The National Human Radiobiology Tissue Repository
– tissue collection at the USTUR –

Sergey Y. Tolmachev and Stacey L. McComish

US Transuranium and Uranium Registries
College of Pharmacy, Washington State University

1845 Terminal Drive, Suite 201, Richland, WA 99354
www.ustur.wsu.edu

"Learning from Plutonium and Uranium Workers"

What is USTUR?

History and Mission

- 1968: National Plutonium Registry established at the Hanford Environmental Health Foundation (HEHF)

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

- 1970: Name changed to the US Transuranium Registry (USTR)
- 1978: US Uranium Registry established at the HEHF
- 1987: Two programs merged into the US Transuranium and Uranium Registries (USTUR)
- 1992: DOE grant to Washington State University for the management and operation of the USTUR
- 1992: Creation of National Human Radiobiology Tissue Repository (NHRTR)

USTUR Registrants

- Voluntary Tissue Donors (Posthumous)

  Whole-body Donors
  Partial-body Donors

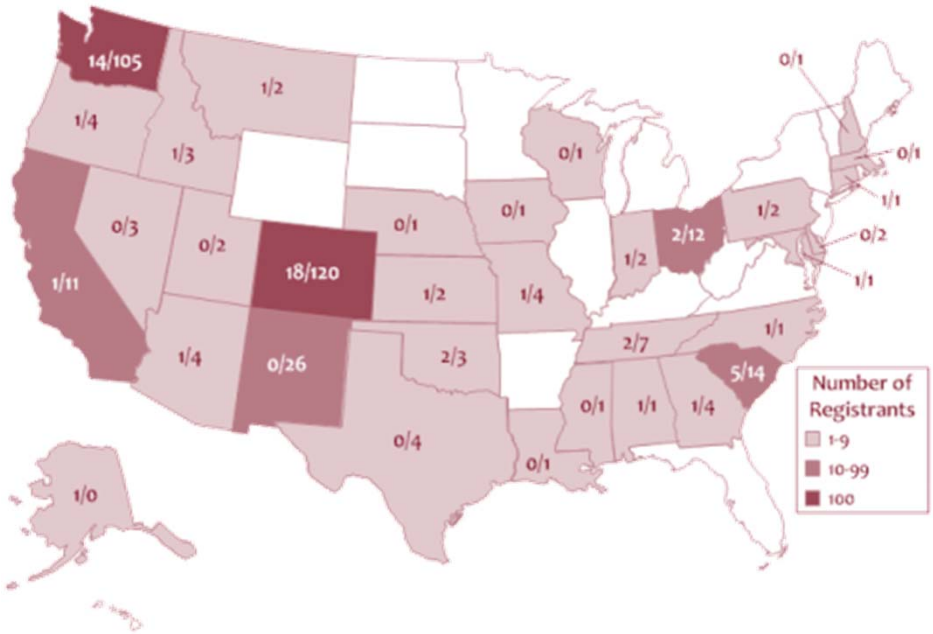
- Former Nuclear Workers from DOE Sites
- Documented Radiation Exposure and Work History
- Exposure Criteria:

  Actinide internal deposition of ≥74 Bq (2 nCi)
  External dose to the whole body ≥0.1 Sv (10 rem)

Registrant Statistics

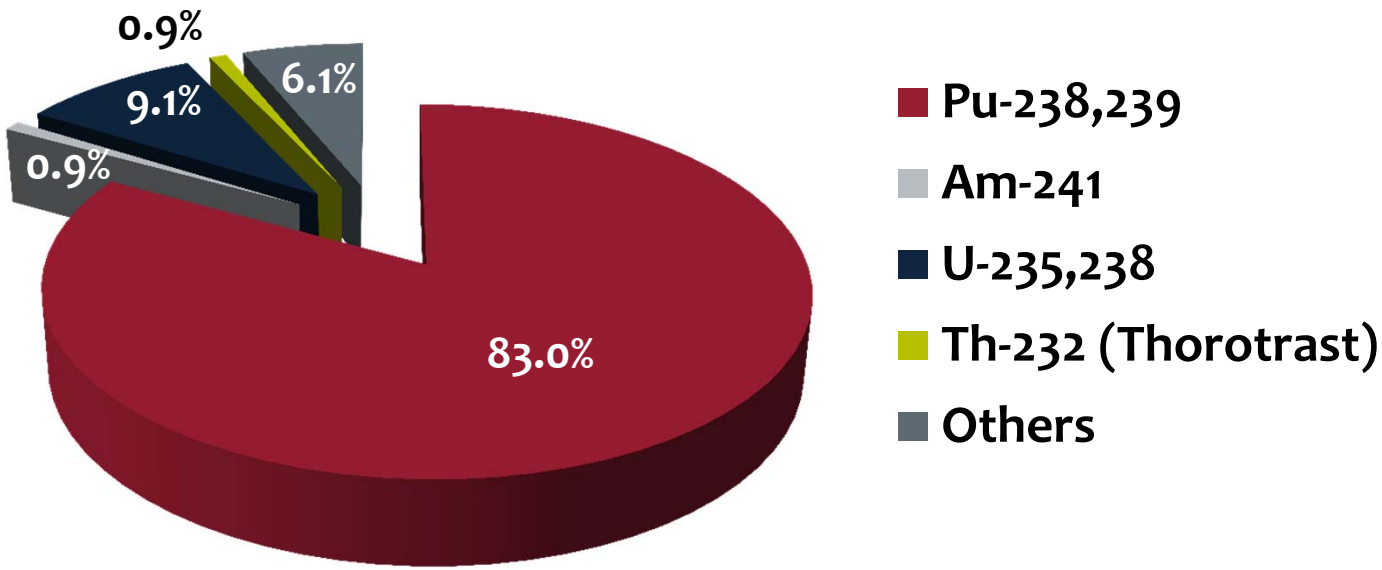
- Living Registrants: 58
  - *Whole-body donors: 8*
  - *Partial-body donors: 44*
  - *Special studies†: 6*
- Deceased Registrants: 347
  - *Whole-body donors: 42*
  - *Partial-body donors: 300*
  - *Special studies: 5*

