Uranium: Sacrifice Method

Summing the amounts of ^{233}U in tissues with that excreted in urine for baboon B704 yields a fractional GI absorption value for the 24-h-fasted animal of 1.25×10^{-2}, or 1.25% (Table 4.1). Of the uranium absorbed through the GI tract, 67% was excreted in urine in the first 8 d. At sacrifice, 83% of the uranium retained in tissues was present in the skeleton, with much smaller percentages (4–6%) in liver, kidney, and muscle (Table 4.1).

GI absorption values obtained at sacrifice of two additional baboons are shown in Table 4.2. These values take into account only the first 8 d of urinary uranium excretion, because urine samples beyond 8 d were not analyzed for the additional baboons. Considering all three animals, the mean fractional GI absorption of uranium in the 24-h-fasted adult baboon by the sacrifice method was 0.026 ± 0.008 (mean ± SE, n = 3), or 2.6%.

Table 4.1 Gastrointestinal absorption of uranium in fasted baboon B704: sacrifice method[a]

Sample	Sample wt.[b] (g)	^{233}U content[c] dpm	$10^2 \times$ fraction of dose	Percentage of retained uranium
Skeleton	476	37.1	0.0852	83.1
Liver	264	7.30 ± 0.17	0.0066	6.4
Left kidney	18.4	3.28 ± 0.06	0.0059	5.8
Right kidney	18.8	3.40 ± 0.06		
Muscle	3990	4.79 ± 1.20	0.0042	4.1
Spleen	..[d]	0.28 ± 0.01	0.0003	0.3
Lungs	68.3	0.36 ± 0.02	0.0003	0.3
Total retained ^{233}U			0.10	100
Days 15-22 urine			0.84	67.2[e]
Days 23-46 urine			0.31	24.8[e]
Total absorbed ^{233}U			1.25	

[a]Baboon B704 was administered 114,000 dpm ^{233}U (1.90 kBq) by i.g. intubation at 0900 on day 14 of experiment 1 after a 24-h fast. Samples other than urine were obtained at sacrifice 32 d after ^{233}U administration. Days 15-22 urine samples were daily 24-h collections obtained on days 15-22, 1-8 d after ^{233}U administration.

[b]Ash weight for skeleton, wet weight for other whole organs.

[c]Values are mean ± SE. Fraction of dose = fraction of intragastrically administered ^{233}U retained per sample. SE values show the uncertainty associated with α-counting ^{233}U in the sample. Values shown were corrected for naturally occurring ^{234}U content. Total retained ^{233}U = sum of samples; the total absorbed ^{233}U = samples + urine.

[d]Not weighed.

[e]Percentage of absorbed (not retained) ^{233}U.

Table 4.2 Gastrointestinal absorption of uranium in three 24-h-fasted adult baboons: sacrifice method[a]

Sample	^{233}U content (10^2 × fraction of dose)		
	B704	B1048	B1050
Skeleton	0.085	0.65	0.57
Liver	0.007	0.02	0.025
Kidneys	0.006	0.02[c]	0.025
Other tissues[b]	0.008	0.01[c]	0.007
Total retained U	0.10	0.70	0.63
Days 15-22 urine	0.84	2.77	2.65
Total absorbed U	0.94	3.47	3.28

[a]Baboons were administered ^{233}U (1.9-6.7 kBq) by i.g. intubation at 0900 on day 14 of experiment 1 after a 24-h fast.

[b]For B704, "other tissues" = kidneys, muscle, lungs, and spleen, analyzed separately and summed. For B1050, "other tissues" = muscle and lungs analyzed separately and summed with a soft tissue composite containing aorta, trachea, spleen, heart, pancreas, uterus, ovaries and tubes, eyes, thyroid, and adrenals.

[c]For B1048, kidneys and "other tissues" were not analyzed. Values were calculated by analogy to these samples for the other two baboons.

4.2 Uranium Metabolism after Oral vs. Intravenous Administration

By 32 d after administration of both oral ^{238}U and i.v. ^{236}U, 84% of the absorbed uranium was excreted in urine for B704 (Table 4.3). In addition, by both modes, the ratio of uranium in liver to skeleton was 1:13 at sacrifice 32 d after administration. These results indicate that, as for plutonium, the major uranium metabolic pathways were independent of whether the uranium entered the bloodstream by i.v. injection or via the GI tract.

Summation of the ^{238}U in all tissues and urine accounted for 91% of the i.v. dose, leaving only 9% unaccounted for (see Other, Table 4.3). For comparison, 29% of the i.v. ^{238}Pu was unaccounted for in these same tissue and urine samples for B704 (Table 3.4). If "other" is mostly made up of fecal radionuclide, these results indicate that plutonium may be excreted in feces to a greater extent than uranium in the adult baboon.

Results of the detailed distribution of oral and i.v. uranium isotopes in skeleton (Table 4.4) showed that the oral/i.v. isotopic ratio was nearly the same for each of 24 skeletal parts, again demonstrating the equivalent handling of i.v. and oral uranium by the body.

In spite of the similar percentages of absorbed uranium appearing in urine by 32 d after oral vs. i.v. uranium (Table 4.3), the time-course of excretion of the oral isotope differed considerably from that of the i.v. isotope (Fig. 4.1). The oral isotope was excreted more slowly and steadily with time, while the i.v. isotope appearing in urine was nearly all excreted within the first 24 h. For example, for the i.v. isotope in baboons B704,

Table 4.3 Comparison of metabolism of uranium in adult baboon B704: oral vs. intravenous administration[a]

Sample	No. of samples analyzed	Uranium content (fraction of administered dose) Oral ^{233}U (10^2 × fraction)	i.v. ^{236}U
Urine (cumulative)			
Days 15-22	8	0.84 (61%)	0.81 (81%)
Days 23-46	6	0.31 (23%)	0.03 (3%)
Total		1.15 (84%)	0.84 (84%)
Tissues on day 46			
Liver	4	0.0066 (0.5%)	0.0045 (0.5%)
Skeleton	25	0.0852 (6.2%)	0.0617 (6.2%)
Other[b]	--	0.1304 (9.5%)	0.160 (9.4%)
Total		0.2222 (16%)	0.2262 (16%)
Total absorbed (urine + tissues)		1.37 (100%)	1.0 (100%)

[a]Baboon B704 was administered ^{233}U (1.90 kBq) by i.g. intubation and ^{236}U (9.5 Bq) by i.v. administration at 0900 on day 14 of experiment 1. B704 was sacrificed on day 46.

[b]Values for "other" were calculated. For the i.g. ^{233}U, "other" was calculated by analogy to the i.v. ^{236}U. For the i.v. ^{236}U, "other" is the amount of the i.v. dose not accounted for by ^{236}U in the urine, liver, and skeleton. A small portion represents ^{236}U in tissues other than liver and skeleton (Table 4.2). The remaining may represent ^{236}U excreted in feces.

B1046, and B1048, 85 ± 2% (mean ± SE, n = 3) of the total amount excreted during the first 8 d was excreted on the first day after administration; in contrast, the first day's urine accounted for only 29 ± 5% of the total amount of oral ^{233}U excreted during the first 8 d for these same animals. For baboon B1048, who urinated just 1 h after isotope administration on day 14, the urine was highly enriched in the i.v. compared with the oral isotope. Consequently, for uranium, the dual isotope method only worked if an oral/i.v. ratio was obtained from values for urinary excretion obtained cumulatively during at least the first 8 d after administration. The 4-d catheterized urine sample alone, for example, was too enriched in the oral isotope compared with the i.v. isotope to give a valid GI absorption value by the dual isotope method.

