The National Human Radiobiology Tissue Repository: a Unique Resource for Scientists

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http://www.ustur.wsu.edu/

Learning from Plutonium and Uranium Workers

Registries' Administrative History

- 1966: US AEC meeting "Plutonium Contamination in Man"
- 1968: founded National Plutonium Registry at the Hanford Environmental Health Foundation (HEHF)
- 1970: name changed to the US Transuranium Registry (USTR)
- 1978: founded the US Uranium Registry (USUR)
- 1987: USTR and USUR administratively merge into the US Transuranium and Uranium Registries (USTUR)
- 1992: a 3-y DOE grant to Washington State University for the management and operation of the Registries
- 1992: Creation of National Human Radiobiology Tissue Repository
- 1996 - 2010: NHRTR holds National Radiobiology Archives (NRA)
- 2009: USTUR/NHRTR new facility in Richland, WA

USTUR Mission

- Follow up occupationally exposed workers, from exposure through full lifespan, by studying the biokinetics (uptake, translocation and retention), and tissue dosimetry of the actinides:

  Evaluate health outcomes, causes of death, and life expectancy of former nuclear workers (volunteer Registrants)

  Obtain, preserve, and make available for future research, samples of tissues at autopsy

  Conduct radiochemical analyses of autopsy tissue samples

  Apply USTUR case study data to refine dose assessment methods

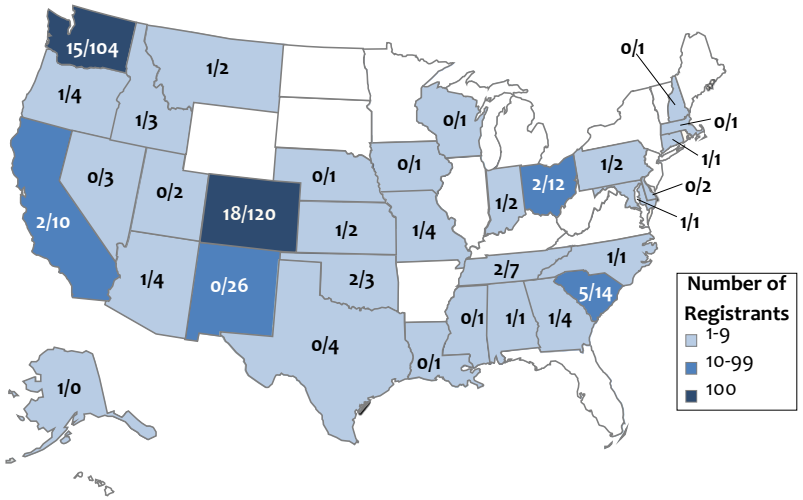
  Assess adequacy of historical and current US regulatory controls and practices in limiting tissue doses to workers

USTUR Registrants

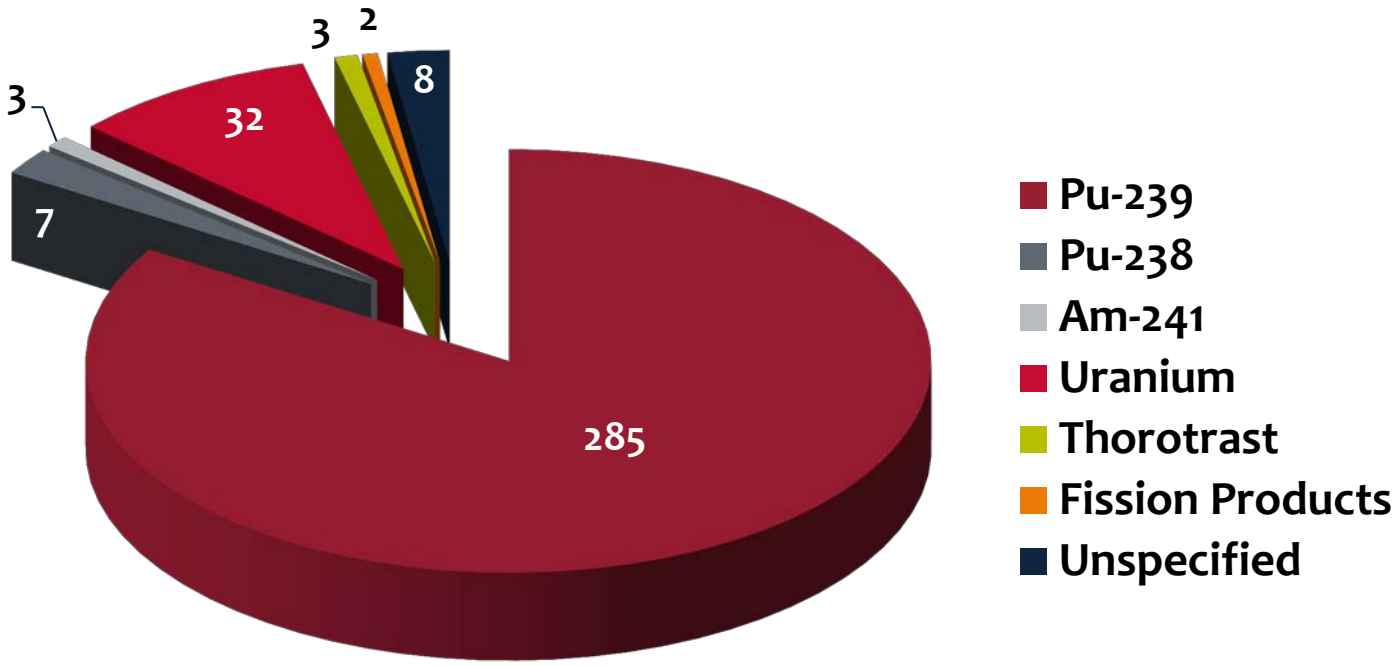
… former nuclear workers, mostly from DOE-owned or leased facilities, with *known history of exposure* to actinides (74 Bq internal deposition or 0.1 Sv external dose) *voluntarily donated* their entire bodies (whole-body donors) or tissues (partial-body donors) for *scientific research*