† - not a tissue donor



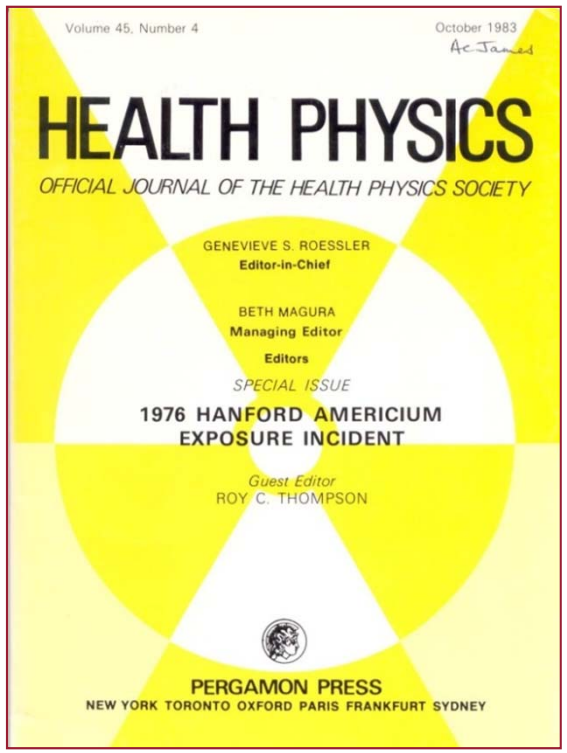
Living/Deceased Registrants

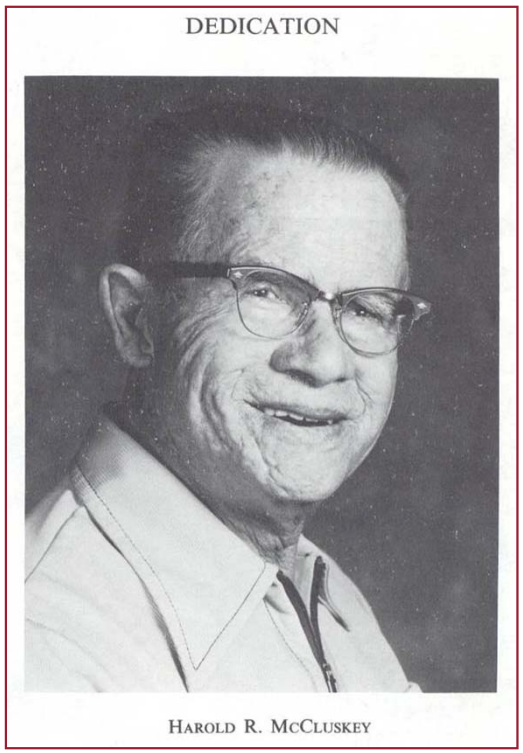
Primary Radionuclide of Exposure

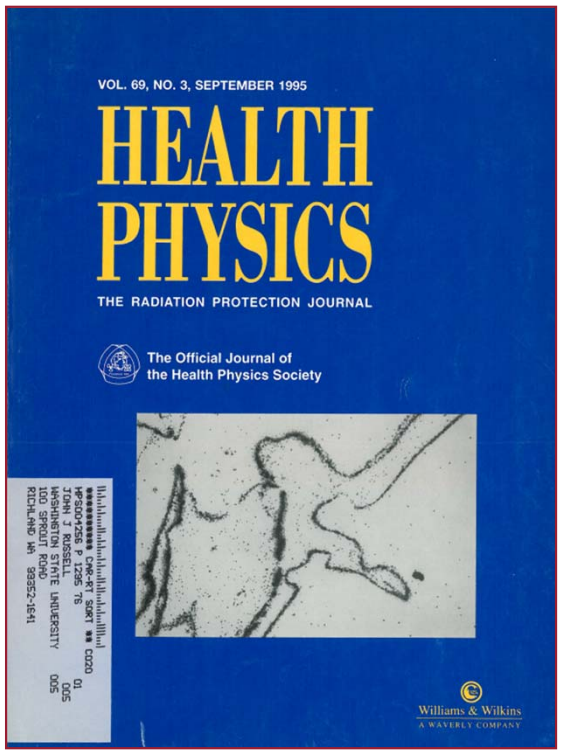


Landmark: (i) 1976 Hanford ^{241}Am Incident – *'Atomic Man'* –

- Explosion of ion-exchange column with ~ 150 g ^{241}Am (19 TBq = 515 Ci)
- Chemical operator injured: acid burns, superficial cuts (face/upper body)
- Estimate of uptake > 40 MBq (1,080 µCi) – Ca/Zn-DTPA chelation therapy