4.3 Gastrointestinal Absorption of Uranium: Dual Isotope Method

GI absorption values for uranium calculated from R_{so}/R_{si} ratios were nearly the same for a number of different sample types for baboon B704, independent of whether the samples contained a large fraction of the absorbed uranium (urine) or a small fraction (rib 5) (Table 4.5). By this method, the fractional GI absorption of uranium in B704 after a 24-h fast was 1.3×10^{-2} (1.3%), much higher than the absorption of plutonium (2.0×10^{-4}, 0.02%; Table 3.7), which was administered at the same time to the same baboon.

Table 4.4 Comparison of distribution of uranium in bones of baboon B704: oral vs. intravenous administration

Bone	Ash wt. (g)	Uranium content: ^{233}U (oral) Ash (dpm/g)	^{233}U (oral) 10^4 × fraction of dose [A]	^{236}U (i.v.) Ash (dpm/g)	^{236}U (i.v.) 10^2 × fraction of dose [B]	Gral/ i.v. ratio [A/B]
Skull (without calvarium)[a]	78.14	0.199	1.367	0.078	1.07	1.3
Calvarium	21.52	0.151	0.285	0.057	0.21	1.4
Total skull[a]	99.66		1.652		1.28	1.3
Cervical vertebrae	9.50	0.186	0.155	0.068	0.11	1.4
Thoracic vertebrae	21.61	0.299	0.567	0.111	0.42	1.4
Lumbar vertebrae	30.06	0.318	0.838	0.122	0.64	1.3
Caudal vertebrae (tail)	13.33	0.156	0.183	0.054	0.13	1.4
Pelvis + sacral vertebrae	53.41	0.332	1.556	0.114	1.07	1.5
Rib 5	2.51	0.255	0.056	0.113	0.050	1.1
Rib 7	2.84	0.261	0.065	0.093	0.046	1.4
Rib 9	2.82	0.220	0.055	0.102	0.050	1.1
Ribs (all other)	19.24	0.229	0.387	0.076	0.26	1.5
Scapula	21.20	0.235	0.438	0.088	0.33	1.3
Clavicle	2.27	0.285	0.057	0.118	0.046	1.2
Sternum	2.26	0.720	0.143	0.238	0.094	1.5
Total axial	181.05		4.500		3.246	1.4
Femora	46.21	0.194	0.786	0.078	0.63	1.2
Patellae	1.84	0.613	0.099	0.054	0.018	5.5
Tibiae - large end	7.83	0.141	0.097	0.049	0.066	1.5
Tibiae - shaft	18.74	0.026	0.043	0.012	0.038	1.1
Tibiae - small end	3.51	0.080	0.025	0.031	0.018	1.4
Fibulae	5.67	0.056	0.028	0.021	0.022	1.3
Hands and feet	35.28	0.134	0.415	0.035	0.22	1.9
Humeri	40.17	0.187	0.660	0.070	0.50	1.3
Radii	18.85	0.054	0.089	0.016	0.052	1.7
Ulnae	18.34	0.081	0.130	0.027	0.088	1.5
Total appendicular	196.44		2.372		1.652	1.4
Total skeleton[a]	477.15		8.524		6.178	1.4

[a]Not including teeth.

Table 4.5 Gastrointestinal absorption of uranium in fasted baboon B704: dual isotope method

Sample	Uranium content[a] (10^2 × fraction of dose)		10^2 × calculated fractional GI absorption[b]
	^{233}U (R_{so})	^{236}U (R_{si})	
Blood, 8 h	0.017[c]	2.1[c]	0.8
Urine, days 15-22	0.84	81	1.0
Urine, days 15-46	1.15	84	1.4
Liver	0.0066	0.45	1.5
Total skeleton	0.089	6.17	1.4
Caudal vertebrae	0.0016	0.11	1.4
Skull	0.014	1.07	1.3
Pelvis + sacral vertebrae	0.016	1.07	1.5
Rib 5	0.00056	0.050	1.1
Mean ± SE (n)			1.3 ± 0.1 (9)

[a]Values are the fraction of administered uranium retained by the sample (^{233}U administered orally; ^{236}U administered intravenously). Samples other than blood and urine were obtained at sacrifice 32 d after administration of ^{233}U (1.90 kBq) and ^{236}U (9.5 Bq) (day 46 of experiment 1).

[b]For a sample calculation, see Table 3.7, footnote b.

[c]Value is for total blood in the animal at 8 h (assuming blood equals 7% of body weight), indicating that, for example, 2.1% of the i.v. dose was present in blood at 8 h after administration.

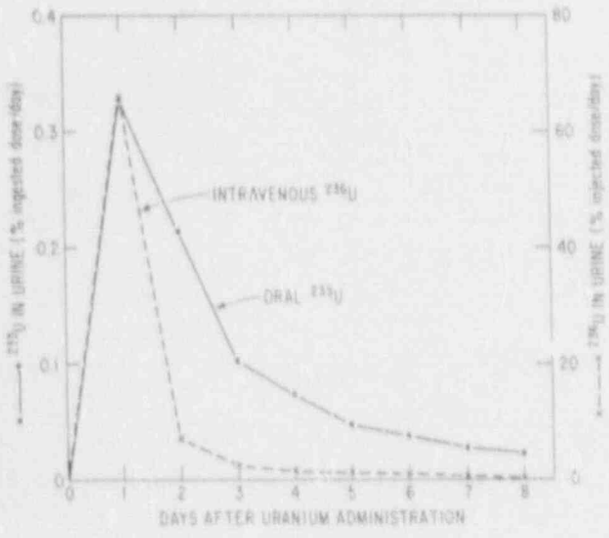

Figure 4.1 Uranium content of urine during days 1–8 after oral or intravenous uranium administration to baboon B704

With the dual isotope method, GI absorption values were obtained for four 24-h-fasted and two fed adult baboons. Values for uranium isotope retention (R_{so} and R_{si}) for the various samples that were used to determine GI absorption values are presented in Table 4.6, with calculated GI absorption values presented in Table 4.7. Mean fractional GI absorption values for the 24-h-fasted baboon, considering all samples, ranged from 1.2×10^{-2} for baboon B704 to 4.7×10^{-2} for B1048, a smaller range than was observed for the GI absorption of plutonium administered at the same time to these same fasted animals (Table 3.9). The calculated GI absorption value based on the 8-h blood sample was uniformly low compared with the mean value for each of the four baboons. In contrast, the value based on the caudal vertebrae was uniformly close to the mean for each

Table 4.6 Uranium content of samples used to determine GI absorption by the dual isotope method

