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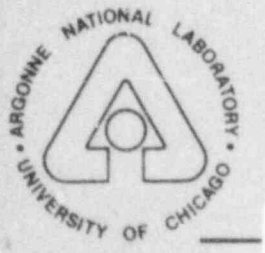
GASTROINTESTINAL ABSORPTION OF PLUTONIUM IN MICE, RATS, AND DOGS: APPLICATION TO ESTABLISHING VALUES OF f_1 FOR SOLUBLE PLUTONIUM

by

M. H. Bhattacharyya, R. P. Larsen, R. D. Oldham,
E. S. Moretti, and M. I. Spaletto



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Division of Biological and Medical Research

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ABSTRACT

The gastrointestinal (GI) absorption of plutonium was measured in mice, rats, and dogs under conditions relevant to setting drinking water standards. The fractional GI absorption of Pu(VI) in adult mice was 2×10^{-4} (0.02%) in fed mice and 2×10^{-3} (0.2%) in fasted mice. The GI absorption of plutonium was independent of plutonium oxidation state, administration medium, and plutonium concentration; absorption was dependent upon animal species, state of animal fasting, state of Pu(IV) hydrolysis, and age of the animal. Fractional GI absorption values ranged from 3×10^{-5} (0.003%) for hydrolyzed Pu(IV) administered to fed adult mice to 7×10^{-3} (0.7%) for Pu(VI) administered to fed neonatal rats.

From analysis of our data, we suggested values of f_1 (the fraction transferred from gut to blood in humans) for use in establishment of oral limits of exposure to plutonium. For an acute exposure in the occupational setting, we proposed one value of f_1 for fed (2×10^{-4}) and one for fasted (2×10^{-3}) individuals. For the environmental setting, we developed two approaches to obtaining values of f_1; suggested values were 6×10^{-4} and 4×10^{-3}, respectively. Both approaches took into account effects of animal age and fasting. We discussed uncertainties in proposed values of f_1 and made recommendations for further research.

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Gastrointestinal Absorption of Plutonium in Mice, Rats, and Dogs: Application to Establishing Values of f_1 for Soluble Plutonium

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PREFACE AND ACKNOWLEDGMENTS

Nuclear power production results in the formation of very significant amounts of plutonium and other transuranics, elements whose assimilation by man in very small amounts is detrimental to health. The setting of standards for these elements is therefore an important task. Inhalation is the main route of exposure to actinides in the occupational setting, whereas ingestion is the more likely route for long-term human exposure to actinides in the environment. Three areas must be considered in evaluating potential consequences of releases of plutonium into the environment: (a) the movement and chemical forms of plutonium in the environment; (b) the uptake, deposition, retention, and excretion by humans of forms of plutonium relevant to environmental exposures; and (c) dose-response functions for the assimilated material. The focus of our study is primarily the gastrointestinal (GI) absorption of plutonium, a part of area (b). Investigations in area (a) are also being conducted at Argonne under a program titled "Actinide Movement in Freshwater Systems," supported by the U.S. Department of Energy (DOE) and directed by D. M. Nelson (formerly directed by R. P. Larsen). A second complementary program supported by DOE and directed by M. H. Bhattacharyya concerns the GI absorption of compounds of cadmium and lead. Experience gained in both of these programs has been used directly in the design and conduct of experiments in the study reported here.

Since we initiated our studies on the GI absorption of plutonium, Dr. Maurice Sullivan at Pacific Northwest Laboratories in Richland, Washington, and Drs. John Stather and John Harrison at the National Radiological Protection Board (NRPB) in England have been engaged in similar investigations. Initially there was little consensus on values for the GI absorption of Pu(IV) and Pu(VI). With time, however, reasons for the differences were, to a major degree, identified. It was established, for example, that problems exist in the preparation of solutions of tetravalent plutonium, and that the uptake of plutonium varies with animal species. Scientists at these various laboratories have now obtained data indicating that GI absorption values for soluble forms of plutonium range from 2×10^{-3} to 5×10^{-3} in the fasted mouse or rat (1, 2), and from 2×10^{-4} to 5×10^{-4} in the fed mouse or rat (1, 3-5). These values for rodents must still be translated into meaningful limits of human intake.

In the final section of this document, we have responded to a request by the Nuclear Regulatory Commission (NRC) to derive from our rodent data recommended values of f_1 (the fraction transferred from gut to blood) for humans. We have addressed the problems of deriving a value of f_1 for environmental exposure to plutonium in drinking water, where persons of all ages and of various dietary habits must be considered. We have presented and discussed two alternative approaches to arriving at a

recommended value of f_1 that applies to the establishment of drinking water standards. We hope that our discussions are helpful and stimulating to those members of national and international committees that make final recommendations for values of f_1 based on our data and those of others.

During our several years of work for the NRC, we have enjoyed our association with its personnel. Special thanks go to Dr. Judith D. Foulke for helping us to initiate our program in March, 1980, and for carefully guiding us during the subsequent years. We appreciate the interest shown by Dr. Michael J. Bell of the Waste Management Branch of the NRC. Thanks also go to Dr. William A. Mills, Chief, Health Effects Branch, for his thoughtful support of our program.

Prior to publication, our document was internally reviewed at Argonne National Laboratory by Dr. Robert A. Schlenker and Dr. Douglas Grahn of the Division of Biological and Medical Research. We thank them for their carefully considered suggestions. We also thank Dr. Roy C. Thompson of Pacific Northwest Laboratory for providing us with his valuable insights. Finally, we thank Terri Harper and Rose Pausche for typing, Karen Haugen for editing, and Carol Fox for computer assistance. Their efforts and talents were much appreciated.

M. H. Bhattacharyya

LIST OF ABBREVIATIONS

ALI	Annual Limit on Intake
DOE	U.S. Department of Energy
f_1	fraction of an element transferred from gut to blood in humans
GI	Gastrointestinal
ICRP	International Commission on Radiological Protection
MPC	Maximum permissible concentration
NRC	U.S. Nuclear Regulatory Commission
NRPB	National Radiological Protection Board, England
%UF	Percentage of ultrafilterable plutonium

Gastrointestinal Absorption of Plutonium in Mice, Rats, and Dogs: Application to Establishing Values of f_1 for Soluble Plutonium

M. H. Bhattacharyya, R. P. Larsen, R. D. Oldham,
E. S. Moretti, and M. I. Spaletto

EXECUTIVE SUMMARY

The objective of this study was to determine the gastrointestinal (GI) absorption of plutonium in animals under conditions relevant to the establishment of drinking water standards for humans. A drinking water standard for plutonium is required as a part of the regulation of releases of plutonium from nuclear reactor facilities and from nuclear waste disposal sites. This study was necessitated by the following considerations: (a) at the start of this study, the maximum permissible concentration (MPC) for soluble forms of plutonium in drinking water was based on a value of f_1 (the fraction of an element transferred from gut to blood in humans) of 3×10^{-5}. The latter value was the GI absorption value obtained experimentally by administering solutions of tetravalent plutonium, Pu(IV), to animals (6); (b) the plutonium in chlorinated drinking water was shown to be hexavalent, Pu(VI), and not Pu(IV) (7); and (c) the value obtained experimentally for the fractional GI absorption of Pu(VI) was 1.9×10^{-2} (8). It thus appeared that the MPC for plutonium in drinking water was too high by three orders of magnitude. To investigate this possibility, a study of the GI absorption of plutonium in its various oxidation states was undertaken.

In our study, mice, rats, and dogs were exposed to solutions of plutonium either *ad libitum* via drinking water or by gavage (direct administration into the stomach). Plutonium concentrations were 1×10^{-10} M, the molar concentration of ^{239}Pu at the MPC for plutonium in drinking water (5 pCi/mL). The administration medium was 0.01 M sodium bicarbonate, a medium similar to Lake Michigan water. The oxidation state was, in general, Pu(VI), the oxidation state present in chlorinated drinking water. Plutonium concentrations in liver and eviscerated carcasses were analyzed by gamma spectroscopy (^{237}Pu) or by alpha spectrometric isotope dilution (^{236}Pu, ^{238}Pu, ^{239}Pu) at 2 to 6 days (mice and rats) or 5 weeks (dog) after plutonium administration. Effects of the following factors on the gastrointestinal absorption of plutonium were investigated:

- 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)

Results included the following:

- The fractional GI absorption of Pu(VI) in the fasted rat was 3.2×10^{-3}, not 1.9×10^{-2}.
- The fractional GI absorption of Pu(IV) in the fasted mouse (2.0×10^{-3}) was the same as that for Pu(VI) (1.5×10^{-3}).
- The fractional GI absorption of Pu(VI) in the fasted dog (0.66×10^{-3}) was somewhat lower than that in the fasted mouse (1.5×10^{-3}) and rat (3.2×10^{-3}).
- The fractional GI absorption of Pu(VI) in the fed mouse (1.4×10^{-4}) was 10- to 15-fold less than in the fasted mouse (1.9×10^{-3}).
- The fractional GI absorption of Pu(VI) was independent of plutonium concentration over the range 10^{-12} M to 10^{-6} M.
- The fractional retention of absorbed Pu(VI) in the fed rat prior to weaning (3×10^{-3} to 7×10^{-3}) was 30 to 70 times greater than in the fed rat during the period from 7 days after weaning through adulthood (1×10^{-4}).

Differences between our results and those of earlier investigators were discussed. Our data for rodents were used to recommend values of f_1 for plutonium relevant to setting limits for human exposure in the occupational and environmental settings.

For acute exposures in the occupational setting, we suggest that separate consideration be given to two different cases of oral exposure to soluble forms of plutonium. For fed individuals, we recommend an f_1 value of 2×10^{-4} (0.02%), which is comparable to the value currently recommended by the ICRP for calculating an Annual Limit on Intake (ALI) for soluble forms of plutonium, 1×10^{-4} (0.01%). However, we propose a value of f_1 of 2×10^{-3} (0.2%) for fasted individuals (i.e., those who skip breakfast and are exposed to plutonium prior to their first meal of the day). According to this analysis, the ALI for fasted individuals would be 10-fold lower than that for fed individuals in the occupational exposure setting.

We considered two alternative approaches for recommending values of f_1 relevant to setting a maximum permissible concentration for plutonium in drinking water in the environmental setting. Approach #1 is based on the concept of limiting lifetime dose from deposited plutonium. Proposed values of f_1 are 3×10^4 (0.03%) if the protected population is defined as fed individuals of all ages, and 6×10^{-4} (0.06%) if the protected population also includes persons who are fasted in their adult years (i.e., skip breakfast). With Approach #1, a 3-fold decrease in

the MPC from that calculated for fed adults is sufficient to protect both young and fasted individuals.

Approach #2 is 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 industrial setting. The proposed value of f_1 is 4×10^{-3} (0.4%), the GI absorption value applied to the first year of human life. With Approach #2, a 30-fold decrease in the MPC from that calculated for fed adults is required to protect both young and fasted individuals. Advantages and disadvantages of these two approaches are discussed.

Finally, recommendations for further research are presented. These recommendations include (a) investigations into the relevance of fasted GI values to setting limits for oral exposure to plutonium and (b) studies of GI absorption in a neonatal nonhuman primate that would elucidate the time course of change in GI absorption from birth through the postweaning period.

1. INTRODUCTION

1.1 Background

The maximum permissible concentration (MPC) of soluble plutonium in drinking water, 5 pCi/mL (9), is based on a value of f_1 (the fraction of an element transferred from gut to blood in humans) of 3×10^{-5} (0.003%). This f_1 value was derived primarily from the results of experiments by Katz et al. (8) and Weeks et al. (10) in which rats were administered 0.01 M nitric acid solutions of tetravalent plutonium [Pu(IV)] at plutonium weight concentrations between 10^{-2} and 10^{4} times that of ^{239}Pu at MPC, 80 pg/mL. The mean value obtained in these experiments for the fraction of the administered plutonium absorbed through the GI tract and retained in bone and liver was 2.5×10^{-5} (0.0025%), in good agreement with values obtained when 0.01 M nitric acid solutions having plutonium concentrations in the range 0.1 to 1 mg/mL were administered to rats (10-12) and to swine (10).

In 1972, Committee 2 of the International Commission on Radiological Protection (ICRP) reviewed data on the gastrointestinal absorption of plutonium and concluded that "the current value of 3×10^{-5} for the fraction of plutonium transferred from the gastrointestinal tract to blood (f_1) appears to be reasonable for soluble plutonium compounds" (6). When the medium of the administered plutonium was a citrate solution, absorption was higher by two orders of magnitude (10-12), but this increase seems to have been attributed to the special nature of the medium. In 1979, the ICRP reconsidered its estimate of f_1 for plutonium and increased it to 1×10^{-4} (0.01%) (13). This threefold increase was based mainly on data of Sullivan et al. reviewed by Stather et al. (14).

In 1978, Larsen and Oldham (7) reported that chlorination of drinking water results in the oxidation of plutonium to the VI state. Because earlier research showed that the fraction of plutonium retained after Pu(VI) administration was 1.9×10^{-2} (10), three orders of magnitude higher than that of Pu(IV), the ICRP value of f_1 for soluble forms of plutonium might have been too low by several orders of magnitude (and the MPC for drinking water correspondingly too high). However, the reduction of Pu(VI) to Pu(IV), which is expected to occur naturally in the gastrointestinal tract, might have been forestalled in the early Pu(VI) experiments (10), since the Pu(VI) solution contained an unspecified amount of dichromate, the oxidant used to convert Pu(IV) to Pu(VI). The dichromate may have acted as a holding oxidant, inhibiting reduction of Pu(VI) to Pu(IV) in the GI tract. The limited and questionable data on the GI absorption of Pu(VI), coupled with the realization that plutonium in chlorinated drinking water is in the VI state, makes critical the establishment of a reliable value for the GI absorption of Pu(VI).

1.2 Overview and Objectives

A drinking water standard for plutonium is required to regulate the release of plutonium into drinking water supply systems from nuclear power facilities or from nuclear waste disposal sites. In the study reported here, the retention of plutonium following oral administration to mice, rats, and dogs was determined under conditions relevant to setting drinking water standards. Effects of the following parameters were investigated: plutonium oxidation state, animal species, feeding regimen, plutonium concentration, age of the animal, administration medium, and plutonium hydrolysis (polymerization). Results are compared with those of earlier investigators. Based on analysis of our data, GI absorption values are suggested for use in setting limits for exposure to plutonium in environmental and occupational exposure settings.

2. MATERIALS AND METHODS

2.1 Plutonium solutions

2.1.1 Isotopes

The plutonium isotopes used in this study either were obtained from other investigators at Argonne National Laboratory (^{238}Pu, ^{239}Pu and ^{242}Pu) or were produced by irradiation in the Laboratory's cyclotron (^{236}Pu and ^{237}Pu). All of the alpha-emitting nuclides had an isotopic purity (on an activity base) of greater than 99.9%. Where necessary, this purity was achieved by using the laboratory's mass separator. Purity was established by alpha spectrometric assay of material that had been electrodeposited onto stainless steel discs.

The ^{237}Pu (half-life, 46 days), which decays by electron capture to ^{237}Np (half-life, 2×10^6 years) with emission of neptunium K x-rays, contained ^{236}Pu, ^{238}Pu, and ^{239}Pu (byproducts in the cyclotron irradiation). The isotopic composition of this plutonium varied depending on both the conditions of the irradiation (energy, target thickness, etc.) and the time between production and use in an experiment. The abundances of the alpha-emitting isotopes relative to that of ^{237}Pu were established by electrodepositing the plutonium and counting the disc in a 2π alpha counter, an alpha spectrometer, and a gamma ray spectrometer. An isotopic composition of "^{237}Pu" that was typical of the materials used in these studies is given in Table 2-1.

Table 1 Isotopic composition of a typical preparation of ^{237}Pu

Plutonium Isotope	Weight Percent
237	23
236	5
238	7
239	< 65

The other isotopes present in the ^{237}Pu were considered in calculating the molar concentrations of the solutions administered to animals. These other isotopes, however, did not interfere in the assays for plutonium in tissue samples because such assays were performed exclusively by counting x-rays. The uranium K x-rays that are emitted in very low abundance in the decay of ^{236}Pu, ^{238}Pu, and ^{239}Pu were not distinguished from the neptunium K x-rays emitted in the decay of ^{237}Pu because of the very small energy differences; hence, if they were present to a significant degree, they were attributed to ^{237}Pu. (Because of the presence of ^{239}Pu, the ^{237}Pu solutions are designated as $^{237/239}Pu$ solutions in later sections of this document.)

Each of the plutonium isotopes used in these experiments was separated from other elements, including other actinides, prior to administration by using the anion exchange procedure of Larsen and Oldham (15). The absence of other actinides (less than 0.1% of the total alpha activity) was confirmed in the alpha spectrometric assays of the electrodeposited plutonium. (All the actinide elements are electrodeposited with plutonium.)

2.1.2 Preparation of Solutions

The plutonium isotopes used in this study were obtained from various sources as solutions whose compositions (acidity and plutonium oxidation state) were uncertain. To assure a known composition of the administered solutions, particularly with respect to oxidation state, the plutonium used in each experiment was converted to a common form: Pu(IV) in a drop or two of 15 M HNO_3. This was done by evaporating a plutonium stock solution (generally in 8M HNO_3) to incipient dryness, adding 9 M HBr and evaporating to incipient dryness, then adding 15 M HNO_3 and evaporating to incipient dryness. The hydrobromic acid treatment insured that the Pu(IV) and Pu(VI) in the nitric acid were converted to Pu(III); the nitric acid treatment eliminated bromide and

converted the plutonium to Pu(IV). Additional steps taken to prepare the individual solutions are described below.

Pu(IV) in 0.01 M $NaHCO_3$ After evaporation of the 15 M HNO_3 (see above), Pu(IV) was taken up in about 0.5 mL of 4 M HNO_3 and titrated dropwise with 1 M $NaHCO_3$ (0.01 mL/drop) until the pH of the solution was between 7.0 and 7.5. Additional 1 M $NaHCO_3$ and 0.1 M NaI were added, and the solution was diluted to volume with water, such that the final solution was 0.01 M in both $NaHCO_3$ and NaI. This final solution had a pH of 8.3. (The $NaNO_3$ concentration of these solutions varied from 0.01 M to 0.2 M.)

Pu (VI) in 0.01 M $NaHCO_3$ (Chemical Oxidation) After evaporation of the 15 M HNO_3, Pu(IV) was taken up in about 0.5 mL of 4 M HNO_3 and titrated dropwise with 1 M $NaHCO_3$ (0.01 mL/drop) until the pH of the solution was between 7.0 and 7.5. The plutonium was oxidized to the VI state by making the solution 0.00015 M in NaOCl (10 ppm in chlorine) and heating for 2 hours at 90°C. Volatilization of chlorine reduced the chlorine concentration to about 1 ppm (as determined with diethyl-p-phenylenediamine). Sufficient additional 1 M $NaHCO_3$ was added to produce a final solution that was 0.01 M in bicarbonate, pH 8.3, when the solution was diluted to volume with water. (The $NaNO_3$ concentration of the solution was 0.2 M.)

Pu (IV) in 0.01 M HNO_3 After evaporation of the 15 M HNO_3, Pu(IV) was taken up in sufficient 1 M HNO_3 to produce a final HNO_3 concentration of 0.01 M when the solution was diluted to volume with water.

Pu (IV) in 0.17 M sodium citrate (pH 4.5) After evaporation of the 15 M HNO_3, Pu(IV) was taken up in 0.25 mL of 4 M HNO_3, and 5 mL of a 5% (0.17 M) solution of sodium citrate was added. The final pH was 4.5.

Pu (VI) in 0.01 M $NaHCO_3$ (Electrolytic Oxidation) After evaporation of the 15 M HNO_3, Pu(IV) was taken up in about 0.5 mL of 1 M HNO_3. The solution was transferred to the anode compartment of an H-style electrolysis cell, and 1 M HNO_3 was added to the cathode compartment. The electrodes were platinum. The plutonium was oxidized to the VI state by applying a 4-V potential to the cell for 3 h. The plutonium solution was removed and titrated dropwise with 1 M $NaHCO_3$ (0.01 mL/drop) until the pH of the solution was between 7 and 7.5. Sufficient 1 M $NaHCO_3$, 0.0015 M NaOCl (100 ppm in chlorine), and water were added to obtain a solution that was 0.01 M in $NaHCO_3$ and 1 ppm in chlorine (pH 8.3). (The $NaNO_3$ concentration of these solutions varied from 0.005 M to 0.05 M.)

