

## USTUR WHOLE BODY CASE 0269: DEMONSTRATING EFFECTIVENESS OF I.V. CA-DTPA FOR PU

A. C. James<sup>†,\*</sup>, L. B. Sasser<sup>†</sup>, D. B. Stuit<sup>†</sup>, S. E. Glover<sup>‡</sup> and E. H. Carbaugh<sup>§</sup>

<sup>†</sup>U.S. Transuranium and Uranium Registries, College of Pharmacy, Washington State University, 2710 University Drive, Richland, WA 99354, USA.

<sup>‡</sup>Dept. of Mechanical, Industrial and Nuclear Engineering, University of Cincinnati, 598 Rhodes Hall, Cincinnati, OH 45221, USA

<sup>§</sup>Pacific Northwest National Laboratory, P.O. Box 999, Richland, WA 99354, USA

*Received October 2, 2006, amended ???? , accepted ????*

**Abstract** — This whole body donation case (USTUR Registrant) involved a single acute inhalation of an acidic Pu(NO<sub>3</sub>)<sub>4</sub> solution in the form of an aerosol ‘mist.’ Chelation treatment with i.v. Ca-EDTA was initiated on the day of the intake, and continued intermittently over 6 months. After 2½ years with no further treatment, a course of i.v. Ca-DTPA was administered. A total of 400 measurements of <sup>239+240</sup>Pu excreted in urine were recorded; starting on the first day (both before and during the initial Ca-EDTA chelation), and continuing for 37 years. This sampling included all intervals of chelation. In addition, 91 measurements of <sup>239+240</sup>Pu-in-feces were recorded over this whole period. The Registrant died about 38 years after the intake, at age 79 y, with extensive carcinomatosis secondary to adenocarcinoma of the prostate gland. At autopsy, all major soft tissue organs were harvested for radiochemical analyses of their <sup>238</sup>Pu, <sup>239+240</sup>Pu and <sup>241</sup>Am content. Also, all types of bone (comprising about half the skeleton) were harvested for radiochemical analyses, as well as samples of skin, subcutaneous fat and muscle. This comprehensive dataset has been applied to derive ‘chelation-enhanced’ transfer rates in the ICRP Publication 67 plutonium biokinetic model, representing the behaviour of blood-borne and tissue-incorporated plutonium during intervals of therapy. The resulting model of the separate effects of i.v. Ca-EDTA and Ca-DTPA chelation shows that the therapy administered in this case succeeded in reducing substantially the long-term burden of plutonium in all body organs, except for the lungs. The calculated reductions in organ content at the time of death are approximately 40% for the liver, 60% for other soft tissues (muscle, skin, glands, etc.), 50% for the kidneys, and 50% for the skeleton. Essentially all of the substantial reduction in skeletal burden occurred in trabecular bone. This modeling exercise demonstrated that 3-y-delayed Ca-DTPA therapy was as effective as promptly administered Ca-EDTA.

### INTRODUCTION

This voluntary whole body donation to the United States Transuranium and Uranium Registries (USTUR) provides a detailed and complete data record of one of the earliest cases of accidental acute inhalation of ‘soluble’ plutonium treated promptly with intravenously (i.v.) administered Ca-EDTA (in 1956). The donation is also unique because it traces the early evolution of chelation treatments, including several unsuccessful trials of orally-administered agents and, most notably, the introduction of i.v. Ca-DTPA therapy (2½ years after the intake, in late 1958). Over the succeeding four decades, intravenous injections of Ca-DTPA, or the potentially less toxic Zn-DTPA, have been used quite often as ‘experimental’ drugs to ‘de-corporate’ high intakes of plutonium.<sup>(1,2)</sup> However, to date, no mechanistic model has been developed to predict quantitatively the effectiveness of a given course of therapy.<sup>(3)</sup> The objective of this study is to quantify (model) the effects of both the Ca-EDTA and Ca-DTPA

treatments on plutonium elimination from the various tissue compartments represented in the ICRP Publication 67 Pu biokinetic model (IC67).<sup>(4)</sup> Concerns over a terrorist radionuclide dispersal threat have recently prompted regulatory approval of diethylenetriaminepentaacetic acid (DTPA) for medically supervised use to treat people internally contaminated with transuranics (plutonium, americium, or curium) (<http://www.fda.gov/cder/drug/infopage/dtpa/>).

