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the Health Effects of Incorporated Radionuclides
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The United States Transuranium and Uranium Registries: Fifty-year History of Actinide Biokinetic Research

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*“Learning from Plutonium and
Uranium Workers”*

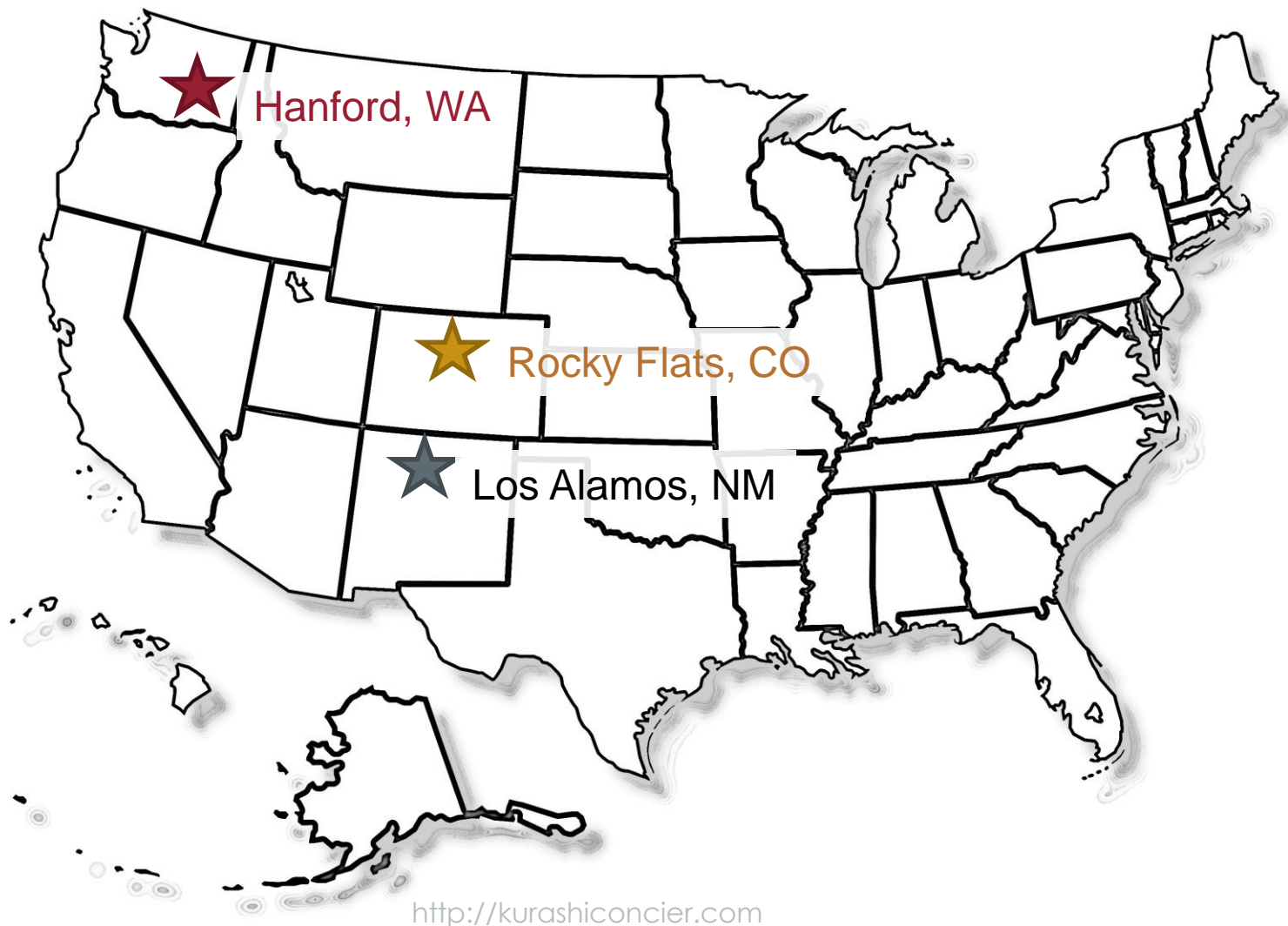




U.S. Transuranium and Uranium Registries: History and Mission



Early Autopsy Studies





U.S. AEC 1966 Meeting on Plutonium Contamination in Man (Rocky Flats Plant)





National Plutonium Registry: 1968 Advisory Committee Meeting



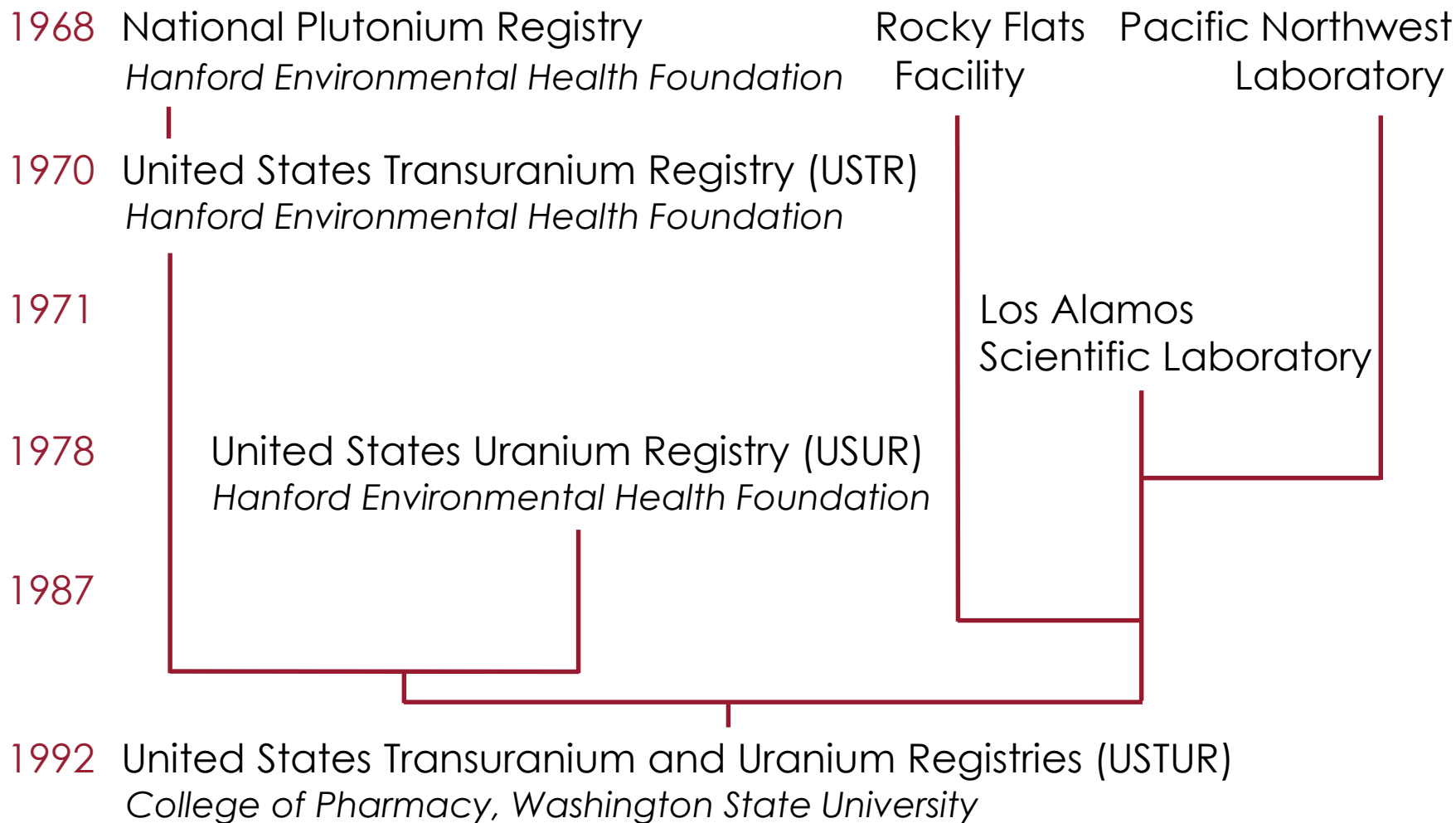
Standing left to right: Carlos E. Newton, Jr., W. Daggett Norwood, H.D. Bruner, Philip A. Fuqua
Seated left to right: Thomas F. Mancuso, J.H. Sterner, Robley D. Evans, Herbert M. Parker
Not photographed: Clarence C. Lushbaugh, Lloyd M. Joshel



Genealogy of the USTUR

REGISTRIES MANAGEMENT

ANALYTICAL SUPPORT





USTUR Today

- The United State Transuranium and Uranium Registries (USTUR) is a federal-grant program funded by the U.S. DOE Office of Domestic and International Health Studies (AU-13)
- Operated by College of Pharmacy and Pharmaceutical Sciences at Washington State University under Central DOE Institutional Review Boards
- Budget: \$5,500,000 (April 1, 2017 – March 31, 2022)
- Faculty and staff:



- Location: Richland, WA
- Website: www.ustur.wsu.edu



Current Mission

- Follow up occupationally-exposed individuals (volunteer Registrants) by **studying the biokinetics** (deposition, translocation, retention, and excretion) and tissue dosimetry of **uranium and transuranium elements**, such as plutonium, americium, curium, and neptunium
- Obtain, analyze, preserve, and **make available for future research**, materials from individuals who had documented intakes of uranium and transuranium elements
- Apply USTUR data to **refine dose assessment methods** in support of reliable epidemiological studies, radiation risk assessment, and regulatory standards **for radiological protection of workers and general public**