2.1.3 Characterization of Solutions

The amounts of plutonium in the administered solutions, as well as the percentages in the IV and VI states, were determined by the lanthanum fluoride method (16). In this method, lanthanum fluoride is precipitated and separated from solution both prior to and subsequent to the addition of ferrous sulfate, a reagent that reduces Pu(VI) to Pu(III). The Pu(IV) that is present initially is carried on the first precipitate; the Pu(VI) that is present initially remains in solution and is reduced to Pu(III) upon addition of the ferrous sulfate. This Pu(III) is then carried on the second precipitate. Assays of plutonium in the first and second lanthanum fluoride precipitates give the amounts of Pu(IV) and Pu(VI), respectively, present in the original solution. For those nuclides that decay by alpha emission, the individual precipitates were dissolved in an aluminum chloride-hydrochloric acid solution, an isotopic diluent was added (usually ^{242}Pu), and the solution was subjected to the same analytical procedure as that used for solutions of tissue samples (see Section 2.5.2). For ^{237}Pu, which decays by neptunium K x-ray emission, the precipitates were assayed by using a sodium iodide-gamma ray spectrometer.

The percentage of ultrafilterable plutonium (% UF) in the administered solutions was determined by the procedure of Lindenbaum and Westfall (17), in which a solution of plutonium is placed in a bag made of cellophane dialysis tubing (Union Carbide Corp.) and centrifuged. The concentration of plutonium in the solution that passes through the dialysis membrane is compared to the concentration in the original solution. Results provide an operational definition of the fraction of plutonium in a solution that is in monomeric vs. polymeric form. (The percentage that passes through the dialysis membrane is monomeric and the percentage retained is polymeric.) The ultrafilterability (% UF) is reported as the percentage that passes through the membrane.

2.2 Animals

2.2.1 Mice

Mice used were adult $B6CF_1$/Anl males or females (Argonne National Laboratory, Argonne, IL), 80 to 90 days old, weighing 18 to 20 g, unless otherwise specified. They were maintained on Wayne Lab Blox rodent chow, in plastic cages at 37° C, in an animal care facility with a lighting schedule of 12 h of light (0600 to 1800) followed by 12 h of dark (1800 to 0600). (In one experiment, this lighting schedule was altered to accommodate plutonium administrations during working hours.) Mice were housed individually in stainless steel metabolism cages from approximately one week prior to plutonium administration until sacrifice.

2.2.2 Rats

Adult rats used were Sprague-Dawley females (CD strain, Charles River Laboratory, North Wilmington, MA), 64 days old, weighing 203 to 233 g. Timed-pregnant rats were Sprague-Dawley females (Harlan Sprague Dawley, Inc., Indianapolis, IN) obtained on day 9 of gestation.

2.2.3 Dogs

Dogs used were adult male beagles (Argonne National Laboratory, Argonne, IL). They ranged in age from 558 to 592 days and in mass from 9.1 to 14.2 kg. They were housed in stainless steel metabolism cages from 8 days prior to plutonium administration until sacrifice 35 days after administration.

2.3 Administration of solutions

2.3.1 Administration by Gavage

Administration of solutions to adult mice by gavage was accomplished by using a syringe and a No. 23 needle with a 2-mm-diameter spherical tip. The volume of solution administered to mice was 0.1 to 0.2 mL. Except where otherwise indicated, lungs of each animal were analyzed to determine whether plutonium had entered the animal via the respiratory tract. If the amount detected in the lungs was greater than 0.01% of the amount administered, the data for that animal were discarded.

Administration of solutions by gavage to neonatal, weanling, young growing, and adult rats was accomplished by using ball-tipped needles of various sizes purchased from Popper and Sons, Inc. (New Hyde Park, NY). All rats except 100-day-old adults were administered 0.1 mL of solution; 100-day-old adults were administered 1.0 mL of solution. Preliminary experiments were performed for each age group to determine (a) the optimum needle size and (b) the incidence of lung contamination with the chosen needle size for each age. Lung contamination was determined by sacrificing rats immediately after solution administration and removing and assaying lungs for radioactivity. (Lung contamination was defined as occurring when the fraction of administered dose retained in the lungs at sacrifice immediately after administration of the radioactive solution was greater than 1×10^{-4}.)

2.3.2 Administration via Drinking Water

To allow mice and rats to drink solutions containing plutonium throughout their normal period of food and water consumption, a glass tube, 8 mm in diameter and 50 mm long, sealed at one end, with a 2-mm-diameter hole in the other end, was used. The tube was filled by introducing the plutonium solution with an Eppendorf micropipet. The tube was mounted inside the cage at a 45° angle with the open end

pointing downward. The volume of solution provided varied with the experiment and animal species. A test of the system in which dye was added to the water and white absorbent paper was placed under the grid bottoms of the stainless steel cages established that the amount of spillage was negligible. A comparison of the absorbent papers with a paper onto which 250 µL of dye solution had been stippled indicated that spillage was quite small, less than 5% of the volume administered. Examination of the animals showed no dye on their pelts. The amount of plutonium consumed was determined by subtracting the amount of plutonium activity measured in the tube after the administration period from the amount provided. The percentage consumed ranged from 44 to 95% for mice and 31 to 99% for rats.

2.3.3 Administration via Intravenous Injection

Following the discovery that plutonium adsorbs to teeth during oral administration of plutonium in drinking water (see Appendix A), we placed three additional animals in each group that received plutonium via gavage or drinking water. These additional mice received no oral plutonium but were injected with 0.1 mL of plutonium solution via the tail vein. Intravenously injected mice were sacrificed at the same time as the mice receiving oral plutonium. A ratio of plutonium in the total carcass (Pu_C) to plutonium in the carcass minus head section (Pu_{C-H}) was determined for the intravenously injected mice. This distribution ratio was used to calculate the plutonium content of the total carcass for the mice receiving plutonium orally (see Appendix A.3).

2.3.4 Administration via Gelatin Capsule

Plutonium solutions were administered to dogs via gelatin capsules. One mL of the solution was placed in the capsule just prior to administration. The capsule was placed in the back of the dog's mouth until the dog swallowed. No anesthesia was administered.

2.3.5 Times of Administration

For mice and rats, the active, waking phase of maximum food and water consumption is during the period of darkness (from 1800 to 0600 in our study). Water consumption by mice during this active phase is approximately 4 mL per mouse. The inactive, sleeping phase is during the period of light (from 0600 to 1800 in our study). During the inactive phase, water consumption is approximately 0.5 mL per mouse. In our experiments, plutonium solutions were administered during both of these phases of the daily cycle, with most data obtained during the dark period of normal food and water consumption.

2.4 Sacrifice and Sampling Procedures

At sacrifice of mice and rats, pelts were removed, bodies were eviscerated, and plutonium was assayed in lungs, livers, and skinned, eviscerated carcasses. This procedure was established on the basis of results obtained in the first experiment, in which Pu(VI) was administered to fasted mice (see Section 3.1, Effect of Plutonium Oxidation State). In that experiment, pelts were removed at sacrifice, and plutonium was assayed in the pelts and the whole (uneviscerated) skinned bodies. Each mouse was then eviscerated, and the skinned, eviscerated carcass, the liver, and the other organs (except the GI tract) were analyzed for plutonium content. The sum of the amounts of plutonium in these three tissue samples was always greater than 90% of the amount in the whole (uneviscerated) skinned animal. More than 95% of the sum was present in the eviscerated body and the liver, with the remainder (less than 5%) in the other organs.

Because the above results were in agreement with the observation of Weeks et al. (10) that the percentage retained in "other soft tissue" of 12 rats ranged from 5 to 15% with a mean of 8%, the only tissues analyzed for plutonium in subsequent experiments were skinned, eviscerated bodies and livers. The amount of plutonium in the skeleton relative to that in the skinned, eviscerated body was determined in several animals by partially decomposing the soft muscle tissue with ethylenediamine, separating the bones, and analyzing them. More than 95% of the activity in the eviscerated body was in the bones. The pelts were analyzed to establish whether plutonium-bearing excrement could have contaminated the carcasses. No activity was found on the pelts.

Following the discovery of occasional lung contamination in the earliest experiments when the method of administration was gavage, lungs were analyzed in all subsequent experiments, both for gavage and drinking water administrations. In all groups where lungs were found to contain plutonium above the limits of detection, the amount of plutonium in the lungs ranged from 0.11% to 5.5% of the plutonium retained in the whole animal at sacrifice, with a mean value of 1.1 ± 0.4% per group (mean ± SEM, n = 20 groups). Expressed as a fraction of the administered dose, the fractional retention of plutonium in the lungs at sacrifice ranged from 2×10^{-7} to 5×10^{-5}, with the highest values in the animals with the highest GI absorption values (the young and the fasted).

2.5 Plutonium Determinations

2.5.1 ^{237}Pu Determinations

The amounts of ^{237}Pu administered and the amounts retained by the animals were determined by counting the neptunium K x-rays emitted in the decay of ^{237}Pu. Two detectors were used, a 2-in.-thick, 4-in.-

diameter sodium iodide crystal for the mice and an 8-in.-diameter Phoswich for the rats. The background count rates for these detectors were 15 and 8 cpm, respectively; the counting time was 40 min; and the sample was located on the face of the detector. The geometry-mass absorption factor in counting skinned, eviscerated carcasses was 45% for the mice and 38% for the rats. These factors were established by ashing eviscerated bodies containing ^{237}Pu and analyzing the ash. The amount of ^{237}Pu administered ranged from 3×10^4 to 1×10^5 pCi; the limit of detection was 3 pCi per animal, equivalent to fractional retentions of 3×10^{-5} to 1×10^{-4}.

2.5.2 ^{236}Pu, ^{238}Pu, ^{239}Pu Determinations

Solutions of tissue samples that contained ^{236}Pu, ^{238}Pu, or ^{237}Pu, or a combination thereof, were prepared in two ways: (a) Skinned, eviscerated carcasses were ashed in a muffle furnace at 600°C, dissolved in concentrated HNO_3, and diluted to a known volume with 6 M HNO_3; (b) Livers were directly digested in concentrated HNO_3. The amount of each alpha-emitting isotope was determined by alpha spectrometric isotope dilution. A known amount (picocuries) of ^{242}Pu was added to an aliquot of the solution to be analyzed, and the solution was evaporated to incipient dryness. An excess of 9 M HBr was added, and the solution was again evaporated to incipient dryness. (This procedure insured isotopic exchange between the isotopes that were in the sample and the ^{242}Pu used as the isotopic diluent.) The plutonium was taken up in 9 M HCl containing about 100 ppm chlorine and was separated from the other sample constituents through the anion exchange procedure of Larsen and Oldham (15). The separated plutonium was electrodeposited with the technique reported by Kressin (18), and the deposit was assayed in an alpha spectrometer. The amounts of ^{236}Pu and ^{238}Pu administered ranged from 2×10^2 pCi to 2×10^3 pCi; the limit of detection for the amount in an animal was 0.002 pCi per animal, equivalent to fractional retentions of 1×10^{-6} to 1×10^{-5}. The amount of ^{239}Pu administered was 4×10^4 pCi; the limit of detection was 0.002 pCi per animal, equivalent to a fractional retention of 5×10^{-6}.

2.6 Format for Presentation of Results

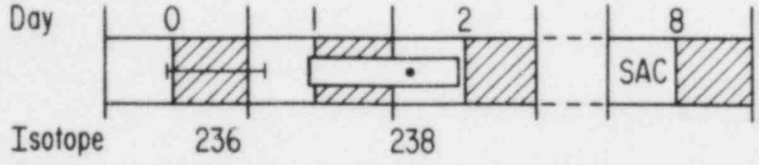
For each experiment, the fraction of the administered plutonium retained in the whole animal and in the liver are presented in tabular form. GI absorption values are not included because the difficulty of collecting urine samples free of fecal contamination prevented reliable measurement of plutonium excretion in urine of mice and rats. Rosenthal et al. showed that urine collected after intravenous injection of ^{239}Pu to mice contains only 10% of the administered dose (16). By analogy, after oral administration of plutonium to the fed mouse, urine would contain 0.002% of the administered dose (0.02% absorbed and retained; 0.002% excreted

into urine), while feces would contain close to 100% of the administered dose. Thus, the potential for contamination of urine by feces is great.

Sullivan et al. reported values for urinary excretion of plutonium after oral administration to rats (1). Cumulative urine samples collected during the 5 to 7 days after plutonium administration contained 0.004% to 0.059% of the administered dose (10% to 150% of the plutonium retained in the whole animals), with large variation between groups. The lowest value, 10% of the retained dose, is similar to the value observed after intravenous injection. Therefore, GI absorption values, which are the sum of fractional retention and fractional excretion in urine, are likely to be only 10% higher than the values of fractional retention. In this document, we report the fractional retention values actually determined in our assays rather than calculated fractional GI absorption values, which would be 10% higher.

3. EXPERIMENTS AND RESULTS

In this section each experiment is described in detail along with its results. For each study, a diagram is presented that has the following general format:



The open squares indicate daily 12-h periods of light when the animals were asleep; shaded squares indicate daily 12-h periods of darkness when the animals were awake and active. The light/dark cycle generally was light from 0600 to 1800 and dark from 1800 to 0600. A horizonal rectangle within the squares represents a period of fasting. A horizonal line with bars on either end represents a period of administration of plutonium via drinking water tube. A dot represents a gavage. The letters SAC indicate the time of animal sacrifice.

In the diagram shown above, mice received two plutonium isotopes: a ^{236}Pu solution was administered via drinking water tube to fed animals from 1700 on day 0 to 0900 on day 1; a ^{238}Pu solution was administered by gavage to the same animals in the fasted condition at 0900 on day 2. The period of fast was from 1700 on day 1 to 1700 on day 2. Mice were sacrificed on day 8.

3.1 Effect of Plutonium Oxidation State

Objective: To determine the effect of the oxidation state of plutonium on its GI absorption. The plutonium was in either the IV or the VI oxidation state. The IV state was used in most earlier investigations (8, 10). Larsen and Oldham (7) demonstrated that plutonium in chlorinated drinking water is in the VI state.

Experiment Conditions:

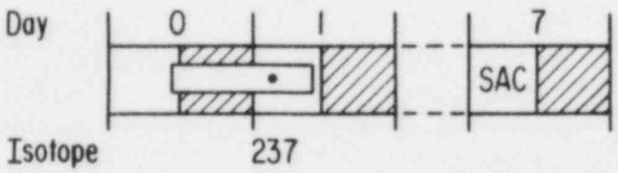
Solutions:

- $^{237/239}Pu$(IV) (6×10^{-10} M) in 0.01 M NaI, pH 8.3
- $^{237/239}Pu$(VI) (6×10^{-10} M) in 0.01 M $NaHCO_3$, 1 ppm Cl_2, pH 8.3

Animals: B6CF$_1$/An1 female mice (80 to 90 days old at administration)

Administrations: 0.2 mL plutonium solutions administered to fasted mice by gavage during the inactive phase

Experiment Diagram: Effect of Plutonium Oxidation State



Experiment Protocol: Two groups of adult female mice (20-21 mice/group) were fasted for 24 h, from 1700 on day 0 to 1700 on day 1. At 0900 on day 1, during the inactive phase, plutonium solutions were administered by gavage, Pu(VI) to one group and Pu(IV) to the other. Mice were sacrificed on day 7. Pelts were removed, bodies were eviscerated, and the amount of ^{237}Pu in the liver and in the skinned, eviscerated carcass of each animal was determined.

Results:

Table 2 Retention of plutonium in adult mice after gastrointestinal absorption: Effect of oxidation state of plutonium

	Pu Oxidation State (%)				Fraction Retained ($\times 10^4$)[a]	
Isotope	IV	VI	% UF	n	Total	Liver
Pu (VI)	12	88	85	20	15 ± 3	2.5 ± 0.7
Pu (IV)	100	0	70	21	20 ± 2	2.8 ± 0.5

[a]Values presented are means ± standard deviation of the mean for the number of animals shown, n. Total fraction retained is the sum of plutonium in skinned, eviscerated carcass and liver. Fraction absorbed is approximately 10% greater than fraction retained (Section 2.6). Lungs of these animals were not assayed for plutonium. Data from several mice with exceptionally high skeletal burdens, presumably due to lung contamination, were excluded as described in Reference 2.

Conclusions: In the fasted mouse, the fraction of plutonium retained 6 days after GI absorption was about 2×10^{-3}; this fraction was the same for both Pu(VI) and Pu(IV).

3.2 Effect of Animal Species

Objective: To determine the effect of animal species on the GI absorption of hexavalent plutonium. The species studied were the mouse, the rat, and the dog.

Experiment Conditions:

Solutions: $^{237/239}Pu(VI)$ ($\sim 6 \times 10^{-10}$ M) in 0.01 M $NaHCO_3$, 1 ppm Cl_2, pH 8.3

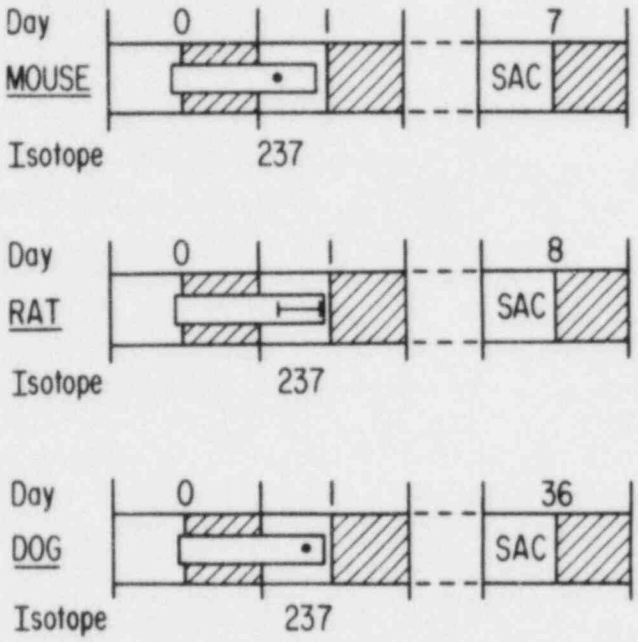
Animals:

- $B6CF_1$/An1 female mice (80-90 days old at administration)
- Sprague-Dawley female rats (64 days old at administration)
- Beagle male dogs (558-592 days old at administration)

Administrations:

- 0.2 mL plutonium solution administered to fasted mice by gavage during the inactive phase
- 2 mL plutonium solution administered to fasted rats via drinking water tube during the inactive phase
- 1 mL plutonium solution administered to fasted dogs via gelatin capsule during the active phase

Experiment Diagram: Effect of Animal Species



Experiment Protocol: Groups of adult female mice and adult female rats (12-20 animals/group) were fasted for 24 h, from 1700 on day 0 to 1700 on day 1. At 0900 on day 1, during the inactive phase, mice were administered a solution of $^{237/239}Pu(VI)$ by gavage. Administration to rats was also during the inactive phase, but via drinking water tube from 0900 to 1700 on day 1. Both groups of rodents were sacrificed on day 7, and the amount of ^{237}Pu in the liver and in the skinned, eviscerated carcass of each animal was determined.

For the study in dogs, each of six adult male beagle dogs was administered a 1-mL portion of the plutonium solution via a gelatin capsule at 1400 following a 21-h fast. Food was returned to the dogs three hours later. Urine and feces were separately collected each day for 7 days. At 5 weeks the dogs were sacrificed, and their pelts and entire GI tracts were removed. Their livers with gall bladders, lungs, and skeletons (in sections), were removed, dried, and separately ashed in a muffle furnace at 500°C. Feces were similarly ashed. The amount

of ^{237}Pu in each sample of ash was determined by dissolving it in concentrated HNO_3 and adjusting the concentration to 8 N HNO_3 in a 200-mL volume. Amounts of ^{237}Pu in solutions of ash and in urine samples were determined by measuring neptunium K x-rays with a Phoswich detector. Lungs were analyzed for ^{236}Pu by alpha spectrometric-isotope dilution. [Details of this dog study were reported in Toohey et al. (20)].

Results:

Table 3 Retention of plutonium after GI absorption: Effect of animal species

Species	Pu Oxidation State (%)		% UF	n	Fraction Retained (x 10^4)[a]	
	IV	VI			Total	Liver
Mouse	12	88	85	20	15 ± 3	2.5 ± 0.7
Rat	3	97	89	12	32 ± 5	6 ± 1
Dog	10	90	93	5	6.6 ± 1.2	3.3 ± 1.0

[a]Values presented are means ± the standard deviation of the mean for the number of animals shown, n. Total fraction retained is sum of plutonium in skinned, eviscerated carcass and liver. Fraction absorbed is approximately 10% greater than fraction retained (Section 2.6).

Conclusions: In the fasted rat, the fraction of plutonium retained 6 days after GI absorption of Pu(VI) was 3.2×10^{-3}, a value two times that in the fasted mouse, 1.5×10^{-3}. Retention in the fasted dog at 35 days was 6.6×10^{-4}, about one-half that in the fasted mouse.

3.3 Effect of Feeding Regimen

3.3.1 Experiment 1. Effect of Food Deprivation

Objective: To determine the effect of food deprivation on the GI absorption of hexavalent plutonium.