### THE DONOR’S INTAKE AND TREATMENT

This gentleman was an operator of the Pu reduction-oxidation (REDOX) process at the Hanford Engineering Works (HEW). He was accidentally contaminated externally and internally following a substantial release of plutonium in the form of an acidic Pu(NO<sub>3</sub>)<sub>4</sub> aerosol mist. The precise time of the release was indicated by the instantaneous response of a stationary “poppy” survey meter in an adjacent change room. The donor provided 3 urine samples

within 12 h of the intake, when a 'week-on, week-off' course of 1-g i.v. Ca-EDTA injections was started. The donor was restricted from all further work in radiation zones.

Intermittent treatments with i.v. Ca-EDTA were continued through about 6 months after the intake. The daily urinary excretion of Pu was then monitored several times per week through about 3-y after the intake, when intermittent treatment with 1-g i.v. Ca-DTPA was started. This treatment was continued for about 2 y. Faecal excretion of Pu was monitored, from day 1 through 35 y. In 1962, i.e., 6 y after the intake, the employer estimated that the donor's initial systemic 'burden' was 0.42  $\mu\text{Ci}$  (15.5 kBq), based on the contemporary graphical methods of analysing Pu

excretion in urine.<sup>(5,6)</sup> This was about 10 $\times$  the 'maximum permissible body burden' (MPBB).<sup>(7)</sup>

BIOASSAY DATA

Figure 1 shows that daily i.v. injections of Ca-EDTA increased the excretion of Pu in urine about 8-fold over the 'baseline' (untreated) rate. Within a day of finishing each series of Ca-EDTA injections, the urinary excretion rate dropped back to the baseline value. The approximate 8-fold enhancement in Pu excretion was maintained throughout the 6-month period of treatment. These Ca-EDTA injections had no effect on the faecal excretion of Pu (Figure 2).

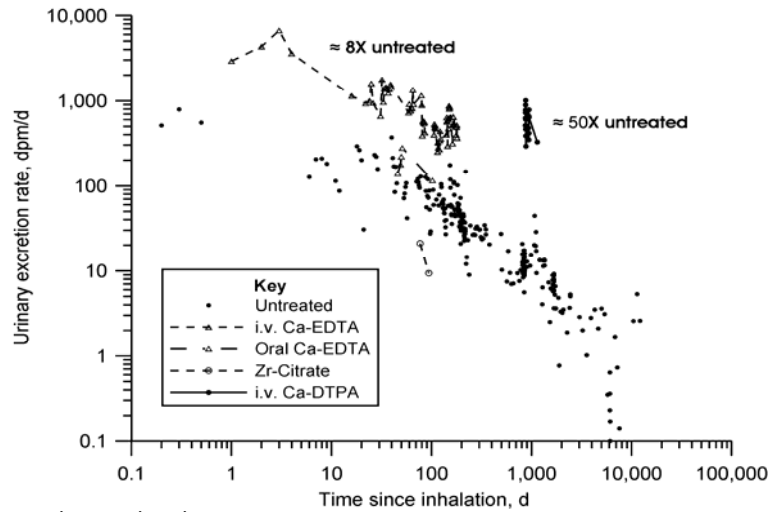


Figure 1. Pu- $\alpha$  excretion rate in urine.