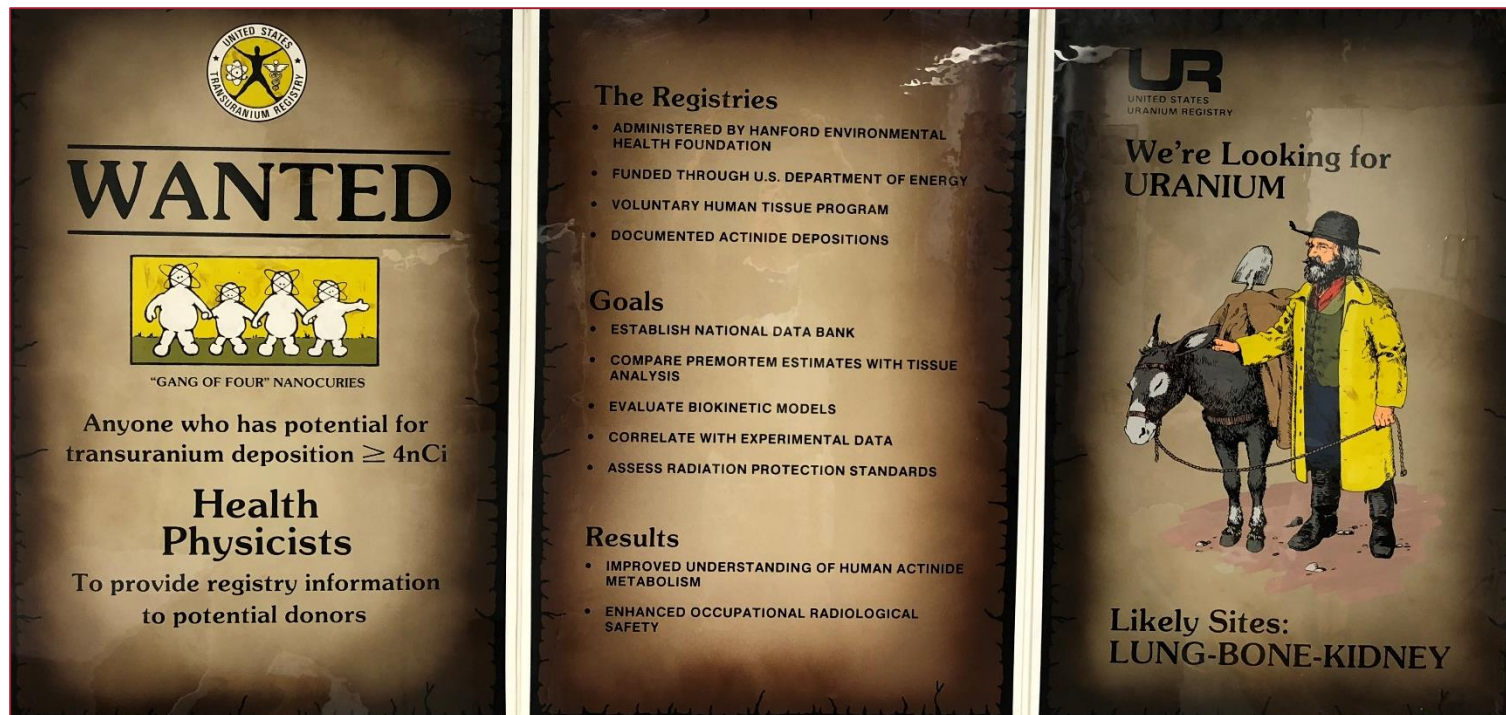


USTUR Registrants



USTUR Registrants (I)

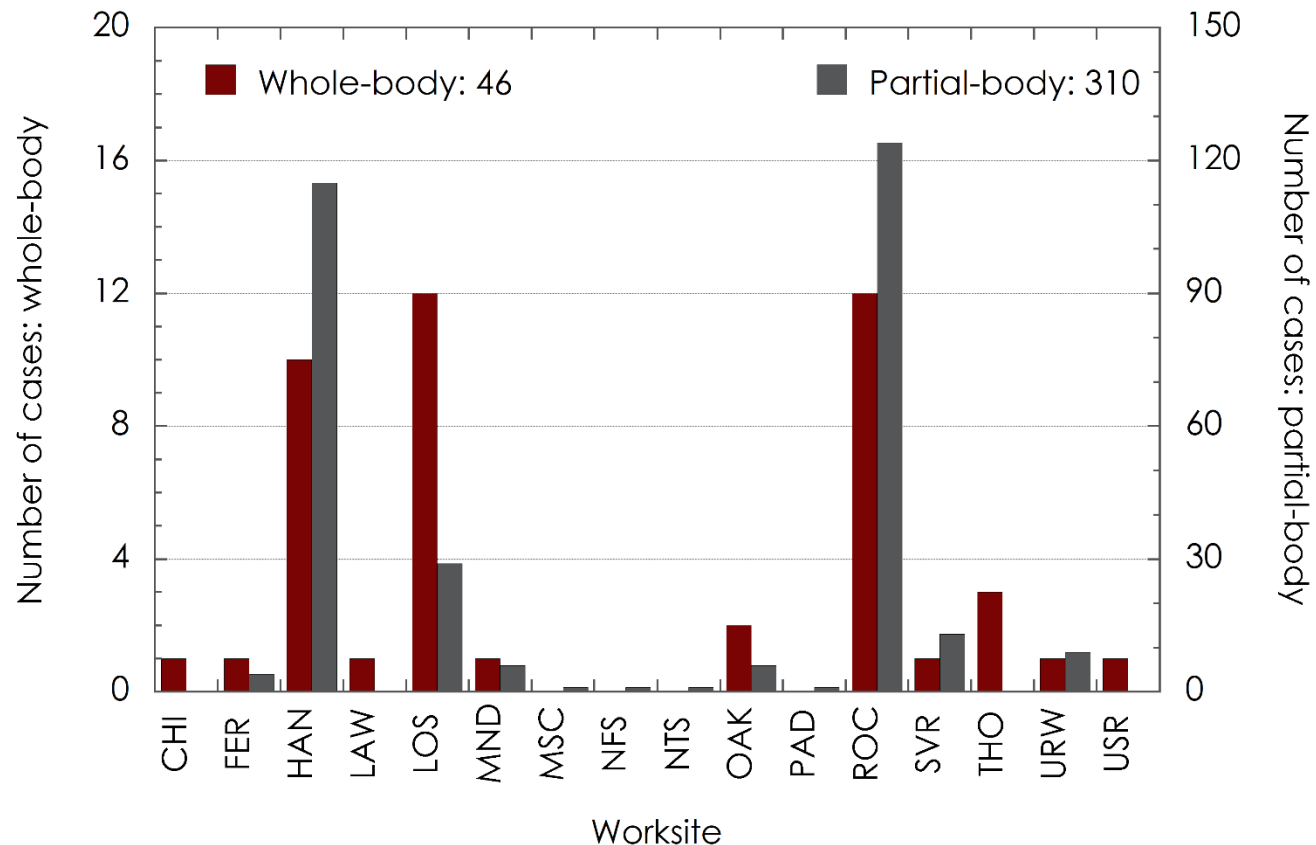
- Voluntary tissue donors (posthumous)
- Documented radiation exposure and work history
- Acceptance criteria:
 - i. actinide internal deposition of ≥ 74 Bq (2 nCi)
 - ii. external dose to whole body ≥ 0.1 Sv (10 rem)