Sample[a]	Uranium content (fraction of dose)											
	B704		B1048		B1050		B1046		B358		B889	
	^{233}U ($10^4 \times R_{so}$)	^{236}U ($10^2 \times R_{si}$)	^{233}U ($10^4 \times R_{so}$)	^{236}U ($10^2 \times R_{si}$)	^{233}U ($10^4 \times R_{so}$)	^{236}U ($10^2 \times R_{si}$)	^{233}U ($10^4 \times R_{so}$)	^{236}U ($10^2 \times R_{si}$)	^{233}U ($10^5 \times R_{so}$)	^{236}U ($10^2 \times R_{si}$)	^{233}U ($10^5 \times R_{so}$)	^{236}U ($10^2 \times R_{si}$)
Fasted animals												
Blood, 8 h[b]	1.7	2.1	2.2	1.1	1.6	1.8	2.9	1.9	–	–	–	–
Urine, 1-8 d[c]	8.	81	280	83	270	86	230	82	–	–	–	–
Caudal vertebrae[d]	0.17	0.13	1.3	0.26	0.44	0.10	0.10	0.028	–	–	–	–
Liver, biopsy[e]	–	–	0.025	0.0030	0.039	0.0049	0.058	0.0063	–	–	–	–
Total liver	0.66	0.45	–	–	–	–	–					
Fed animals												
Caudal vertebrae[d]	–	–	–	–	–	–	–	–	0.13	0.028	0.40	0.069

[a]Fasted animals received uranium doses on day 14 after a 24-h fast and were sacrificed 32 d later (exp. 1). Fed animals received uranium doses 2 h after the morning feeding on day 56 and caudal vertebrae biopsies were removed on day 70, 14 d later (exp. 2).

[b]Values are for whole blood based on blood = 7% of body weight.

[c]Urine collected during the first 8 d after isotope administration; i.e., days 15-22 of experiment 1 (Fig. 2.2).

[d]For fasted animals, values are for the caudal vertebrae shown in Table 3.8, footnote g. For fed animals, values are for caudal vertebrae #1-16.

[e]Values are uranium contents of biopsy sample. See Table 3.8, footnote h, for biopsy/liver weights.

Table 4.7 Gastrointestinal absorption of uranium in fed and fasted adult baboons: dual isotope method[a]

Sample	10^2 × calculated fractional GI absorption[b]					
	B704	B1048	B1050	B1046	B358	B880
Fasted animals						
Blood, 8 h	0.8	2.0	0.9	1.5	--	--
Urine, 1-8 d	1.0	3.4	3.1	2.8	--	--
Bone, caudal vert.	1.3	5.0	4.4	3.6	--	--
Liver, biopsy	1.5	8.3	8.0	9.2	--	--
Mean ± SE (4)	1.2 ± 0.2	4.7 ± 1.4	4.1 ± 1.5	4.3 ± 1.7		
Fed animals[c]						
Caudal vertebrae	--	--	--	--	0.46	0.58

[a]On day 14 of experiment 1, 24-h-fasted baboons were administered ^{233}U (1.9-6.7 kBq) by i.g. intubation at 0900 and ^{236}U (10-19 kBq) by i.v. injection immediately afterwards. Bone and liver samples were obtained on day 46, 32 d later. On day 56 of experiment 2, fed animals were administered ^{233}U (12-14 kBq) by i.g. intubation at 0900, 2 h after the morning feeding, and ^{236}U (16 Bq) by i.v. injection immediately afterwards. Caudal vertebrae were removed on day 70, 14 d later.

[b]Values calculated by dual isotope method from values of R_{ao} and R_{ai} presented in Table 4.6. See Table 3.7, footnote b, for sample calculation.

[c]Uranium was administered to three fed baboons, but only two provided GI absorption data, because B230 regurgitated shortly after administration.

animal. For fed animals, uranium GI absorption values were about 10-fold lower (Table 4.7).

4.4 Comparison of Sacrifice vs. Dual Isotope Methods

Uranium GI absorption values obtained by the dual isotope method agreed well with those obtained by the sacrifice method (Table 4.8). On the average, sacrifice method values were 79% of the dual isotope method values. The sacrifice method values may have been lower because they included uranium excretion in days 1–8 urines only, while results show that about 20% of the absorbed oral isotope was excreted in urine after day 8 (see "Urine, Days 23–46," Table 4.3).

4.5 Effects of Feeding Regimen and Animal Species on the Gastrointestinal Absorption of Uranium

For adult baboons and mice, fasting resulted in a 7- to 11-fold increase in the GI absorption of uranium (Table 4.9). A substantial increase due to fasting in humans also appeared to occur. However, the GI absorption of uranium in both fed and fasted adult baboons was significantly greater than in fed and fasted adult mice, and uranium GI absorption values for baboons agreed closely with values reported for fed and fasted humans. Results of this interspecies comparison of the GI absorption of uranium differ significantly from those for plutonium (Table 3.13), which indicated that the GI absorption of plutonium in fed and fasted animals were similar for the three species.

Table 4.8 Uranium GI absorption in fed and fasted adult baboons: comparison of sacrifice and dual isotope methods[a]

Feeding Regimen	10^2 × fractional GI absorption		
	Sacrifice [A]	Dual isotope [B]	A/B
Fasted			
B704	1.0	1.2	0.83
B1048	3.5	4.7	0.74
B1050	3.3	4.1	0.80
B1046	--	4.3	--
Mean ± SE (n)	2.6 ± 0.8 (3)	3.6 ± 0.8 (4) 3.3 ± 1.1 (3)[b]	
Fed			
B358	--	0.46	--
B880	--	0.58	--
Mean ± SE (n)		0.52 ± 0.06 (2)	

[a]Values for sacrifice method are from Table 4.2; values for dual isotope method are from Table 4.7.

[b]Mean for dual isotope method excluding B1046, which was not sacrificed. This mean is therefore directly comparable to the sacrifice method mean.

Table 4.9 GI absorption of uranium: an interspecies comparison

Feeding regimen	Percentage absorbed		
	Mice[a]	Baboons	Humans
Fed			
Mean	0.069	0.52	0.5[b]
SE	0.009	0.06	0.1
n	5	2	2
Fasted[c]			
Mean	0.80	3.6	>1.9[d]
SE	0.19	0.8	--
n	5	4	4

[a]Data from Bhattacharyya et al. (1989).

[b]Data from Larsen and Orlandini (1984).

[c]Animals were fasted for 24 h.

[d]Data from Hursh et al. (1969). Persons were administered uranium before breakfast, after an overnight fast. Range of values was 0.5–5.

5 Results: Neptunium

5.1 Gastrointestinal Absorption of Neptunium: Sacrifice Method

Summing the amounts of ^{237}Np in tissues with that excreted in urine for baboon B704 yields a fractional GI absorption for the 24-h-fasted animal of 0.33×10^{-2}, or 0.33% (Table 5.1). Of the neptunium absorbed through the GI tract, 33% was excreted in urine in the first 8 d. At sacrifice 32 d after administration, 85% of the neptunium retained in tissues was present in the skeleton, 15% in liver, and much smaller percentages in kidneys and lungs (0.3%).

GI absorption values obtained at sacrifice after two additional neptunium administrations are shown in Table 5.2. For the 24-h-fasted animals, the mean fractional GI absorption value of ^{239}Np by the sacrifice method was 0.0093 ± 0.0003 (mean ± SE, n = 2), or 0.93%. For ^{237}Np administration on day 14 to 24-h-fasted baboon B704, the value was about 3-fold lower, 0.0033 (0.33%).