Experiment Conditions:

Solutions:

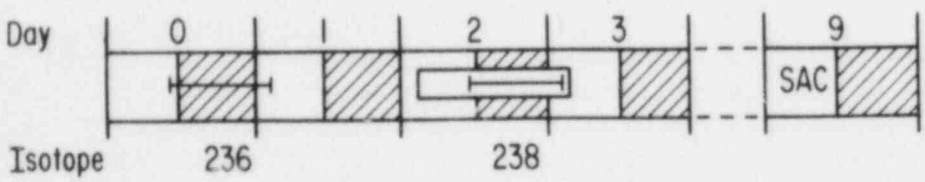
- $^{236}Pu(VI)$ (1×10^{-10} M) in 0.01 M $NaHCO_3$, 1 ppm Cl_2, pH 8.3
- $^{238}Pu(VI)$ (1×10^{-10} M) in 0.01 M $NaHCO_3$, 1 ppm Cl_2, pH 8.3

Animals: $B6CF_1$/Anl male mice (80 to 92 days old at administration)

Administrations:

- 3 mL of ^{236}Pu solution administered to fed mice via drinking water tube during the active phase
- 3 mL of ^{238}Pu solution administered to fasted mice via drinking water tube during the active phase

Experiment Diagram: Effect of Food Deprivation



Experiment Protocol: Two 0.01 M $NaHCO_3$ solutions, each containing a particular plutonium isotope, were administered to the same group of animals, one while the animals were being fed and the other while they were being fasted. GI absorption values under two experimental conditions were thus determined in the same group of animals.

Twelve adult, male mice being fed ad libitum were provided 3 mL of a solution of $^{236}Pu(VI)$ via drinking water tube from 1700 on day 0 to 0900 on day 1 (during the active phase). At 0900 on day 2, food was removed from the cages, and from 1700 on day 2 to 0900 on day 3, the mice were provided 3 mL of a 1×10^{-10} M solution of $^{238}Pu(VI)$. At 0900 on day 3, the plutonium solution was replaced by normal drinking water, and food was returned to the cages. All mi#e were sacrificed on day 9. The ^{236}Pu and ^{238}Pu contents of the liver and the skinned, eviscerated carcass of each animal were determined by alpha spectrometric-isotope dilution. (See Appendix A for further details.)

Results:

Table 4 Retention of plutonium in adult mice after GI absorption: Effect of food deprivation

Feeding Regimen	Pu Oxidation State (%) IV	VI	% UF	n	Fraction Retained ($\times 10^4$)[a] Total	Liver
Fasted	8	92	69	12	19 ± 2	6.3 ± 1.0
Fed	0	100	99	12	1.4 ± 0.2	0.42 ± 0.04

[a]Values presented are means ± the standard deviation of the mean for the number of animals shown, n. Total fraction retained is sum of plutonium in skinned, eviscerated carcass and liver. Fraction absorbed is approximately 10% greater than fraction retained (Section 2.6).

Conclusions: The fraction of plutonium retained 7 to 9 days after GI absorption of Pu(VI) in the fasted mouse (1.9×10^{-3}) was 13-fold higher than in the fed mouse (1.4×10^{-4}).

3.3.2 Experiment 2: Effect of Time of Day of Plutonium Administration

Objective: To determine the effect of Pu(VI) administration during the active vs. the inactive phase of the mouse's daily cycle.

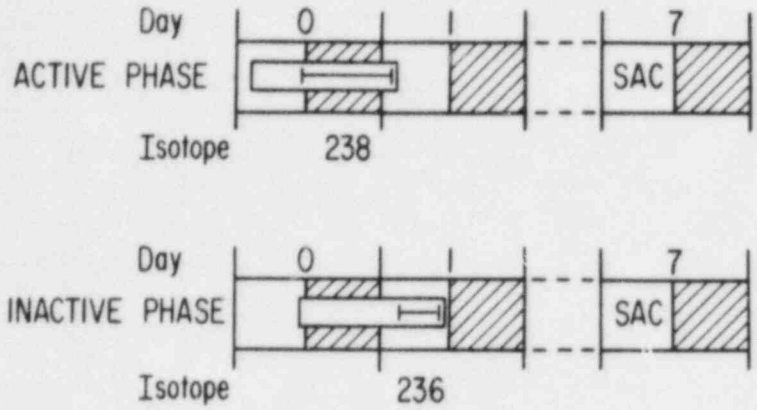
Experiment Conditions:

Solutions: Same as 3.3.1, Effect of Food Deprivation

Animals: Same type as 3.3.1

Administrations: $^{238}Pu(VI)$ or $^{236}Pu(VI)$ solutions administered to fasted mice via drinking water tube during the active (3.0 mL) or inactive (0.25 mL) phases

Experiment Diagram: Effect of Time of Day of Plutonium Administration



Experiment Protocol: Twelve male mice were fasted for 24 h, from 0900 on day 0 until 0900 on day 1. From 1700 on day 0 until 0900 on day 1 (during the active phase), they were provided 3 mL of a 1×10^{-10} M solution of $^{238}Pu(VI)$. At 0900 on day 1, the plutonium solution was replaced by normal drinking water, and food was returned to the cages. An additional eight adult, male mice were also fasted for 24 h, from 1700 on day 0 until 1700 on day 1. From 0900 until 1700 on day 1 (during the inactive phase), they were provided 0.25 mL of a 1×10^{-10} M solution of $^{236}Pu(VI)$. At 1700 on day 1, the plutonium solution was replaced by normal drinking water, and food was returned to the cages. Both groups of mice were sacrificed 6 days after plutonium administration. The ^{238}Pu and ^{236}Pu contents of the liver and of the skinned, eviscerated carcass of each animal were determined by alpha spectrometric-isotope dilution. (See Appendix A for further details.)

Results:

Table 5 Retention of plutonium in adult mice after GI absorption: Effect of time of day of plutonium administration

Time of Pu Administration	Pu Oxidation State (%) IV	VI	% UF	n	Fraction Retained ($\times 10^4$)[a] Total	Liver
1700, Active Phase	8	92	69	12	19 ± 2	6.3 ± 1.0
0900, Inactive Phase	1	99	90	8	18 ± 5	5.0 ± 1.3

[a]Values presented are means ± the standard deviation of the mean for the number of animals shown, n. Total fraction retained is sum of plutonium in skinned, eviscerated carcass and liver. Fraction absorbed is approximately 10% greater than fraction retained (Section 2.6).

Conclusions: The fraction of plutonium retained 6 days after administration of Pu(VI) during the active phase to the fasted mouse was the same as the fraction retained after administration during the inactive phase to a similarly fasted mouse.

3.4 Effect of Plutonium Concentration

Objective: To determine the effect of plutonium concentration on the GI absorption of hexavalent plutonium in the range from two orders of magnitude below to two orders of magnitude above the current MPC for plutonium in drinking water (1×10^{-10} M for ^{239}Pu).

Experiment Conditions:

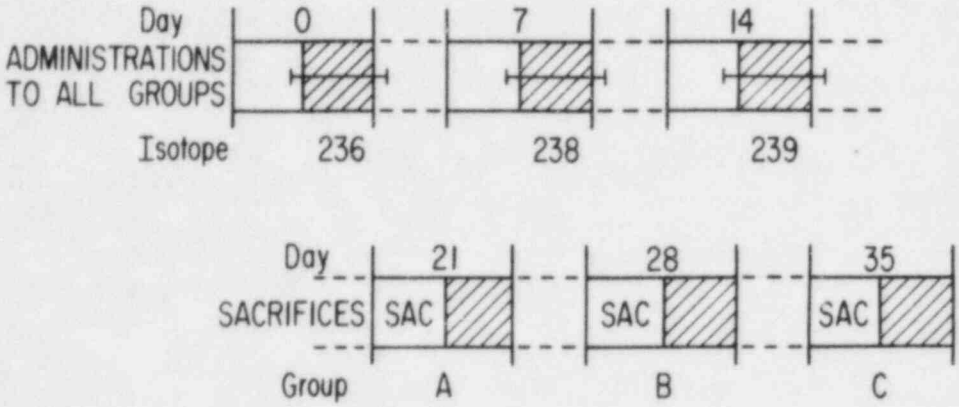
Solutions:

- $^{236}Pu(VI)$ (1×10^{-12} M) in 0.01 M $NaHCO_3$, 1 ppm Cl_2, pH 8.3
- $^{238}Pu(VI)$ (1×10^{-10} M) in 0.01 M $NaHCO_3$, 1 ppm Cl_2, pH 8.3
- $^{239}Pu(VI)$ (1×10^{-8} M) in 0.01 M $NaHCO_3$, 1 ppm Cl_2, pH 8.3

Animals: $B6CF_1$/Anl male mice (80-94 days old at administration)

Administrations: 3 mL plutonium solution administered to fed mice via drinking water tube during the active phase

Experiment Diagram: Effect of Plutonium Concentration



Experiment Protocol: Each mouse in three groups (A, B, and C) of fed adult, male mice (10 mice/group) was provided 3 mL of a 1×10^{-12} M solution of $^{236}Pu(VI)$ via drinking water tube from 1700 on day 0 to 0900 on day 1 (during the active phase), when the plutonium solution was replaced by normal drinking water. This administration protocol was repeated on day 7 with a 1×10^{-10} M solution of $^{238}Pu(VI)$ and again on day 14 with a 1×10^{-8} M solution of $^{239}Pu(VI)$. Each mouse in each group thus received three solutions of plutonium, the molar concentration of the first being 100 times lower than the present MPC for ^{239}Pu in drinking water, the second being equal to it, and the third being 100 times higher. Because the body does not distinguish between one isotope of plutonium and another, care was taken to wait between isotope administrations to allow for clearance of the GI tract and blood of one isotope at a given concentration before administration of the next isotope at the next concentration. The times of the administrations (on successive weeks rather than successive days) and their order (from lowest concentration to highest) minimized the potential effect of plutonium at one concentration on the metabolic behavior of plutonium at the next concentration.

Mice in Group A were sacrificed on day 21, those in Group B on day 28, and those in Group C on day 35, and the amounts of ^{236}Pu, ^{238}Pu, and ^{239}Pu in the liver and in the skinned, eviscerated carcass of each mouse were determined by alpha spectrometric-isotope dilution. (See Appendix A for further details.) Information was thus obtained on the retention of plutonium subsequent to its GI absorption at three plutonium concentrations, and at three times after administration of each isotope, i.e., at 21, 28, and 35 days after administration of the 1×10^{-12} M $^{236}Pu(VI)$ solution; at 14, 21, and 28 days after administration of the 1×10^{-10} M $^{238}Pu(VI)$ solution; and at 7, 14, and 21 days after administration of the 1×10^{-8} M $^{239}Pu(VI)$ solution. The effect of plutonium concentration on GI absorption was established by

comparing retention values of the three isotopes at 21 days after the administration of each.

Results:

Table 6 Retention of plutonium in adult mice after GI absorption: Effect of plutonium concentration

Plutonium Conc.	Pu Oxidation State (%) IV	VI	% UF	n	Fraction Retained ($\times 10^4$)[a] Total	Liver
1×10^{-12}	2	98	81	10	1.6 ± 0.2	0.40 ± 0.07
1×10^{-10}	16	84	78	10	2.4 ± 0.3	0.59 ± 0.07
1×10^{-8}	2	98	87	10	2.4 ± 0.2	0.58 ± 0.05

[a]Values presented are means ± the standard deviation of the mean for the numbers of animals shown, n. Values are for mice sacrificed at 21 days after Pu(VI) administration. Total fraction retained is sum of plutonium in skinned, eviscerated carcass and liver. Fraction absorbed is approximately 10% greater than fraction retained (Section 2.6).

Conclusions: The fraction of plutonium retained by fed mice 21 days after GI absorption of Pu(VI) was independent of plutonium concentration in the range from 1×10^{-12} M to 1×10^{-8} M plutonium. Retention values obtained (1.6×10^{-4} to 2.4×10^{-4}) were similar to the value obtained earlier for the fed mouse (1.4×10^{-4}, Table 3-3).

3.5 Effect of Age of the Animal

Objective: To determine the effect of animal age on the GI absorption of hexavalent plutonium in the rat.

Experiment Conditions:

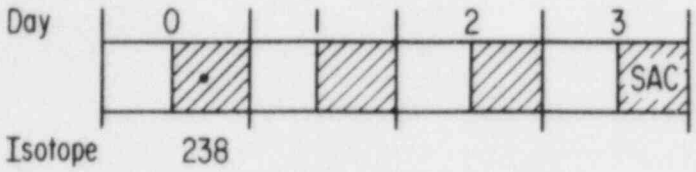
Solutions: $^{238}Pu(VI)$ (1×10^{-9} M) in 0.01 M $NaHCO_3$, 1 ppm Cl_2, pH 8.3

Animals: Pups from Harlan Sprague-Dawley female rats (1 day to 100 days old at administration)

Administrations:

- 0.1 mL plutonium solution administered by gavage during the active phase to fed rats of all ages except 100 days old
- 1.0 mL plutonium solution administered by gavage during the active phase to fed 100-day-old rats

Experiment Diagram: Effect of Animal Age



Experiment Protocol: To prevent lung contamination when gavaging the many ages and therefore sizes of rats involved in this experiment, we conducted a preliminary test of our gavage technique. Gavage needles of different sizes, to accommodate the different ages of rats we planned to study, were tested for their ability to deliver a dose of radioactive solution to the stomach of the fed, active phase rat, such that less than 0.01% of the dose appeared in the lungs when the rats were sacrificed immediately after gavage. (0.01% of the dose is the amount absorbed through the GI tract of the adult, fed rat. Lung contamination must be kept below that level.)

Following establishment of acceptable gavage procedures, timed-pregnant rats were obtained 9 days after conception; they delivered their pups either 12 or 13 days later. Litters were equalized to 10 pups per dam when pups were 1 day old (delivery day = 0 days of age for the pups). Plutonium was administered to groups of fed rat pups (4-7 rats/group) when pups were 1, 2, 10, 19, 29, 52, and 100 days old. Pups were weaned when 22 days old. Solutions of Pu(VI) (0.1 mL or 1.0 mL) were administered by gavage to each group of fed rat pups at 2300 (during the active phase). Two or three days after administration, they were sacrificed, and the amounts of ^{238}Pu in livers and skinned, eviscerated carcasses were determined by alpha spectrometric-isotope dilution.

Results:

Table 7 Retention of plutonium in rats after GI absorption: Effect of animal age

Age of Rat (days)	Pu Oxidation State (%) IV	VI	% UF	n	Fraction Retained ($\times 10^4$)[a] Total	Liver
1	1	99	98	5	74 ± 4	12 ± 1
2	1	99	98	5	74 ± 9	15 ± 2
10	0	100	100	4	47 ± 7	4 ± 0.4
19	1	99	100	6	31 ± 10	2 ± 0.6
Weaning (22)						
29	6	94	100	7	1.1 ± 0.2	0.11 ± 0.03
52	1	99	95	6	1.1 ± 0.4	0.10 ± 0.02
100	1	99	100	4	0.9 ± 0.4	0.10 ± 0.03

[a]Values presented are means ± the standard deviation of the mean for the numbers of animals shown, n.

Conclusions: The fraction of plutonium retained by the fed rat after GI absorption of Pu(VI) at 1 day of age was 7.4×10^{-3}, 70-fold higher than the GI absorption value of 1×10^{-4} measured in the adult rat at 100 days of age. At 19 days of age, just prior to weaning, the fraction retained by the fed rat was 3.1×10^{-3}, the same value as that for the fasted adult rat. By 29 days of age, one week after weaning, the fraction of plutonium retained after GI absorption by the fed rat had decreased to adult levels, 1×10^{-4}.

3.6 Effect of Administration Medium

Objective: To determine the effect of administration medium on the GI absorption of tetravalent plutonium. Results of previous investigators showed 10- to 100-fold differences in absorption due to differences in administration medium (10-12). In these previous investigations, the media used were 0.01 M HNO_3 and citrate buffer. In our present investigation, the media used were 0.01 M HNO_3, citrate buffer, and 0.01 M $NaHCO_3$.

Experiment Conditions:

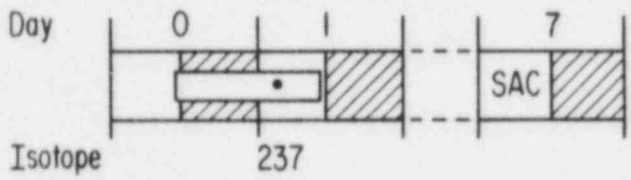
Solutions:

- $^{237/239}Pu(IV)$ (6×10^{-10} M) in 0.01 M $NaHCO_3$, 0.01 M NaI, pH 8.3
- $^{237/239}Pu(IV)$ (1×10^{-9} M) in 0.01 M HNO_3, pH 2.0
- $^{237/239}Pu(IV)$ (6×10^{-10} M) in 0.17 M citrate buffer, pH 4.5

Animals: $B6CF_1$/Anl female mice (80 to 90 days old at administration)

Administrations: 0.2 mL plutonium solution administered to fasted mice by gavage during the inactive phase

Experiment Diagram: Effect of Administration Medium



Experiment Protocol: Three groups of adult, female mice (8-20 mice/group) were fasted for 24 h, from 1700 on day 0 to 1700 on day 1. At 0900 on day 1, during the inactive phase, each group was administered a particular solution of $^{237/239}Pu(IV)$ by gavage. The solution media were (1) 0.01 M $NaHCO_3$ (pH 8.3), (2) 0.01 M HNO_3 (pH 2.0), and (3) 0.17 M citrate buffer (pH 4.5). Mice were sacrificed on day 7, and the amount of ^{237}Pu in the liver and in the skinned, eviscerated carcass of each animal was determined.

Results:

Table 8 Retention of plutonium in adult mice after GI Absorption: Effect of administration medium

Medium	Pu Oxidation State (%)				Fraction Retained ($\times 10^4$)[a]	
	IV	VI	% UF	n	Total	Liver
0.01 M Sodium Bicarbonate	100	0	70	21	20 ± 2	2.8 ± 0.5
0.01 M Nitric Acid	100	0	53	12	17 ± 3	4.2 ± 0.9
0.17 M Citrate Buffer	100	0	84	8	24 ± 5	5 ± 1

[a]Values presented are means ± the standard deviation of the mean for the number of animals shown, n. Total fraction retained is sum of plutonium in skinned, eviscerated carcass and liver. Fraction absorbed is approximately 10% greater than fraction retained (Section 2.6).

Conclusions: The retention of plutonium after GI absorption in the fasted mouse was not significantly affected by the nature of the medium in which the plutonium was administered.

3.7 Effect of Plutonium Hydrolysis

3.7.1 Experiment 1: Effect of Storage on Properties of a Plutonium Solution

Objective: To determine whether solutions of Pu(IV) that are low in both plutonium and nitric acid concentrations (1×10^{-6} M and 1×10^{-2} M, respectively) are stable with respect to polymerization of plutonium over a period of several hundred days. Results were expected to provide an explanation for the low fractional GI absorption value for plutonium (2×10^{-5} to 3×10^{-5}) obtained by Katz et al. (8) and Weeks et al. (10). Our values for fed animals are higher than theirs by a factor of 10; for fasted animals, our values are higher by a factor of 100. Because their administrations were for periods of up to 300 days, we postulated that the plutonium in their solutions (0.01 M HNO_3) had polymerized with time.

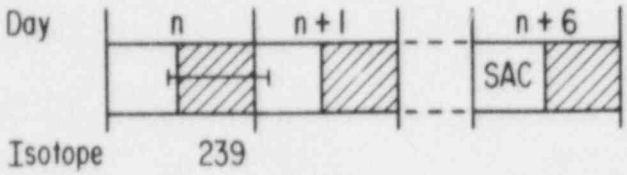
Experiment Conditions:

Solution: $^{239}Pu(IV)$ (1×10^{-6} M) in 0.01 M HNO_3, pH 2.0

Animals: $B6CF_1$/Anl male mice (86-116 days old at administration)

Administrations: 3 mL plutonium solution administered to fed mice via drinking water tube during the active phase

Experiment Diagram: Effect of Solution Storage



Experiment Protocol: A 1×10^{-6} M solution of $^{239}Pu(IV)$ in 0.01 M HNO_3 was prepared on day 0 as described in Section 2.1.2 and was administered to groups of fed adult male mice (5 mice/group) on days 0, 1, 3, 9, 30, and 217. The higher plutonium concentration used in this study, 1×10^{-6} M, was required to detect the low specific activity isotope, ^{239}Pu, in the animal; ^{239}Pu was the isotope used by Weeks et al. in their chronic administration study (10). Our plutonium solution was stored at room temperature for the duration of the experiment in a stoppered Pyrex glass bottle. Three-mL aliquots of the solution were administered to mice via drinking water tube from 1700 on day n until 0900 on day n+1. The plutonium concentration, oxidation state, and percent ultrafilterability of the solution were determined at each time of administration. Mice were sacrificed 6 days after administration of plutonium, and the amount of ^{239}Pu in the liver and the skinned, eviscerated carcass of each animal was determined by alpha spectrometric-isotope dilution. (See Appendix A for further details.)