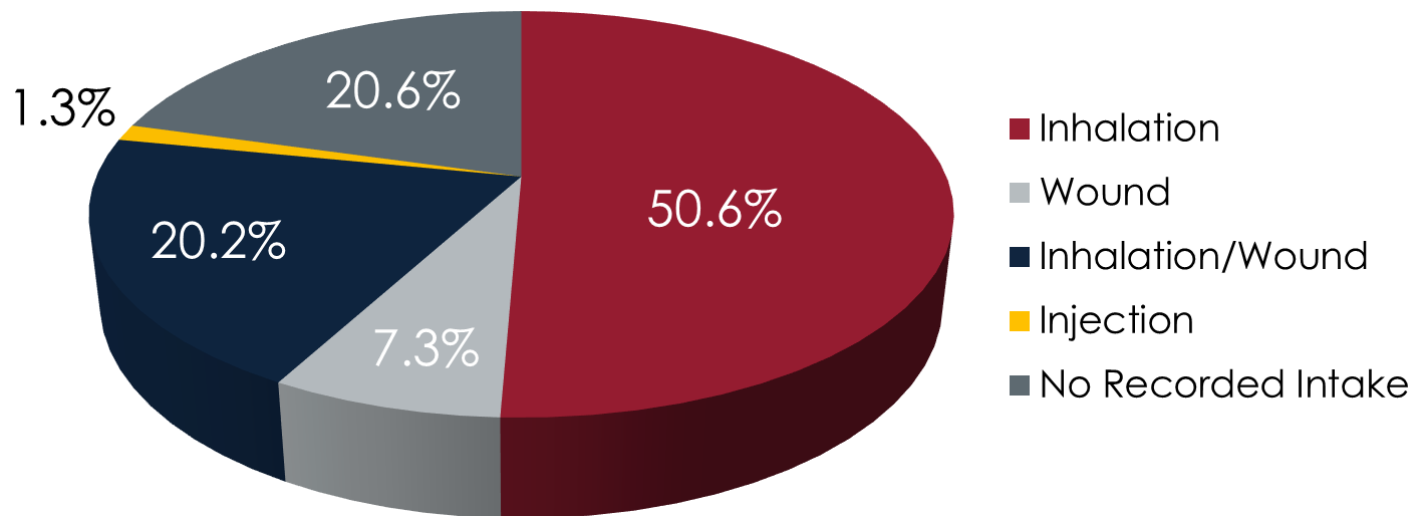
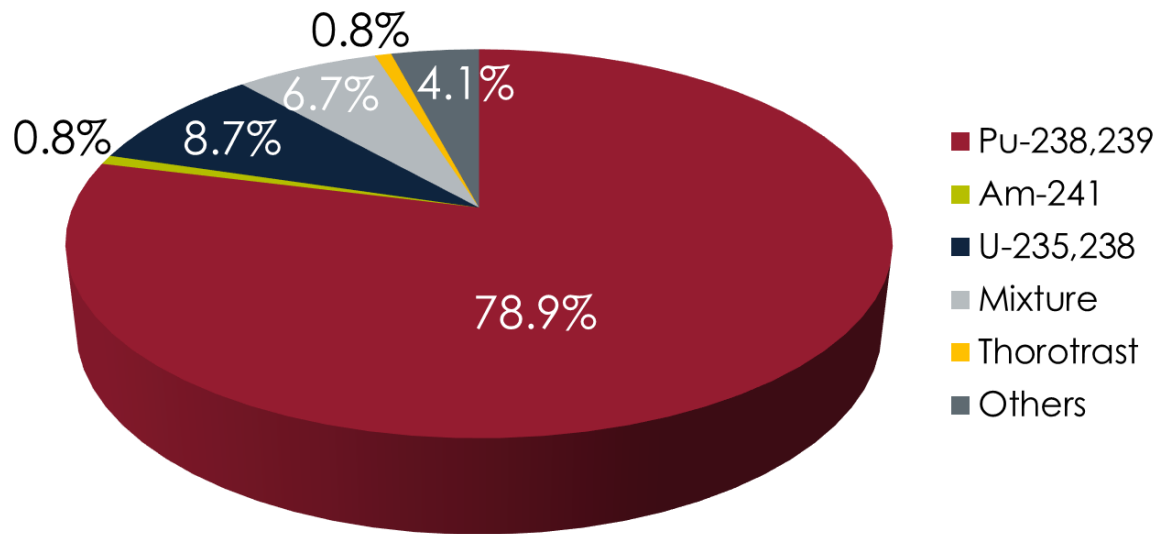
USTUR Registrants (II)

- Voluntary tissue donors (posthumous)
whole- (46) and/or partial-body (310) donation
- Former nuclear workers from DOE sites