- Systemic deposition – 0.5 MBq (13 µCi)

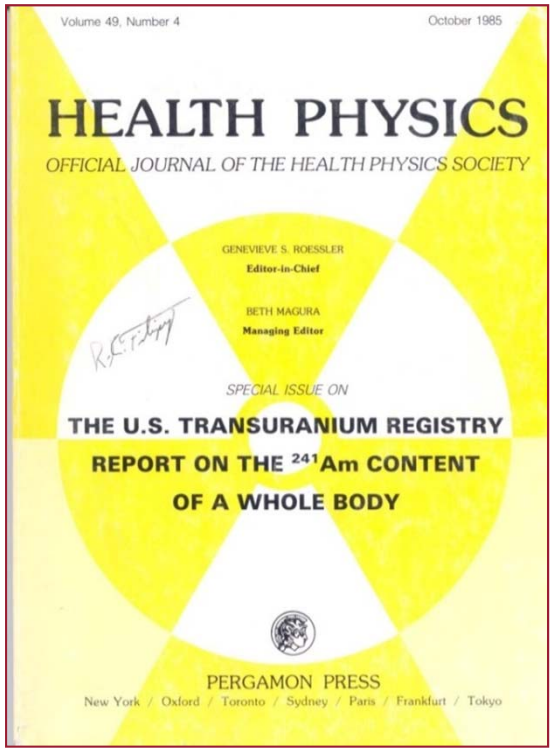


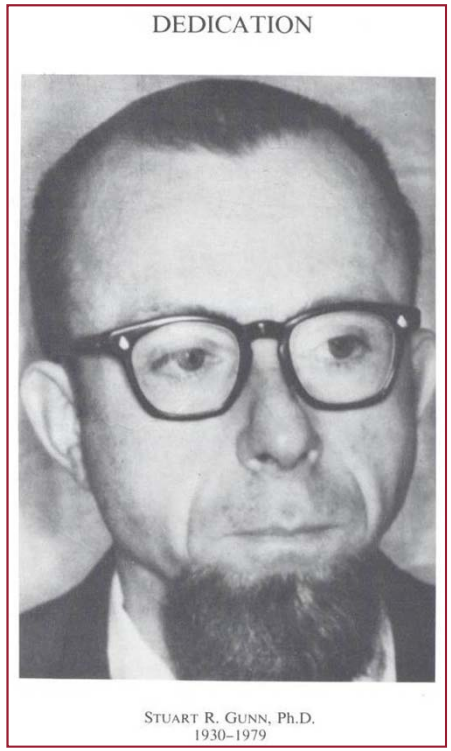




Landmark: (ii) 1979 First Whole-Body Donation

- Donor (radiochemist) worked with unsealed ^{241}Am source (1952 – 1954)
- First indication of intake was detection of ^{241}Am in urine sample (1958 routine surveillance program) – No chelation therapy
- Contemporary estimate of intake: 8 – 40 kBq (0.23 – 1.1 µCi)