USTUR Today

- Living Registrants: 60
  - *Whole-body donors: 8*
  - *Partial-body donors: 46*
  - *Special studies: 6*
- Deceased Registrants: 345
  - *Whole-body donors: 42*
  - *Partial-body donors: 298*
  - *Special studies: 5*



Primary Radionuclide of Exposure



† - deceased Registrants

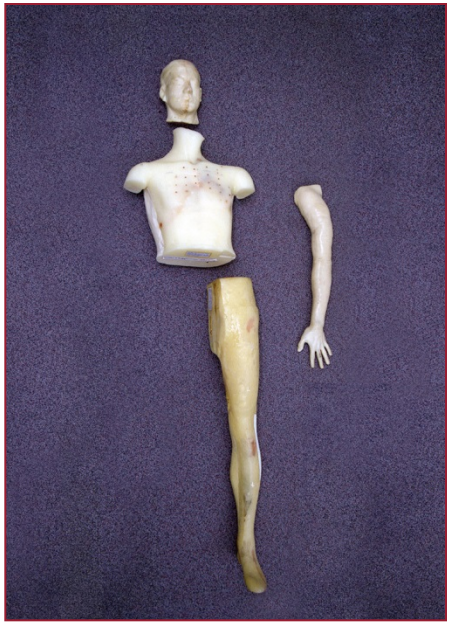
National Human Radiobiology Tissue Repository

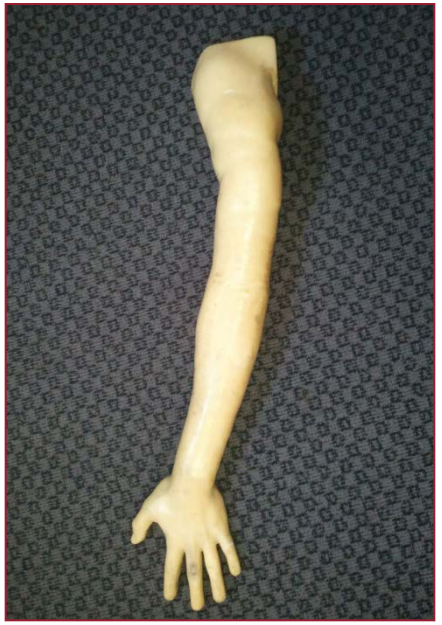
- Tissues from:

  Whole-body donors: 41

  Partial-body donors: 101

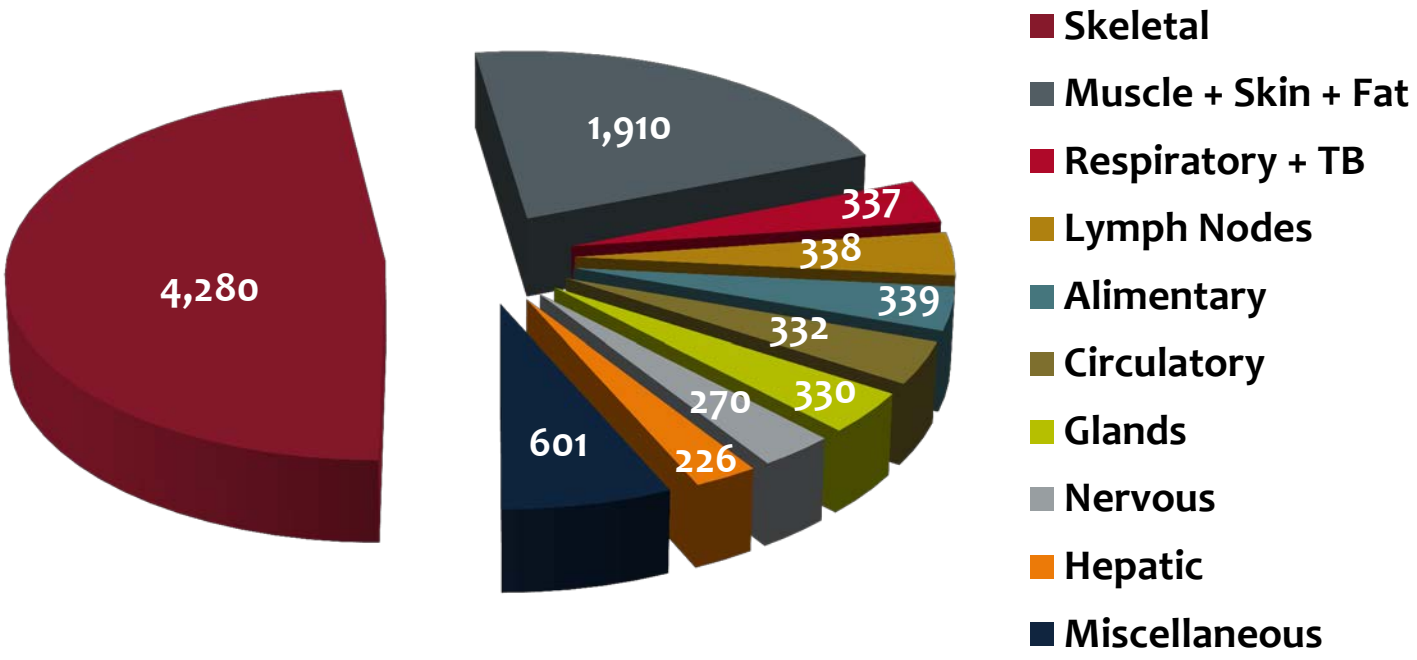
- USTUR Case 0102:





USTUR/NHRTR Tissues

- NHRTR holds 8,963 frozen tissues from 142 donations



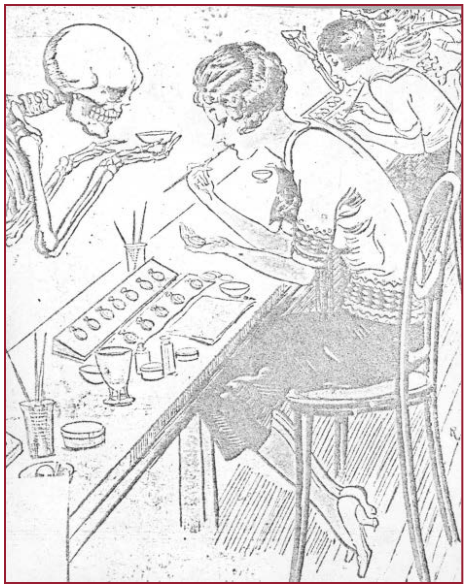
Inside NHRTR

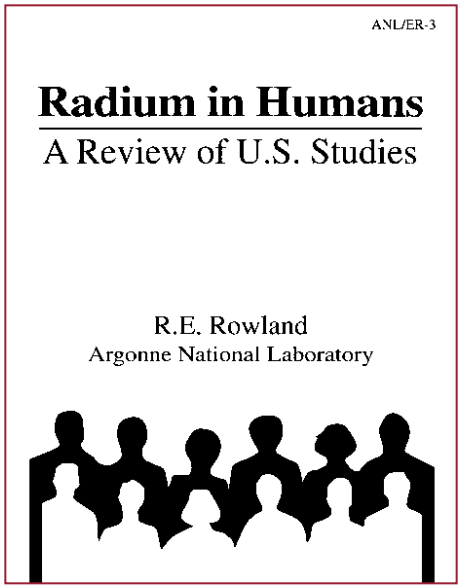
NHRTR: *US Radium Studies*

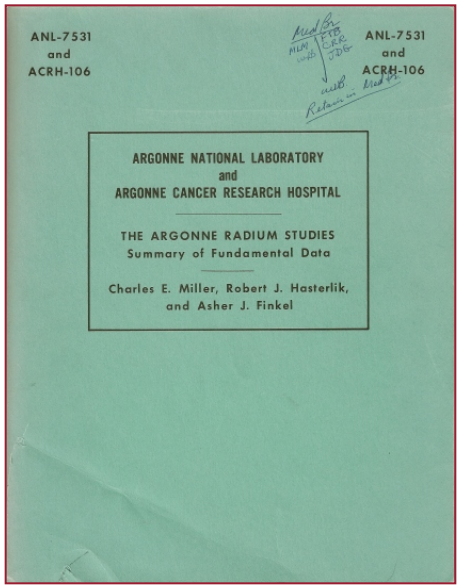
- Frozen tissues, dry/plastic-embedded bones, pathology slides

  Radium Dial Painters: NJRRP → MIT → ANL

  Medical Exposures (Radiothor)







NHRTR: *Plutonium Injection Studies*

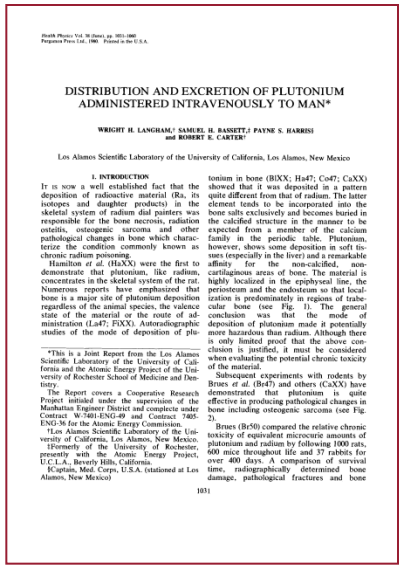
- Dry and plastic-embedded bones

  CHI-1: 6.5 µg (14.9 kBq)i.v. injection $^{239}Pu^{4+}$- citrate; M 68

  HP-2: 5.1 µg (11.7 kBq) i.v. injection $^{239}Pu^{4+}$- citrate; M 49

  HP-4: 4.9 µg (11.2 kBq) i.v. injection $^{239}Pu^{4+}$- citrate; F 18

  HP-9: 6.3 µg (14.5 kBq) i.v. injection $^{239}Pu^{4+}$- citrate; M 66



DISTRIBUTION AND EXCRETION OF PLUTONIUM ADMINISTERED INTRAVENOUSLY TO MAN*

WRIGHT H. LANGHAM,† SAMUEL H. BASSETT,† PAYNE S. HARRIS‡ and ROBERT E. CARTER†

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1. INTRODUCTION

It is now a well established fact that the deposition of radioactive material (Ra, its isotopes and daughter products) in the skeletal system of radium dial painters was responsible for the bone necrosis, radiation osteitis, osteogenic sarcoma and other pathological changes in bone which characterize the condition commonly known as chronic radium poisoning.

Hamilton *et al.* (HaXX) were the first to demonstrate that plutonium, like radium, concentrates in the skeletal system of the rat. Numerous reports have emphasized that bone is a major site of plutonium deposition regardless of the animal species, the valence state of the material or the route of administration (La47; FiXX). Autoradiographic studies of the mode of deposition of plutonium in bone (BlXX; Ha47; Co47; CaXX) showed that it was deposited in a pattern quite different from that of radium. The latter element tends to be incorporated into the bone salts exclusively and becomes buried in the calcified structure in the manner to be expected from a member of the calcium family in the periodic table. Plutonium, however, shows some deposition in soft tissues (especially in the liver) and a remarkable affinity for the non-calcified, non-cartilaginous areas of bone. The material is highly localized in the epiphyseal line, the periosteum and the endosteum so that localization is predominately in regions of trabecular bone (see Fig. 1). The general conclusion was that the mode of deposition of plutonium made it potentially more hazardous than radium. Although there is only limited proof that the above conclusion is justified, it must be considered when evaluating the potential chronic toxicity of the material.

Subsequent experiments with rodents by Brues *et al.* (Br47) and others (CaXX) have demonstrated that plutonium is quite effective in producing pathological changes in bone including osteogenic sarcoma (see Fig. 2).