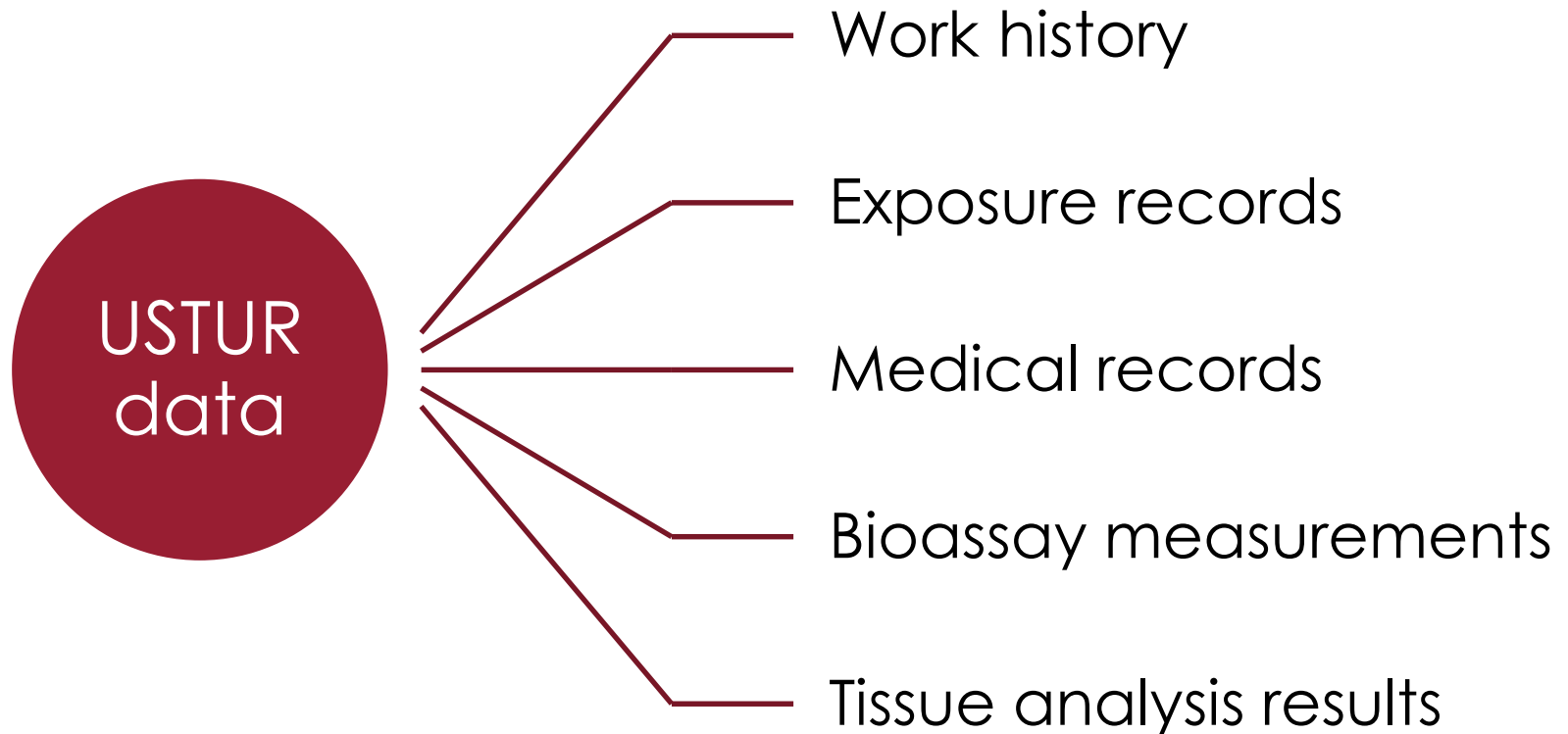


Primary Intakes



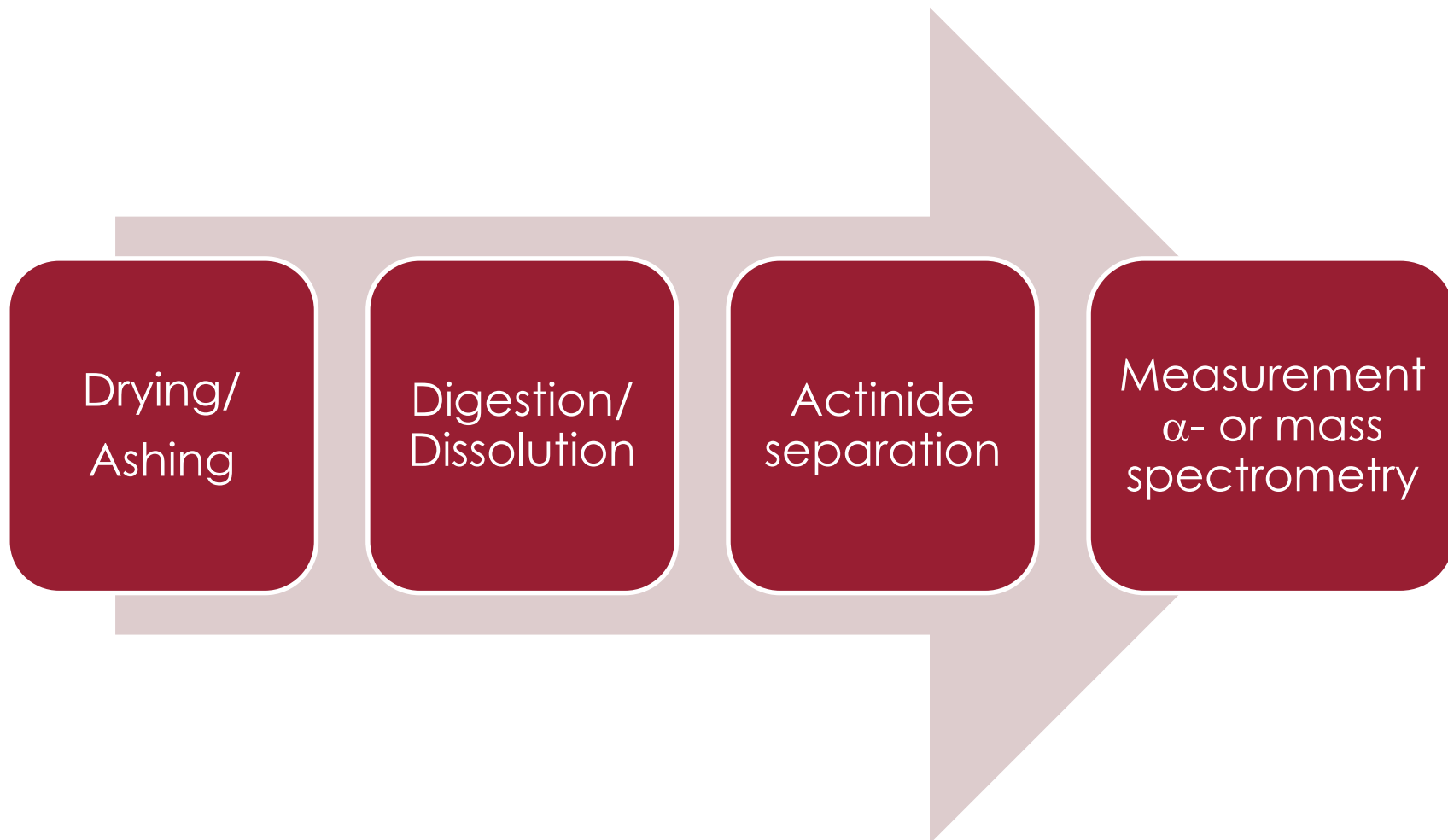


Unique Data Resource



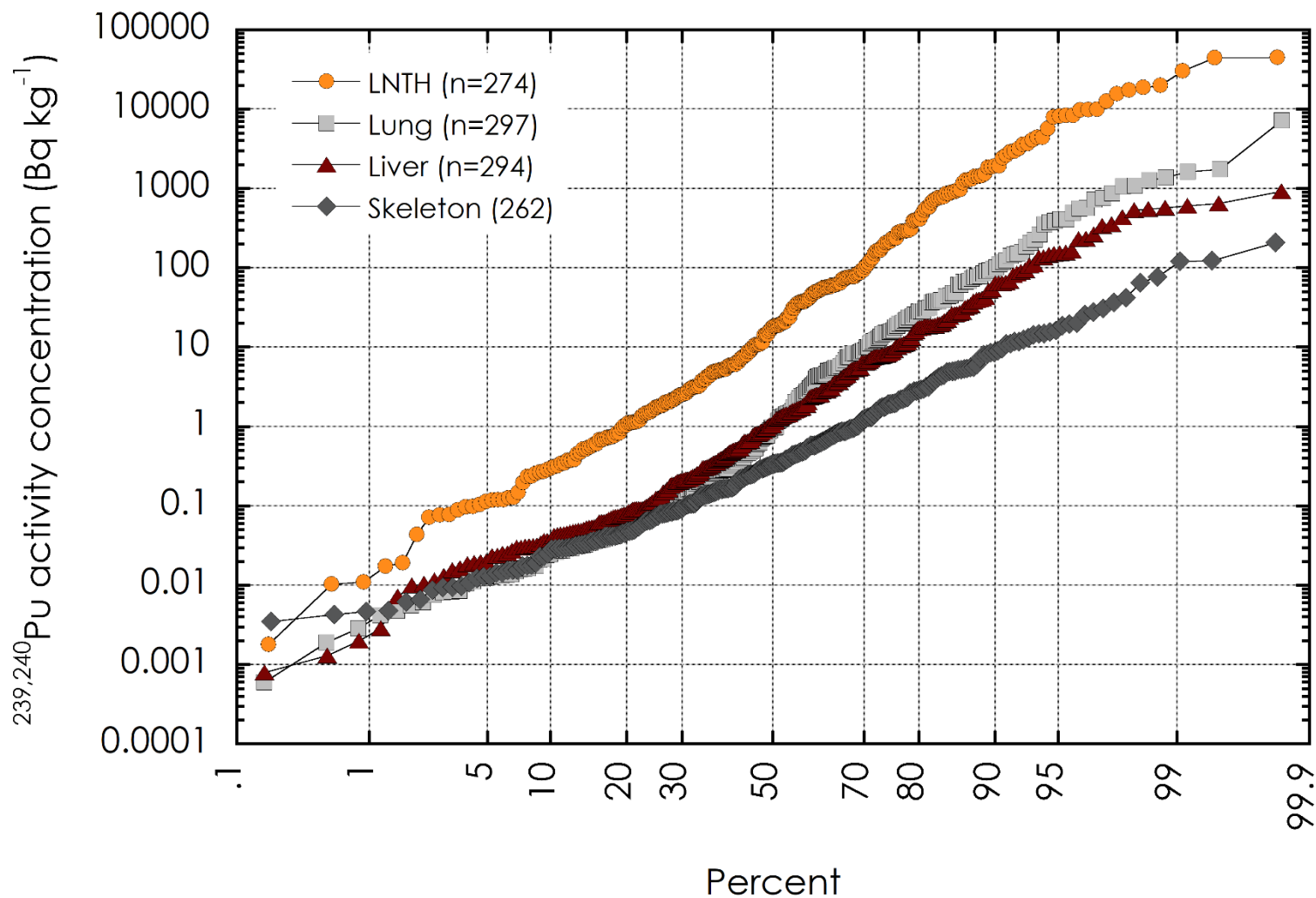


Tissue Analysis: *Backbone of the USTUR*



- 300 – 400 tissue analysis for Pu/Am and U per year

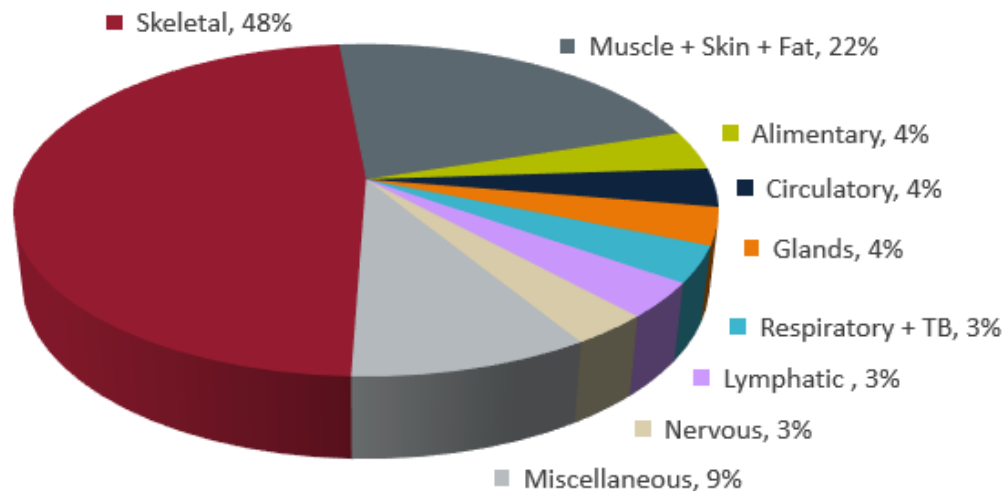
Plutonium in Tissues of USTUR Donors





National Human Radiobiology Tissue Repository (NHRTR)

- USTUR tissue donations: 9,000+ frozen tissues
- Argonne National Laboratory (ANL) historical samples
 - ✓ Radium dial painters
 - ✓ Plutonium injection studies
- Los Alamos National Laboratory (LANL) population studies

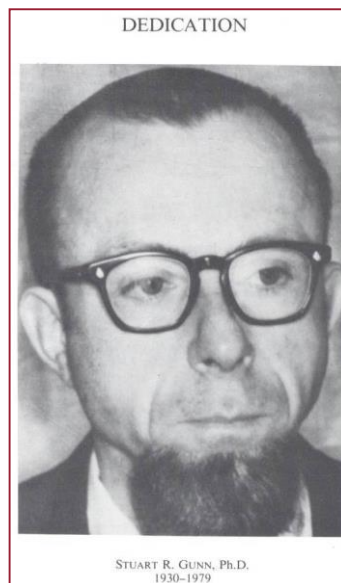
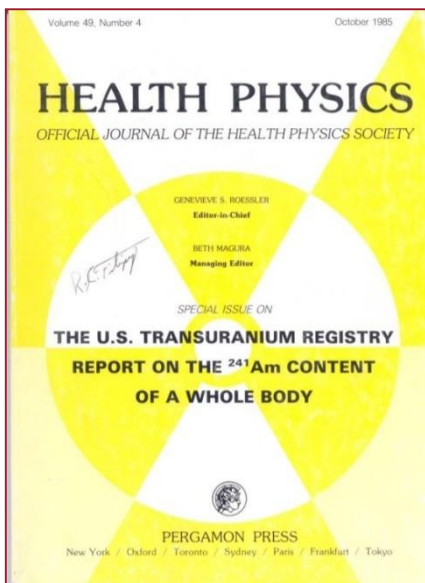




Historical Landmarks

First Whole-Body Donation: Case 0102

- Worked with unsealed ^{241}Am source for 2 years
- ^{241}Am was detected later in routine urine samples
- Contemporary estimate of intake: 8 – 40 kBq
- Systemic deposition: 82% skeleton, 6.3% liver; 11% other tissues
- *In vivo* calibration phantoms of skull, torso, arm and leg