National Human Radiobiology Tissue Repository

NHRTR Sample Collections

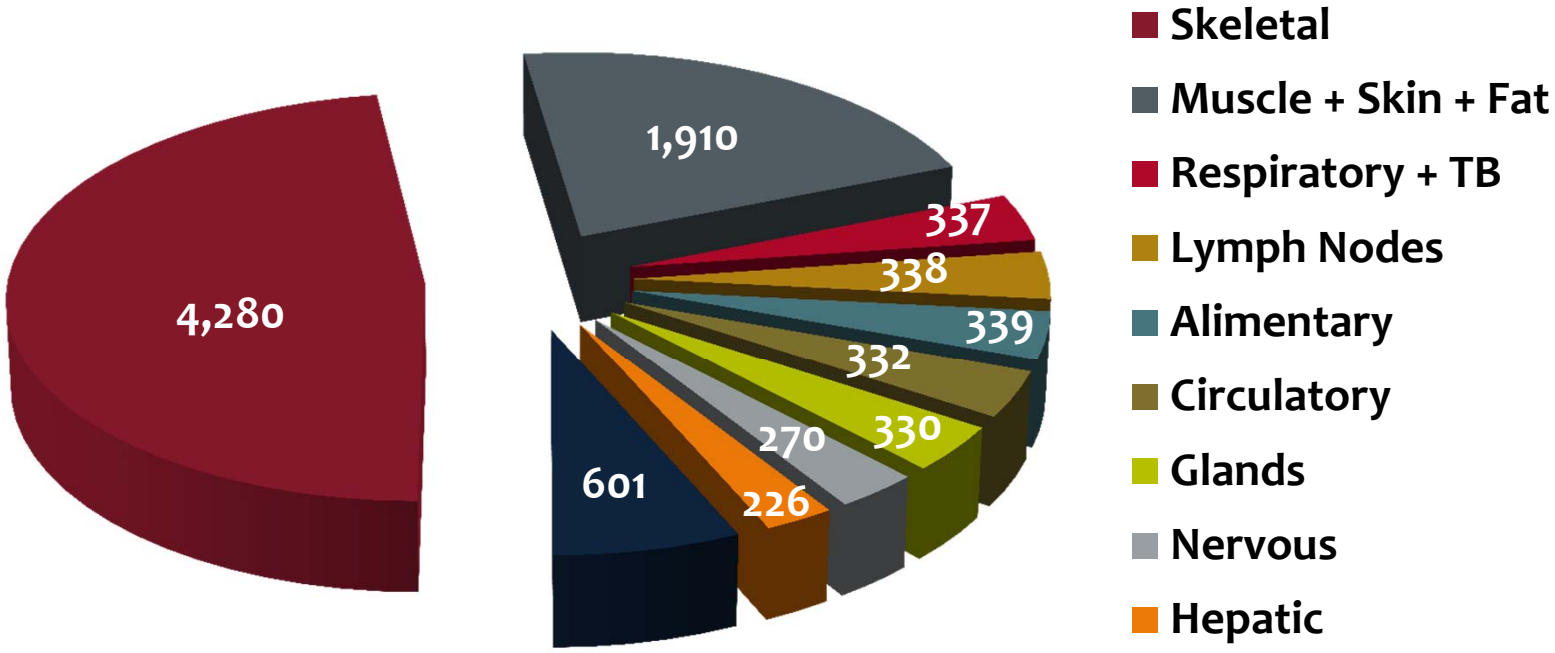
- USTUR Research (1968 – present)
- US Radium Studies (1957 – 1990)
- Los Alamos Plutonium Autopsy Tissue Study (1959 – 1976)
- Health and Safety Laboratory Bone Program (1953 – 1959)
- Plutonium Injection Studies (1945 – 1947)

1996 – 2010: National Radiobiology Archives → Northwestern University (Chicago, IL)

Inside NHRTR

USTUR Tissue Samples

- NHRTR holds 8,963 frozen tissue samples from 142 donations



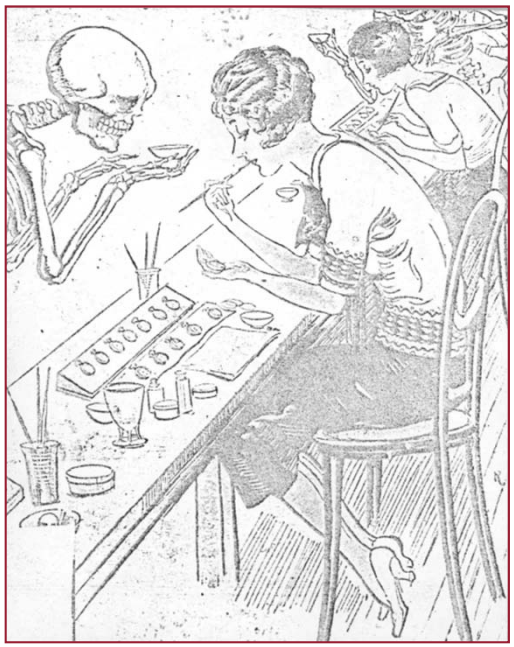
THEMIS Electronic Inventory Database Statistics