Table 5.1 Gastrointestinal absorption of neptunium in fasted baboon B704: sacrifice method[a]

Sample	Sample wt.[b] (g)	^{237}Np content[c] dpm	$10^2 \times$ fraction of dose	Percentage of retained neptunium
Skeleton	476	79.4 ± 2.2	0.148	84.6
Liver	264	14.1 ± 0.7	0.026	14.9
Left kidney	18.4	0.18 ± 0.01	0.00057	0.3
Right kidney	18.8	0.13 ± 0.01		
Muscle	3990	nd[d]	nd	--
Spleen	--[e]	nd	nd	--
Lungs	68.3	0.28 ± 0.02	0.00052	0.3
Total retained ^{237}Np			0.18	100
Days 15-22 urine			0.11	33.3[f]
Days 23-46 urine			0.04	12.1[f]
Total absorbed ^{237}Np			0.33	

[a]Baboon B704 was administered 53,540 dpm ^{237}Np (892 Bq) by i.g. intubation at 0900 on day 14 of experiment 1 after a 24-h fast. Samples other than urine were obtained at sacrifice on day 46, 32 d after ^{237}Np administration. Days 15-22 urine samples were daily 24-h collections obtained on experiment days 15-22, 1–8 d after ^{237}Np administration.

[b]Ash weight for skeleton; wet weight for other whole organs.

[c]Values are mean ± SE. Fraction of dose = fraction of intragastrically administered ^{237}Np retained per sample. SE values show the uncertainty associated with α-counting ^{237}Np in sample. Total retained ^{237}Np = sum of samples; the total absorbed ^{237}Np = samples + urine.

[d]nd = not determined.

[e]Not weighed.

[f]Percentage of absorbed (not retained) ^{237}Np.

Table 5.2 Gastrointestinal absorption of neptunium in fasted adult baboons: sacrifice method[a]

	Neptunium content (10^2 × fraction of dose)		
	^{237}Np	^{239}Np	
Sample	B704	B704	B1050
Skeleton	0.15	0.45	0.51
Liver	0.03	0.07	0.04
Kidneys	0.001	--	0.01
Other tissues	--	--	0.01
Total retained Np	0.18	0.52	0.57
Urine	0.15	0.38	0.40
Total absorbed Np	0.33	0.90	0.97

[a]Baboons were administered neptunium by i.g. intubation at 0900 on day 14 (^{237}Np to B704) or on day 45 (^{239}Np to B704 and B1050) after a 24-h fast. Baboons were sacrificed on day 46, one day after ^{239}Np administrations and 32 d after ^{237}Np administration. Urine samples were either 1-d collections (^{239}Np) or 32-d cumulative (^{237}Np). Data are from Ralston (1990, Table 4.9).

5.2 Neptunium Metabolism after Oral vs. Intravenous Administration

By 32 d after oral ^{237}Np or 30 d after i.v. ^{237}Np, 39–44% of the absorbed neptunium was excreted in urine (Table 5.3). In addition, by both modes, the ratio of neptunium in liver to skeleton was 1:6 at sacrifice 30–32 d after administration. These results indicate that, as for plutonium and uranium, the major neptunium metabolic pathways were the same, independent of whether the neptunium entered the bloodstream by i.v. injection or via the GI tract.

Results of the detailed distribution of oral ^{237}Np (B704) and i.v. ^{237}Np (B880) in the skeleton (Table 5.4) showed a fairly consistent oral/i.v. ratio for the 24 skeletal parts, taking into consideration the fact that the comparison involves two separate baboons. These results again demonstrate the equivalent handling of i.v. and oral neptunium by the body.

5.3 Gastrointestinal Absorption of Neptunium: Dual Isotope Method

GI absorption values for neptunium calculated from R_{so}/R_{si} ratios were close to one another for a number of different sample types for baboon B704, independent of whether the sample contained a large fraction of the absorbed neptunium (days 15–22 cumulative urine) or a small fraction (liver, caudal vertebrae) (Table 5.5). Calculated GI absorption values for different samples varied more for neptunium than for uranium (Table 4.5) and plutonium (Table 3.7), most likely because for neptunium, the R_{so} values were from B704 whereas the R_{si} values were from B880. For uranium and plutonium, the i.v. and oral isotopes were simultaneously administered to the same animal, B704 (Fig. 2.2).

GI absorption values were out of range when R_{so}/R_{si} ratios from 8-h blood or day-15 urine (collected 1 d after ^{237}Np administration on

Table 5.3 Comparison of metabolism of neptunium in adult baboons: oral vs. intravenous administration[a]

Sample	No. of samples analyzed	Neptunium content (fraction of administered dose) Oral ^{237}Np (10^2 × fraction)	i.v. ^{237}Np
Urine (cumulative)			
Days 15-22	8	0.108 (31%)	0.35 (35%)
Days 23-46	6	0.042 (12%)	0.04 (4%)
Total		0.150 (44%)	0.39 (39%)
Tissues on day 46			
Liver	4	0.026 (7.6%)	0.081 (8.1%)
Skeleton	24	0.148 (43%)	0.46 (46%)
Other[b]	--	0.020 (5.8%)	0.069 (6.9%)
Total		0.194	0.610
Total absorbed (urine + tissues)		0.34 (100%)	1.00 (100%)

[a]Baboon B704 was administered ^{237}Np (892 Bq) by i.g. intubation at 0900 on day 14 of experiment 1 and was sacrificed on day 46, 32 d later. Baboon B880 was separately administered ^{237}Np (45 kBq) by i.v. injection 30 d before sacrifice. Values for i.v. ^{237}Np were obtained from Ralston (1990; Tables 3.14 and 3.22).

[b]Values for "other" were calculated. For the i.g. ^{237}Np, "other" was calculated by analogy to the i.v. ^{237}Np. For the i.v. ^{237}Np, "other" is the amount of the i.v. dose not accounted for by ^{237}Np in urine, liver, and skeleton.

day 14) were used for calculation. This is because of differences in the early kinetics of the oral vs. i.v. neptunium, with the 8-h blood relatively deficient in the i.v. neptunium and the 1-d urine relatively enriched in the i.v. neptunium. When a cumulative urine sample was used for the calculation (urine, days 15–22), an accurate GI absorption value was obtained (Table 5.5). Note that i.v. neptunium cleared the blood very quickly, with only 1.4% of the injected neptunium remaining in blood 8 h after injection (Table 5.5). For comparison, 8-h blood samples contained 2.1% of intravenously injected uranium (Table 4.5) and 25% of intravenously injected plutonium (Table 3.7).

With the dual isotope method, the fractional GI absorption of neptunium in B704 after a 24-h "fast" was 0.34×10^{-2} (0.34%), about 4-fold lower than for uranium (1.3×10^{-2}, or 1.3%; Table 4.5) and 17-fold higher than for plutonium (2.0×10^{-4}, or 0.02%; Table 3.7), both of which were administered at the same time as neptunium to the same baboon (Fig. 2.2).

With the dual isotope method, GI absorption values were obtained for two additional neptunium administrations. Values for neptunium isotope retention (R_{so} and R_{si}) for the samples that were used to determine GI absorption values are presented in Table 5.6, with calculated GI absorption values presented in Table 5.7. The first two administrations were for ^{239}Np to 24-h-fasted animals and showed GI absorption values of about 1%. The third administration (^{237}Np to B704 after a similar fast, which was suspect) was absorbed to a somewhat lesser extent, 0.3%.