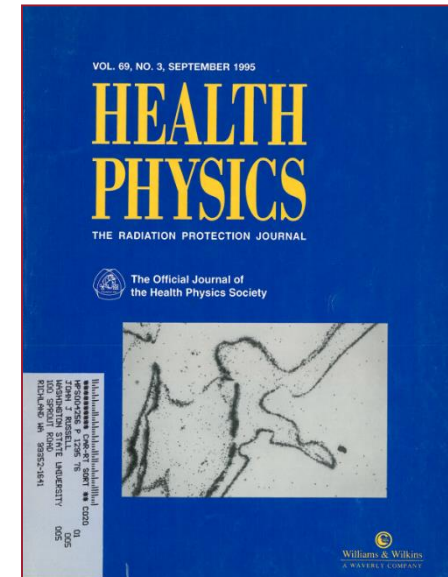
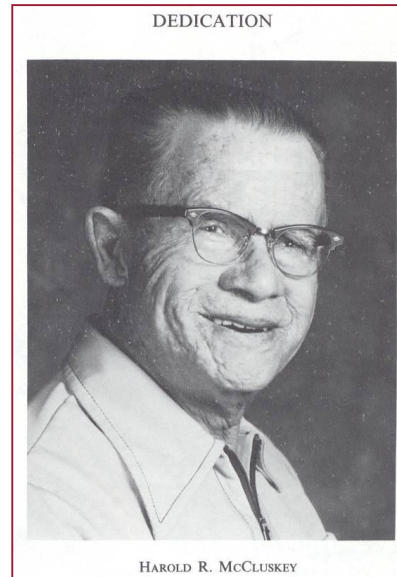
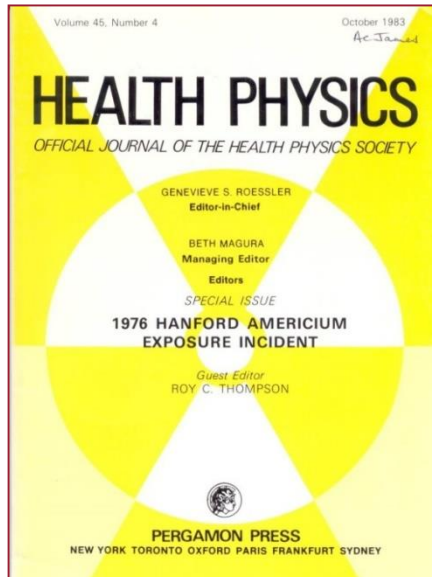




The Atomic Man: Case 0246

Largest recorded Am intake !!!

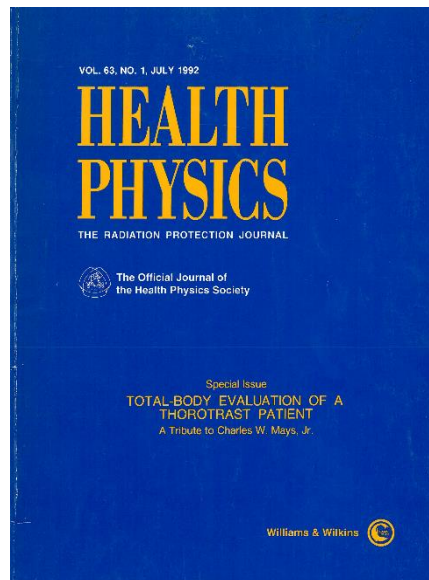
- Explosion of ion-exchange column with ~150 g of ^{241}Am
- Estimated uptake > 40 MBq
- Extensive Ca/Zn-DTPA chelation therapy
- Systemic deposition after treatment – 0.5 MBq





Thorotrast Study: Case 1001

- First study of thorium distribution in a human body
- Female whole-body donor
- Medical exposure to Thorotrast® ($^{232}\text{ThO}_2$ colloidal)



- Findings
 - ✓ Alpha risk coefficients for liver, skeleton, and leukemia
 - ✓ Spleen destruction
 - ✓ Clarified epidemiologic studies
 - ✓ DNA analysis: deleted region of *c-fms* gene, possibly radiation induced

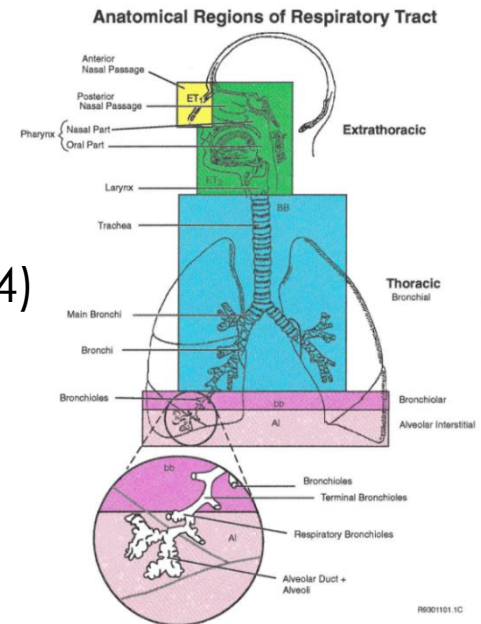


Current Research and Collaborations



Primary Research: *Biokinetic Modeling and Internal Dosimetry of Actinides*

- Testing, improving and parameterizing biokinetic models for radiological protection
 - ✓ Human Respiratory Tract Model (ICRP 130)
 - ✓ Wound Model (NCRP 156)
 - ✓ Systemic models for U, Pu, Am (ICRP OIR3 & OIR4)
- Evaluating uncertainties in internal radiation dose assessment
- Modeling actinide decorporation



Courtesy of W.J. Bair

USTUR Presentations

- I. Avtandilashvili and Tolmachev. Biokinetics of soluble plutonium after wound injury treated with Ca-DTPA
- II. Leggett *et al.* Case studies in brain dosimetry for internal emitters: Is more detail needed for epidemiology?
- III. Tolmachev *et al.* USTUR: Expanding horizons for actinide biokinetics and dosimetry



IMBA Professional Plus® Software

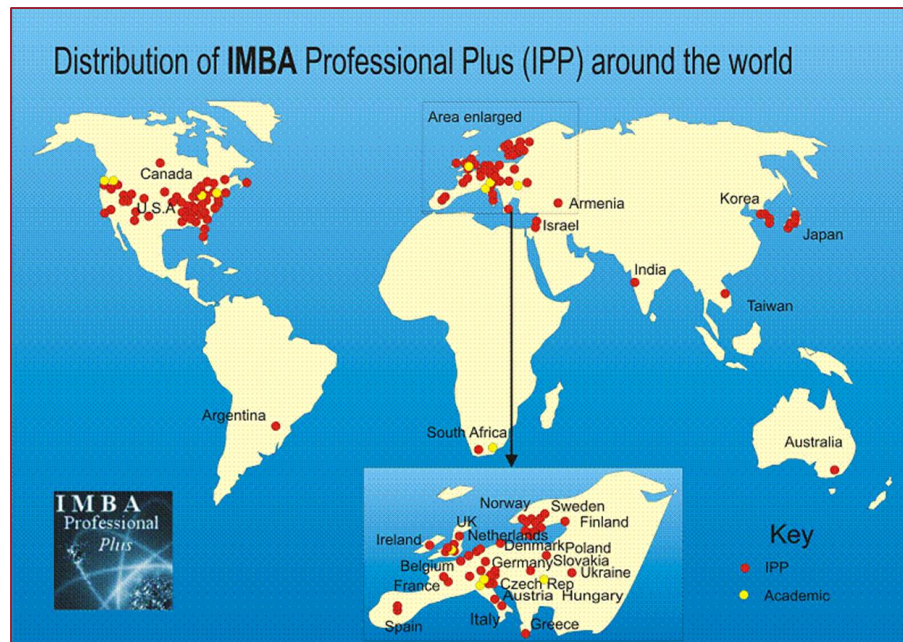
- Developed: ACJ & Associates (USA) and Health Protection Agency (UK)
- Funded: U.S. DOE, COG, and NIOSH



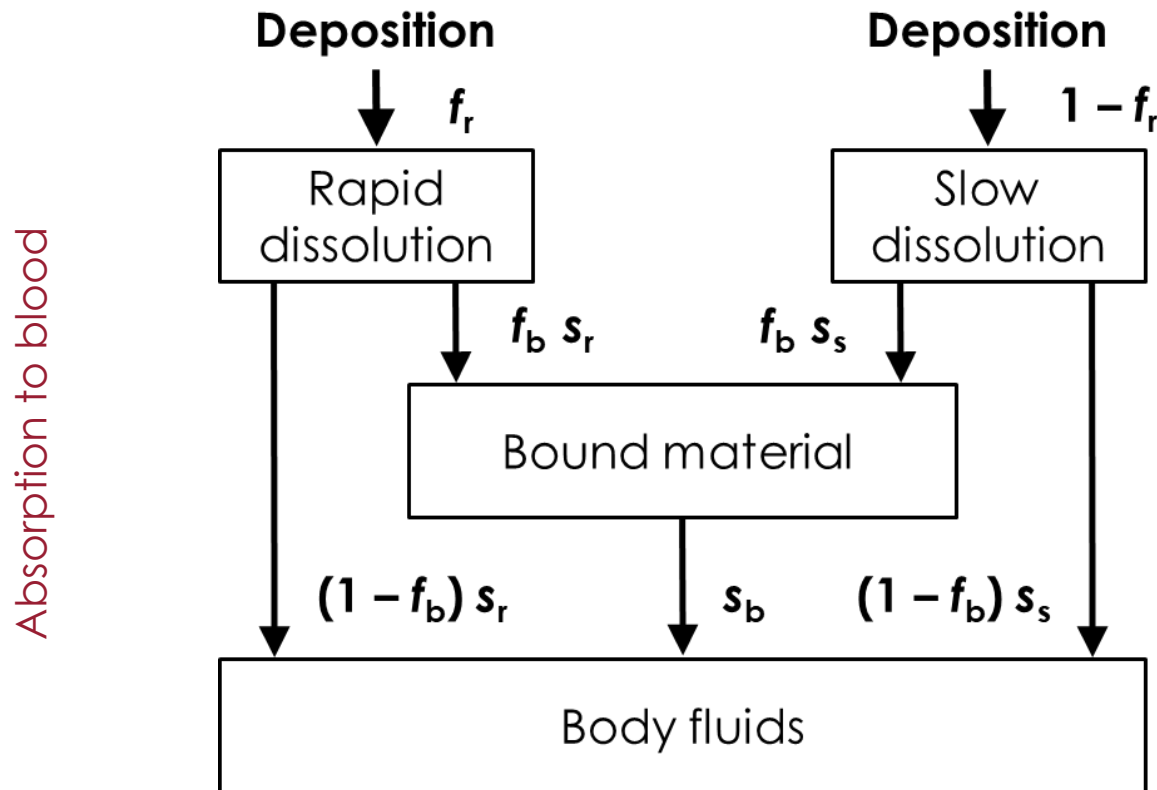
Dr. Anthony James
WSU/USTUR, Research
Professor & Director