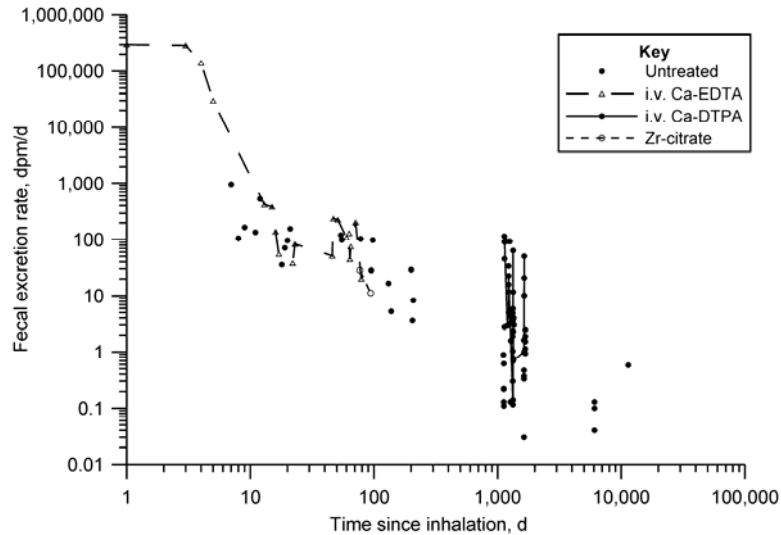


Figure 2. Pu- $\alpha$  excretion rate in faeces.

Figure 1 also shows that orally administered Ca-EDTA (tried periodically between 50 and 100 d after the intake) had no substantial effect on urinary Pu excretion. Orally administered Zr-citrate (at around 100 d) reduced Pu urinary excretion. The effect of these additional (test) treatments was negligible compared to that of i.v. Ca-EDTA, and was ignored for modeling purposes.

Intravenous administration of Ca-DTPA (intermittently between 865 and 1,642 d after the intake) increased urinary excretion of Pu on the days of injection about 50-fold (Figure 1). Again, Pu excretion fell back rapidly to the baseline rate on subsequent days. Although the faecal data show greater scatter, i.v. Ca-DTPA tended to shift the faecal excretion of Pu to the high end of the range (Figure 2).

#### AUTOPSY TISSUE DATA

Table 1 summarizes the total  $^{238+239}\text{Pu}$  activity measured in body organs by radiochemical analysis. Tables of primary measurement data (including the  $^{238}\text{Pu}$  and  $^{241}\text{Am}$  contents) for individual soft tissue samples and all individual bones are available from <http://www.ustur.wsu.edu/Montpellier/index.html>. The sub-division of skeletal activity between trabecular and cortical bone was estimated by the method described for an earlier USTUR  $^{238}\text{PuO}_2$  case analysis.<sup>(8)</sup>

Table 1. Measured  $^{239+240}\text{Pu}$  tissue contents

Organ/Tissue	Activity at Death, Bq
Lungs, larynx, trachea	26.7
Thoracic lymph nodes (LNTH)	0.19
Skeleton	1197
Trabecular bone	≈ 230
Cortical bone	≈ 970
Liver	937
Kidneys	1.7
Testes	0.83
All other soft tissues (total)	180
Total 'Systemic'	2317

Remarkably, Table 1 shows that about 1% of the total  $^{239+240}\text{Pu}$  body burden at death remained in the lungs (38 y after the intake). This residue is about 2 orders of magnitude higher than the amount expected in blood, and is inconsistent with that expected (zero) for 'soluble' Pu (ICRP default Type M). Also, the  $^{239+240}\text{Pu}$  concentration in the thoracic lymph nodes (LNTH) was about the same as that in the lungs. If the long-term retention had resulted from an 'insoluble' (particle) component in the inhaled aerosol, the LNTH concentration would have been two orders of magnitude higher than that in the lungs. Therefore, it can be inferred that this observed long-term retained

Pu is the residue of material initially 'bound' to lung tissues.

#### ANALYSIS OF INTAKE

The IMBA Expert™ USDOE-Edition code<sup>(9)</sup> was used to define the absorption and lung retention behaviour of the inhaled  $\text{Pu}(\text{NO}_3)_4$  aerosol, by fitting simultaneously the baseline (untreated) urinary and faecal Pu excretion data and the lung and lymph node contents measured at the time of death (14,054 d post intake), as described for Case 0262.<sup>(10)</sup> Again, the fitting procedure was constrained to predict exactly the measured lung and LNTH contents, while simultaneously minimizing the value of  $(\sum \chi^2_{\text{urine}} + \sum \chi^2_{\text{faeces}})$ . The resulting 'maximum likelihood' values of the critical intake and absorption parameters for the ICRP Publication 66 model (IC66)<sup>(11)</sup> were:

- Intake  $\approx 58$  kBq.
- AMAD  $\approx 2$   $\mu\text{m}$ .
- Gut absorption fraction,  $f_1 \approx 0.0005$ .
- $s_p \approx 10$   $\text{d}^{-1}$ ,  $s_{pt} \approx 100$   $\text{d}^{-1}$ ,  $s_t \approx 0.02$   $\text{d}^{-1}$ .
- Bound fraction,  $f_b \approx 8\%$ .
- $s_b \approx 2 \times 10^{-4}$   $\text{d}^{-1}$ .