Brues (Br50) compared the relative chronic toxicity of equivalent microcurie amounts of plutonium and radium by following 1000 rats, 600 mice throughout life and 37 rabbits for over 400 days. A comparison of survival time, radiographically determined bone damage, pathological fractures and bone

*This is a Joint Report from the Los Alamos Scientific Laboratory of the University of California and the Atomic Energy Project of the University of Rochester School of Medicine and Dentistry.

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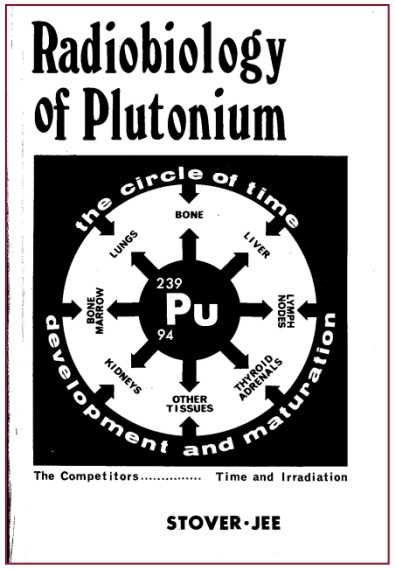

The Human Plutonium Injection Experiments

The Plutonium Experiment

Until now.

similar radiation experiments with humans.

This article is intended to tell the Los Alamos story of these experiments and their aftermath. The article is based on memos and other documents that were collected by one of the authors (Moss) and were released to the public as a result of Secretary O'Leary's openness initiative. Los Alamos was not directly involved in choosing the subjects for the experiments nor in carrying out the clinical studies. Nevertheless, the motivation for the experiments arose at Los Alamos and scientists at Los Alamos were involved in planning the experimental protocols, preparing the material to be injected in the subjects, and analyzing the results. They were involved both at the time the experiments took place and years later when it became clear that reanalysis was appropriate.

Our intent in reviewing this story is to give enough scientific and quantitative details to bring out two areas that are usually not adequately addressed in the press and other popular reports. The first area is the purpose of the studies. What was to be learned, and how well did the experiments succeed in accomplishing the stated goals? The second area is the significance of the results for the protection of plutonium workers. How have those results aided our current understanding of the uptake, distribution, and retention of plutonium, and how have the results helped us to minimize the risks of internal exposure from plutonium? We will, in fact, show a new analysis of the data from the 1940s that, coupled with a recent human plutonium injection study using plutonium-237, strengthens our understanding of the manner in which plutonium, once it has reached the bloodstream, distributes itself in the body.

But first, we examine motivations and try to reconstruct why things were done as they were. For that we need to go back to the atmosphere of World War II and the enormous pressures attendant on using unknown and uncharacterized materials to build the first atomic weapons.

The Manhattan Project and Its Need for Plutonium

In planning the development of the atomic bomb, scientists considered using two fissionable materials capable of sustaining a chain reaction—uranium-235 and plutonium-239. Each presented a different set of production and health-related problems.

Uranium-235 was present in natural uranium in small amounts (0.7 per cent). Scientists faced the daunting task of separating kilogram amounts of uranium-235 from the much more plentiful uranium-238 isotope by taking advantage of the slight difference in the mass of the two isotopes. For example, in the gaseous-diffusion method, gaseous compounds of the two isotopes diffuse through porous barriers or membranes at rates that differ by about 6 parts per thousand. Similarly, the electromagnetic method passes a beam of ionized uranium through a magnetic field, and the two isotopes follow circular paths that very gradually diverge.

In 1942, it was problematic whether enough uranium-235 could be separated by such painstaking techniques to achieve the goal of having an atomic bomb by January 1945. It was deemed necessary to pursue plutonium-239 as another possible weapon material. Because plutonium is chemically different from uranium, it was thought that it could be produced in reactors through neutron absorption and then separated easily from its uranium parent and fission products by chemical means.

Scientists had created tiny amounts of plutonium with the cyclotron at the University of California Radiation Laboratory in 1941 and demonstrated its favorable nuclear properties (see "The Making of Plutonium-239"). The physical properties and the chemistry of plutonium were determined using only microgram (micro = 10^{-6}) quantities. Such small amounts and the fact that plutonium emits alpha radiation, which doesn't penetrate the skin, meant the risk of handling plutonium, compared to gamma-emitting radionuclides, was not a major concern. In fact, the alpha activity of these small quantities was the only means to track and account for the material.

The discovery of plutonium led the Office of Scientific Research and Development to inaugurate work on plutonium for a weapon design. The work

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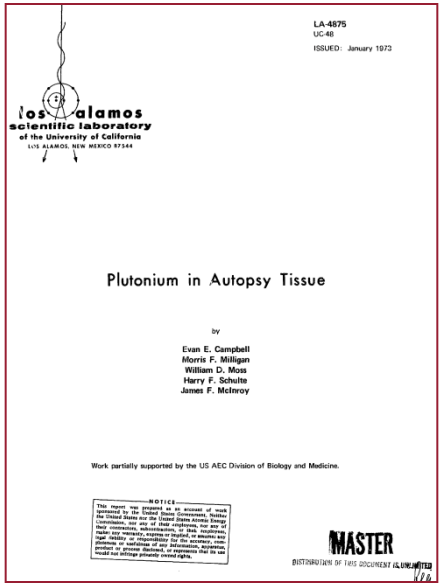
Los Alamos Science Number 23 1995

NHRTR: *Los Alamos Environmental Study*

- Acid digested tissues (acid solutions): ~2,000 samples



LA-4875
UC-48
ISSUED: January 1972

los alamos
scientific laboratory
of the University of California
LOS ALAMOS, NEW MEXICO 87544

Plutonium in Autopsy Tissue

by

Evan E. Campbell
Morris F. Milligan
William D. Moss
Harry F. Schulte
James F. McInroy

Work partially supported by the US AEC Division of Biology and Medicine.