Table 5.4 Comparison of distribution of neptunium in bones after oral vs. intravenous administration[a]

			Neptunium content				
			$^{237}Np^{b}$ (oral)		$^{237}Np^{c}$ (i.v.)		
Bone	Ash wt.[b] (g)	Wet wt.[c] (g)	Ash (dpm/g)	10^2 × % dose/ bone [A]	10^2 × % dose/g wet bone	% dose/ bone [B]	Oral/ i.v. ratio [A/B]
Skull + teeth	106.63	353.3	0.155	3.05	2.22	7.95	0.38
Cervical vertebrae	9.50	43.9	0.171	0.30	3.81	1.67	0.18
Thoracic vertebrae	21.61	121.4	0.319	1.29	5.72	6.94	0.19
Lumbar vertebrae	30.03	137.4	0.352	1.98	6.25	8.73	0.23
Sacral vertebrae	53	44.8	0.206	2.05	2.56	5.42	0.38
Pelvis		149.5			2.87		
Caudal vertebrae	13.33	--	0.113	0.28	--	1.16	0.24
Ribs	27.41	84.0	0.233	1.26	3.67	3.07	0.41
Scapulae	21.20	75.3	0.191	0.75	2.67	1.89	0.40
Clavicles	2.27	8.25	0.259	0.11	3.84	0.32	0.34
Sternum	2.26	15.5	0.577	0.24	5.56	0.86	0.28
Total axial	180.78	680.1		8.26		30.06	0.27
Femura	46.21	155.5	0.152	1.31	1.38	2.14	0.61
Patellae	1.84	11.0	0.094	0.034	2.56	0.28	0.12
Tibiae	30.08	118.2	0.080	0.45	0.63	0.74	0.61
Fibulae	5.67	16.8	0.073	0.078	0.70	0.12	0.65
Hands	35.28	81.6	0.067	0.44	0.99	1.64	0.27
Feet		127.3			0.52		
Humeri	40.17	107.6	0.129	0.97	1.85	1.99	0.49
Radii	18.85	64.1	0.048	0.17	0.74	0.47	0.36
Ulnae	18.34	59.1	0.055	0.19	1.18	0.69	0.28
Total appendicular	196.44	741.2		3.64		8.07	0.45
Total skeleton	483.85	1774.6		14.95		43.08	0.32

[a]Oral ^{237}Np data are for B704 sacrificed on day 46, 32 d after i.g. administration of ^{237}Np (892 Bq) on day 14 of experiment 1. The i.v. data are for B880 sacrificed 30 days after i.v. injection of ^{237}Np (45 kBq). Data for B880 are from Ralston (1990; Tables 3.27 and 3.28).

[b]Values are for B704.

[c]Values are for B880.

Table 5.5 Gastrointestinal absorption of neptunium in fasted baboon B704: dual isotope method

Sample	Neptunium content[a] (fraction of dose)		$10^2 \times$ calculated fractional GI absorption[b]
	^{237}Np ($10^2 \times R_{so}$)	^{237}Np (R_{si})	
Blood, 8 h	0.013[c]	0.014[c]	0.93
Urine, day 15[d]	0.029	0.30	0.10
Urine, days 15-22 (cumulative)[d]	0.108	0.35	0.31
Liver	0.026	0.081	0.32
Total skeleton	0.148	0.46	0.32
Caudal vertebrae	0.0028	0.012	0.23
Skull + teeth	0.031	0.080	0.39
Pelvis + sacral vertebrae	0.021	0.054	0.39
Ribs	0.013	0.031	0.42
Mean ± SE (n)			0.34 ± 0.02 (7)[c]

[a]Values are fraction of administered neptunium retained by the sample (^{237}Np administered orally to B704 on day 14 of experiment 1, 32 d before sacrifice; ^{237}Np separately administered intravenously to B880 30 d before sacrifice). Values for R_{si} are from Ralston (1990, Tables 3.8, 3.14, and 3.22).

[b]For a sample calculation, see Table . footnote b.

[c]Value is for total blood in the animal at 8 h (assuming blood equals 7% of body weight), indicating that, for example, 1.4% of i.v. neptunium was present in the blood at 8 h after administration.

[d]Urine days refer to experiment days for B704 (Fig. 2.2). For example, day-15 urine was collected from the time of ^{237}Np administration to 1 d later. Urine values for R_{si} were correspondingly obtained from urines collected 1 d and 1-8 d (cumulative) after i.v. ^{237}Np administration to B880.

[e]Mean value does not include values for 8-h blood or day-15 urine, because the latter values were clearly out of range.

5.4 Comparison of Sacrifice vs. Dual Isotope Methods

Neptunium GI absorption values obtained by the dual isotope method agreed very well with those obtained by the sacrifice method (Table 5.8). On the average, sacrifice method values were 102% of the dual isotope method values.

5.5 Effects of Feeding Regimen and Animal Species on the Gastrointestinal Absorption of Neptunium

5.5.1 Feeding Regimen

A summary of the effects of various feeding regimens on the GI absorption of neptunium in adult

Table 5.6 Neptunium content of samples used to determine GI absorption by the dual isotope method

	Neptunium content (fraction of dose)[a]					
	B704[b]		B1050[b]		B704[c]	
Sample	^{239}Np (R_{so})	$^{237}Np/^{239}Np$ (R_{si})	^{239}Np (R_{so})	$^{237}Np/^{239}Np$ (R_{si})	^{239}Np (R_{so})	^{237}Np (R_{si})
Urine, 1 d	0.38	0.35	0.40	0.35	--	--
Urine, 1-7 d	--	--	--	--	0.11	0.35
Skeleton, whole	0.45	0.59	0.51	0.59	0.15	0.46
Liver, whole	0.065	0.063	0.037	0.063	0.026	0.081

[a]Values are fraction of administered dose per sample. Values for R_{so} were obtained after i.g. administration of ^{239}Np or ^{237}Np. Values for R_{si} were obtained after i.v. injection of ^{239}Np or ^{237}Np to baboons as indicated in footnotes b and c.

[b]Baboons B704 and B1050 received ^{239}Np (2.6-5.8 MBq) by i.g. intubation on day 45 after a 24-h fast and were sacrificed on day 46, 1 d later. R_{so} values were obtained from these baboons. R_{si} values were means obtained from baboons B1048 and B830, which received ^{239}Np (B1048, 51 kBq) or ^{237}Np (B830, 13 kBq) by i.v. injection and were sacrificed 1 d later (Ralston, 1990; Table 3.22). For both oral and i.v. neptunium, urine samples were 24-h collections made 1 d post administration.

[c]R_{so} values were obtained from baboon B704, who received ^{237}Np (892 Bq) by i.g. intubation on day 14 after a 24-h fast and was sacrificed on day 46, 32 d later. R_{si} values were obtained from baboon B880, who received ^{237}Np (45 kBq) by i.v. administration 30 d before sacrifice (Ralston 1990, Table 3.22). For both oral and i.v. neptunium, urine samples were cumulative collections made 1-7 d post administration.

baboons is shown in Table 5.9. Data are from Ralston (1990; table 5.2). In the 14-h- to 24-h-fasted animal, the GI absorption of neptunium was 1.2%–1.5%. As was the case for plutonium, ^{237}Np GI absorption decreased significantly upon feeding, by 5- to 10-fold, and did not rise significantly even 8 h after a morning meal. In the absence of that morning meal, however, the GI absorption of neptunium was at the level of the 24-h-fasted animal by 2 h after the usual mealtime (Table 5.9, condition 2).