These estimated parameter values were obtained by using the default transfer rates for systemic Pu recommended by ICRP for Reference Man.<sup>(4)</sup> Thus, no account was taken of any effect of the chelation therapies in accelerating the elimination of Pu from the body; the analysis was carried out using only the observed baseline (untreated) excretion rates. It was determined that a 'reasonable' statistical fit to the observed baseline excretion rates yielded a projected value of the 'untreated' body burden at the time of death (38 y post intake) of 3.9 kBq. This projected value is about  $1.7\times$  the measured total body burden (2.3 kBq), indicating a substantial overall effect of the chelation treatments in this case.

#### BIOKINETIC MODEL SYSTEM

The combined respiratory tract and systemic Pu biokinetic model system solved by the IMBA Expert™ software is shown in Figure 3. In order to examine the effects of modifying the values of key rate constants in the IC67<sup>(4)</sup> systemic Pu model on the urinary and faecal excretion of Pu (in specified time intervals), together with their effects on projected Pu tissue contents (at the time of death), the 'rate matrix' algorithm was used to solve the complete biokinetic system. This was done in time steps corresponding to all discrete chelation treatments (i.v. Ca-EDTA or i.v. Ca-DTPA) and the corresponding excreta collection periods (treated or untreated).

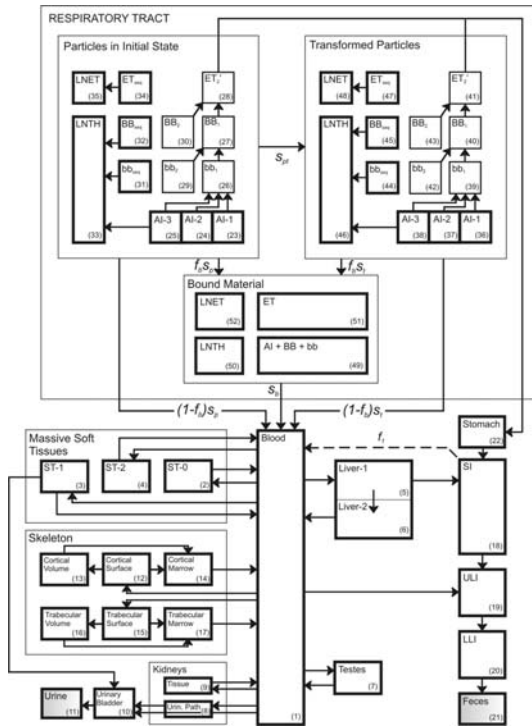


Figure 3. Combined implementation of IC66 (HRTM) and IC67 systemic Pu model.

MODELING EFFECTS OF CHELATION

Figure 4 shows (as thickened lines) the transfer pathways in the IC67 systemic Pu biokinetic model considered in this study as potentially influenced by Ca-EDTA or Ca-DTPA chelation therapy.

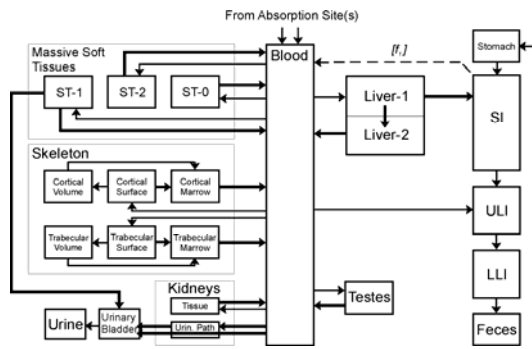


Figure 4. Hypothetical chelation pathways considered.