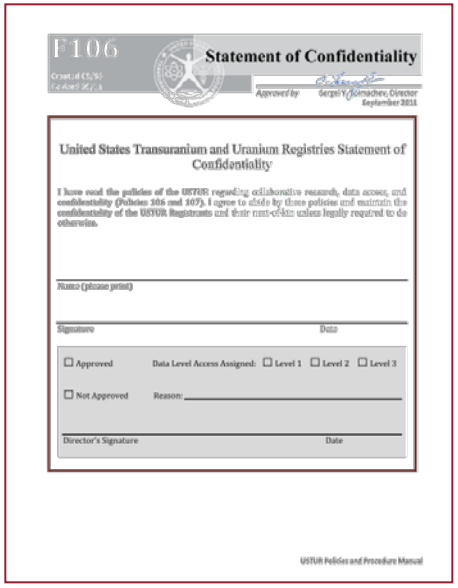
NOTICE

MASTER

McInroy JF, Campbell EE, Moss WD, Tietjen GL, Eutsler BC, Boyd HA. *Plutonium in Autopsy Tissue: A Revision and Updating of Data Reported in LA-4875*. Health Physics 37: 1-136; 1979

How to Request

- Provide a brief summary of the proposed sample usage
- Sign a confidentiality statement
- Provide a copy of Institutional Review Board approval for protection of human subject



F106 Statement of Confidentiality

Approved by Sergei V. Tolmachev, Director September 2011

United States Transuranium and Uranium Registries Statement of Confidentiality

I have read the policies of the USTUR regarding collaborative research, data access, and confidentiality (Policies 106 and 107). I agree to abide by these policies and maintain the confidentiality of the USTUR Registrants and their next-of-kin unless legally required to do otherwise.

Name (please print)

Signature Date

☐ Approved Data Level Access Assigned: ☐ Level 1 ☐ Level 2 ☐ Level 3

☐ Not Approved Reason:

Director's Signature Date

USTUR Policies and Procedure Manual

P106 Scientific Collaboration and Data Access

Created 06/93
Revised 01/13

Approved by Sergei V. Tolmachev, Director January 2013

This policy applies to research collaboration with other scientists and institutions, and to sharing Registries' data and materials with others.

Collaboration with other institutions is encouraged

To maximize the scientific worth and output of the unique materials and data under its purview, the Registries encourages and actively seeks collaboration with other investigators and institutions. Collaboration is sought to compliment rather than duplicate the capabilities of the Registries, and to facilitate the efforts of the Registries in achieving its primary goal. Collaboration may take the form of joint evaluations of data, tissues, or other Registries materials, preparation of articles for peer-reviewed literature, or preparation of joint research proposals to a potential sponsor.

Definition of collaborative researchers

Data, tissue and other unique materials collected by the Registries may be made available to other scientists under the following conditions:

1. Potential research collaborators must submit to the Registries a written proposal that describes the specific materials requested, and includes the proposed usage of the requested materials.
2. Research collaborators must provide written assurance that the Registries' policies with respect to human subjects, informed consent, privacy of the Registrants and their next-of-kin, and national security will be followed as agreed in Form 106.
3. Research collaborators must furnish copies of the approval documents issued by their Institutional Review Boards.

Dissemination of Registries' data and biological materials

Registries' data are classified into three levels, based on the potential for identification of the donors and dissemination of the data to other researchers. Access to the data will be restricted as follows:

Level 1: Data include personal identifiers and specific dates of events with specific sites of employment. These data are available, by written request, to medical and radiation protection groups from the worksites of the Registrants. Access to these data is restricted by site. For example, medical and radiation protection personnel at a work site may access data of Registrants only from that site. Signed confidentiality statements (Form 106) must be received from the responsible person(s) at the sites requesting data.

Level 2: Data include no personal identifiers; however, specific dates of events and general descriptions of the sites of employment are included. These data are available to collaborative researchers as defined above.

Level 3: Data include no personal identifiers, only general times of employment and radiologic events, and general information regarding worksites. These data are available on the USTUR website (www.ustur.wsu.edu).

USTUR Policies and Procedure Manual

P107 Publications

Approved by Sergei V. Tolmachev, Director September 2011

This policy applies to all publications of the United States Transuranium and Uranium Registries. All collaborative researchers are subject to this policy.

Peer-reviewed publication of scientific findings is encouraged

It is the policy of the Registries to encourage publication of scientific findings and the associated data upon which these findings are based as expeditiously as practicable. Peer-reviewed scientific literature is the preferred vehicle for this purpose. To expedite publication, further, preliminary results may be published in Registries Annual Reports, or in special topical reports.

Publication in peer-reviewed literature includes the following: articles; unless abstracts; letters to the editor; other technical communications; or oral presentations of findings that have undergone independent review for scientific content and merit, given at scientific and technical meetings. Publication by the Registries scientific staff is encouraged, and, in keeping with the true spirit of academic freedom, does not require external or internal prior approval. The author(s) is(are) responsible for the scientific content of the publication, and for ensuring that there is no breach or violation of confidentiality, or other legal and ethical requirements.

Privacy of Registrants must be maintained

The USTUR has pledged confidentiality to the Registrants and their next-of-kin, and that pledge will pertain to all publications. No publicly available or open-literature publication shall be made in which Registrants are identified by name or other personal identifiers without the prior consent of the Registrant, or the legally responsible next-of-kin, unless legally required by law, regulation, or court order.

Specific dates of radiological or medical incidents, specific dates of employment, or the exact place of employment shall not be used in publications. Also, the use of specific descriptors of radiological incidents, health conditions, or causes of death should be avoided if they might assist a reader in the identification of a subject. Such information will be presented in general terms so that an individual reading the publication would be forced to perform additional research in order to identify the research subject. For example, times of events shall be stated as time (days, months, years) before or after the beginning of work, the end of work, or death. An individual might be identified as working at Rocky Flats, Hanford, or other sites, but no specific work location or employer will be identified.