Results:

Table 9 Effect of storage time on properties of a plutonium solution[a]

Age of Pu Solution (days)	Pu Concentration (% of 0-Time)	Pu Oxidation State (%) IV	VI	% UF
0	100	97	3	55
1	95	--	--	57
3	98	95	5	39
9	97	92	8	72
30	94	85	15	68
217	97	52	48	87

[a]A 1×10^{-6} M solution of Pu(IV) in 0.01 M HNO_3 was stored in a Pyrex bottle at room temperature.

Table 10 Retention of plutonium in adult mice after GI absorption: effect of solution storage time

Age of Solution (days)	n	Fraction Retained ($\times 10^4$)[a] Total	Liver
0	5	0.46 ± 0.06	0.16 ± 0.04
1	5	1.12 ± 0.13	0.36 ± 0.02
3	5	1.12 ± 0.10	0.32 ± 0.01
9	5	1.09 ± 0.14	0.31 ± 0.01
30	5	0.98 ± 0.05	0.32 ± 0.02
217	8	1.33 ± 0.09	0.46 ± 0.05

[a]Values presented are means ± the standard deviation of the mean for the numbers of animals shown, n. Total fraction retained is sum of plutonium in skinned, eviscerated carcass and liver. Fraction absorbed is approximately 10% greater than fraction retained (Section 2.6).

Conclusions: The 1×10^{-6} M solution of Pu(IV) in 0.01 M HNO_3 did not polymerize with time or adsorb to the Pyrex holding vessel on standing for 217 days (Table 3-8). The Pu(IV) did slowly oxidize with time; after 217 days, half of the Pu(IV) had oxidized to Pu(VI). As might be expected, the GI absorption and subsequent retention of plutonium in the fed mouse did not change with aging of the 0.01 M HNO_3 solution of plutonium (Table 3-9).

The GI absorption value obtained for this 1×10^{-6} M solution of Pu(IV) in 0.01 M HNO_3, approximately 1×10^{-4}, corresponds closely to the value of 1.4×10^{-4} obtained in the fed mouse for the GI absorption of a 1×10^{-10} M solution of Pu(VI) in 0.01 M $NaHCO_3$ (Table 3-3). In agreement with our other results, the GI absorption of plutonium was independent of plutonium concentration, oxidation state, and administration medium. Note that this experiment was conducted in the fed mouse, while the other experiments, studying effects of these parameters, were conducted in the fasted mouse.

3.7.2 Experiment 2: Effect of Plutonium Hydrolysis (Polymerization) on GI Absorption

Objective: To determine the GI absorption of polymeric plutonium in the mouse, with the degree of polymerization defined by the ultrafilterability (% UF) of the plutonium in solution. This experiment was not designed as a whole; results from several otherwise unrelated experiments were brought together and compared.

Experiment Conditions:

Solutions:

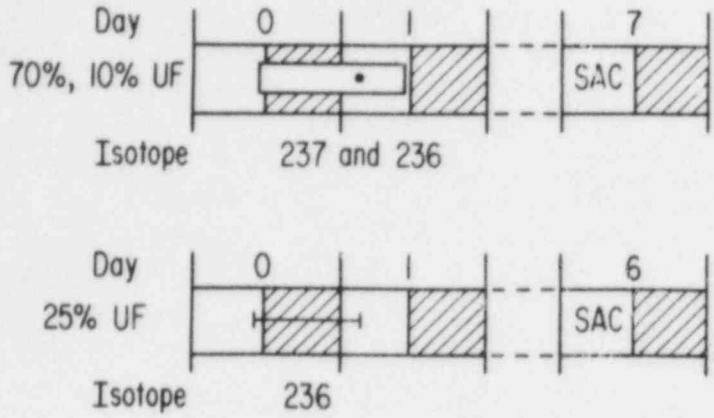
- ^{236}Pu(IV) (2×10^{-10} M) in 0.01 M $NaHCO_3$, 0.01 M NaI, pH 8.3 (10 and 25% UF)
- $^{237/239}Pu$(IV) (6×10^{-10} M) in 0.01 M $NaHCO_3$, 0.01 M NaI, pH 8.3 (70% UF)

Animals: $B6CF_1$/Anl male and female mice (80-90 days old at administration)

Administrations:

- 0.2 mL plutonium solution administered to fasted mice by gavage during the inactive phase
- 3 mL plutonium solution administered to fed mice via drinking water tube during the active phase

Experiment Diagram: Effect of Plutonium Hydrolysis



Experiment Protocol: Values for the ultrafilterability of solutions of tetravalent plutonium varied considerably, despite the fact that the same method was used to prepare them and the final plutonium concentration was only 1×10^{-10} M. To establish the relationship, if any, between ultrafilterability and GI absorption for Pu(IV) in solution, data were compared from experiments where solutions of Pu(IV) had low (10%, 25%) and high (70%) ultrafiltration values. In these experiments, 1×10^{-10} M solutions of Pu(IV) in 0.01 M $NaHCO_3$ were administered on day 0 either to fasted mice by gavage during the inactive phase (for the 70 and 10% UF solutions) or to fed mice via drinking water tube during the active phase (for the 25% UF solution). Mice were sacrificed on day 6 or 7, and the amounts of plutonium in the livers and skinned, eviscerated carcasses were determined (see Appendix A, Table A-3, for details of 25% UF group).

Results:

Table 11 Retention of plutonium in adult mice after GI absorption: Effect of plutonium hydrolysis (polymerization)

% UF	Pu Oxidation State (%) IV	VI	Administration Conditions	n	Fraction Retained ($\times 10^4$)[a] Total	Liver
70%	100	0	fasted, inactive phase	21	20 ± 2	2.8 ± 0.5
10%	97	3	fasted, inactive phase	3	3.1 ± 0.7	0.92 ± 0.28
25%	99	1	fed, active phase	8	0.31 ± 0.02	0.098 ± 0.008

[a]Values presented are means ± the standard deviation of the mean for the numbers of animals shown, n. Total fraction retained is sum of plutonium in skinned, eviscerated carcass and liver. Fraction absorbed is approximately 10% greater than fraction retained (Section 2.6).

Conclusions: A decrease from 70% UF to 10% UF for Pu(IV) solutions resulted in a decrease in GI absorption from 2×10^{-3} to 3×10^{-4} in the fasted mouse. An additional 10-fold decrease in GI absorption was observed when fed mice were administered a solution of Pu(IV) of low ultrafilterability. (This latter decrease is consistent with the decrease in the fed vs. fasted mouse observed in our feeding regimen study, Table 3-3.) The GI absorption of the 25% UF solution administered to the fed mouse, 3.1×10^{-5}, was the same as the GI absorption reported by Katz et al. (8) and Weeks et al. (10) for Pu(IV) in the fed rat (2.5×10^{-5}). These results lend support to the postulate that the plutonium in the solutions used by Katz et al. and Weeks et al. was polymerized at the time of administration.

4. DISCUSSION

In our investigation of the gastrointestinal absorption and retention of plutonium, experiments were designed to meet two general objectives. The first was to provide data for establishment of an f_1 value for plutonium in humans under conditions that simulate as closely as possible the uptake of plutonium from drinking water. The second was to resolve large differences between our results and those of earlier investigators. Experiments performed in this study are categorized according to these two objectives as follows:

Objective 1: Establishment of an f_1 value for humans:

(a) Pu(VI) in dilute $NaHCO_3$ administered to fasted mice (Section 3.1)

(b) Pu(VI) in dilute $NaHCO_3$ administered to fasted rats and dogs (Section 3.2)

(c) Pu(VI) administered to fed and fasted mice (Section 3.3)

(d) Pu(VI) in dilute $NaHCO_3$ at various plutonium concentrations administered to mice (Section 3.4)

(e) Pu(VI) administered to rats of various ages (Section 3.5)

(f) Pu(IV) in dilute $NaHCO_3$ administered to fasted mice (Section 3.1)

In studies (a) through (e), the GI absorption of Pu(VI), the form of plutonium in chlorinated drinking water, was determined under various conditions relevant to the setting of human drinking water standards. In study (f), the GI absorption of Pu(IV), a form of plutonium present in unchlorinated drinking water, was determined.

Objective 2: Resolution of differences between our results and those of earlier investigators:

(a) Pu(IV) in citrate solution administered to mice (Section 3.6)

(b) Pu(IV) in 0.01 M HNO_3 administered to mice (Section 3.6)

(c) Pu(IV) in 0.01 M HNO_3 administered to mice after prolonged solution storage (Section 3.7)

(d) Hydrolyzed Pu(IV) solutions administered to mice (Section 3.7)

In studies (a) and (b), effects of administration medium on GI absorption of plutonium were investigated; effects of administration medium had been reported by Weeks et al. (10). In studies (c) and (d), effects of hydrolysis (polymerization) of plutonium on its GI absorption were determined; these studies are relevant to explaining early data of Katz et al. (Ka55) and Weeks et al. (10).

We have discussed results relating to Objective 2 first in order to establish the validity of our results with respect to earlier studies. In the same section, we have also compared our data with resuits recently reported by investigators from other laboratories, in order to put our findings into current perspective.

4.1 Resolution of Differences between Our Results and Those of Earlier Investigators

Results of several earlier studies, of our studies, and of several recent studies reported by others are given in Table 4-1 for comparison. In the earlier studies, when the administration medium was 0.01 M HNO_3 and the form administered was Pu(IV), the fraction of plutonium retained by the fed rat was 3×10^{-5} (Table 4-1, a). The GI absorption of Pu(IV) in these earlier studies appeared to be highly dependent upon administration medium, with higher fractions of plutonium retained when solutions were more acidic [2.8×10^{-3} for Pu(IV) in 0.1 M HNO_3 (Table 4-1, b)], or when they contained citrate [4.1×10^{-3} for Pu(IV) citrate (Table 4-1, c)]. The fraction of plutonium retained after administration of hexavalent plutonium was also very high [1.87×10^{-2} (Table 4-1, d)].

Table 12 Retention of plutonium in the mouse and rat after gastrointestinal absorption

Oxidation State	Species (number of animals)	Administration Medium			Feeding regimen	Fraction retained ($\times 10^4$)	Reference
		Medium	Molarity	pH			
Early Data:							
a. IV	rat (160)	HNO_3	0.01	2.0	Fed	0.3	8
b. IV	rat (6)	HNO_3	0.10	1.0	Fasted (?)	28	10
c. IV	rat (6)	citrate	0.02	2.0	Fasted (?)	41	10
d. VI	rat (6)	HNO_3	0.01	2.0	Fasted (?)	187	10
Recent Data:							
e. VI	mouse (20)	$NaHCO_3$	0.01	8.3	Fasted	15	2
f. IV	mouse (21)	$NaHCO_3$	0.01	8.3	Fasted	20	2
g. IV	mouse (12)	HNO_3	0.01	2.0	Fasted	17	2
h. IV	mouse (8)	citrate	0.17	4.5	Fasted	24	2
i. VI	rat (12)	$NaHCO_3$	0.01	8.3	Fasted	32	2
j. VI	rat (8)	HNO_3	0.01	2.0	Fasted	45	1
k. VI	mouse (12)	$NaHCO_3$	0.01	8.3	Fed	1.4	3,21
l. VI	rat (8)	HNO_3	0.01	2.0	Fed	2.4	1
m. IV	rat (6)	HNO_3	0.10	1.0	Fed	1.0-2.0	5
n. IV	rat (5-14)	HNO_3	0.01	2.0	Fed	1.3-4.8	1,22

One must ask why the results of the early investigations differ so strikingly from ours. In our experiments, the fraction of plutonium retained after oral administration of either Pu(IV) or Pu(VI) to the fasted mouse was approximately 2×10^{-3}, independent of oxidation state (Table 4-1, e and f). The fraction retained was also independent of medium: the values for Pu(IV) administered in 0.17 M citrate buffer, in 0.01 M $NaHCO_3$, or in 0.01 M HNO_3 were the same (Table 4-1, f, g, h). In the earlier studies, citrate complexation enhanced the GI absorption of Pu(IV) (Table 4-1, a vs. c).

Two factors seem to contribute to the 100-fold difference between our GI absorption value for Pu(IV) (2×10^{-3}) and that of Katz et al. (3×10^{-5}). The first factor is feeding regimen. We have found that absorption in the fasted mouse is 10-fold higher than in the fed mouse. Katz et al. administered Pu(IV) in 0.01 M HNO_3 solution to adult rats daily for a period of 9 1/2 months (285 days). Had the plutonium been administered on a given day to fasted rats, the resulting GI absorption value would have been 10-fold higher, or 3×10^{-4}. However, this projected value for the fasted rat is still lower by a factor of 10 than the GI absorption value we measured in the fasted rat (3×10^{-3}, Table 3-2), indicating that the effect of fasting on GI absorption accounts for only a part of the difference between Katz's value and ours.

The second factor that contributes to the difference in values is the tendency of solutions of Pu(IV) to hydrolyze/polymerize. Our experience shows that during preparation of solutions of Pu(IV), even when the final concentration is as low as 1×10^{-10} M, polymerization cannot always be predicted or prevented. The data presented in Table 3-10 show that polymerized Pu(IV) is not as readily absorbed as is monomeric Pu(IV). The solutions of Pu(IV) used in the studies of Katz et al. and Weeks et al. may have been polymerized, explaining the remainder of the 100-fold difference between their values and ours. Originally we thought that their plutonium in 0.01 M HNO_3 solution might have been polymerizing with time during the 285 days of the experiment, but we demonstrated that this probably did not occur. Our solutions of Pu(IV) in 0.01 M HNO_3 were stable to polymerization over a period of 210 days (Tables 3-8 and 3-9). More likely, the plutonium in their original stock solution, the one they diluted to obtain the administered solutions, was polymerized to an extent similar to that in several of our studies. In fact, our value for the fraction of plutonium retained after administration of Pu(IV) in 0.01 M $NaHCO_3$, 3×10^{-3} (Table 3-2), is very close to the high values reported by Weeks et al. for administration of Pu(IV) in 0.1 M (rather than 0.01 M) acid solution, 3×10^{-3}, and in citrate solution, 4×10^{-3} (Table 4-1). Therefore, our results are in agreement with those of Weeks et al. in those cases where polymerization of plutonium in their solutions was least likely. The lack of predictability of polymer formation during preparation of solutions of Pu(IV) makes crucial the analysis of solutions of Pu(IV) for polymers (e.g., by a UF determination) prior to their use in GI absorption studies.

Differences between our data on the GI absorption of Pu(VI) and those of Weeks et al. also require explanation. The latter investigators obtained a value of 2×10^{-2} for the GI absorption of Pu(VI) in the rat (feeding regimen unspecified), while our value for Pu(VI) in the fasted rat is 10-fold lower (3×10^{-3}). As was mentioned in the introduction, information obtained about the early Pu(VI) experiments of Weeks et al. indicates that their rats were probably fasted, and that their Pu(VI) solutions may have contained significant amounts of dichromate. We suggest that their Pu(VI) value was about 10-fold higher than ours because the dichromate acted as a holding oxidant (preventing the reduction of Pu(VI) to Pu(IV) in the GI tract), and that the absorption of Pu(VI) is indeed higher by a factor of 10 than that of Pu(IV). This explanation for the high GI absorption values for Pu(VI) in the studies of Weeks et al. is supported by recent work of Sullivan et al. (1), who recently showed that when Pu(VI) in the presence of 0.15 M dichromate is administered to fasted rats, a GI absorption value of 0.8×10^{-2} is obtained.

In our studies, Pu(VI) and Pu(IV) were absorbed to the same extent, probably because Pu(VI) is rapidly reduced to Pu(IV) in the GI tract. Recent data of Sullivan et al. (1) in the rat and Stather et al. (23) in the hamster support this view by demonstrating that GI absorption values for Pu(IV) and Pu(VI) are the same.

4.2 General Discussion of Results

Given that a plausible explanation exists for the differences between our GI absorption values for plutonium and those of Katz et al. and Weeks et al., we can focus on the relevance of our values to environmental exposures of humans to soluble forms of plutonium. Studies of plutonium in natural water systems show that the plutonium in these systems is monatomic, that the oxidation states are Pu(IV) and Pu(V), with the Pu(IV) fraction increasing with increasing concentrations of dissolved organic carbon (humic acids) (24,25), and that the molar solubility of plutonium in natural waters is higher by orders of magnitude than the molar concentration of ^{239}Pu at the present MPC for plutonium in drinking water (26). (A 1×10^{-10} M plutonium solution is 5 pCi/mL.) Because Pu(IV) and Pu(V) are oxidized to Pu(VI) when drinking water is chlorinated (7), Pu(VI) must be administered if GI absorption studies are to be relevant to potential human exposures caused by releases into the environment and the subsequent consumption of contaminated drinking water by humans. Therefore, we have studied the absorption of Pu(VI) rather than Pu(IV).

The fact that the oxidation state of administered plutonium [Pu(IV) vs. Pu(VI)] has little effect on its GI absorption has already been discussed (Section 4.1).

With regard to effects of animal species, we have observed some differences between values for the retention of plutonium after GI absorption in the rat, mouse, and dog (Table 3-2). Stather et al. (23) have obtained GI absorption values for plutonium in the hamster that are 5- to 10-fold lower than our values for the mouse and rat. Recently, J. D. Harrison, a colleague of Stather, reported GI absorption values for plutonium in rats that are similar to our values (5), confirming a significant difference between rat/mouse and hamster.

A number of investigators have reported effects of fasting on the GI absorption of plutonium. Both their data and ours indicate that the GI absorption of plutonium is 10 to 15 times greater in the fasted than in the fed mouse (Table 3-3), rat (1), and hamster (23). Values recently reported for the GI absorption of lead (^{203}Pb) in the fed and fasted human show similar large differences between the fed and 24-h-fasted states (27). The relevance of a fasted GI absorption factor to the recommendation of an f_1 factor for plutonium in humans is considered below.

Our studies on effects of plutonium concentration show that the GI absorption value for Pu(VI) in the fed mouse, 1×10^{-4} to 2×10^{-4}, is independent of plutonium concentration from 10^{-12} M to 10^{-6} M (Tables 3-5 and 3-9). This range includes the concentration of ^{239}Pu at the present MPC for plutonium (1×10^{-10} M) and the concentration of ^{239}Pu if the value of f_1 were higher by a factor of 100 and the MPC correspondingly lower (1×10^{-12} M). These data imply that if a new MPC for plutonium in drinking water were recommended based on an increased value of f_1 for plutonium, additional measurements of absorption at these concentrations would not be necessary.

The effect of animal age on the GI absorption of plutonium is dramatic. In fed rats that are 1 to 2 days old, retention is 70 times that in the fed adult; just prior to weaning, retention is 30 times that in the fed adult (Table 3-6). However, retention in the fed rat just prior to weaning is the same as that in the fasted adult (3×10^{-3}), while retention one week after weaning is the same as that in the fed adult (1×10^{-4}). These data suggest that much of the 30-fold decrease in GI absorption of plutonium that occurs on weaning is due to adsorption of plutonium onto a component of rodent chow and not to a dramatic change in gut physiology. Increases similar to those we report here for GI absorption in the neonatal rat have been previously reported for plutonium and other actinide elements (28, 29), as well as for lead (30), cadmium (31), and iron (30).

In summary, we have demonstrated that the GI absorption of plutonium is independent of the oxidation state of plutonium, the administration medium (citrate vs. bicarbonate vs. nitric acid), and the plutonium concentration in the range 10^{-12} M to 10^{-6} M. We have also shown that the GI absorption of polymeric Pu(IV) is much lower than that of monomeric Pu(IV). The retention of plutonium after GI absorption varies with species in the following order: rat $\geq$ mouse > dog > hamster, with the fraction retained by the fasted rat being 3×10^{-3} and that retained by the fasted hamster being 1×10^{-4}. Finally, the GI absorption of plutonium by animals is highly dependent upon their feeding regimen and age, being strikingly higher in the fasted animal and in the preweaned neonatal animal.

5. VALUES OF f_1 FOR PLUTONIUM IN HUMANS

5.1 Introduction

In this section we have responded to a request by the NRC to use our data on the GI absorption of plutonium in animals to recommend values for f_1, the fraction of plutonium transferred from gut to blood in humans. Our GI absorption values in the fasted adult mouse and the fed neonatal rat are higher by factors of 10 to 35 than those in the fed adult mouse, and higher by factors of 20 to 70 than the current value of

f_1 recommended by the ICRP for soluble forms of plutonium, 1×10^{-4} (13). Because the effects of fasting and age are large, we evaluated their importance for setting limits of exposure to plutonium prior to suggesting values of f_1. We present here the results of our evaluation.