We showed that, when the animal was fasted, similar high GI absorption values (ca. 1%) were observed after both high mass (^{237}Np) and low mass (^{239}Np) neptunium exposures (Tables 5.9 and 5.10). In contrast, in fed animals, GI absorption values for low masses of neptunium (0.03% for ^{239}Np, Table 5.10) were significantly lower than for higher masses (0.12–0.53% for ^{237}Np, Table 5.9).

5.5.2 Animal Species

The GI absorption of ^{239}Np in fed animals was similar for mice, baboons, and humans (Table 5.10). In fasted animals, values for humans were not available, but in both mice and baboons, substantial increases in the GI absorption of ^{239}Np occurred due to fasting. The increase was somewhat greater in baboons than in mice.

Table 5.7 Gastrointestinal absorption of neptunium in fasted adult baboons: dual isotope method

Sample	10^2 x calculated fractional GI absorption[a]		
	B704[b]	B1050[b]	B704[c]
Urine, 1 d	1.1	1.1	--
Urine, 1-7 d, cumulative	--	--	0.31
Skeleton, whole	0.76	0.86	0.33
Liver, whole	1.0	0.59	0.32
Mean ± SE (3)	0.95 ± 0.1	0.85 ± 0.2	0.32 ± 0.1

[a]Values calculated by dual isotope method from values of R_{ss} and R_{sl} presented in Table 5.6. See Table 3.7, footnote h, for sample calculation.

[b]Baboons B704 and B1050 received ^{239}Np (2.6-5.8 MBq) by i.g. intubation on day 45 after a 24-h fast (Fig. 2.2) and were sacrificed on day 46. Urine sample was a 24-h collection obtained one day after administration (on day 46).

[c]Baboon B704 received ^{237}Np (892 Bq) by i.g. intubation on day 14 after a 24-h fast (Fig. 2.2) and was sacrificed on day 46, 32 d later. Urine sample was a 7-d cumulative sample collected on days 15-21 of the experiment (1-7 d after administration).

Table 5.8 Neptunium GI absorption in fasted adult baboons: comparison of sacrifice and dual isotope methods[a]

Animal	Duration of fast (h)	Fractional GI absorption		
		Sacrifice [A]	Dual isotope [B]	A/B
B704	24	0.90	0.95	0.95
B1050	24	0.97	0.85	1.1
B704	24	0.33	0.32	1.0
Mean ± SE (n)		0.73 ± 0.20 (3)	0.71 ± 0.20 (3)	

[a]Values for sacrifice method are from Table 5.2; values for dual isotope method are from Table 5.7.

Table 5.9 GI absorption of ^{237}Np in adult baboons before and at various times after a "breakfast" meal

Condition at administration	Duration of fast (h)	Percentage absorbed[a] (mean ± SE)
1. 24-h fasted	24	1.5 ± 0.2 (3)
2. No breakfast + 2 h	14[b]	1.2 ± 0.6 (1)
3. Breakfast + 2 h	2	0.30 ± 0.10 (3)
4. Breakfast + 4 h	4	0.12 ± 0.05 (3)
5. Breakfast + 6 h	6	0.13 ± 0.05 (3)
6. Breakfast + 8 h	8	0.33 ± 0.29 (2)

[a]Values are from Ralston (1990, Table 5.2). They were obtained by the dual isotope method from analyses of samples of blood, urine, liver, and caudal vertebrae. $^{237}Np(VI)$ bicarbonate was the form administered intragastrically.

[b]The value for a baboon with no breakfast was obtained by administering neptunium at 1000 after a 14-h overnight fast. Baboons with breakfast were fed as described in the text and were administered neptunium 2, 4, 6, or 8 h later (Fig. 2.3).

Table 5.10 GI absorption of ^{239}Np: an interspecies comparison

Feeding regimen	Percentage absorbed		
	Mice	Baboons	Humans
Fed			
Mean	0.027[a]	0.03[b]	0.020[c]
SE	0.003	0.02	0.002
n	10	3	5
Fasted			
Mean	0.35[a]	1.5[b]	--
SE	0.04	0.3	--
n	10	8	--

[a]Values from Larsen et al. (1982). Mice were fasted for 24 h.

[b]Values from Ralston (1990). For ^{237}Np, GI absorption in fasted baboons was the same as for ^{239}Np, but in fed baboons, ^{237}Np absorption (Table 5.9) was ca. 10-fold greater than the values for ^{239}Np shown here.

[c]Values from Popplewell et al. (1991). Humans were fed ^{239}Np citrate with their mid-day meal. Values calculated with i.v./oral method based on 1- to 7-d cumulative urinary excretion.

6 Discussion

6.1 Gastrointestinal Absorption Values by Sacrifice vs. Dual Isotope Methods

6.1.1 Metabolism of Intravenously and Orally Administered Plutonium, Uranium, and Neptunium

To apply the dual isotope method of determining GI absorption values, an isotope must be injected intravenously. With knowledge of the metabolic pattern of the i.v. isotope, we can determine a GI absorption value for a number of elements from analysis of samples of urine or blood after oral administration of an isotope. This method has been used to determine the GI absorption of calcium (DeGrazia et al., 1965), iron (Inameto, 1970), and neptunium (Popplewell et al., 1991) in humans.

With regard to the metabolic pattern after i.v. administration, the percentage of dose excreted in urine during the first 8 d was in the order uranium > neptunium > plutonium (Table 6.1). The value shown here for plutonium in adult baboons (8.3%) is higher than the 1.1% reported for humans by Hunt et al. (from Langham et al. [1956]; as evaluated by Durbin [1972], and Hunt et al. [1990]). For neptunium, 1- to 8-d cumulative urinary excretion in adult baboons (41.0%) was identical to that for two of five adult humans given ^{239}Np intravenously (Popplewell et al., 1991) and was similar to the mean for all five people (33.3 ± 3.5, n = 5). For uranium, the fraction excreted in urine early after i.v. injection to adult baboons (82.7% in 8 d) was also similar to that reported for humans (72% in 1 d; Hursh and Spoor [1973]).

For all three elements, a major fraction of the dose retained in the body of the baboon after i.v. injection resided in the skeleton (Table 6.1). GI absorption values in fasted baboons were in the order uranium > neptunium > plutonium. Similarly, the fractions of the retained dose present in skeleton were in the same order, with 93% of the body's uranium present in the skeleton 32 d after uranium injection.

Next to the skeleton, the liver was the organ with the highest fraction of dose after i.v. injection of plutonium, neptunium, and uranium (Table 6.1). For uranium, the percentage of injected dose in liver (0.32%) was similar to that in kidneys (0.24% for B704).