Approval may be required for non-peer-reviewed publications

The author(s) is(are) responsible for obtaining the Registries' approval of press releases and publications that do not undergo external scientific peer review prior to release or distribution. Customarily, it is the responsibility of the senior author to obtain the approval. This should not be construed to impose any constraints on formal or informal communications between Registries staff and external persons on technical or scientific matters, and applies only to 1) documents specifying Registries policy or administrative position, or existing commitments of Registries

USTUR Policies and Procedure Manual

How to Publish

- Registries as a co-author:

  Unpublished data - bioassay, in-vivo counting, analytical results, use of tissue samples or other materials
  Collaborative effort by Registries staff

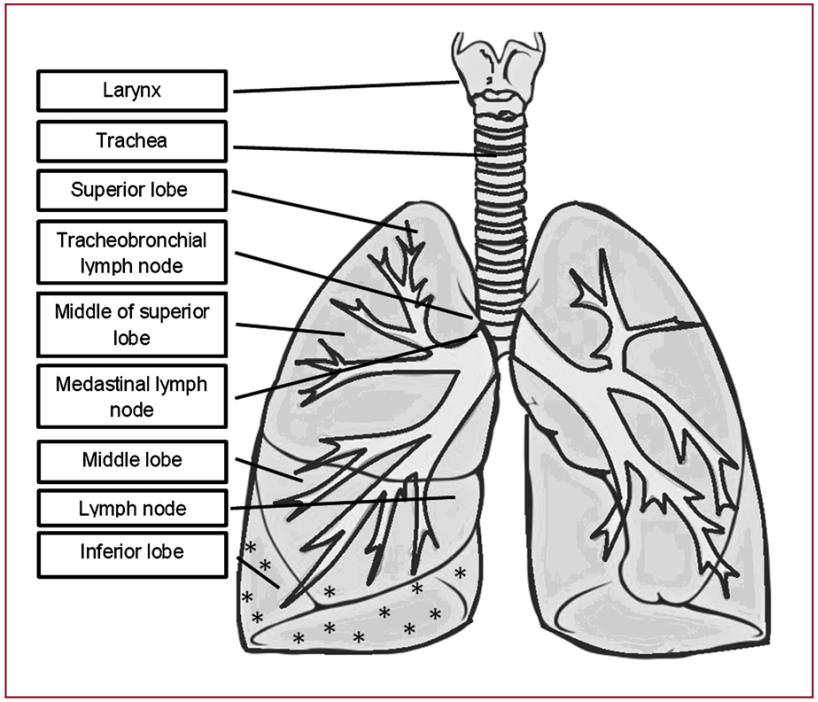
- Acknowledgment to the Registries:

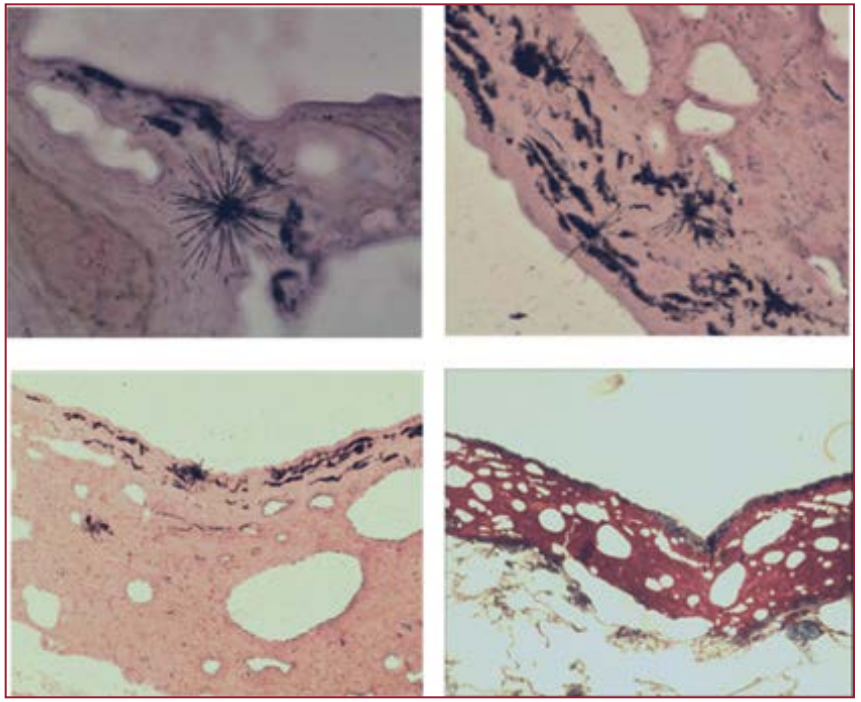
  Loan or provision of tissues or other materials

  Only published Registries' data or evaluation

  Manuscript exclusively prepared by other investigators without consulting the Registries

Microdistribution and Long-term Retention of $^{239}Pu(NO_3)_4$





Nielsen, C. E., Wilson, D. A., Brooks, A. L., McCord, S. L., Dagle, G. E., James, A. C., Tolmachev, S. Y., Thrall, B. D. and Morgan, W. F. *Microdistribution and Long-term Retention of $^{239}Pu\ (NO_3)_4$ in the Respiratory Tracts of an Acutely Exposed Plutonium Worker and Experimental Beagle Dogs.* Cancer Research. 72, 5529-36 (2012).