In order to represent the direct effects of these chelating agents, the ICRP-recommended transfer rates for each pathway highlighted in Figure 4 were multiplied by an agent-specific ‘trial’ factor

( $K_{\text{pathway,agent}}$ ). These trial values of  $K_{\text{pathway,agent}}$  were then varied iteratively (in pairs) to minimise the value of  $(\sum \chi^2_{\text{urine}} + \sum \chi^2_{\text{faeces}})$ , while preserving a reasonably accurate prediction of the  $^{239+240}\text{Pu}$  contents of the measured tissue contents. As an example, Figure 5 shows the  $\chi^2$  ‘hyper-surface’ obtained by co-varying the K-factors for the ‘blood  $\rightarrow$  urinary path’ and ‘blood  $\rightarrow$  bladder content’ pathways during periods of i.v. Ca-EDTA therapy.

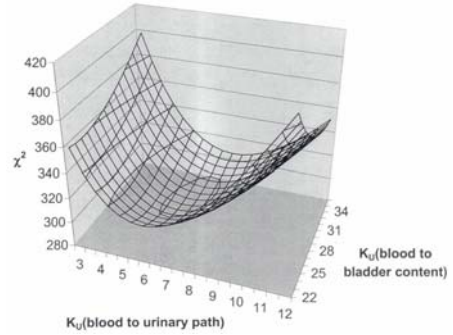


Figure 5.  $\chi^2$  hyper-surface resulting from co-varying a pair of trial EDTA transfer-rate enhancement factors.

This process was repeated iteratively to include examination of all highlighted pathways shown in Figure 4, under the specific influence of both the initial i.v. Ca-EDTA and later i.v. Ca-DTPA therapy regimes.

MODELED EXCRETION BEHAVIOUR

Figures 6 and 7 compare the ‘modeled’ urinary excretion of Pu under the influence of the i.v. Ca-EDTA and Ca-DTPA therapy regimes administered in this case with the respective case bioassay data. Figure 8 shows this comparison for faecal excretion (influenced by i.v. Ca-DTPA).

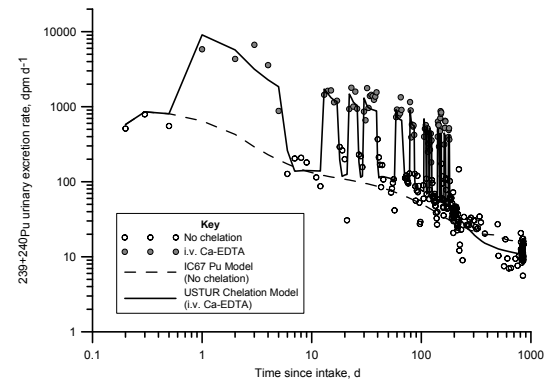


Figure 6. Measured and modeled effects of prompt i.v. Ca-EDTA therapy on Pu urinary excretion.

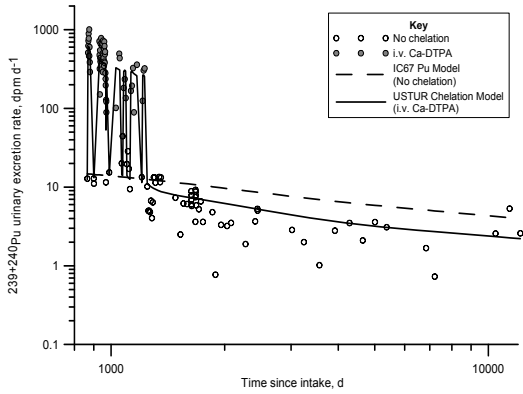


Figure 7. Measured and modeled effects of 3-y-delayed i.v. Ca-DTPA therapy on Pu urinary excretion.

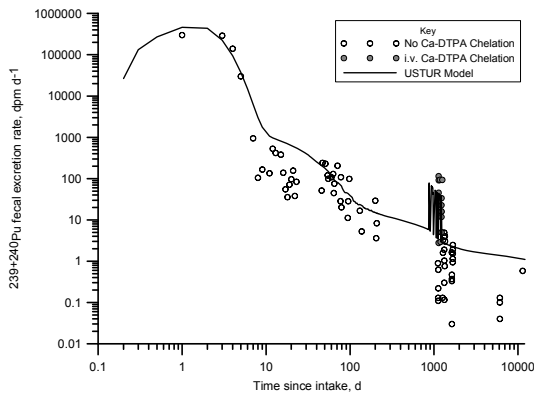


Figure 8. Measured and modeled effects of 3-y-delayed i.v. Ca-DTPA therapy on Pu faecal excretion.