Dr. Alan Birchall
WSU/USTUR
Adjunct Professor

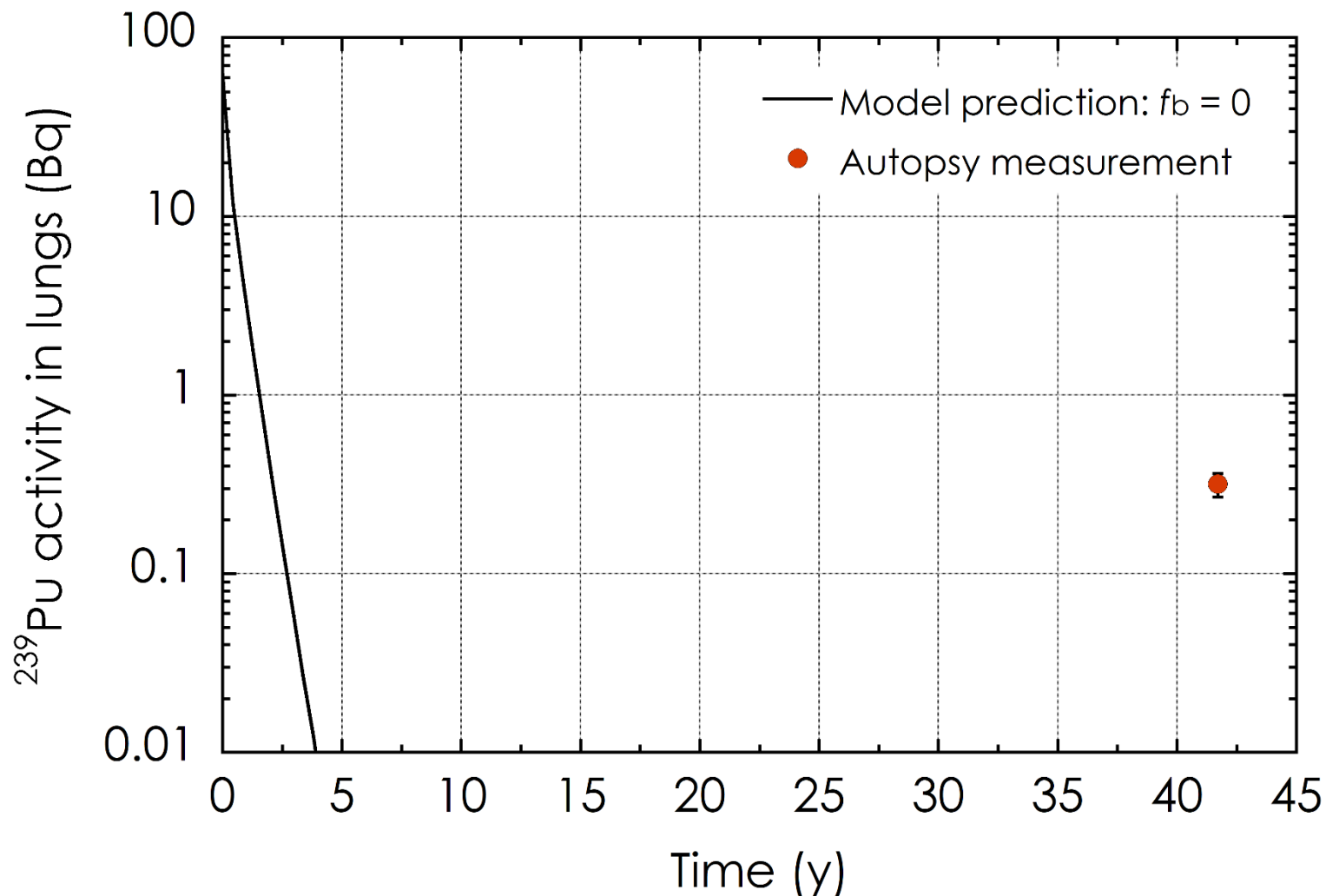


Human Respiratory Tract Model: *Plutonium Bound Fraction*

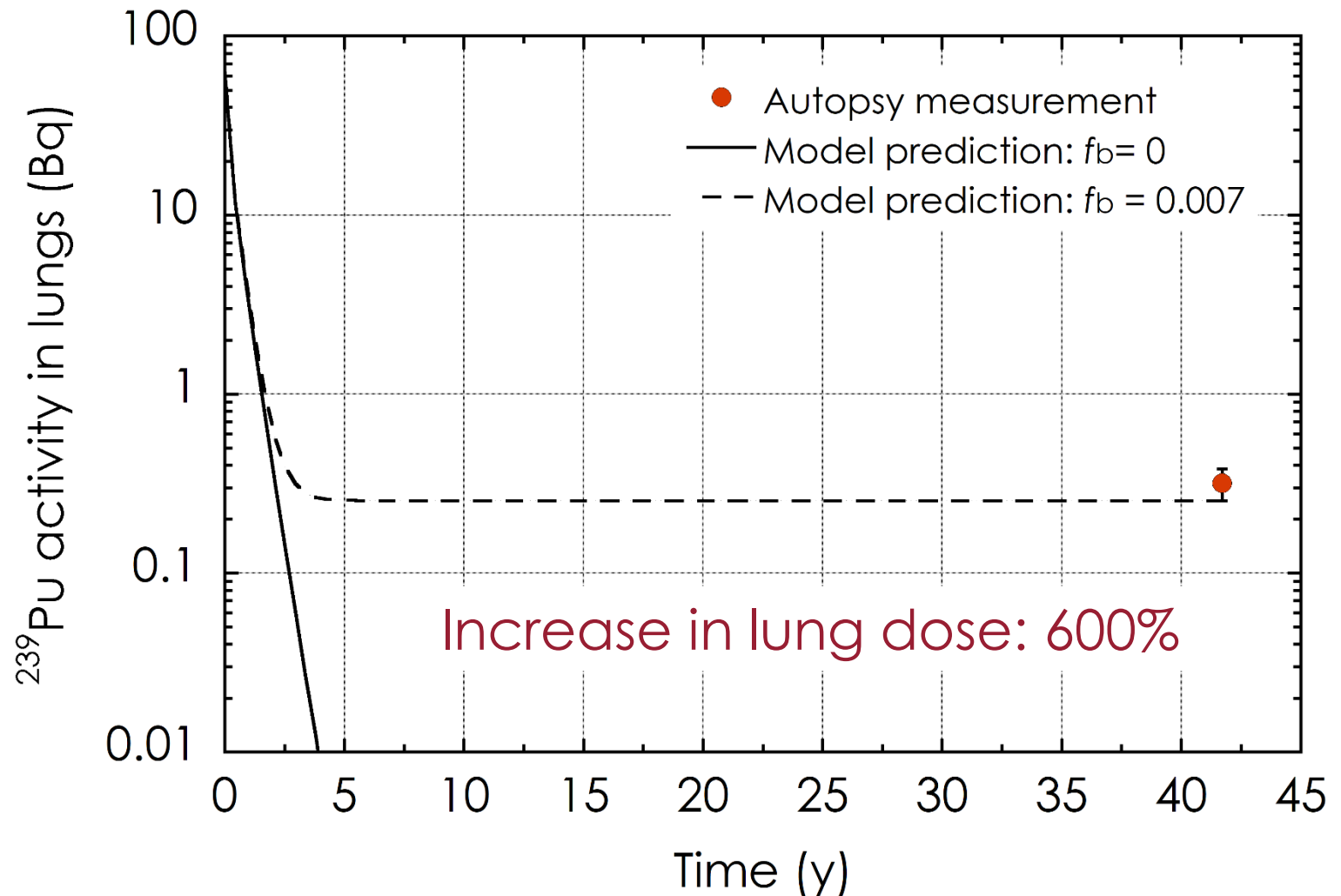


- Bound material fraction: f_b
- ICRP 66, ICRP 130 HRTM: $f_b = 0$
- OIR Part 4 (*upcoming*): $f_b = 0.002$