In Section 5.2 we have considered the occupational setting. The value of f_1 for plutonium currently recommended by the ICRP applies to this setting. In Section 5.3 we have considered values of f_1 for the environmental setting. Our studies are primarily directed toward the establishment of an MPC for plutonium in drinking water rather than toward a limit for exposure to plutonium in food. The MPC in turn affects limits for plutonium concentrations in liquids released into natural water systems from both nuclear reactor facilities and nuclear waste disposal sites.

All of our proposed values of f_1 are based on our rodent data. Extrapolation of rodent data to humans is discussed in Section 5.4, as are the uncertainties in our proposed values of f_1 and suggestions for further research.

5.2 Suggested Values of f_1: Occupational Exposure to Soluble Forms of Plutonium

Exposures to plutonium in the workplace occur mainly as a result of accidents, making the exposures punctate rather than continuous, as in the environmental setting. In establishing values of f_1 for oral exposure to plutonium in the occupational setting, we suggest that separate consideration be given to two groups of individuals: (a) workers who eat a normal breakfast and (b) workers who skip breakfast and are exposed to plutonium prior to eating the first meal of the day. The latter individuals would absorb plutonium at the fasted level, i.e., at a rate 10-fold greater than the average worker (Appendix B).

For the fed worker, a value of f_1 of 2×10^{-4}, our value for the fed adult mouse, is applicable. This value is comparable to the f_1 value currently recommended by the ICRP for soluble forms of plutonium in the occupational setting, 1×10^{-4} (13). Our value is slightly lower than the value recommended by the National Radiological Protection Board (NRPB) in England, 5×10^{-4} (32).

For the fasted worker exposed to plutonium prior to his first meal of the day, we suggest a value of f_1 of 20×10^{-4}, our GI absorption value for the fasted animal. 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 the soluble forms of plutonium that is 10-fold lower than that for the insoluble forms.

In suggesting values of f_1 for the occupational setting, we note that exposure via inhalation is the main route encountered in the workplace, while exposure via ingestion predominates in the environmental setting. A value of f_1 for oral exposure to soluble forms of plutonium therefore has only minimal relevance to exposures in the occupational setting. The value of f_1 is much more relevant to considerations of environmental exposure.

5.3 Suggested Values of f_1: Environmental Exposure to Plutonium in Drinking Water

5.3.1. Presentation of Alternatives

We consider here two approaches to establishing values of f_1 for plutonium in drinking water. In both approaches we deal with the effects of animal age and fasting on the GI absorption of plutonium, because exposure to plutonium in drinking water affects persons of all ages and of various dietary habits. The derived values of f_1 with these two approaches differ by a factor of 10. The details of our approaches are presented in Appendices C and D. Results are summarized here.

With Approach #1, a particular concentration of ^{239}Pu in drinking water was assumed (1 Bq/L), and the amounts of ^{239}Pu and the doses[a] accumulated with age due to the consumption of drinking water from birth to 70 years were calculated with age-dependent values of f_1, of fluid consumption, and of body weight (Appendix C, Section 1).

Calculations were performed for two groups. Individuals in the first group were breakfast eaters in their adult years; water consumption when they were in the fasted state was negligible. The calculated amount of plutonium accumulated from drinking water in the bodies of these fed individuals by 1 year of age was 1.3 Bq and by 70 years of age was 9.1 Bq (Appendix D, Table D-2). The cumulative dose at one year was 0.09 Bq·y/kg and at 70 years was 5.5 Bq·y/kg. (1 Bq·y/kg = 2.6×10^{-5} Gy or 5.2×10^{-4} Sv for ^{239}Pu.)

Individuals in the second group were not breakfast eaters in their adult years, and water consumption in the fasted state (prior to their first meal of the day) was one-third of their daily intake. The amount of plutonium accumulated from drinking water in the bodies of these fasted individuals by one year of age was 1.3 Bq and by 70 years of age was 27.7 Bq (Appendix D, Table D-3). The cumulative dose at one year was 0.09 Bq·y/kg and at 70 years was 12.1 Bq·y/kg.

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[a]The term "dose" in this document refers to absorbed dose to the whole body delivered by internally deposited plutonium.

As a final step in Approach #1, we derived a single, age-independent value of f_1 for each of the above groups such that, when we calculated lifetime dose with this single value of f_1, we obtained the same dose as the lifetime dose obtained with the multiple, age-dependent values of f_1. This single value of f_1 could then be used, along with a single age-weighted average value of fluid consumption, to calculate an MPC, taking into account effects of age and fasting on the GI absorption of plutonium.

The single, age-independent value of f_1 derived for the group of fed individuals (breakfast eaters) was 2.6×10^{-4} (Figure C-2). The value for the group of fasted individuals (not breakfast eaters) was 5.6×10^{-4} (Figure C-5). The latter value of f_1 is only 3-fold greater than the experimental GI absorption value of the fed adult, 2×10^{-4}, indicating in an indirect way that neither high values of GI absorption in the very young nor high values of GI absorption applied to periods of fasting in adults had a dramatic effect on the cumulative 70-year dose from deposited plutonium.

Based on these results with Approach #1, we suggest a value of f_1 of 3×10^{-4} (rounded from 2.6×10^{-4}) for calculation of an MPC if the protected population is defined as fed individuals of all ages. We suggest a value of 6×10^{-4} (rounded from 5.6×10^{-4}) if the protected population is individuals of all ages who are fasted in their adult years (i.e., skip breakfast).

With Approach #2 (Appendix C, Section 2), we calculated the dose commitment over a 70-year lifetime from each year's uptake of plutonium from drinking water containing ^{239}Pu at 1 Bq/L. We identified the single year of human life during which uptake of plutonium resulted in the greatest commitment of lifetime dose. This approach is based on the current approach of the ICRP in deriving Annual Limits on Intake (ALIs) for radionuclides in the occupational setting. The ICRP limits intake of radionuclides in the workplace such that the 50-year commitment of dose from any one year's intake does not exceed a given value (0.05 Sv for consideration of stochastic effects and 0.5 Sv for nonstochastic effects, Reference 13).

From our analysis, the first year of human life is the year during which uptake of plutonium from drinking water results in the greatest commitment of lifetime dose. Of the lifetime dose, 14.4% is committed by uptake during the first year of life, while only 2.9% is committed by uptake during the next highest year (Figure C-7). Three factors that apply to the first year of human life contribute to this result: (a) high GI absorption values, (b) low body weight, and (c) long residence times for plutonium in the body after uptake early in life.

By applying our GI absorption values for rodents to humans, we obtained a single value of f_1 for the first year of human life of 4×10^{-3} (0.4%)

(Appendix C, Section 2). If lifetime dose commitment is to be limited on an annual basis, the approach now being followed by the ICRP in the occupational setting, this value of f_1 must be considered in establishing limits for intake of plutonium in the environmental setting.

5.3.2. Discussion: Suggested Values of f_1 and Corresponding MPCs

In this section, we follow Approaches #1 and #2 to derive values of the MPC for plutonium in drinking water. We also discuss various issues related to these approaches. However, resolution of these issues is beyond the scope of this document. Our thoughts are presented to stimulate members of national and international committees who make final recommendations for values of f_1 based on our data and those of others.

With Approach #1, we consider setting limits for exposure to plutonium in drinking water by evaluating a 70-year lifetime accumulation of dose; it is presented as a contrast to Approach #2. The current MPC for soluble forms of plutonium in drinking water, 5 pCi/mL, is based on a value of f_1 of 3×10^{-5}, the experimental GI absorption value of Pu(IV) in fed adult animals obtained in early investigations (6,9). If this MPC were recalculated for the GI absorption value for fed adults reported in this document, 2×10^{-4}, the new MPC would be 7-fold lower, 0.8 pCi/mL. Following Approach #1, an MPC that protects fed individuals of all ages ($f_1 = 3 \times 10^{-4}$) would be 0.5 pCi/mL, and one that also protects fasted individuals ($f_1 = 6 \times 10^{-4}$) would be 0.3 pCi/mL.

The problem with focusing on lifetime accumulation of dose is that lifetime commitment of dose during the first year of human life is expected to be greater than that in any subsequent year, based on application of GI absorption values for the neonatal rat (Figure C-7). The ICRP currently limits dose commitment in the occupational setting on an annual basis. This criterion is not met by Approach #1, and therefore Approach #2 must also be considered.

On the basis of Approach #2, we propose a value of f_1 of 4×10^{-3} (0.4%) for use in calculating an MPC for plutonium in drinking water. This approach limits exposure by applying an ALI to the first year of human life. The MPC with this approach is 0.02 pCi/mL, approximately 30-fold lower than the MPC for fed adults (0.8 pCi/mL) and 10-fold lower than the MPC based on Approach #1 that considers both young and fasted persons (0.3 pCi/mL). The MPC based on Approach #2 is low because the lifetime dose commitment from exposure to plutonium in drinking water during the first year of life is high (1.7 Bq·y/kg, Table D-6); this commitment is 30-fold higher than the dose commitment from exposure during the twentieth year of life (0.06 Bq·y/kg, Table D-6).

Problems also exist with Approach #2, which applies the ALI concept to the environmental setting. In the occupational setting, all potentially exposed individuals are adults. Therefore, a single GI absorption value applies to each year of employment, and a single ALI can be set to restrict the dose commitment equally for each year during the working life of the individual. In the environmental setting, the first year of high GI absorption of plutonium and low body weight is without exception followed by many years of much lower GI absorption and higher body weight. The result is that the calculated lifetime commitment of dose from plutonium uptake during the first year of life is much greater than the lifetime commitment of dose from uptake during the adult years at a given concentration of plutonium in drinking water (Figure C-7 and Table D-6). A limit for the ingestion of plutonium that restricts the lifetime commitment of dose resulting from uptake during the first year of human life would restrict the dose commitment during later years to a much greater extent than is required.

In addition, however, if annual dose rather than annual commitment of dose is considered, the first year of human life is not singled out as a year of maximum risk. The calculated dose for the first year of life is 0.09 Bq• y/kg (Tables D-2 and D-3), while the dose during the seventieth year is either 0.13 Bq• y/kg for fed individuals (Table D-2) or 0.39 Bq• y/kg for fasted individuals (Table D-3). These results support the view that the GI absorption value for the first year of more rapid absorption of plutonium may not be appropriate to determining the limit of intake of plutonium for all subsequent years. As suggested by Approach #1, decreasing the MPC for plutonium in drinking water by a factor of three from that calculated for the fed adult individual may be sufficient to protect both young and fasted individuals.

5.4 Uncertainties in Suggested Values of f_1: Recommendations for Research

5.4.1 The Occupational Setting

We have suggested, in our analysis of the occupational setting (Section 5.2), that the GI absorption value for the fasted animal applies to persons orally exposed to soluble forms of plutonium prior to eating their first meal of the day, i.e., to persons who do not eat breakfast before coming to work. This conclusion is based on a feeding regimen study in mice (Appendix B). Because the GI absorption value for the fasted adult animal is 10-fold greater than that for the fed adult, the relevance of the fasted GI absorption value to setting limits for exposure to plutonium must be determined. The influence of a reasonable fasting schedule in a species more similar to humans than mice should be investigated. Experimental work is needed in an animal like the baboon, where transit times of foods through the GI tract are similar to those in humans. The time after the start of the active phase when the fasted

GI absorption value is reached should be determined for the baboon that eats no "breakfast."

The possibility also exists that if food or another substance were consumed shortly after plutonium ingestion, the GI absorption of plutonium might be decreased to the fed level, independent of the fasting state of the person at the time of plutonium ingestion. The GI absorption of lead in humans was decreased from 70% in fasted individuals to 2-4% in individuals who had consumed lead concurrently with either food or calcium phosphate solutions (27, 33). Experiments are needed to determine whether administration of food or a calcium phosphate solution shortly after ingestion of plutonium decreases the GI absorption of plutonium by the fasted animal. If proven effective, oral calcium phosphate could be administered in the occupational setting to limit the GI absorption of plutonium in cases of oral exposures to plutonium.

5.4.2 The Environmental Setting

One area of uncertainty particularly relevant to the environmental setting is the application of GI absorption values for the preweaned rodent to preweaned humans. The rodent-based GI absorption values that we have applied to the first year of human life, 7×10^{-3} (0.7%) and 3×10^{-3} (0.3%) (Table C-1), are considerably lower than GI absorption values reported for the young of several higher species: 6×10^{-2} (6%) for the 2-day-old dog (34); 2×10^{-1} to 3×10^{-1} (20 to 30%) for the 1-day-old miniature swine (29, 34). The GI absorption of plutonium in the 1- to 2-day-old animal, independent of species, is clearly greater than that in the adult.

At present very little information is available on GI absorption values for neonatal humans or the time course of change during the first year(s) of human life. Sullivan et al. have shown that by 21 days of age, the GI absorption value of plutonium in miniature swine has fallen to 3×10^{-3} (0.3%), a 100-fold decrease from the value at 1 day of age (34). This value at 3 weeks is similar to the value we obtained for the preweaned, neonatal rat and is still 10- to 20-fold greater than that for the adult rat or swine. These data of Sullivan et al. imply that GI absorption values in neonatal swine, as in rats, remain considerably greater than in adults throughout the period prior to weaning. However, their study did not include animals up to the time of weaning, typically at 6 weeks of age for miniature swine (35). To substantiate the theory that GI absorption values in neonatal humans during the first year(s) of life remain well above the adult values, we recommend investigations into the GI absorption of plutonium during the first year of life in a long-lived nonhuman primate, such as the baboon or chimpanzee. Such an investigation is required if a standard for exposure to plutonium in the environment is to be reliably set.

5.4.3 GI Absorption and Species Extrapolation

In recommending a value of f_1 for plutonium or any other element, a most important and difficult task is the extrapolation of laboratory animal data to humans. Values of f_1 proposed in this report are based solely on rodent data and do not include a factor for extrapolation of rodent data to humans. We note, however, that GI absorption values of plutonium, cadmium, and lead share several common features: (a) our values for these elements in adult mice are comparable to one another; (b) the values are greater in iron-deficient animals than in animals with normal iron levels (36-38); and (3) the values are greater in neonatal animals than in adults (4, 29-31). These commonalities suggest that extrapolation of rodent data to humans may also be comparable for these elements.

For cadmium and lead, GI absorption values determined directly in humans (3% to 10%, References 37, 39, 40) are approximately 10-fold greater than our values in mice (0.3% to 0.8%). The values of f_1 for plutonium that we have proposed in this report may therefore be low by an order of magnitude, although this assumption is clearly tenuous. GI absorption values for cadmium in the monkey (5-6%, Reference 41) and for lead in the baboon (10%[a]) are very close to those for humans (3-10%, References 37, 39, 40). The problem of extrapolation of data between species could therefore be circumvented by determining the GI absorption of plutonium in the baboon. We are currently making such determinations.

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APPENDIX A
ADSORPTION OF PLUTONIUM TO TEETH DURING ADMINISTRATION OF PLUTONIUM TO MICE VIA DRINKING WATER

During studies of the distribution of retained lead in mice, we found that most of the ^{210}Pb in the mouse was located in the head section of mice that had consumed ^{210}Pb in drinking water (1). In our actinide studies, we observed that plutonium was adsorbed onto mouth surfaces in mice that had consumed plutonium in drinking water (1). In this appendix we present a method for calculating GI absorption values from data obtained in experiments in which adsorption occurred, together with results of such calculations.

1. IDENTIFICATION OF TOOTH CONTAMINATION IN PLUTONIUM GI ABSORPTION STUDIES

Objective: To determine the extent of adsorption of plutonium to teeth and other exposed mouth surfaces when Pu(IV) and Pu(VI) bicarbonate solutions are administered to mice via a) gavage and b) drinking water.

Experiment Conditions:

Solutions:

- $^{236}Pu(VI)$ (1×10^{-10} M) in 0.01 M $NaHCO_3$, 1 ppm Cl_2, pH 8.3
- $^{236}Pu(IV)$ (1×10^{-10} M) in 0.01 M $NaHCO_3$, 0.01 M Na_2I, pH 8.3

Animals: $B6CF_1$/Anl male mice (80 days old at administration)

Administrations: 0.2 mL plutonium solution administered to fasted mice by gavage or by drinking water tube during the inactive phase

Experimental Protocol: Four groups of mice were fasted from 1700 on day 0 to 1700 on day 1. Mice were administered a 1×10^{-10} M solution of ^{236}Pu in 0.01 M bicarbonate via drinking water tube from 0900 to 1700 on day 1 or via gavage at 1000 on day 1 (during the inactive phase). The administration method and oxidation state for each group are shown in Table A-1.

All mice were sacrificed 6 days after plutonium administration. The following samples were analyzed for ^{236}Pu content: (a) headless eviscerated carcass, (b) teeth, (c) remaining mouth portions exposed to fluid during drinking process, (d) skull, (e) liver, and (f) lungs.

Table A-1. Experimental protocol for identification of plutonium adsorption to teeth

Group	Administration Method	Pu Oxidation State (%) IV	VI	% UF
1	gavage	1	99	90
2	drinking water	1	99	90
3	gavage	97	3	9.7
4	drinking water	97	3	9.7

Results:

See Table A-2.

Conclusions:

(a) Significant amounts of plutonium were adsorbed to teeth of mice following administration of either Pu(VI) or Pu(IV) in drinking water. Adsorption was much greater for Pu(VI) than for Pu(IV).

(b) The amounts of plutonium in the headless carcasses were the same for mice receiving plutonium either in drinking water or by gavage. Therefore a factor (the ratio of plutonium in total carcass to that in headless carcass) can be applied to the plutonium content of the headless carcass of a mouse receiving either treatment to calculate the plutonium content of its total carcass. The mean value of this factor is 1.24 for the two groups of mice in our study receiving plutonium by gavage (Table A-2). The method for use of such a ratio for calculating GI absorption values is presented in Appendix A, Section 2.

(c) The mean ratio of plutonium content in the headless carcass to that in liver for all groups of mice is 2.03 (Table A-2); the ratio is independent of plutonium oxidation state and administration method. The method for use of such a ratio for calculating GI absorption values is presented in Appendix A, Section 2.

Table A-2 Distribution of plutonium in the mouse after oral administration via gavage or drinking water[a]

Group	Fraction of Administered Plutonium Retained ($\times 10^4$)						
	Headless Carcass	Teeth	Remaining Mouth	Skull	Liver	$\frac{\text{Total}^b \text{ Carcass}}{\text{Headless Carcass}}$	$\frac{\text{Headless}^b \text{ Carcass}}{\text{Liver}}$
1. Pu(VI) gavage	9.4±0.7 (7)	0.32±0.16 (3)	0.79±0.04 (3)	1.3±0.2 (3)	4.6±0.3 (7)	1.27±0.06 (5)	2.05±0.06 (7)
2. Pu(VI) in drinking water	10.3±3.0 (8)	53±14 (3)	3.1±1.2 (3)	1.2±0.5 (3)	5.0±1.3 (8)	11.0±5.3 (3)	2.08±0.09 (8)
3. Pu(IV) gavage	1.9±0.4 (3)	0.05±0.01 (3)	0.14±0.03 (3)	0.23±0.05 (3)	0.90±0.28 (3)	1.21±0.06 (3)	2.24±0.41 (3)
4. Pu(IV) in drinking water	2.1±0.3 (6)	1.70±0.50 (3)	0.60±0.10 (3)	0.66±0.36 (3)	1.23±0.19 (6)	2.69±0.78 (3)	1.76±0.18 (6)

[a]Values presented are means ± standard deviation of the mean. Number of animals is shown in parentheses.

[b]Ratios were obtained for each individual mouse in a group prior to calculation of the mean ratio for each group.

2. METHOD FOR CALCULATION OF GI ABSORPTION VALUES FROM EXPERIMENTS WHERE PLUTONIUM WAS ADMINISTERED IN DRINKING WATER

Three experiments required reanalysis because plutonium was administered in drinking water with resulting tooth contamination and because unsectioned carcasses of a number of mice in each group had already been analyzed before adsorption of plutonium to teeth was identified. The three experiments requiring reanalysis were those to determine (a) the effect of feeding regimen (Section 3.3), (b) the effect of plutonium concentration (Section 3.4), and (c) the effect of plutonium hydrolysis (Section 3.7). The following is a description of the method by which accurate and reliable data were obtained from these three experiments by using the four or five remaining mice in each experimental group. (Fortunately, sample analysis was the rate-limiting step in these experiments, so that unanalyzed mice still existed for all but one group when adsorption to teeth was identified.)

2.1 Method

(a) The plutonium content of the livers (Pu_L) of all mice administered plutonium in drinking water was used as a reliable measure of plutonium absorbed from the GI tract.