The transfer rate modifying factors derived for both i.v. Ca-EDTA (Figure 6) and Ca-DTPA (Figure 7) accurately predict the observed enhancements in daily excretion of Pu in urine. They also predict the upward shift in the baseline urinary Pu excretion rate compared to that predicted for ‘no treatment’ (by the IC67 Pu biokinetic parameter values). The observed enhancement of faecal Pu excretion influenced by i.v. Ca-DTPA therapy (Figure 8) is also predicted. However, the modeled enhancement factor for the ‘Liver-1 → SI’ pathway (Figure 4), fitted in combination with the other rate enhancement factors, does not yet represent accurately the long-term ‘baseline’ (systemic) faecal Pu excretion.

#### DERIVED DECORPORATION EFFECTIVENESS

Table 2 compares the  $^{239+240}\text{Pu}$  tissue contents measured in this case at the time of death with those predicted by the derived models of i.v. Ca-EDTA and

Ca-DTPA transfer rate enhancements. The table also shows the final body burden predicted in the absence of these decorporation effects, i.e., for ‘no treatment.’

Table 2. Measured and modeled tissue contents

Tissue	$^{239+240}\text{Pu}$ Content at Death, kBq			
	Autopsy	USTUR Model		
		Treated	Untreated	Saved
Whole body	2.29	2.29	4.22	46%
Lungs	0.027	0.027	0.027	0%
LNTH	0.00019	0.00021	0.00021	0%
Liver	0.94	0.81	1.62	50%
Skeleton	1.20	1.21	2.18	45%
Muscle, Skin, etc.	0.18	0.23	0.38	39%
Testes	0.83	0.83	1.47	44%
Kidneys	0.0017	0.0017	0.0032	47%

The inferred ability of delayed i.v. Ca-DTPA to decorporate a significant amount of Pu from bone surfaces and bone marrow confirms the much earlier quantitative observations of these processes in experimental animals (weanling rats).<sup>(12)</sup> In this human case, the ratios of  $^{239+240}\text{Pu}$  concentrations measured in trabeculated bones : that measured in cortical bone was significantly lower than the range found in other (non-chelated) USTUR cases.

#### CONCLUSION AND COMMENTS

The study outlined here is a ‘work in progress.’ The analytical methods applied and the resulting detailed model of the effects of i.v. Ca-EDTA and Ca-DTPA treatment in terms of specific ‘transfer-rate-enhancement’ factors will be described elsewhere.<sup>(13)</sup>

These case data are currently being re-analysed for final publication by substituting the recently reported ‘modified’ Pu biokinetic model of Leggett et al.<sup>(14)</sup> as the ‘baseline,’ in place of the IC67 model used here. The newer model treats the early kinetics of Pu transfer between two blood compartments and tissue fluid in a manner that is consistent with the results of European biokinetic studies with human volunteers.<sup>(15,16)</sup> Planned further study of the Case 0269 data includes extension of the modeling process to evaluate the effects of the Ca-EDTA and Ca-DTPA therapies in decorporating in-grown  $^{241}\text{Am}$  from body tissues. USTUR has determined the  $^{241}\text{Pu}$  content of the inhaled Pu material by measuring the amount of  $^{241}\text{Am}$  in-growth in the original urine planchets (5 decades after the original chemical separation).

However, it is already clear from this initial study that both the i.v. Ca-EDTA and i.v. Ca-DTPA therapies administered in this case had substantial

(quantifiable) effects in decorporating Pu from the liver, soft tissues, bone marrow and bone surfaces. In fact, even after a 3-y delay in starting i.v. Ca-DTPA therapy, this was about equally effective in decorporating Pu from these tissues as the prompt treatment with i.v. Ca-EDTA.