Carcinogenic and Inflammatory Effects of $^{239}Pu(NO_3)_4$

- Analysis: to determine genetic and inflammatory response pathways following plutonium exposure

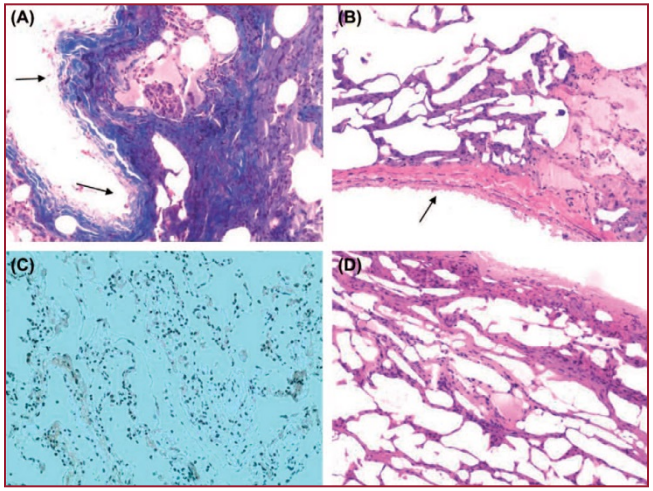
  Possible pathways - tissue injury, apoptosis, and gene expression modifications

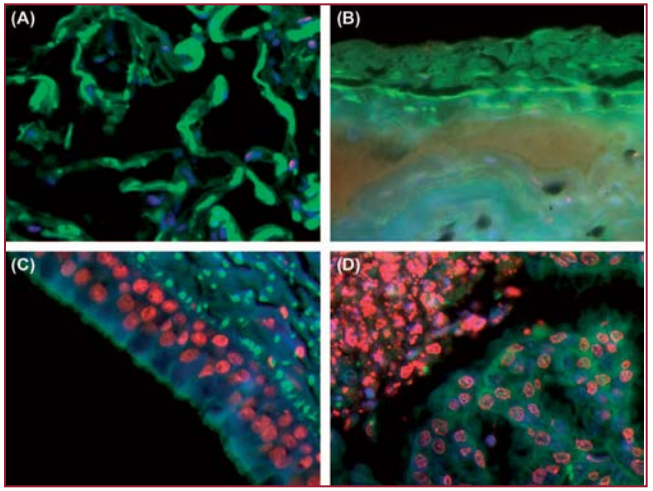
- Immunohistochemistry: to characterize lung lesions, visualize interstitial fibrosis, and other pathology
- RT-PCR: to quantify the expression of chemokine/cytokine regulatory genes thought to be involved in inflammation and carcinogenesis

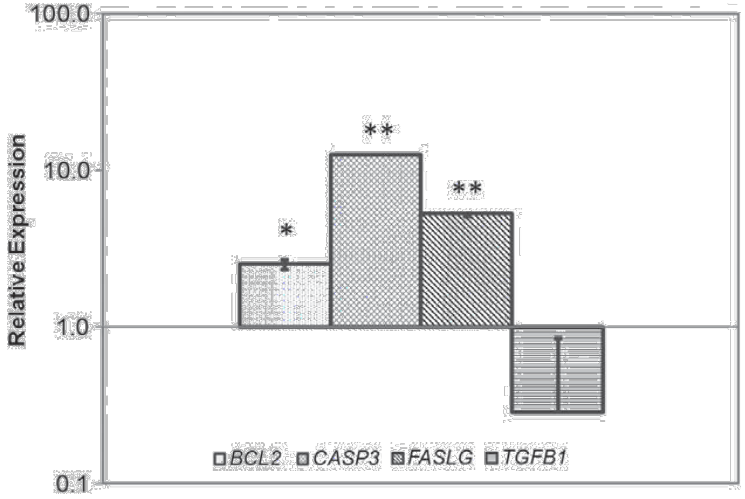
  BCL-2, CASP-3, FASL, IL4, IL8 and TGFß-1

Nielsen, C. E., Wang, X., Robinson, R. J., Brooks, A. L., Lovaglio, J., Patton, K. M., McComish, S. L., Tolmachev, S. Y. and Morgan, W. F. *Carcinogenic and inflammatory effects of plutonium-nitrate retention in an exposed nuclear worker and beagle dogs.* Int J Radiat Biol. 90, 60-70 (2014).

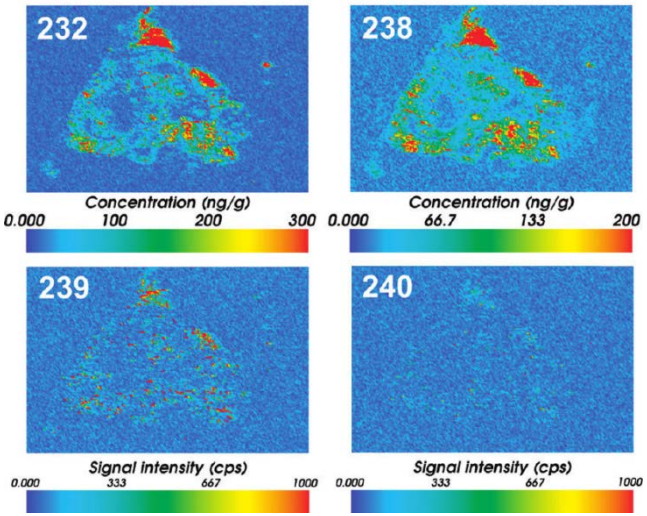
C. E. Nielsen *et al.* (2014) Int J Radiation Biology