(b) A ratio of the amount of plutonium in the eviscerated carcass minus head (Pu_{C-H}) to that in the liver (Pu_L) was determined for mice in those groups with four to five mice remaining to be analyzed.

(c) The ratio Pu_{C-H}/Pu_L was used to calculate the plutonium content of the headless, eviscerated carcass from the plutonium content of the liver for every mouse in each group.

(d) The plutonium content of the eviscerated carcass plus head (Pu_C) was calculated by using the ratio Pu_C/Pu_{C-H} obtained from mice administered plutonium by intravenous injection.

2.2 Summary of Steps in the Method

(a) Determine: Plutonium content of liver for all animals in a group = Pu_L.

(b) Determine from remaining unanalyzed mice: $\frac{Pu_{C-H}}{Pu_L}$, where Pu_{C-H} = plutonium content of the eviscerated carcass minus head.

(c) Determine from mice injected with plutonium intravenously: $\frac{Pu_C}{Pu_{C-H}}$, where Pu_C = plutonium content of whole, eviscerated carcass.

(d) Calculate total retained plutonium (Pu_T), by using the equation

$$Pu_T = Pu_L + Pu_C, \text{ where } Pu_C = Pu_L \times \frac{Pu_{C-H}}{Pu_L} \times \frac{Pu_C}{Pu_{C-H}}$$

from all mice

from remaining mice

from intravenously injected mice

3. CALCULATION OF GI ABSORPTION VALUES FOR MICE ORALLY ADMINISTERED PLUTONIUM IN DRINKING WATER OR BY GAVAGE

For those experiments that were partially analyzed when adsorption of plutonium to teeth was identified, the fraction of administered plutonium retained in the whole mouse was calculated by using the Pu_L values and the distribution ratios shown in Table A-3. The total fraction of plutonium retained in the whole mouse (Pu_T) was calculated by using the equation shown at the end of Appendix A, Section 2. The values of Pu_T shown in Table A-3 are the same as those given in the text in Tables 3-3, 3-4, 3-5, and 3-10.

In subsequent experiments where Pu(VI) was administered by gavage to mice, adsorption of Pu(VI) to mouth surfaces also occurred. One or two mice in a group of ten mice treated by gavage had a disproportionately high amount of plutonium in the head section compared to that in the carcass minus head (1). Therefore, we adopted the following standard procedure for determining the plutonium content of the eviscerated carcasses (Pu_C) of mice or rats orally administered plutonium either by gavage or in drinking water: (a) Pu_{C-H} was determined for all animals administered plutonium via the oral route; (b) Pu_C/Pu_{C-H} was determined for additional mice administered plutonium via intravenous injection. [Pu_C/Pu_{C-H} is the same for mice administered plutonium either orally or intravenously (1)]; (c) Pu_C for mice receiving oral plutonium was then determined by multiplying Pu_{C-H} for orally treated mice by the ratio Pu_C/Pu_{C-H} for intravenously injected mice. This procedure is similar to that presently used by Stather, et al. (2). It eliminates the effect of contamination of mouth surfaces during oral administration, which is especially important when GI absorption values are low, as in the case of plutonium.

Table A-3 Plutonium distribution ratios and their use in calculation of GI absorption values for mice administered plutonium in drinking water

Section	Experiment	Group	Fraction Retained ($\times 10^4$) and Plutonium Distribution Ratios[a]				
			Pu_L (all mice)	Pu_{C-H}/Pu_L (remaining mice)	Pu_C/Pu_{C-H} (intravenously injected mice)	Pu_C (calculated)	Pu_T ($Pu_C + Pu_L$)
3.3	Food Deprivation	Fasted	6.3±1.0 (12)	1.65±0.03 (4)	1.22±0.01 (3)	12.8±2.0 (12)	19.1±2.2 (12)
3.3	Food Deprivation	Fed	0.42±0.04 (12)	2.0±0.3 (4)[b]	1.23±0.01 (3)	1.01±0.17 (12)	1.43±0.17 (12)
3.3	Time of Day	Active Phase	6.3±1.0 (12)	1.65±0.03 (4)	1.22±0.01 (3)	12.8±2.0 (12)	19.1±2.2 (12)
3.7	Plutonium Hydrolysis	25% UF	0.098±0.008 (8)	(1.76±0.05)[c]	(1.20±0.01)[c]	0.21±0.02 (8)	0.31±0.02 (8)
3.4	Plutonium Conc.	1×10^{-12} M Pu	0.40±0.07 (10)	2.50±0.22 (5)[d]	1.22±0.01 (3)	1.2±0.2 (10)	1.6±0.2 (10)
3.4	Plutonium Conc.	1×10^{-10} M Pu	0.59±0.07 (10)	2.50±0.22 (5)[d]	1.22±0.01 (3)	1.8±0.3 (10)	2.4±0.3 (10)
3.4	Plutonium Conc.	1×10^{-8} M Pu	0.58±0.05 (10)	2.50±0.22 (5)[d]	1.22±0.01 (3)	1.8±0.2 (10)	2.4±0.2 (10)

[a] Values presented are means ± standard deviation of the mean. The number of mice is shown in parentheses. Pu_L, Pu_C and Pu_T indicate plutonium contents of liver, carcass, and whole mouse, respectively, expressed as fraction of the oral dose retained 6 days after plutonium administration ($\times 10^4$). The first plutonium distribution ratio, Pu_{C-H}/Pu_L, was calculated from mice administered plutonium in drinking water that were not yet analyzed when adsorption to teeth was identified. The second ratio, Pu_C/Pu_{C-H}, was obtained from additional mice that were administered plutonium via intravenous injection. Pu_C was calculated from the equation, $Pu_C = Pu_L \times [Pu_{C-H}/Pu_L] \times [Pu_C/Pu_{C-H}]$.

[b] Plutonium content of carcass minus head section and liver was so low for the fed mice in this group that only one decimal place could be justified for the Pu_{C-H}/Pu_L ratio.

[c] Unanalyzed mice receiving plutonium in drinking water and additional intravenously injected mice were not available for this group; mean values from other relevant groups were applied.

[d] This ratio is slightly higher than those for the other groups because mice were sacrificed 21 days rather than 6 days after plutonium administration. Data from one set of five remaining mice were used for all three plutonium concentrations.

4. REFERENCES

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2. J. W. Stather, J. D. Harrison, P. Rodwell, and A. J. David, "The gastrointestial absorption of plutonium and americium in the hamster," Phys. Med. Biol. 24, 396-407 (1979).

APPENDIX B
EFFECT OF FEEDING REGIMEN ON THE GI ABSORPTION OF PLUTONIUM IN MICE

1. EXPERIMENT

Our earlier studies showed that the fractional GI absorption of plutonium is 1×10^{-4} to 2×10^{-4} (0.01-0.02%) in fed mice (1) and 10×10^{-4} to 20×10^{-4} (0.1-0.2%) in fasted mice (2). The latter mice were fasted for 24 h, and the plutonium was typically administered during the last 16 h of the fast. The experiment reported here established the time required after the start of a 24-h fasting period for the fasting GI absorption level to be reached. Two sets of mice were used, each containing four groups of animals (5 to 7 mice per group). Plutonium solution was administered by gavage 0, 2, 4, or 8 h after the start of a 24-h fasting period. In Set A, the fasting period began at 1800 h, at the start of the mouse's active, waking phase (1800 to 0600); in Set B, the fasting period began at 2200 h, after the mice had eaten for 4 h during their active, waking phase. Mice were sacrificed 3 days after plutonium administration.

Results are presented in Table B-1. GI absorption values for both sets of mice at the start of the fast (0 h) agreed with our earlier values for the fed adult mouse. GI absorption values for mice whose fast started at the beginning of the active phase (Set A) rose to a level typical of the fully fasted mouse after 2 h of fasting. In mice allowed to eat for 4 h prior to initiation of the fast (Set B), GI absorption values rose to a level typical of the fasted mouse only after 8 h of fasting.

Results of this mouse study, if applied to humans, suggest that at the start of a day, a person may absorb plutonium from drinking water at a significantly elevated level until he eats his first meal of the day. Once a meal has been eaten, plutonium absorption from drinking water would most likely be at the fed level for the remainder of the day. (Subsequent meals usually follow in less than 8 h.) The large difference in the GI absorption value for the fasted vs. fed animal (10-fold) makes important the question of the relevance of these results to humans.

Table B-1 Gastrointestinal absorption and retention of plutonium in mice: Effects of length of fasting period and the time of its initiation

Time of Administration		Length of	Fractional retention of Pu ($\times 10^4$)[c]	
Set A[a]	Set B[b]	fast (h)	Set A	Set B
1800	2200	0	2.8 ± 0.3	2.1 ± 0.3
2000	2400 (0000)	2	17 ± 5	2.4 ± 0.5
2200	0200	4	18 ± 4	1.7 ± 0.1
0200	0600	8	16 ± 5	9 ± 3

[a]Fast was initiated at 1800, at the start of the mouse's active phase.

[b]Fast was initiated at 2200, 4 h after the start of the mouse's active phase.

[c]Values are mean ± SE for 5-7 mice/group.

2. REFERENCES

1. R. P. Larsen, M. H. Bhattacharyya, R. D. Oldham, E. S. Moretti, and M. T. Spaletto, "Continued studies of the gastrointestinal absorption of plutonium by rodents," Part II, pp. 105-116, Radiological and Environmental Research Division Annual Report, Argonne National Laboratory Report Number ANL-81-85, March 1982.

2. R. P. Larsen, R. D. Oldham, M. H. Bhattacharyya, E. S. Moretti, and D. J. Austin, "Plutonium retention in mice and rats after gastrointestinal absorption," Radiat. Res. 87, 37-49 (1981).

APPENDIX C
DERIVATION OF VALUES OF f_1 FOR THE ENVIRONMENTAL SETTING

The ICRP is currently working on recommendations for values of f_1 for the environmental setting.[a] In Appendix C, we discuss two alternate approaches to obtaining an environmental f_1 factor, with particular reference to the setting of standards for plutonium in drinking water. Our first approach allows for a limitation of dose accumulation on a lifetime basis[b]; it is somewhat analogous to the former approach of the International Commission on Radiological Protection (ICRP) in setting a maximum permissable body burden for lifetime accumulation of plutonium. The second approach allows for a limitation of dose commitment on an annual basis; it is analogous to the current approach of the ICRP in setting an Annual Limit on Intake (ALI) for plutonium in the occupational setting. We have considered both approaches because the MPCs for plutonium in drinking water derived by using them differ by a factor of 10.

1. APPROACH #1: LIMITATION OF LIFETIME DOSE AS THE CRITERION FOR LIMITATION OF EXPOSURE TO PLUTONIUM IN THE ENVIRONMENTAL SETTING

1.1 Summary of Approach #1

- Calculations are made of amounts of plutonium accumulated in the human body with age during a 70-year lifetime, from consumption of drinking water containing ^{239}Pu at 1 Bq/L. Age- and feeding regimen-dependent values of GI absorption are used.

- Lifetime dose from deposited plutonium is calculated from the amounts of plutonium accumulated during a lifetime, taking into account changes in body weight with age (see Appendix D, Section 1).

- A constant value of f_1 is determined that results in the same lifetime dose as do gastrointestinal (GI) absorption values that change with age and feeding regimen (see Appendix D, Section 2).

- The latter constant value of f_1 can be used, along with an age-weighted average value for daily water consumption, to calculate a standard concentration for plutonium in drinking water. By using this value of f_1, lifetime dose from deposited plutonium is limited to a certain value.

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[a]Personal communication, R. C. Thompson, Pacific Northwest Laboratory, Richland, Washington, 1984.

[b]The term "dose" in this document refers to absorbed dose to the whole body delivered by internally deposited plutonium.

1.2 Derivation of Values of f_1

The age-dependent values of GI absorption and of fluid consumption used in the above calculations are presented in Table C-1. As is explained in footnotes b-d of that table, the GI absorption values for humans are assumed to be the same, for corresponding periods of life, as the values presented in this report for mice/rats.

1.3 Effect of Animal Age

In this first analysis, we have evaluated the effect of increased GI absorption in the young on accumulation of plutonium and of lifetime dose. The age effect is considered independently of other factors, such as fasting. The accumulation of plutonium in the fed individual with age because of consumption of drinking water containing ^{239}Pu at 1 Bq/L is shown by the solid line in Figure C-1. Amounts of ^{239}Pu accumulated during specific age periods and methods of calculation are presented in Table C-2 (fed individuals).

Table C-1. Assumptions for derivation of an f_1 factor for plutonium in drinking water

Age		Fraction Retained ($\times 10^4$)	Consumption of Water and Water-Based Fluids (L/d)[a]
Mouse/Rat	Man		
1-2 d	0-2 month	70[b]	0.8
19 d	2-12 month	30[c]	1.0
26 d-adult	1-20 y	2[d]	1.2
adult	20-70 y	2 (fed)[d] 20 (fasted)[d]	1.7

[a]Values are estimated from data in Reference 1 (Reference Man). Milk consumption values for infants are included to simulate the formula-fed infant. For children older than 12 months, milk consumption values are excluded from the fluid consumption model; only water and water-based fluid consumption is estimated.

[b]The GI absorption value used for the 0- to 2-month old child (7×10^{-3}) is that for the fed, 1- to 2-day old rat, assuming that this value applies to the infant consuming only milk or formula.

[c]The value used for the 2- to 12-month old child (3×10^{-3}) is that for the fed, 19-day-old rat, assuming that this value applies to the child consuming a mixture of milk (or formula) and solid food.

[d]After one year of age, values for the fed and fasted adult mouse are used, 2×10^{-4} and 2×10^{-3}, respectively, on the assumption that the transition to solid food at weaning in humans is accompanied by a decrease in GI absorption, as is the case for the rat (Table 3-6).

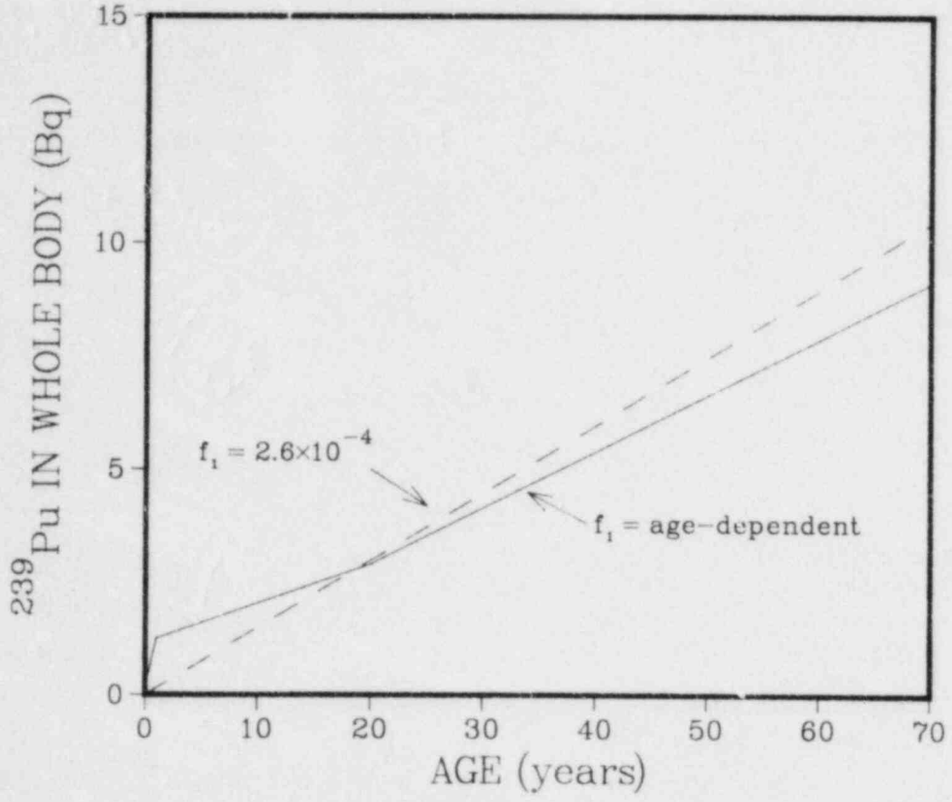


Figure C-1 Accumulation of ^{239}Pu in humans with age from drinking water containing ^{239}Pu at 1 Bq/L: The fed individual. Methods of calculation are shown in Table C-2. The solid line is for the case in which age-dependent values of GI absorption and fluid consumption are used. The dashed line is for the case in which constant values of GI absorption, 2.6×10^{-4}, and fluid consumption, 1.6 L/d, are used.

Table C-2. Accumulation of ^{239}Pu with age in humans from consumption of drinking water

Age Period (y)	Water Intake (L/d)	GI Absorption Value ($x10^4$)		Plutonium Accumulation[a] (Bq ^{239}Pu)	
		Fed Persons	Fasted[b] Persons	Fed Persons	Fasted[b] Persons
0-2 month	0.8	70	70	0.34	0.34
2-12 month	1.0	30	30	0.91	0.91
1-20 y	1.2	2	2	1.66	1.66
20-70 y	1.7	2	8[b]	6.21	24.82
			Total 0-70 y =	9.12	27.73
0-70 y	1.6[c]	2.6[d]	5.6[d]	10.63	23.71

[a]Plutonium accumulation is calculated with the values for GI absorption and water consumption shown, assuming a concentration of ^{239}Pu in drinking water of 1 Bq/L. For example, for the first age period,

Plutonium accumulation
0-2 mo = (0.8 L/d) (365 d/y) (1 Bq/L) (1/6 y) (70×10^{-4})
= 0.34 Bq
(Note that this approach is conservative in that it does not include a half-life for removal of deposited plutonium.)

[b]Fasted persons are those who, after the age of 20, consume one-third of their daily water before consuming their first meal of the day (i.e., persons who eat no breakfast). Plutonium in that one-third of the daily water intake is assumed to be absorbed at the level of the fasted animal, with a GI absorption value of 2×10^{-3}. The GI absorption value for 20 to 70 years of age is therefore: $1/3\ (2 \times 10^{-3}) + 2/3\ (2 \times 10^{-4}) = 8 \times 10^{-4}$, as shown. (Note that GI absorption values for 0-20 years for the fasted persons are the same as those for the fed persons; i.e., the fasted condition is considered only for persons over 20 y).

[c]This value for water intake is an age-weighted average for the 70 year lifetime: $(0.8 \times 1/6 + 1.0 \times 5/6 + 1.2 \times 19 + 1.7 \times 50) \div 70 = 1.6$

[d]These single, age-independent GI absorption values result in the same lifetime doses as do the multiple, age-dependent values.

The rapid rate of accumulation of plutonium during the first year of life, in the case where age-dependent GI absorption values are used (solid line, Figure C-1), is clearly evident. Fourteen percent of the lifetime body burden is deposited during the first year of life; accumulation during later years is much less rapid. When a constant value for GI absorption, 2.6×10^{-4}, is used along with a constant value for water consumption, 1.6 L/d (dashed line, Figure C-1), plutonium accumulation during the early years is much lower.

Figure C-2 shows the age-dependent accumulation of dose from deposited plutonium for two cases: (a) the case in which age-dependent values of GI absorption and fluid consumption are used (solid line) and (b) the case in which constant values of GI absorption (2.6×10^{-4}) and water consumption (1.6 L/d) are used (dashed line). Figure C-3 shows annual rather than cumulative dose for case (a).

As can be seen, use of the constant GI absorption value, 2.6×10^{-4}, results in nearly the same projected lifetime dose to the body by age 70 as does use of age-dependent GI absorption values (Figure C-2). The annual dose for the first year of life (0.09 Bq·y/kg) is slightly lower than the annual dose during the seventieth year of life (0.13 Bq·y/kg; Figure C-3). The constant f_1 value, 2.6×10^{-4}, is only 20% higher than the value for the fully fed adult rodent, 2×10^{-4}, indicating that only a small increase in the f_1 value is required to offset the effect of increased GI absorption in the young individual when lifetime dose from deposited plutonium is limited to a particular value. Results in Figure C-3 also indicate that the first year of human life is not a year of maximum risk from the standpoint of annual dose.