States Government nor any agency thereof, nor any of their employees, makes any warranty, expressed or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

#### ACKNOWLEDGEMENT AND DISCLAIMER

This paper is based upon work supported by the U.S. Department of Energy, Office of Epidemiology and Health Surveillance, under Award Number DE-FG06-92EH89181. It was prepared as an account of work sponsored by an agency of the United States Government. Neither the United

#### REFERENCES

1. Gerber, G. B. and Thomas, R. S. (eds). *Guidebook for the treatment of accidental internal radionuclide contamination of workers*. Radiat. Prot. Dosim. **41**(1) (1992).
2. Henge-Napoli, M. H., Stradling, G. N. and Taylor, D. M. *Decorporation of radionuclides from the human body*. Radiat. Prot. Dosim. **87**(1) (2000).
3. Taylor, D. M., Stradling, G. N. and Ménétrier. *Biokinetics of radionuclides and treatment of accidental intakes*. Radiat. Prot. Dosim. **105**(1-4), 637-640 (2003).
4. International Commission on Radiological Protection. *Age-dependent dose to members of the public from intake of radionuclides: Part 2, ingestion dose coefficients*. ICRP Publication 67. Ann. ICRP **23**(3/4) (1993).
5. Langham, W. H. *Excretion methods: The application of excretion analyses to the determination of body burden of radioactive isotopes*. Brit. J. Radiol. **Suppl. 7**, 95-113 (1957).
6. Healy, J. W. *Estimation of plutonium lung burden by urine analysis*. Am. Ind. Hyg. Assoc. Quart. **18**, 261-266 (1957).
7. National Committee on Radiation Protection (NCRP). Subcommittee on permissible internal dose. *Maximum permissible amounts of radioisotopes in the human body and maximum permissible concentrations in air and water*. Washington, DC: U.S. Department of Commerce; NCRP Report No. 11. U.S. Bureau of Standards, Handbook 52 (1953).
8. James, A. C., Filipy, R. E., Russell, J. J., McInroy, J. F. *USTUR case 0259 whole body donation: A comprehensive test of the current ICRP models for the behavior of inhaled  $^{238}\text{PuO}_2$  ceramic particles*. Health Phys. **84**, 2-33 (2003).
9. James, A. C., Birchall, A., Marsh, J. W. and Puncher, M. User Manual for *IMBA-EXPERT<sup>TM</sup> USDOE-Edition (Phase II)*. Richland, WA: ACJ & Associates, Inc. (2004). Available in pdf from [www.imbaexpert.com](http://www.imbaexpert.com).
10. James, A. C., Sasser, L. B., Stuit, D. B., Wood, T. G., Glover, S. E., Lynch, T. P. and Dagle, G. E. *USTUR whole body case 0262: 33-y follow-up of  $\text{PuO}_2$  in a skin wound and associated lymph node*. Radiat. Prot. Dosim. (In press) (This issue).
11. International Commission on Radiological Protection. *Human respiratory tract model for radiological protection*. ICRP Publication 66. Ann. ICRP **24**(1-3) (1994).
12. James, A. C. and Taylor, D. M. *DTPA therapy for chelation of  $^{239}\text{Pu}$  in bone: The influence of bone remodeling*. Health Phys. **21**, 31-39 (1971).
13. James, A. C., Filipy, R. E., Sasser, L. B., Stuit, D. B., Glover, S. E. and Carbaugh, E. H. *USTUR whole body case 0269: I. Modeling the effectiveness of i.v. Ca-EDTA and Ca-DTPA therapy in reducing  $^{239}\text{Pu}$  tissue burdens. (in preparation)*.
14. Leggett, R. W., Eckerman, K. F., Khokhryakov, V. F., Suslova, K. G., Krahenbuhl, M. P. and Miller, S. C. *Mayak worker study: An improved biokinetic model for reconstructing doses from internally deposited plutonium*. Radiat. Res. **164**, 111-122 (2005).
15. Talbot, R. J., Newton, D. and Warner, A. J. *Metabolism of injected Pu in two healthy men*. Health Phys. **65**, 41-46 (1993).
16. Ham, G. J. and Harrison, J. D. *The gastrointestinal absorption and urinary excretion of Pu in male volunteers*. Radiat. Prot. Dosim. **87**, 267-272 (2000).