Table 6.1 Tissue distribution and urinary excretion of plutonium, neptunium, and uranium in the adult baboon after intravenous administration[a]

	Percentage of injected dose, mean ± SE (n)		
Sample	Plutonium	Neptunium	Uranium
A. Day 1 urine	7.2 ± 0.7 (4)	34.7 ± 2.2 (14)	71.3 ± 2.3 (4)
B. Day 1-8 urine	8.3 ± 0.7 (4)	41.0 ± 2.2 (14)	82.7 ± 1.4 (4)
C. Liver	26.3 ± 5.0 (3)	8.1 (1)	0.32 ± 0.07 (3)
D. Skeleton	37.5 ± 5.5 (3)	46.3 (1)	9.6 ± 1.8 (3)
E. Other tissues	1.7 ± 0.5 (2)	2.2 (1)	0.45 ± 0.05 (2)
Total (lines B to D)	73.8	92.6	93.1

[a]For plutonium and uranium, ^{238}Pu(VI) bicarbonate and ^{236}U(VI) bicarbonate were injected i.v. into baboons B704, B1048, B1050, and B1046 on day 14 of experiment 1, and the first three baboons were sacrificed on day 46, 32 d later. Data for neptunium are from Ralston (1990); tissues were taken 30 d after ^{237}Np administration to baboon B880.

For plutonium, the liver and skeleton contained 40% and 57%, respectively, of the plutonium retained in the whole body (C + D + E, Table 6.1), similar to the value of 45% each in liver and skeleton recommended by the ICRP for humans (ICRP, 1979; 1986). Surprisingly, summation of the amounts of plutonium in day 1–8 urine, liver, and skeleton accounted for only a mean of 73.8% of the i.v. injected ^{238}Pu (Table 6.1), implying that a significant fraction of the plutonium absorbed through the GI tract was also missing. In fact, GI absorption values for plutonium determined by the sacrifice method on the average were lower by 30% than those obtained by the dual isotope method (Table 3.10). For baboons B704 and B1050, samples of all soft tissues except the pelt were analyzed, and the balance of the intravenous isotope could not be accounted for in these tissues. The possibility exists that ca. 25% of both the intravenously injected plutonium and the absorbed plutonium was excreted in feces. It is interesting that, for both neptunium and uranium, the same tissues from the same baboons accounted for 93–97% of the intravenously injected isotopes. Similarly, there was closer agreement between GI absorption values determined by the sacrifice vs. dual isotope methods for these elements (Tables 4.8 and 5.8).

For uranium, retention in the skeleton at sacrifice 32 d after administration was 9.6% of the total injected uranium, in the range of the 5% and 10% values reported for two humans at similar times after i.v. injections (Hursh and Spoor, 1973).

For all three elements, metabolic pathways for excretion and tissue deposition were the same, independent of whether the element entered the bloodstream by i.v. injection or by absorption from the GI tract (Tables 3.4, 4.3, and 5.3). This was true even for the many parts of the baboon skeleton as indicated by i.v./oral isotopic ratios that were reasonably similar for all of these parts (Tables 3.5, 4.4, and 5.4). Interestingly, the relative distributions in the latter skeletal parts were also similar for plutonium, neptunium, and uranium, with the sternum, lumbar vertebrae, and thoracic vertebrae showing the highest concentrations for each element, and the humeri, radii, and ulnae showing the lowest.

6.1.2 Comparison of Values by Sacrifice vs. Dual Isotope Methods

When GI absorption values for plutonium, uranium, and neptunium were calculated by the dual isotope method from the relative amounts of the oral and i.v. isotopes in various tissue samples, reasonable agreement was obtained between the individual values calculated based on R_{so}/R_{si} ratios for blood, urine, caudal vertebrae, and liver (Tables 3.9, 4.7, and 5.7).

For plutonium, the amount of the oral isotope excreted in urine was low enough that contamination of urine by feces was a problem for cage-collected samples (Table 3.6). Consequently, urine was obtained by catheterization 4 d after isotope administration. The kinetics of plutonium appearance and disappearance from blood and urine after simultaneous oral and i.v. injection was similar enough for the two modes of administration that R_{so}/R_{si} ratios for 8-h blood or 4-d catheterized urine samples gave good measures of plutonium GI absorption (Table 3.9). For humans, extreme care would have to be taken to prevent contamination of urine samples by feces to apply this method, especially in the fed individual. Evidence that this can be done is provided by the work of Hunt et al., in which he estimated the GI absorption of plutonium in humans fed a meal of plutonium-containing winkles to be 0.008% based on urinary plutonium excretion (Hunt et al., 1986, 1990).

For uranium and neptunium, the amount of oral isotope excreted in urine was much higher than for plutonium, and contamination of urine by the oral isotopes in feces was not a problem for the cage-collected urine samples (Table 3.6). Consequently, R_{so}/R_{si} ratios for the first week's cumulative excretions in urine gave very good measures of the GI absorptions of these elements (Tables 4.7 and 5.7). Popplewell reports using analysis of cumulative urinary excretion to measure the GI absorption of neptunium in humans by the i.v./oral (dual isotope) method (Popplewell et al., 1991).

Besides showing reasonable agreement between GI absorption values calculated from R_{so}/R_{si} ratios

for various tissues, results of our studies also showed that GI absorption values for plutonium, uranium, and neptunium calculated by the dual isotope method agreed well with those obtained by summation of amounts of the oral isotope in excreta and tissues at sacrifice (Tables 3.10, 4.8, and 5.8). From our data, a GI absorption value obtained by analysis of a single biopsy sample of caudal vertebrae, for example, was essentially the same as the value obtained by analysis of urine and all tissues at sacrifice. In the studies reported, use of the dual isotope method in combination with administration of multiple elements (plutonium, uranium, and neptunium) to the same animal enabled us to determine 29 GI absorption values in seven adult baboons, only three of which were sacrificed. The savings in analysis time and animal life afforded by the dual isotope method are clear.

6.2 Interspecies Comparisons of GI Absorption

Pathways for the GI absorption of plutonium were the same for both mice and baboons with respect to the percentages of administered Pu(VI) absorbed in fed (0.01–0.02%) and fasted (0.2%) animals. The GI absorption values for fed animals also agreed well with values estimated for humans who consumed plutonium in winkles (0.008%) (Mussalo-Rauhamaa et al., 1984; Hunt et al., 1986, 1990). These results support the view that GI absorption values in both mice and baboons provide a good basis for estimating the GI absorption of plutonium in humans.

In the case of uranium, GI absorption values in mice differed substantially from those in baboons. In both fed and fasted animals, GI absorption values in baboons were 6–7 times higher than in mice. The higher values in baboons agreed well with values obtained in humans for both fed (0.5%; Larsen and Orlandini, 1984) and fasted (ca. 2%, 0.5–5% range; Hursh et al., 1969) conditions. These results support the view that biochemical pathways for the GI absorption of uranium differ substantially between mice and baboons, and that the pathway in baboons is more similar to that in humans than is the one in mice. A similar finding applies to the GI absorption of cadmium and lead, where GI absorption values in mice are substantially lower than those in nonhuman primates and humans (Bhattacharyya, 1983; Suzuki and Taguchi, 1980; Flanagan et al., 1978; Rabinowitz et al., 1976; Yamagata et al., 1975).

For ^{239}Np, GI absorption values for the fed condition were the same for mice, baboons, and humans (0.02%–0.03%; Table 5.10). In fasted animals, values for humans were not available, but values in baboons were 4-fold higher than in fasted mice. On the basis of the data for uranium, fasted humans would be expected to absorb neptunium to an extent similar to that of baboons.

For all three elements where GI absorption values for humans were available, GI absorption values for baboons agreed well with the human values.