Soluble ^{239}Pu Retention in Lungs: $f_b = 0$



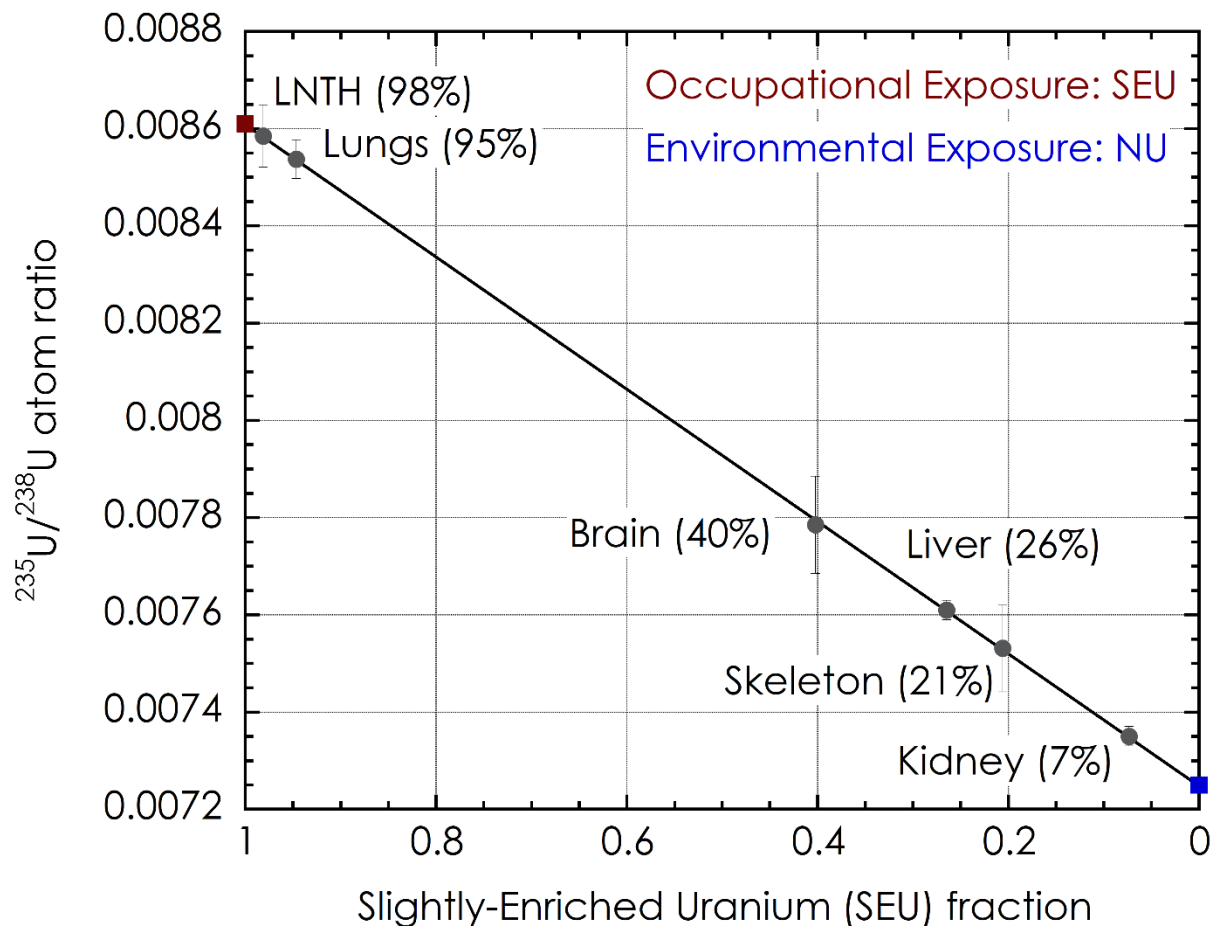
Soluble ^{239}Pu Retention in Lungs: $f_b = 0.007$





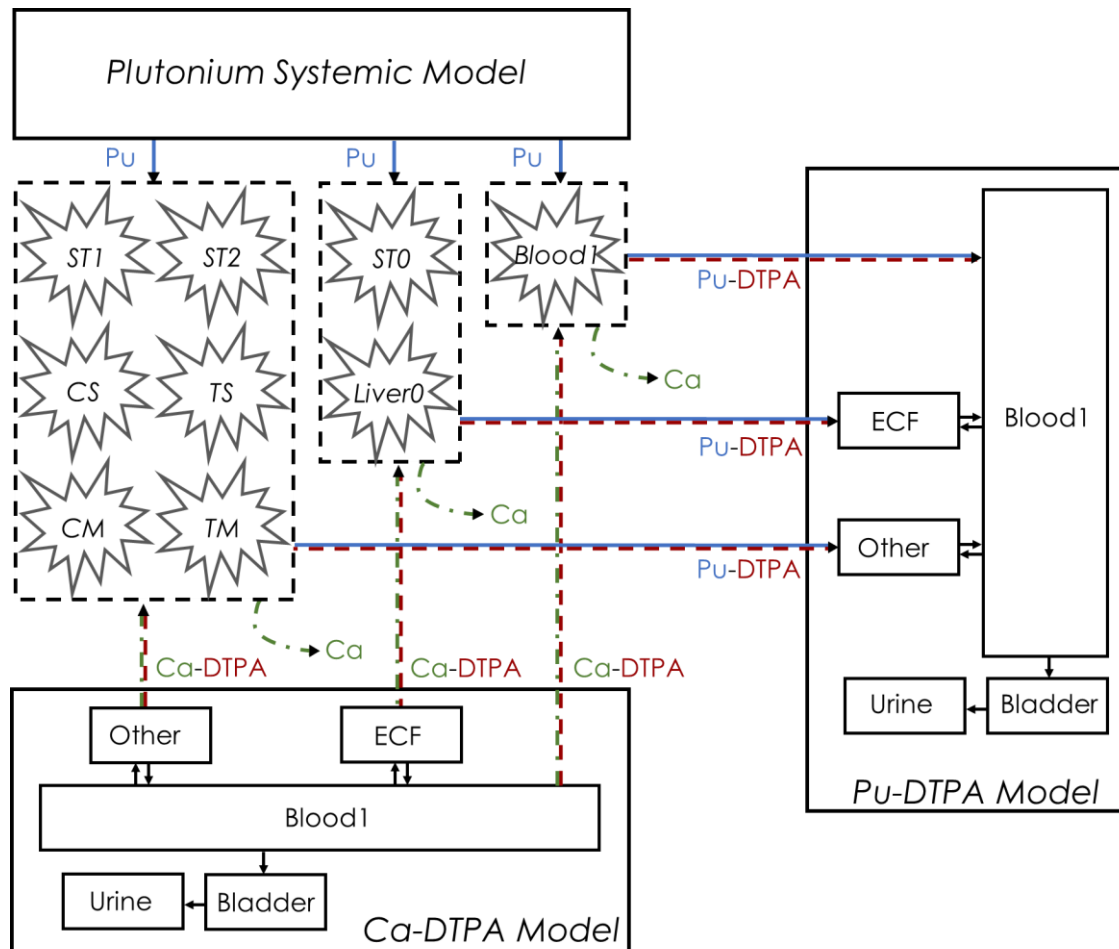
Uranium Hexafluoride Inhalation

- Acute inhalation due to massive explosion of UF_6 tank
- Slightly enriched U retained in lungs 65 y post-intake



Avtandilashvili *et al.* J. Radiol. Prot. 35: 129-151; 2015.

New System of Models for Plutonium Decorporation



Assumptions

- Chelation in extra-cellular fluid, liver, and skeleton in addition to chelation in blood
- Same model structure for the injected Ca-DTPA and Pu-DTPA chelate
- Different kinetics for Ca-DTPA and Pu-DTPA

Dumit *et al.* Radiation Research (submitted); 2018.



Collaborative Research Network

- Actinide biokinetic modeling and dosimetry
- Chelation therapy modeling
- Radiation biomarkers
- Nuclear forensics
- Actinide nanoparticles
- Beryllium and zirconium



National Council on Radiation
Protection and Measurements





USTUR Scientific Contributions





Contribution to National Council on Radiation Protection and Measurements

- Report 164: Uncertainties in Internal Radiation Dose Assessment (2009)
- Report 163: Radiation Dose Reconstruction Principles and Practices (2009)
- Report 156: Development of a Biokinetic Model for Radionuclide-Contaminated Wounds for Their Assessment, Dosimetry and Treatment (2006)
- Report 135: Liver Cancer Risk from Internally-Deposited Radionuclides (2001)
- Report 128: Radionuclide Exposure of the Embryo/Fetus (1998)

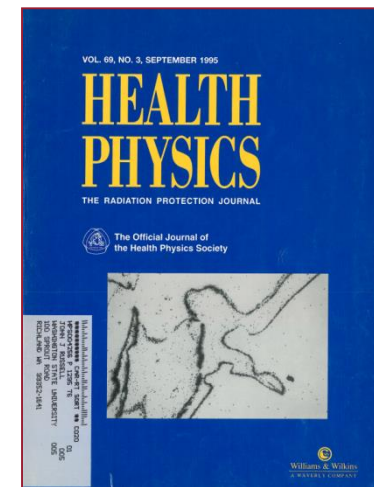
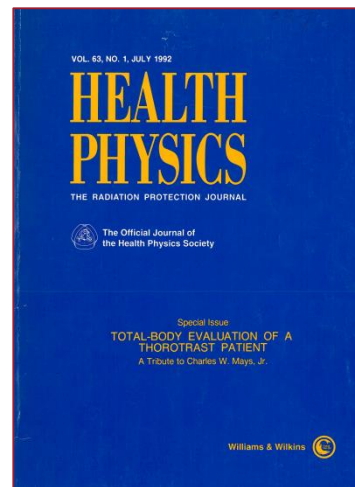
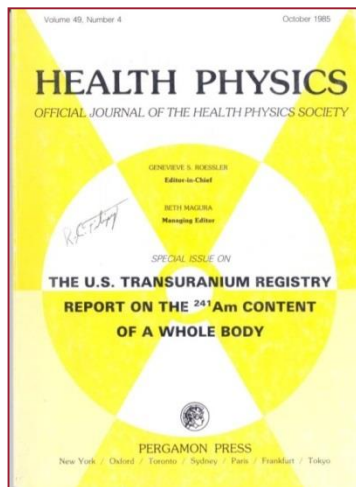