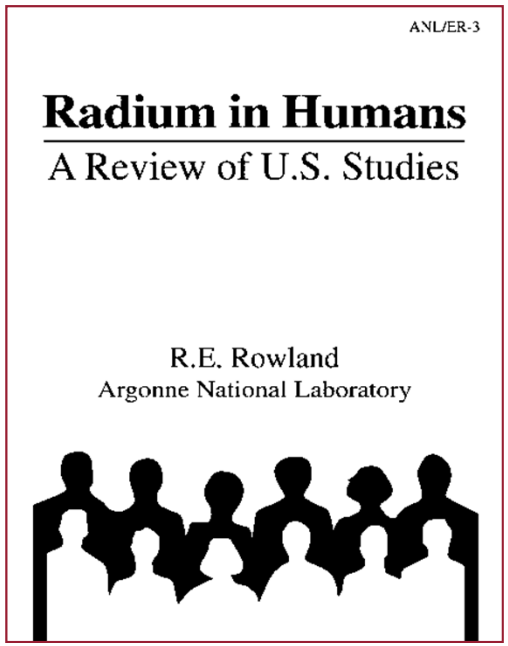
NHRTR: *US Radium Studies*

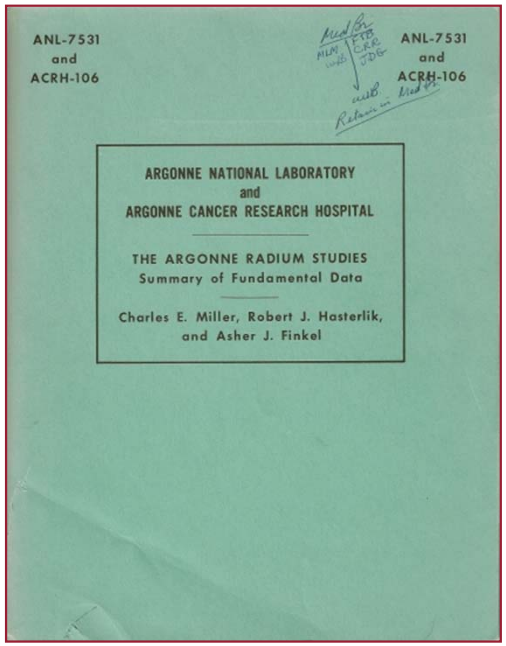
- Frozen tissues, dry/plastic-embedded bones, pathology slides

  Radium Dial Painters: NJRRP → MIT → ANL/CHR

  Medical exposure: therapeutic injections

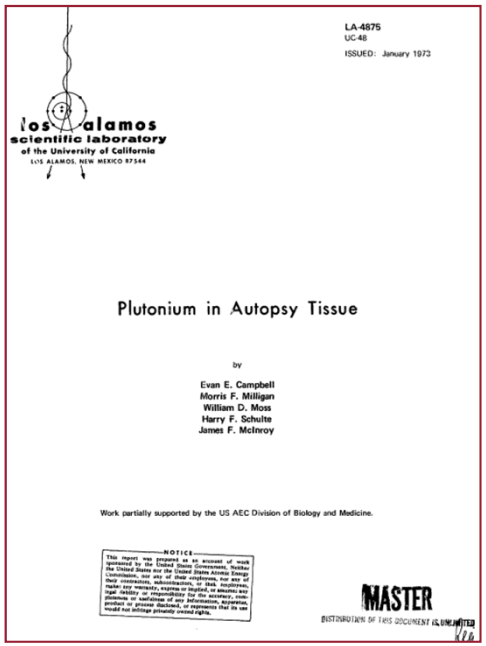






NHRTR: *Los Alamos Autopsy Study*

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



LA-4875
UC-48
ISSUED: January 1973

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
This report was prepared as an account of work sponsored by the United States Government. Neither the United States nor the United States Atomic Energy Commission, nor any of their employees, nor any of their contractors, subcontractors, or their employees, makes any warranty, express 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.

MASTER

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

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 Phys. 37: 1-136; 1979.

NHRTR: *Plutonium Injection Studies*

- Dry and plastic-embedded bones, urine

  CAL-3: 5.5 ng (3.5 kBq) i.m. injection $^{238}Pu^{6+}$- nitrate; M 36

  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†

Los Alamos Scientific Laboratory of the University of California, Los Alamos, New Mexico

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 (BiXX; 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.

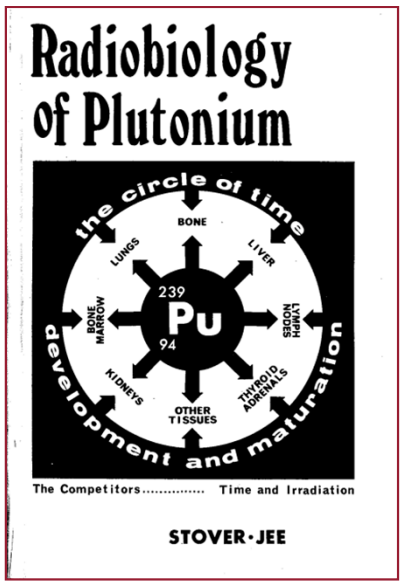
The Report covers a Cooperative Research Project initiated under the supervision of the Manhattan Engineer District and completed under Contract W-7401-ENG-49 and Contract 7405-ENG-36 for the Atomic Energy Commission.

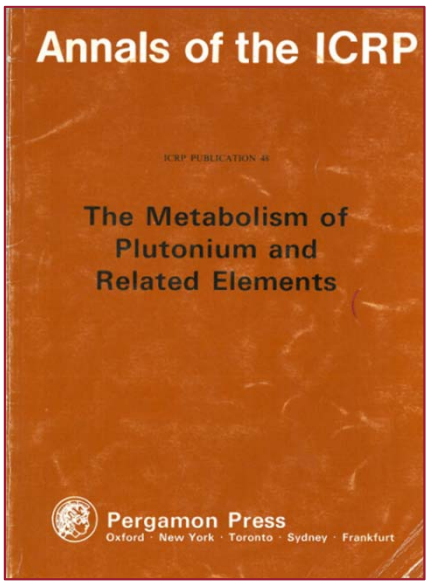
†Los Alamos Scientific Laboratory of the University of California, Los Alamos, New Mexico.