6.3 Effects of Timing and Duration of Fast

Our studies with both plutonium and neptunium show that, in the absence of a morning meal, the extent of GI absorption in baboons is the same as in the 24-h-fasted animal by 2 h after breakfast time (Tables 3.12 and 5.9). Once the animal has eaten breakfast, GI absorption is at the level of the fed animal for at least 8 h. These results provide a rational basis for evaluating the relevance to humans of the significant increase in GI absorption reported by many investigators for 24-h-fasted animals.

With respect to the occupational setting, the results in Tables 3.12 and 5.9 support the hypothesis that persons who arrive at work having had no breakfast and who are orally exposed to plutonium (or neptunium and most likely uranium) prior to their first meal will absorb considerably more of these elements than their counterparts who had consumed a morning meal. Results of Blake et al. (1983) and James et al. (1985) in humans showing high GI absorption values for lead in overnight fasted individuals (70%) also support this interpretation. One resulting approach would be to give separate consideration to these two groups in setting ALIs. For the fed worker, fractional f_1 values of 1×10^{-4} for plutonium (Table 3.13), 5×10^{-3} for uranium (Table 4.9), and 2×10^{-4} for ^{239}Np (3×10^{-3} for ^{237}Np) (Tables 5.9 and 5.10) would be applicable. For fasted workers, fractional f_1 values of 2×10^{-3} for plutonium, 4×10^{-2} for uranium, and 1.5×10^{-2} for neptunium (both ^{239}Np and ^{237}Np) would apply. Selecting two values of f_1, one for fed individuals and another for fasted individuals, is an approach comparable to that currently used by the ICRP in recommending an f_1 value for soluble forms of plutonium that is 10-fold higher than that for the insoluble forms.

Currently, the ALI for oral exposure to plutonium in the workplace (ICRP, 1979) is based on a fractional GI absorption value for soluble forms of plutonium of 1×10^{-4}, 10–60 times lower than values reported for fasted animals (Table 3.10). Recently, after an extensive review of data on the metabolism of plutonium and related elements (ICRP, 1986), the ICRP recommended that a GI absorption value of 1×10^{-3} be applied to setting ALIs for soluble forms of plutonium (identified as forms other than oxides or nitrates). Use of the 1×10^{-3} value, arrived at partly through an accounting for effects of fasting on GI absorption, is consistent with the results reported here.

To apply the results of our research to persons environmentally exposed to plutonium, the two approaches developed in our last NUREG report (Bhattacharyya et al., 1985, pp. 39-42), based on results in mice, should be considered, because GI absorption values for soluble forms of plutonium were found to be the same in mice, baboons, and humans (Table 3.13, this report).

Approach 1 was based on the concept of limiting the lifetime dose from deposited plutonium. Single f_1 values were derived that would yield the same calculated lifetime dose from deposited plutonium as would be obtained by considering effects of animal age and fasting on the GI absorption of plutonium. (The fasting effect would apply to plutonium in drinking water.) These derived f_1 values were (a) 3×10^{-4} (0.03%) for an exposed population of all ages that ingests plutonium only in the fed condition (i.e., does not ingest plutonium-containing water before their first meal of the day) and (b) 6×10^{-4} (0.06%) for an exposed population in which both age and fasting are taken into consideration in a reasonable way. These f_1 values were derived assuming empirical plutonium GI absorption values of 2×10^{-4} for the fed and 2×10^{-3} for the fasted states.

Approach 2 was based on the concept of limiting commitment of lifetime dose on an annual basis and is analogous to the approach used by the ICRP for recommending ALIs for the workplace. With this approach, the single f_1 value that was identified to limit plutonium exposure in the general population, considering all ages and feeding regimens, was 4×10^{-2} (0.4%). This f_1 value is the time-weighted average value that was applied to the first year of life in humans, because the annual commitment of lifetime dose from plutonium absorption after consumption of formula and food during that first year was greater than during any other year. Three factors that apply to the first year of human life contribute to this result: (1) high GI absorption values; (2) low body weights, making organ concentrations high; and (3) long times for retention of plutonium in the body because of accumulation early in life. Approach 2 requires that special attention be given to identifying GI absorption values that are relevant to the first year of human life.

Discussion of the two approaches can be found in Bhattacharyya et al. (1985). Consideration should be given to applying one of these approaches to setting standards for environmental exposures to elements other than plutonium.

6.4 Conclusions

- GI absorption values for plutonium, uranium, and neptunium in adult baboons provide good estimates of GI absorption values in humans.

- The dual isotope method provides an excellent means of determining GI absorption values without requiring sacrifice of the animal (study subject). The method was recently applied to determining the GI absorption of ^{237}Np in fed humans (Popplewell et al., 1991).

- Plutonium, neptunium, and probably uranium consumed before the first meal of the day (in liquids such as coffee, or at work for someone who has skipped breakfast) will be absorbed at the level of the 24-h-fasted state — 0.2% for plutonium, 1% for neptunium, and 4% for uranium.

- These elements consumed either in food, liquids, or other media after the morning meal will be absorbed at the level of the fed state — 0.01% for plutonium, 0.03% for small amounts of neptunium (e.g., 10^{-8} mg ^{239}Np/kg) and 0.3% for large amounts of neptunium (e.g., 10^{-1} mg ^{237}Np/kg), and 0.5% for uranium.

- The above results should be applied to incorporate GI absorption values of fasted animals into standards set for oral exposure of humans to plutonium, uranium, and neptunium in both environmental and workplace settings.

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11. ABSTRACT (200 words or less)

Gastrointestinal (GI) absorption values of plutonium, uranium, and neptunium were determined in fed and fasted adult baboons. A dual isotope method of determining GI absorption, which does not require animal sacrifice, was validated and shown to compare well with the sacrifice method (summation of oral isotope in urine with that in tissues at sacrifice). For plutonium, GI absorption values in baboons were almost identical to those in mice (ca. 0.2% in fasted animals, 0.01% in fed animals), and the values for fed animals agreed with estimates for humans. For uranium, GI absorption values in fed (0.5%) and fasted (4%) baboons agreed well with those in fed and fasted humans and were 6–7 times higher than those in mice. For neptunium, GI absorption values in fed baboons were lower for small amounts of ^{239}Np (0.03%) than for much larger amounts of ^{237}Np (0.3%). Neptunium GI absorption values in fasted baboons (1.5%) were independent of amounts ingested and were considerably higher than those in fed animals. The GI absorption of ^{239}Np in fed animals was essentially the same in mice, baboons, and humans. In fasted animals, mice absorbed 4 times less ^{239}Np than did baboons (values for humans are not available). For one baboon that was not given its morning meal, both plutonium and neptunium GI absorption values at 0900 hours, 2 h after the usual mealtime (14-h overnight fast, baboon "without breakfast"), were the same as those in baboons fasted for 24 h. In contrast, for baboons that received a morning meal, plutonium and neptunium absorptions did not rise to the value found in 24-h-fasted baboons even 8 h after the meal. The authors conclude that GI absorption values for plutonium, uranium, and neptunium in adult baboons are good estimates of the values in humans (and better than those in mice) and that the values for the fasted condition need to be taken into account when standards are set for oral exposures in environmental and workplace settings. A rational way of doing this for plutonium is discussed.

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