Contribution to International Commission on Radiological Protection

- Occupational Intakes of Radionuclides - Part 4 (upcoming)
- Publication 137: Occupational Intakes of Radionuclides - Part 3 (2017)
- Publication 70: Basic Anatomical & Physiological Data for Use in Radiological Protection - The Skeleton (1995)
- Publication 69: Age-dependent Doses to Members of the Public from Intake of Radionuclides - Part 3 Ingestion Dose Coefficients (1995)
- Publication 66: Human Respiratory Tract Model for Radiological Protection (1994)
- Publication 67: Age-dependent Doses to Members of the Public from Intake of Radionuclides - Part 2 Ingestion Dose Coefficients (1993)
- Publication 56: Age-dependent Doses to Members of the Public from Intake of Radionuclides - Part 1 (1989)
- Publication 48: The Metabolism of Plutonium and Related Elements (1986)

Health Physics Journal Special Issues

- 2019, **upcoming**: *The United States Transuranium and Uranium Registries (USTUR): Five Decade Follow-up of Plutonium and Uranium Workers*
- 1995, 69 (3): *1976 Hanford Americium Exposure Incident: Update*
- 1992, 63 (1): *Total-body Evaluation of a Thorotrast Patient*
- 1985, 49 (4): *The U.S. Transuranium Registry Report on the ^{241}Am Content of a Whole Body*





USTUR Special Issues: HPJ PAP

MODELING THE SKELETON WEIGHT OF AN ADULT CAUCASIAN MAN

Abstract—The reference male (10.5 kg) recommended by the International Commission on Radiological Protection (ICRP) was dissected skeletons from uranium and Uranium national Commission on Radiological Protection (ICRP) anatomical data from 3 height demonstrated skeleton weight and body height $W_{\text{skel}} \text{ (kg)} = -10.7 + 0.1 H \text{ (cm)}$ was used to estimate the skeleton weight of the U.S. Transuranium and Uranium Registries (TUR) individual bone weights from which has provided a national Commission on Radiological Protection (ICRP) vs. body height equation on Radiological Protection (ICRP) uranium and Uranium 69 data points represent with body heights and 188 cm and 6.5 to 13.4 kg. A least-squares regression of two parameters was observed vs. body height $W_{\text{skel}} = 0.093 \times H \text{ (cm)}$. In addition, multiple variables included were evaluated using multiple regression fit equation $W_{\text{skel}} = 0.036 \times H \text{ (cm)} + 0.036 \times W_{\text{body}}$ to be used to estimate skeleton weight activities for bone and Uranium Registries (TUR) Health Phys. 115(000):000-000; 2018.

Key words: International Commission; Reference Man; U.S.

THE IMPORTANCE AND QUANTIFICATION OF PLUTONIUM BINDING IN HUMAN LUNGS

Alan B. ...

Abstract—Epidemiological data arising from exposure to plutonium and other detrimental effects of these risks, in dosimetric models used to estimate the lung dose, is extremely important. The International Commission on Radiological Protection (ICRP) model, has been developed for use in the plutonium study involving the plutonium workers in Ozersk, Russia. One important factor in the lung dose is the binding of plutonium, which becomes bound to the lung tissue. It has been shown that if just in the bronchial region, the binding is very difficult to quantify. This paper summarizes the results of a Bayesian analysis of 20 measurements. The results suggest a small fraction for all actinides in internal dosimetry. In an analysis of the International Commission on Radiological Protection (ICRP) considering the adoption of a fraction for all actinides in internal dosimetry. In an analysis of the International Commission on Radiological Protection (ICRP) further experimental work is planned. This paper assesses the direct measurement of tissues of workers who have been cleared by the national Commission on Radiological Protection (ICRP) and corroborate previous information.

EVALUATING PLUTONIUM INTAKE AND RADIATION DOSE FOLLOWING EXTENSIVE CHELATION TREATMENT

Sara Dumit, Maia Avtandilashvili, and Sergei Y. Tolmachev¹

Abstract—A voluntary partial-body donor (TUR Case 0785) was exposed to ^{239}Pu via inhalation and wounds. This individual received treatment including wound excision, treatment with calcium ethylenediaminetetraacetic acid (CaEDTA), and treatment with calcium diethylenetriaminepentaacetic acid (CaDTPA). Major soft tissues and selected bones were and radiochemically analyzed for ^{239}Pu . Mortem systemic retention of ^{239}Pu was estimated to be $32.0 \pm 1.4 \text{ Bq}$, $2.172 \pm 70 \text{ Bq}$, and 39 Bq in the lungs 51 y after the accident indicated by the plutonium material. To estimate the radiation dose, urine measurements not treatment, in vivo chest counts, and post mortem analysis data were simultaneously used. Modules for Bioassay Analysis Professionals currently recommended International Commission on Radiological Protection Publication 130 human and National Council on Radiation Protection Report 156 wound model were used with the intake, adjusted for ^{239}Pu removed by chelation, estimated at approximately 79.5 kBq by inhalation and 32% from the wound. The predominantly insoluble type S material plutonium fragments deposited in the wound in radiation dose was achieved by chelation. The committed effective dose was calculated to be 0.000 Sv for this case, the effect of enhanced urinary excretion enhancement factor as 83 ± 52 and 38 ± 17 for initial and delayed calcium diethylenetriaminepentaacetic acid treatments, respectively. The enhancement factor decreases proportionally to a time after intake. For delayed calcium diethylenetriaminepentaacetic acid treatment, with five consecutive treatments, the enhancement factor increased from 1 to 10.

THE PSEUDO-PELGER HUËT CELL AS A RETROSPECTIVE DOSIMETER: ANALYSIS OF A RADIUM DIAL PAINTER COHORT

Ronald E. Goans,¹ Richard E. Toohey,² Carol J. Iddins,³ Stacey L. McComish,⁴ Sergei Y. Tolmachev,⁴ and Nicholas Dainiak^{3,5}

Abstract—Recently, the pseudo-Pelger Huët anomaly in peripheral blood neutrophils has been described as a new radiation-induced, stable biomarker. In this study, pseudo-Pelger Huët anomaly was examined in peripheral blood slides from a cohort of 166 former radium dial painters and ancillary personnel in the radium dial industry, 35 of whom had a marrow dose of zero above background. Members of the radium dial painter cohort ingested ^{226}Ra and ^{228}Ra at an early age (average age $20.6 \pm 5.4 \text{ y}$; range 13–40 y) during the years 1914–1955. Exposure duration ranged from 1–1,820 wk with marrow dose $1.5\text{--}6,750 \text{ mGy}$. Pseudo-Pelger Huët anomaly expressed as a percentage of total neutrophils in this cohort rises in a sigmoidal fashion over five decades of red marrow dose. Six subjects in this cohort eventually developed malignancies: five osteosarcomas and one mastoid cell neoplasm. The pseudo-Pelger Huët anomaly percentage in these cases of neoplasm increases with marrow dose and is best fit with a sigmoid function, suggestive of a threshold effect. No sarcomas are seen for a marrow dose under 2 Gy. These results indicate that pseudo-Pelger Huët anomaly in peripheral blood is a reasonable surrogate for the estimation of alpha dose to bone marrow in historic radiation cases. Hypotheses are discussed to explain late (months to years), early (hours to days), and intermediate (weeks to months) effects of ionizing radiation, respectively, on the expression of genes encoding inner nuclear membrane proteins and their receptors, on the structure and function of nuclear membrane proteins and lipids, and on cytokinesis through chromatin bridge formation.

Key words: biodosimeter; dial painter dosimetry; biomarker; radium dosimetry

INTRODUCTION

ANALYSIS of peripheral blood smears from a group of former radium dial painters and ancillary personnel in the radium industry points to the existence of a long-term biomarker for radiation dose, pseudo-Pelger Huët anomaly (PHA). The radium dial painter cohort is a well-described group of predominantly young women who incidentally ingested ^{226}Ra and ^{228}Ra as they painted luminescent watch dials in the first half of the twentieth century (Toohey et al. 1983; Rowland 1994, 1996). In the present study, the authors present the dose response of the pseudo-Pelger Huët anomaly in a large cohort of former dial painters. PHA has been recently described as a novel, permanent, radiation-induced biomarker in circulating neutrophils (Goans et al. 2015, 2017), and it appears to be a surrogate for the estimation of radiation dose to bone marrow. Peripheral blood slides prepared in 1960–1975 during patient follow-up at Argonne National Laboratory and a satellite laboratory at Massachusetts Institute of Technology (MIT) were made available in collaboration with the United States Transuranium and Uranium Registries (USTUR).

PHA was initially described by Karl Pelger (Pelger 1928) and later defined by G. J. Huët (Huët 1931) as a mutation with autosomal dominant inheritance. PHA is characterized in myelocytes by bean- or dumbbell-shaped,



USTUR: *Take Home Message*

- In-depth study of actinide biokinetics and tissue dosimetry
- Unique resource of data and preserved tissue materials from former nuclear workers
- Significant contributor to national and international radiation protection advisory bodies
- 50 years of research funded by U.S. DOE



Acknowledgment





USTUR Special Session at 61st Annual Meeting of the Health Physics Society, July 19, 2016, Spokane, WA

Questions?

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