‡Formerly of the University of Rochester, presently with the Atomic Energy Project, U.C.L.A., Beverly Hills, California.

§Captain, Med. Corps, U.S.A. (stationed at Los Alamos, New Mexico)

1031





Tissue Materials: *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

Created 05/93
Revised 09/11

Approved by Sergei Y. 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 06/92
Revised 01/13

Approved by Sergei Y. 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

Created 06/92
Revised 09/11

Approved by Sergei Y. 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; notes; 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 Rgistrants 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 descriptions 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 classified 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 practice, or making commitments of Registries

USTUR Policies and Procedure Manual

USTUR Data: *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:

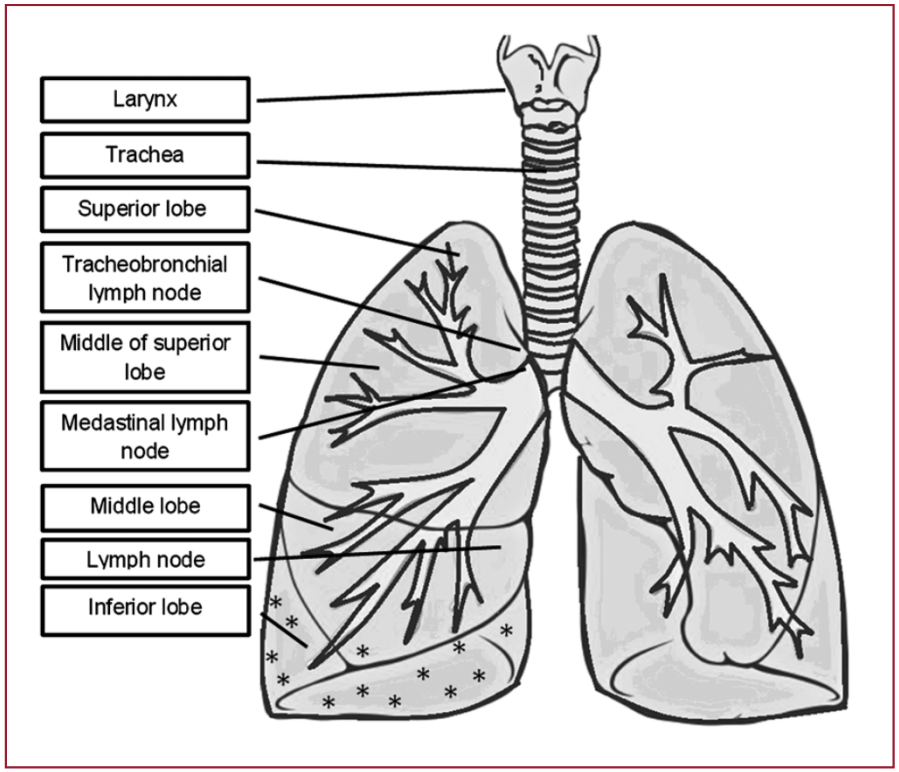
  Loan or provision of tissues or other materials

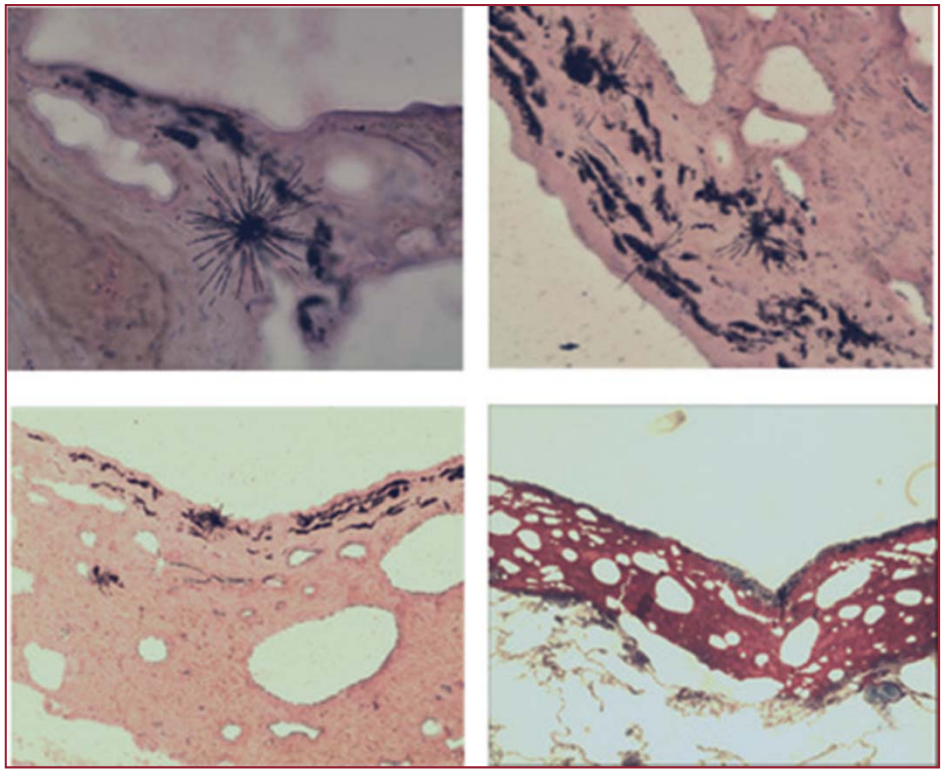
  Only published Registries' data or evaluation