1.4 Effect of Food Consumption as Well as Animal Age

In deriving values of f_1 that apply to the general public, we must consider the relationship between the GI absorption of plutonium and food consumption. Does the ten-fold increase in the GI absorption of plutonium in the fasted vs. fed state in the mouse or rat have relevance to establishing the value of f_1 for humans? We have shown (2) that, when fasting in the mouse is initiated at the beginning of the active, waking phase, the value for the GI absorption of plutonium from drinking water increases from 2×10^{-4} at zero time to 2×10^{-3} after only 2 h of fasting. When the fast is initiated after the mouse has eaten for 4 h into its active phase, however, the increase in the GI absorption value does not occur until after 8 h of fasting (Appendix B). When applied to humans, these data imply that a person may absorb plutonium from drinking water at the fasted GI absorption level at the beginning of his active phase, i.e., during the time from the start of the day until his first full meal of the day. Once a meal has been eaten, plutonium absorption from drinking water would most likely be at the fed level for

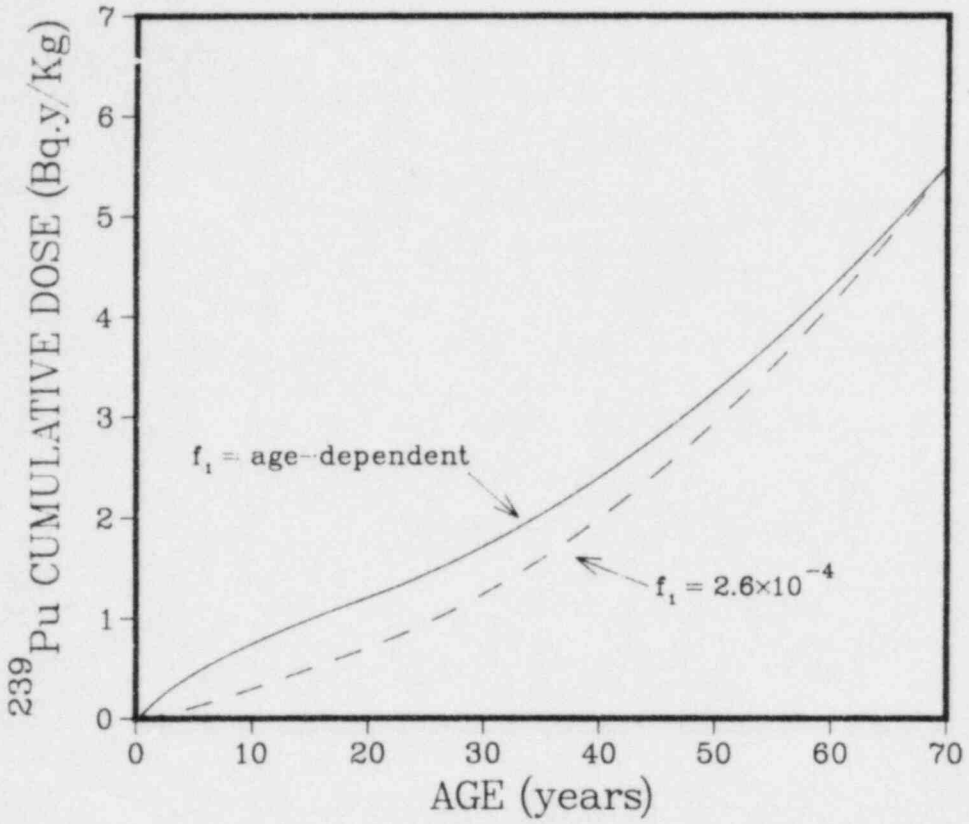


Figure C-2 Accumulation of dose in humans with age from drinking water containing ^{239}Pu at 1 Bq/L: The fed individual. Methods of calculation are shown in Appendix D, Section 1. The solid and dashed lines correspond to the solid and dashed lines, respectively, of plutonium accumulation presented in Figure C-1.

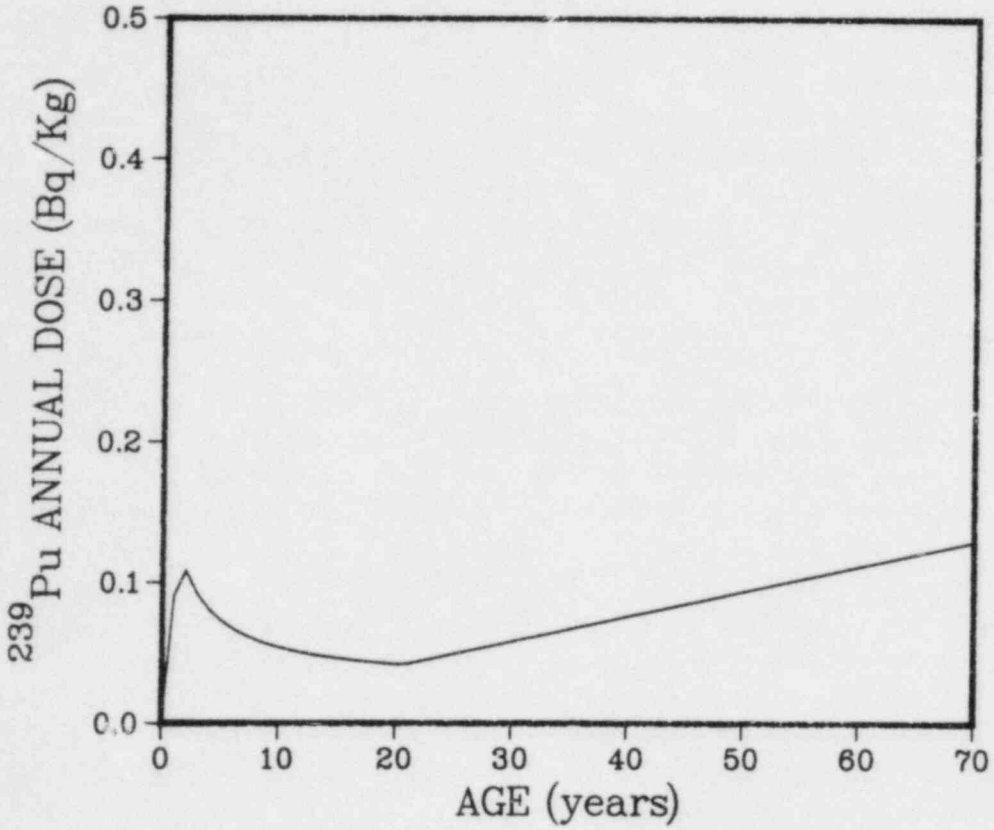
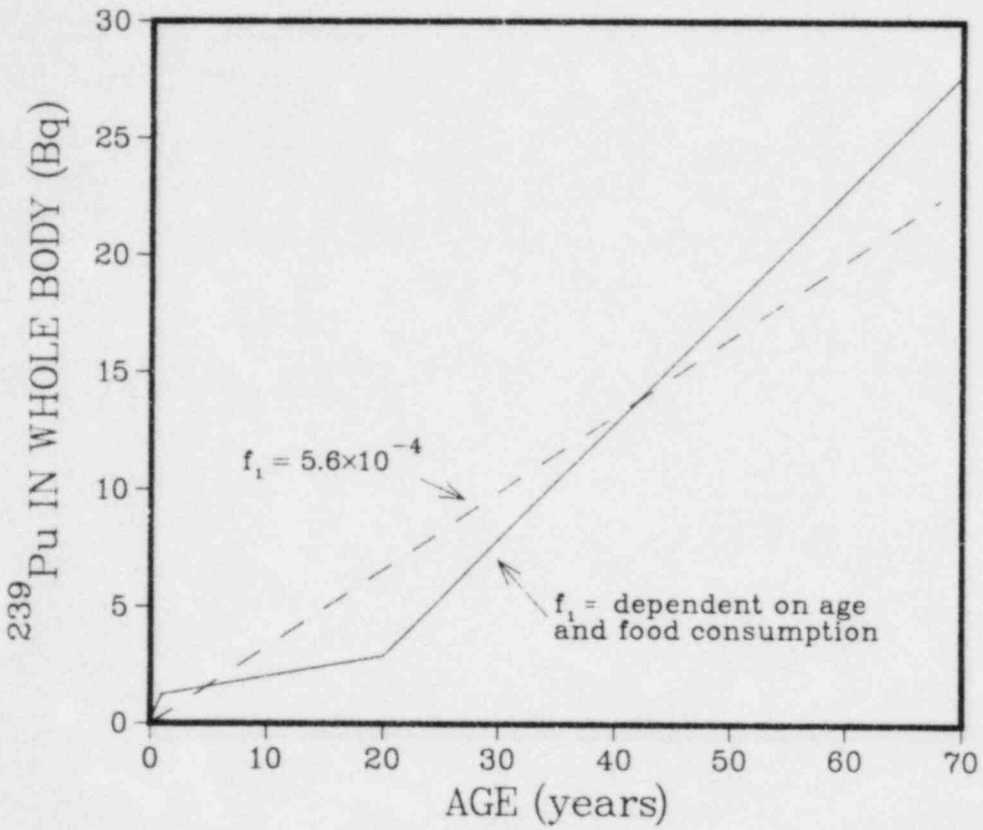


Figure C-3 Annual dose in humans with age from drinking water containing ^{239}Pu at 1 Bq/L: The fed individual. Methods of calculation are shown in Appendix D, Section 1.

the remainder of that day. (Subsequent meals usually follow in less than 8 h.)

The importance of human fasting on the projected accumulation of plutonium with age is demonstrated in Figure C-4. Amounts of ^{239}Pu accumulated from drinking water for the fasted case described above and methods of calculation are presented in Table C-2. Use of the GI absorption value of 8×10^{-4} (see footnote b, Table C-2) for the years between 20 and 70, when daily water intake is at a maximum, results in an accumulation of 27.7 Bq of ^{239}Pu by age 70 (solid line, Figure C-4), compared to only 9.1 Bq when the GI absorption value for the fed adult (2×10^{-4}) is used (solid line, Figure C-1). Lifetime accumulation of plutonium in the fasted case is dominated by rapid accumulation during the adult years, with a smaller percentage of lifetime body burden accumulated during the first year of life (4.5%) than in the case of the fully fed adult (14%).

Figure C-5 shows the age-dependent accumulation of dose from deposited plutonium for two cases: (a) the case in which GI absorption values are dependent upon both age and feeding regimen (solid line) and (b) the case in which GI absorption is independent of age (dashed line). Figure C-6 shows annual rather than cumulative dose for case (a). As can be seen, 5.6×10^{-4} is the constant, age-independent value of f_1 that results in the same lifetime dose to the body by age 70 as do absorption values that change with age and feeding regimen (Figure C-5). The annual dose for the first year of life (0.09 Bq·y/kg) is 4-fold lower than that for the seventieth year of life (0.35 Bq·y/kg) (Figure C-6). The constant f_1 value, 5.6×10^{-4}, is only 3-fold greater than the value used for the fully fed adult (2×10^{-4}). If limitation of lifetime dose is the criterion for limitation of plutonium exposure, this value of f_1, 5.6×10^{-4}, can be used to set a drinking water standard for plutonium. It takes into account, in a reasonable way, effects of both animal age and fasting.



Figures C-4 Accumulation of ^{239}Pu in humans with age from drinking water containing ^{239}Pu at 1 Bq/L: The fasted individual. Methods of calculation are shown in Table C-2. The solid line is the same as that for Figure C-1 during the period 0 to 20 y of age; after 20 y, a GI absorption value for the partially fasted human, 8×10^{-4}, is used, as explained in the text and Table C-2.

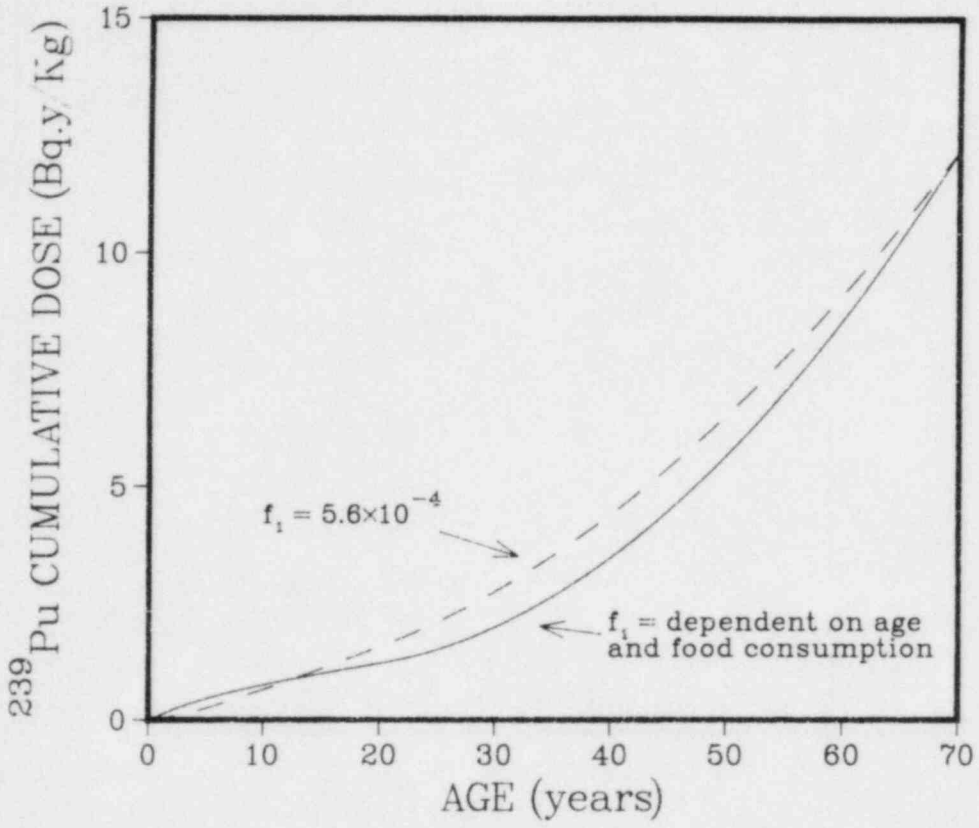


Figure C-5 Accumulation of dose in humans with age from drinking water containing ^{239}Pu at 1 Bq/L: The fasted individual. Methods of calculation are shown in Appendix D, Section 1. The solid and dashed lines correspond to the solid and dashed lines, respectively, of plutonium accumulation presented in Figure C-4.

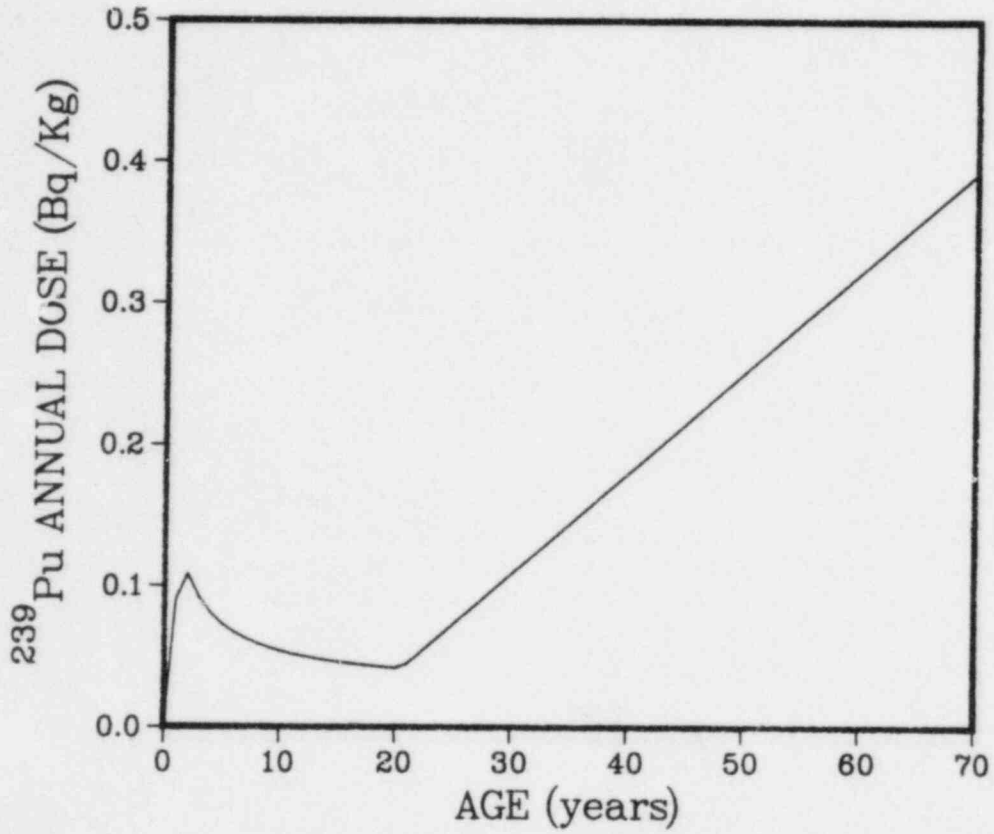


Figure C-6 Annual dose in humans with age from drinking water containing ^{239}Pu at 1 Bq/L: The fasted individual. Methods of calculation are shown in Appendix D, Section 1.

2. APPROACH #2: LIMITATION OF ANNUAL COMMITTMENT OF DOSE AS THE CRITERION FOR LIMITATION OF EXPOSURE TO PLUTONIUM IN THE ENVIRONMENTAL SETTING

2.1 Introduction

In arriving at a value of f_1 for plutonium in the environmental setting, our analysis to this point has been based on the premise that the only requirement for a drinking water standard is that the lifetime dose from deposited plutonium be limited to a particular value. This approach differs from that currently used by the ICRP in addressing the occupational setting. The ICRP now limits commitment of lifetime dose on an annual basis by recommending an ALI for each radionuclide. This type of approach has not yet been addressed by our considerations of f_1 factors.

The following question needs to be addressed in this regard: During what year of life does exposure to plutonium result in the greatest commitment of lifetime dose? The high values of GI absorption in the young animal prior to weaning are obviously very important. If plutonium deposition in the formula-fed infant during the first year of life results in a greater commitment of lifetime dose than does deposition in any subsequent year, then GI absorption values and fluid consumption values during that first year of life are the parameters that must be used to set a drinking water standard that limits commitment of lifetime dose on a yearly basis.

2.2 Summary of Approach #2

- For each year of plutonium intake during a 70-year lifetime of consumption of drinking water containing ^{239}Pu at 1 Bq/L, cumulative dose to the body during the remainder of the 70-year lifetime due to deposition during that one year is calculated (see Appendix D, Section 3).

- Calculations use the values of GI absorption and fluid consumption for the fasted case in Table C-2 and Figure C-4. The calculations take into account increases in body weight with increasing age.

- That year of life is identified during which intake results in the greatest commitment of dose to the body during a 70-year lifetime.

- The values for GI absorption and fluid consumption for the year of greatest commitment of dose can be used to calculate a standard concentration for plutonium in drinking water. Plutonium intake is limited such that lifetime dose from intake during an identified critical year(s) does not exceed a certain value.

2.2 Derivation of Values of f_1

Figure C-7 presents the contribution to total lifetime dose of each year's intake of plutonium from consumption of drinking water containing ^{239}Pu at 1 Bq/L. The case considered is the fasted case from Table C-2. The fed individual was not considered because the first year of his/her life clearly would contribute most to lifetime dose commitment, with the highest GI absorption values, lowest body weights, and longest retention of plutonium in the body after accumulation because of uptake early in life.

For the fasted individual, plutonium deposited during the first year of life (when GI absorption values are high and body weight is low) is projected to deliver 14.4% of the total lifetime dose (Figure C-7), as compared to 2.9% for plutonium deposited during the twenty-first year of life [when plutonium deposition is again projected to be high because of combined effects of fasting and adult levels of water intake (Figure C-4), but when body weight is also high]. After the twenty-first year of life, the contribution to lifetime dose of a given year's intake decreases with increasing age, because plutonium taken up in a given year resides in the body for a shorter time as the year of intake approaches the seventieth year of life (Figure C-7).

Figure C-7 shows clearly that the first year of human life is the year during which plutonium deposition from drinking water results in the greatest commitment of lifetime dose to the body. The GI absorption value for this first year, then, is the one that must be used to set a drinking water standard that limits the commitment of lifetime dose on an annual basis. By using the parameters in Table C-2, we obtained a single value of f_1 for the first year of life of 4×10^{-3} [7×10^{-3} (2/12) + 3×10^{-3} (10/12)]. This value of f_1 allows for limitation of lifetime accumulation of dose on an annual basis from consumption of drinking water, by taking into account the early years of high plutonium uptake and low body weight.

3. SUMMARY

The GI absorption value for plutonium that we experimentally determined in the fed adult mouse is 2×10^{-4} (0.02%). From our experimental data we derived two values of f_1 based on the limitation of lifetime dose as the criterion for limitation of exposure to plutonium. The first value, 2.6×10^{-4} (0.026%), takes into account the greater GI absorption of plutonium projected for the first year of human life. The second value, 5.6×10^{-4} (0.056%), takes into account effects of both animal age and fasting. It focuses on the individual who does not eat breakfast.