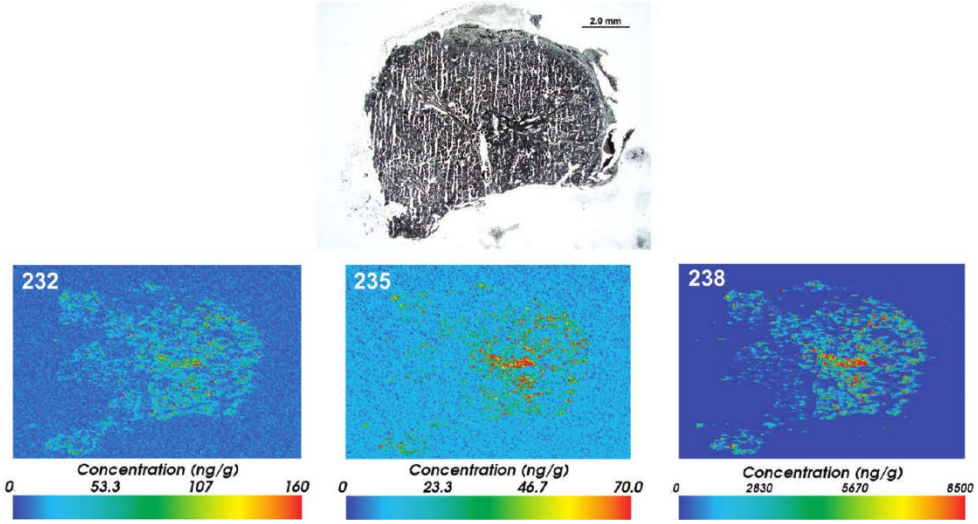






Actinide Elemental Bioimaging





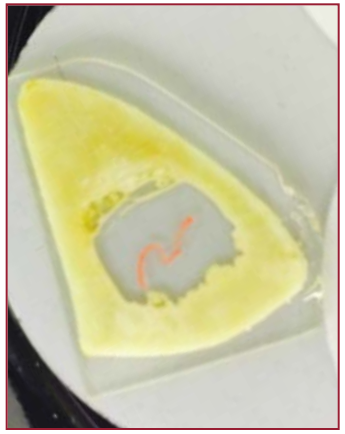
Pu exposure: Paratracheal LN

U exposure: Parabronchial LN

Hare, D., Tolmachev, S., James, A., Bishop, D., Austin, C., Fryer, F. and Doble, P. *Elemental Bio-imaging of Thorium, Uranium, and Plutonium in Tissues from Occupationally Exposed Former Nuclear Workers.* Anal Chem. 82, 3176-82 (2010).

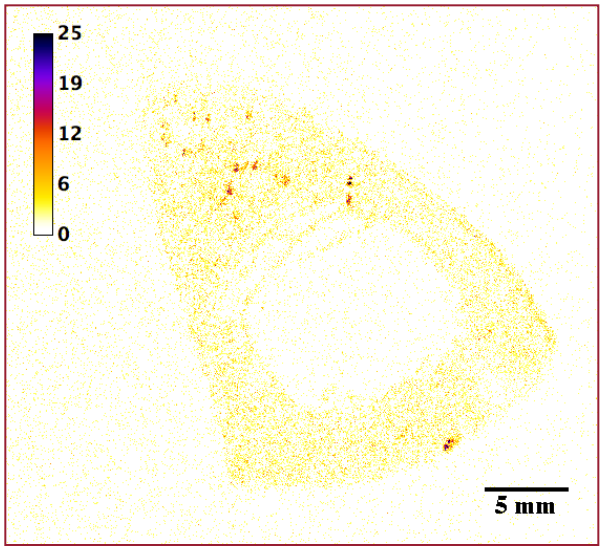
Ra-226 Bone Microdosimetry

- In 1926: therapeutic injection to heal vague arthritic pains and nervousness
- In 1957: 1,350 nCi of ^{226}Ra was measured in whole-body
  Estimated intake of ^{226}Ra: 250.2 µCi (250.2 µg of ^{226}Ra)
  Whole-body dose: 2,236 cGy from ^{226}Ra
- In 1958: died from osteogenic sarcoma with metastases, radium necrosis of bone



Digital Autoradiography

- iQID: ionizing-radiation Quantum Imaging Detector
- Imaging Time: 235 h
- Activity Concentration: 8 - 50 µBq µg^{-1}
- Total Activity: 63.95 mBq



B. W. Miller. *Alpha-particle Imaging Applications with the iQID Camera*. Presentation at USTUR Scientific Advisory Committee Meeting (2014)

Beryllium in Human

Table 3 Concentration of Be in digestate and wet tissues from several USTUR cases measured by ICP-MS—see attached tables

Tissue/organ description	Donation type	Time of exposure[a], *y*	Weight, g		^{9}Be concentration	
			Tissue	Solution	Solution, pg g^{-1}	Tissue, μg kg^{-1}
Case 0262						
Lung (L)	WB	8	433.5	400.1	227±7	0.210±0.006
LN Peribronchial			18.1	300.0	373±4	6.18±0.07
Femur (R) MS			155.8	600.0	4±1	0.015±0.003
Case 0425						
LN Hilar	WB	23	6.5	177.1	300±3	8.17±0.08
Femur (R) MS			95.4	507.2	19±1	0.101±0.005
Case 0706						
Lung (R)	WB	6	389.7	1075.6	1326±6	3.66±0.02
LN Pulmonary			2.1	325.0	382±2	59.11±0.3
Hair			14.8	232.8	18.4±0.4	0.289±0.005
Femur (R) MS			133.7	653.9	825±4	4.03±0.02
Case 0720						
Lung (R)	WB	23	606.1	500.0	126±2	0.104±0.002
LN Hilar (R)			4.0	427.3	969±16	103.5±1.7
LN Paratrechial			6.9	100.0	4928±54	71.4±0.8
Femur (R) MS			124.3	558.5	21±1	0.094±0.004
Case 0744						
Lung (R)	WB	3	60.3	166.2	9.0±0.1	0.025±0.001
LN Pulmonary			1.4	250.0	1427±17	255±3
Femur (R) MS			155.6	813.9	19±4	0.10±0.02
Case 0817						
Lung (R)	PB	38	313.0	997.2	25.6±1.5	0.082±0.005
Femur (R) MS			162.6	933.1	27.7±1.3	0.159±0.007
Case 1002						
Femur (R) MS	WB	27	146.7	600.0	8±1	0.033±0.004

R right side, *L* left side; *MS* middle shaft; *WB* whole body; *PB* partial body

[a] Self-reported years of exposure

Lariviere, D., Tremblay, M., Durand-Jezequel, M. and Tolmachev, S. *Detection of Beryllium in Digested Autopsy Tissues by Inductively Coupled Plasma Mass Spectrometry using a High Matrix Interface Configuration.* Anal Bioanal Chem. 403, 409-18 (2012).