  Manuscript exclusively prepared by other investigators without consulting the Registries

http://www.ustur.wsu.edu/PolicyProcedures/USTURprocedures.html

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

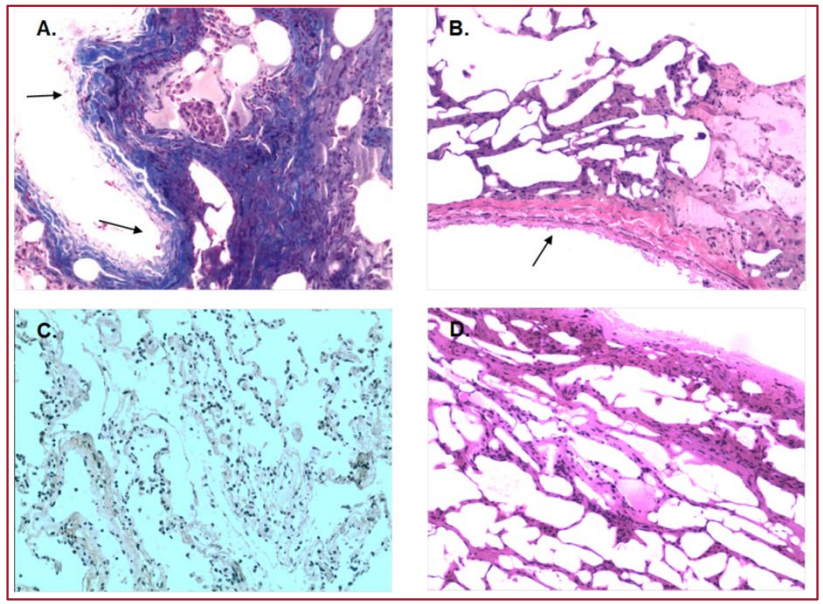
  Possible pathways - tissue injury, apoptosis, and gene expression modifications

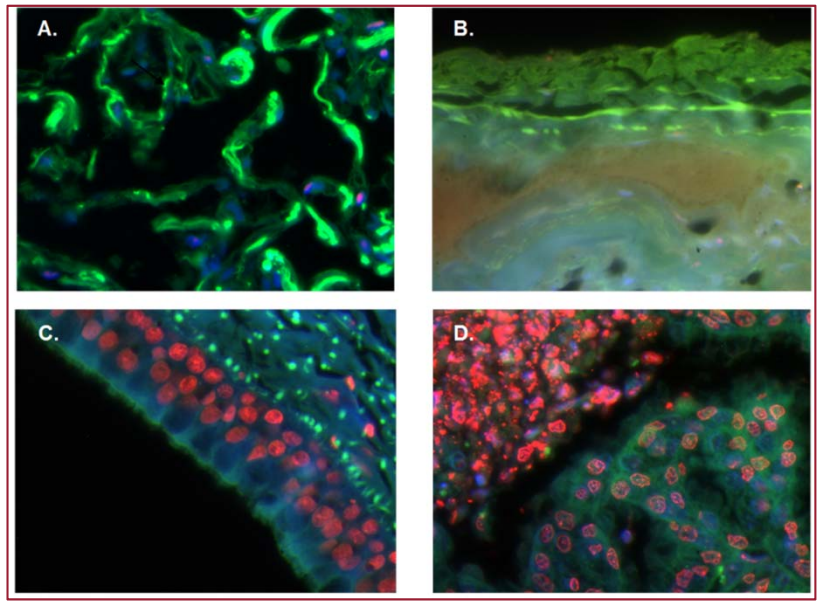
- Immunohistochemistry: to characterize lung lesions, visualize interstitial fibrosis, and other pathology
- RT-PCR: to quantify the expression of chemokine/cytokine regulatory genes thought to be involved in inflammation and carcinogenesis