Both of our derived values of f_1, 2.6×10^{-4} and 5.6×10^{-4}, differ little from our experimentally-determined GI absorption value for the fed adult mouse, 2×10^{-4}. This indicates that only a the small

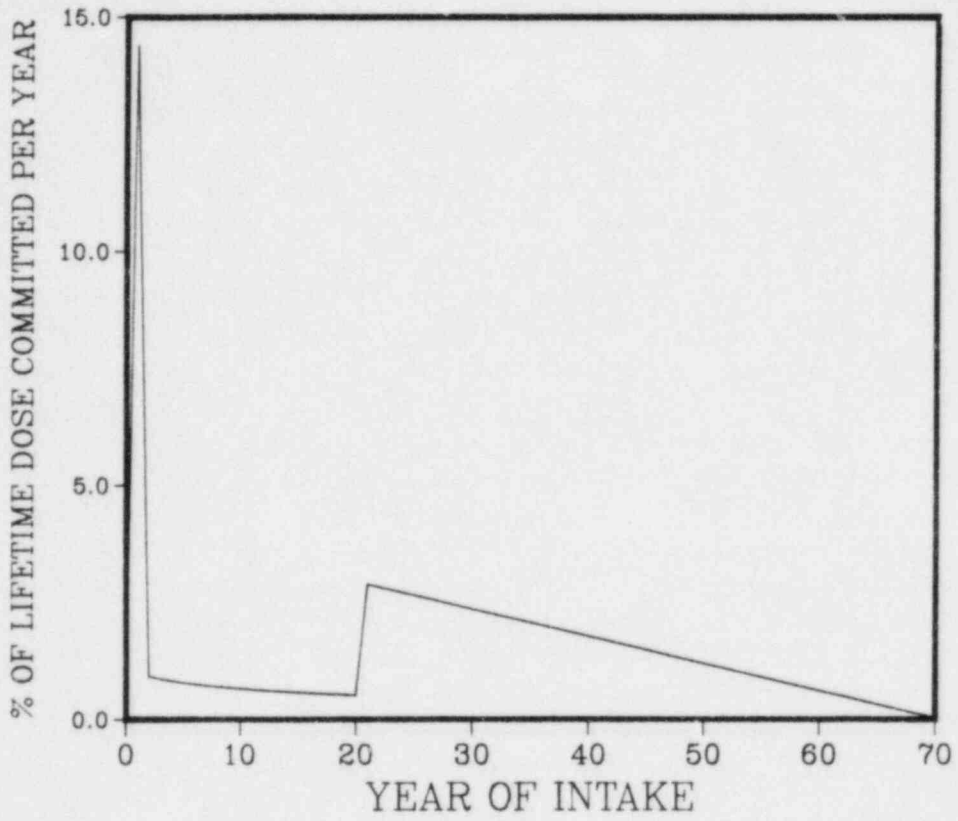


Figure C-7 Contribution to total lifetime dose of each year's intake of plutonium in drinking water: The fasted individual. Methods of calculation are described in Appendix D, Section 3.

increase in f_1 is required to account in a reasonable way for effects of both animal age and fasting when limitation of lifetime dose is the criterion for limitation of exposure to plutonium in the environmental setting.

Finally, by applying the high GI absorption values for animals prior to weaning, and by focusing on the approach taken by the ICRP for the occupational setting in restricting intake of radionuclides to a given annual limit, a value of f_1 of 4×10^{-3} (0.4%) is obtained. This value allows for limitation of dose commitment on an annual basis and should be considered in the evaluation of f_1 values that apply to the environmental setting.

4. REFERENCES

1. International Commission on Radiological Protection, "Report of the Task Group on Reference Man," ICRP Publication 23, Permagon, Oxford, England (1975).

2. R. P. Larsen, M. H. Bhattacharyya, R. D. Oldham, E. S. Moretti, and M. T. Spaletto, "Continued studies of the gastrointestinal absorption of plutonium by rodents: Relationships to feeding regimen and age of animals," Part II, pp. 141-146, Radiological and Environmental Research Division Annual Report, ANL Report Number ANL-82-65, November 1982.

APPENDIX D.
METHODS FOR CALCULATION OF DOSE ACCUMULATION AND AGE-INDEPENDENT VALUES OF f_1

1. DOSE ACCUMULATION WITH AGE FROM LIFETIME ACCUMULATION OF PLUTONIUM IN DRINKING WATER

The amount of plutonium deposited in the body as a function of age to 70 years of life from consumption of drinking water containing ^{239}Pu at 1 Bq/L is described in this report (Figures C-1 and C-4) by a piecewise, but continuous, set of four linear functions covering the age interval 0 to 70 years:

$$P(t) = a + bt$$

where a and b have the sets of values shown in Table D-1, each set corresponding to one of four intervals of age, t_1 to t_2, for a projected 70-year lifetime. Each age interval corresponds to a period during which a given value for the GI absorption of plutonium is assigned (Table C-1).

Body weight in a human male as a function of age is described by the linear function

$$W(t) = e + ft$$

where e and f have sets of values corresponding to the same four intervals of age as were used for P(t) (see Table D-1). A plot of W(t) vs. age is shown in Figure D-1, along with data points from Reference 1 (Reference Man) for comparison.

The dose delivered to the whole body during any time interval dt is calculated by dividing the amount of plutonium in the body at time t [given by P(t)] by the weight of the body at time t [given by W(t)], and multiplying by the time interval over which the dose is delivered, dt. This unit of dose is then integrated over the entire time interval under consideration as follows:

$$_{t_1}^{t_2}D = \int_{t_1}^{t_2} \frac{P(t)}{W(t)}\,dt = \int_{t_1}^{t_2} \frac{a + bt}{e + ft}\,dt$$

where $_{t_1}^{t_2}D$ is an expression of dose with units Bq·y/kg and t_1 and t_2 are the ages in years at the beginning and end of the age interval under consideration. (1 Bq·y/kg = 2.6×10^{-5} Gy or 5.2×10^{-4} Sv for ^{239}Pu.)

Table D-1. Conditions for calculation of lifetime dose from plutonium in drinking water

Factor[a]	Unit	Values of Constants for Integration				
					20-70 y	
		0-2 months	2-12 months	1-20 y	Fed Persons	Fasted Persons
t_1	y	0	1/6	1	20	20
t_2	y	1/6	1	20	70	70
a	Bq	0	0.16	1.16	0.43	-7.01
b	Bq/y	2.04	1.09	0.087	0.124	0.496
e	kg	3.4	3.9	7.3	70.0	70.0
f	kg/y	9.6	6.5	3.1	0	0

[a]Factors used are t_1 and t_2, the intervals of time over which the integration was carried out in the calculation of dose; a and b, the intercepts and slopes, respectively, of the four portions of the plutonium accumulation curves for fed individuals (Figure C-1) and for fasted individuals (Figure C-4); e and f, the intercepts and slopes, respectively, of the four portions of the body weight accumulation curve shown in Figure D-1.

The lifetime accumulation of dose is obtained by integrating over the four intervals of age shown in Table D-1. Results of such calculations are shown in Table D-2 for the fed individual and in Table D-3 for the fasted individual. This method of calculating dose as a function of age accounts for changes in body weight with age; i.e., the dose delivered by a given amount of plutonium taken up during the first year of life, when body weight ranges from 3.4 to 10.4 kg, is much greater than the dose delivered by that amount of plutonium taken up by the 70-kg adult. The calculated dose is a dose to the whole body rather than to the bone surfaces. This expression is considered adequate for the purpose of deriving values of f_1, because little change in these f_1 values would result from use of doses to the bone surfaces.

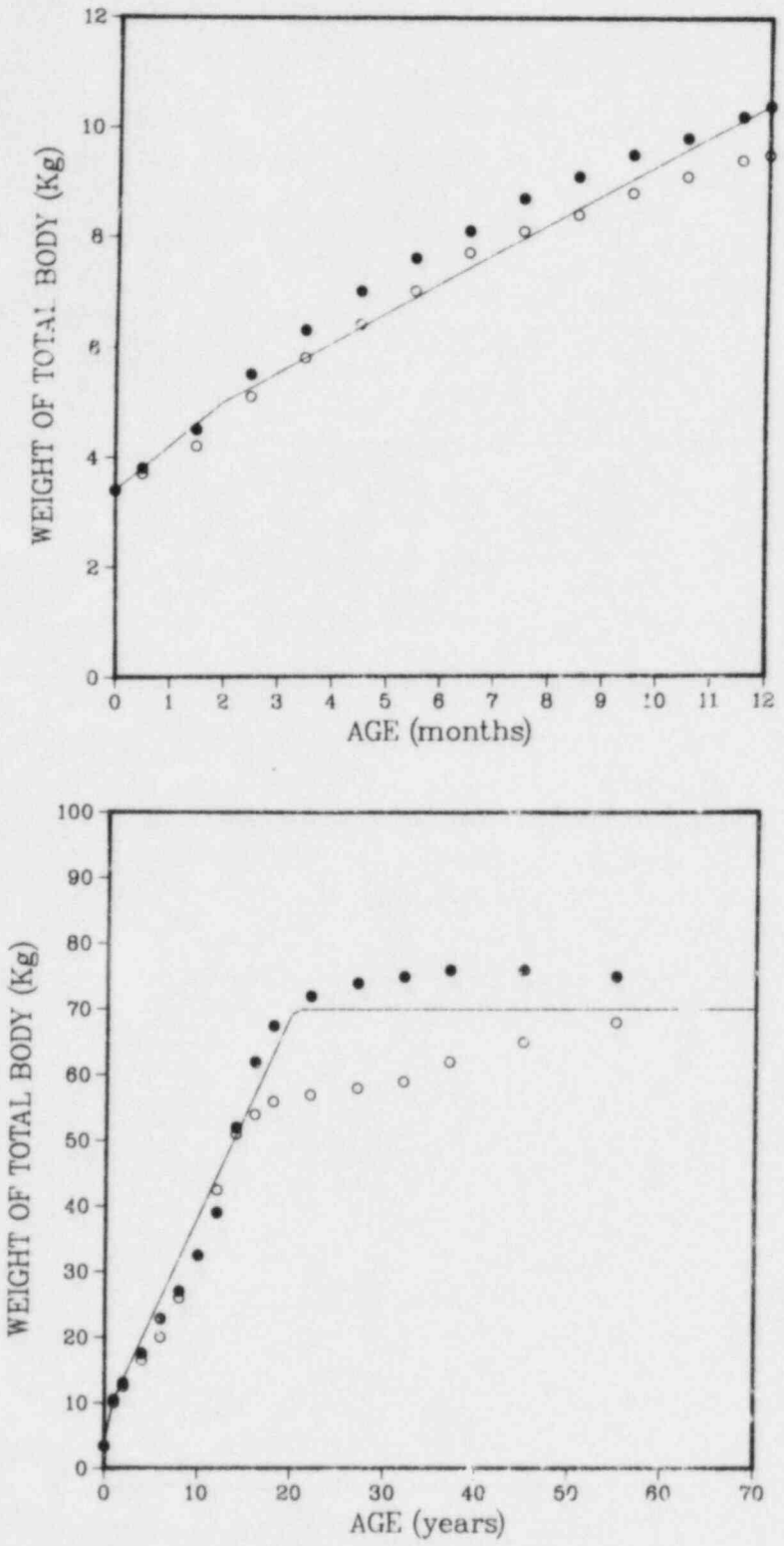


Figure D-1 Weight of total body as a function of age for humans. ● = males, Reference 1; ○ = females, Reference 1; solid line = functions used in dose calculations in this document. Upper graph covers ages 0-12 mo; lower graph covers age 0-70 y.

Table D-2. Accumulation of plutonium and dose with age in humans from drinking water containing ^{239}Pu at 1 Bq/L: The fed individual

Age (y)	^{239}Pu in Whole Body (Bq)	Annual Dose from ^{239}Pu (Bq/kg)	Cumulative Dose from ^{239}Pu (Bq·y/kg)
1/6	0.34	-	0.0064
1	1.25	0.090	0.090
5	1.60	0.073	0.44
10	2.03	0.054	0.75
15	2.47	0.046	0.99
20	2.90	0.042	1.21
21	3.03	0.043	1.25
25	3.53	0.050	1.44
30	4.15	0.058	1.71
35	4.77	0.067	2.03
40	5.39	0.076	2.39
45	6.01	0.085	2.80
50	6.63	0.094	3.25
55	7.25	0.10	3.75
60	7.87	0.11	4.29
65	8.49	0.12	4.87
70	9.11	0.13	5.50

Table D-3. Accumulation of plutonium and dose with age in humans from drinking water containing ^{239}Pu at 1 Bq/L: The fasted individual

Age (y)	^{239}Pu in Whole Body (Bq)	Annual Dose from ^{239}Pu (Bq/kg)	Cumulative Dose from ^{239}Pu (Bq·y/kg)
1/6	0.34	-	0.0064
1	1.3	0.090	0.090
5	1.6	0.073	0.44
10	2.0	0.054	0.74
15	2.5	0.046	0.99
20	2.9	0.042	1.2
21	3.4	0.045	1.3
25	5.4	0.074	1.5
30	7.9	0.11	2.0
35	10.4	0.14	2.6
40	12.8	0.18	3.5
45	15.3	0.22	4.5
50	17.8	0.25	5.6
55	20.3	0.29	7.0
60	22.8	0.32	8.5
65	25.2	0.36	10.3
70	27.7	0.39	12.1

2. CALCULATION OF AN AGE-INDEPENDENT VALUE OF f_1

Once lifetime accumulation of dose by age 70, $^{70}_{0}D$, has been calculated for the fed (or fasted) individual by using GI absorption values that change with age, the following question can be asked: What constant, age-independent value of f_1 results in the same lifetime dose by age 70 as the dose calculated with age-dependent values of GI absorption?

If values of f_1 and water consumption are assumed to be constant with age, then the lifetime plutonium accumulation curve is a single linear function throughout life, with a constant slope b and an intercept of zero at time zero; i.e., $P(t) = bt$. The age-independent value of f_1 can

then be calculated from the following equation. (See Table D-4 for values of constants.)

$$\int_0^{1/6} \frac{bt}{3.4+9.6t}dt + \int_{1/6}^{1} \frac{bt}{3.9+6.5t}dt + \int_1^{20} \frac{bt}{7.3+3.1t}dt + \int_{20}^{70} \frac{bt}{70}dt = {}_0^{70}D$$

where ${}_0^{70}D$ = a known value of lifetime dose. This equation for lifetime dose is based on the assumption that P(t) = bt throughout life. The lifetime function of body weight, W(t), is the same as that described in Appendix D, Section 1.

Solving for b,

$$b\left[\int_0^{1/6} \frac{t}{3.4+9.6t}dt + \int_{1/6}^{1} \frac{t}{3.9+6.5t}dt + \int_1^{20} \frac{t}{7.3+3.1t}dt + \int_{20}^{70} \frac{t}{70}dt\right] = {}_0^{70}D$$

$b\,[\hat{D}] = {}_0^{70}D$, where $\hat{D}$ = the integral in brackets above.

$$b = {}_0^{70}D/\hat{D}$$

Finally, a constant, age-independent value of f_1 is calculated from the above value of b as follows:

$$f_1 = \frac{b\ Bq/y}{(1.6\ L/d)\ (365\ d/y)\ (1\ Bq/L)} = \frac{b}{584}$$

where b = the constant slope of the plutonium accumulation curve, given above,
1.6 L/d = an age-weighted average value for water consumption, and
1 Bq/L = concentration of ^{239}Pu in drinking water.

Constant, age-independent values of f_1 were calculated from values of ${}_0^{70}D$ for the fed and the fasted cases shown in Table D-1. These values are given in Section 5.3 and in Appendix C, Section 1.

Table D-4. Conditions for calculation of an age-independent value of f_1 that delivers a known lifetime dose from deposited plutonium[a]

Factor	Unit	Values of Constants for Integration			
		0-2 months	2-12 months	1-20 y	20-70 y
t_1	y	0	1/6	1	20
t_2	y	1/6	1	20	70
a	Bq	0	0	0	0
b	Bq/y	b	b	b	b
d	kg	3.4	3.9	7.3	70.0
e	kg/y	9.6	6.5	3.1	0

[a]Values for a and b apply to the case where P(t), the lifetime accumulation of plutonium, is a single linear function from age 0 to 70 y. The slope of P(t) throughout life is b, and the intercept at age zero is zero; i.e., P(t) = bt for all age intervals.

3. DOSE ACCUMULATION OVER A 70-YEAR LIFETIME FROM A ONE YEAR ACCUMULATION OF PLUTONIUM IN DRINKING WATER

The purpose of the calculation presented here is to determine which single year of plutonium uptake from drinking water containing ^{239}Pu at 1 Bq/L results in the greatest contribution to lifetime dose. The case considered is the one for the fasted individual, Table C-2 and Figure C-4.

The method of calculations is as follows:

- The accumulation of dose is calculated for a single year of plutonium accumulation from drinking water.
- The plutonium deposited in the body as a result of that year's uptake is assumed to remain constant to 70 years of life. The dose resulting from the residence of that year's plutonium in the body over the remainder of the 70-year lifetime is calculated and added to the dose calculated for the year of uptake.
- A similar calculation of dose is carried out for each year of plutonium uptake over a 70-year lifetime.

The values of a, b, e, and f used in the calculation of lifetime dose committed by each year's uptake are shown in Table D-5. Lifetime dose is calculated by using the integration method presented in Appendix D, Section 1. Results of these calculations are shown in Table D-6 and Figure C-7.

4. REFERENCES

1. International Commission on Radiological Protection, "Report of the Task Group on Reference Man," ICRP Publication 23, Permagon, Oxford, England (1975).

Table D-5 Conditions for the calculation of lifetime dose committed by each year's intake of plutonium in drinking water[a]

Factor	Unit	Values of Constants for Integration			
Age Interval: 0-1 y					
t_1	y	0	1/6	1	20
t_2	y	1/6	1	20	70
a	Bq	0	0.16	1.25	1.25
b	Bq/y	2.04	1.09	0	0
c	kg	3.4	3.9	7.3	70.0
d	kg/y	9.6	6.5	3.1	0
Age Interval: 1-20 y[b]					
t_1	y	y	y+1	20	
t_2	y	y+1	20	70	
a	Bq	-0.087y	0.087	0.087	
b	Bq/y	0.087	0	0	
c	kg	7.3	7.3	70.0	
d	kg/y	3.1	3.1	0	
Age Interval: 20-70 y[c]					
t_1	y	y	y+1		
t_2	y	y+1	70		
a	Bq	-0.496y	0.496		
b	Bq/y	0.496	0		
c	kg	70.0	70.0		
d	kg/y	0	0		

[a]Values of a and b correspond to those of the fasted individual in Table D-1.

[b]Calculations of lifetime dose are carried out for values of y = 1 to 19.

[c]Calculations of lifetime dose are carried out for values of y = 20 to 69.

Table D-6. Contribution to total lifetime dose of each year's consumption of drinking water containing ^{239}Pu at 1 Bq/L: The fasted individual[a]

Age At End of Year of Exposure (y)	Lifetime Dose Commitment	
	Bq• y/kg	Percentage of Total Dose
1	1.7	14.4
5	0.10	0.8
10	0.08	0.7
15	0.07	0.6
20	0.06	0.5
21	0.35	2.9
25	0.32	2.7
30	0.29	2.4
35	0.25	2.1
40	0.22	1.8
45	0.18	1.5
50	0.15	1.2
55	0.11	0.9
60	0.07	0.6
65	0.04	0.3
70	0.00	0.0

[a]Calculations were carried out for the fasted individual to determine which year of intake would contribute the most to the total commitment of lifetime dose. Calculations were not carried out for the fed individual because the first year of life, with the highest GI absorption values and lowest body weights, clearly would contribute most to lifetime dose commitment for this case.

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13. ABSTRACT (200 words or less)

The gastrointestinal (GI) absorption of plutonium was measured in mice, rats, and dogs under conditions relevant to setting drinking water standards. The fractional GI absorption of Pu (VI) in adult mice was 2×10^{-4} (0.02%) in fed mice and 2×10^{-3} (0.2%) in fasted mice. The GI absorption of plutonium was independent of plutonium oxidation state, administration medium, and plutonium concentration; absorption was dependent upon animal species, state of animal fasting, state of Pu(IV) hydrolysis, and age of the animal. Fractional GI absorption values ranged from 3×10^{-5} (0.003%) for hydrolyzed Pu(IV) administered to fed adult mice to 7×10^{-3} (0.7%) for Pu(VI) administered to fed neonatal rats.

From analysis of our data, we suggested values of f_1 (the fraction transferred from gut to blood in humans) for use in establishment of oral limits of exposure to plutonium. For an acute exposure in the occupational setting, we proposed one value of f_1 for fed (2×10^{-4}) and one for fasted (2×10^{-3}) individuals. For the environmental setting, we developed two approaches to obtaining values of f_1; suggested values were 6×10^{-4} and 4×10^{-3}, respectively. Both approaches took into account effects of animal age and fasting. We discussed uncertainties in proposed values of f_1 and made recommendations for further research.

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