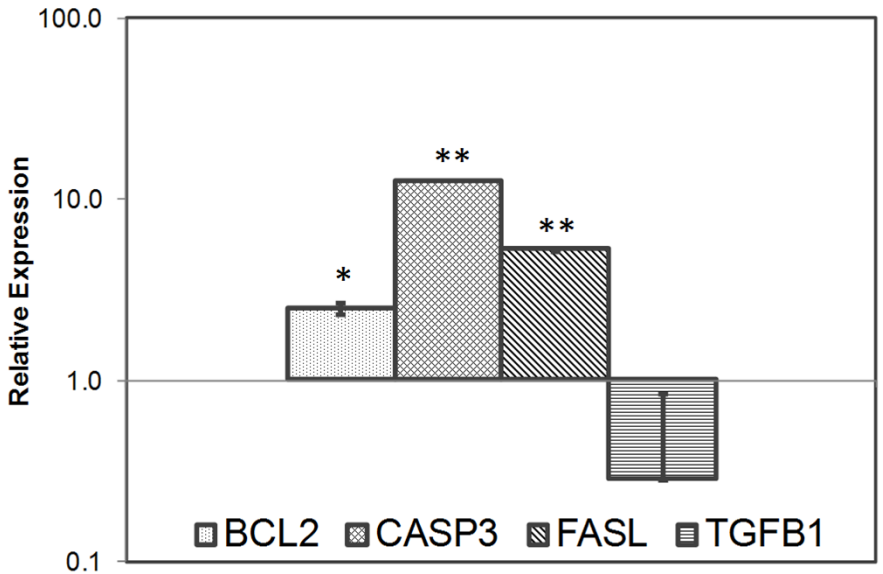
  BCL-2, CASP-3, FASL, IL4, IL8 and TGFß-1

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







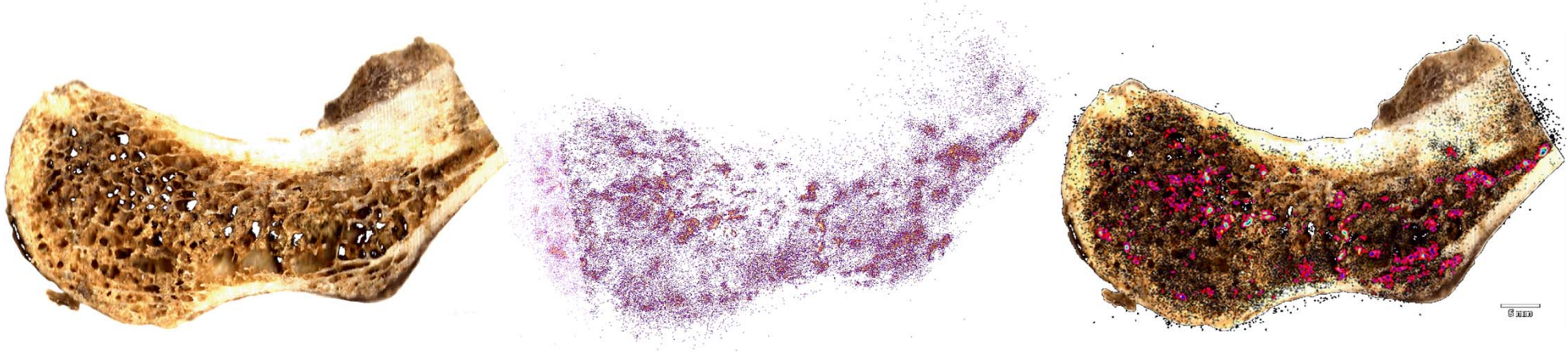
Radionuclide Bone Microdosimetry

- Digital Autoradiography: ionizing-radiation Quantum Imaging Detector (iQID)
- Radionuclides: ^{239}Pu, ^{226}Ra, ^{241}Am

  Plutonium injection study – ^{239}Pu: 14.9 kBq (0.4 µCi)

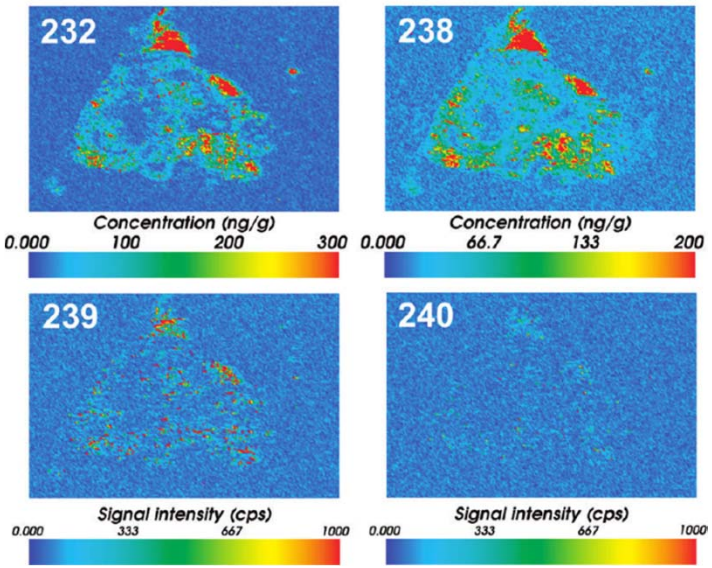
  Radium therapeutic injection – ^{226}Ra: 9.3 MBq (250.2 µCi)

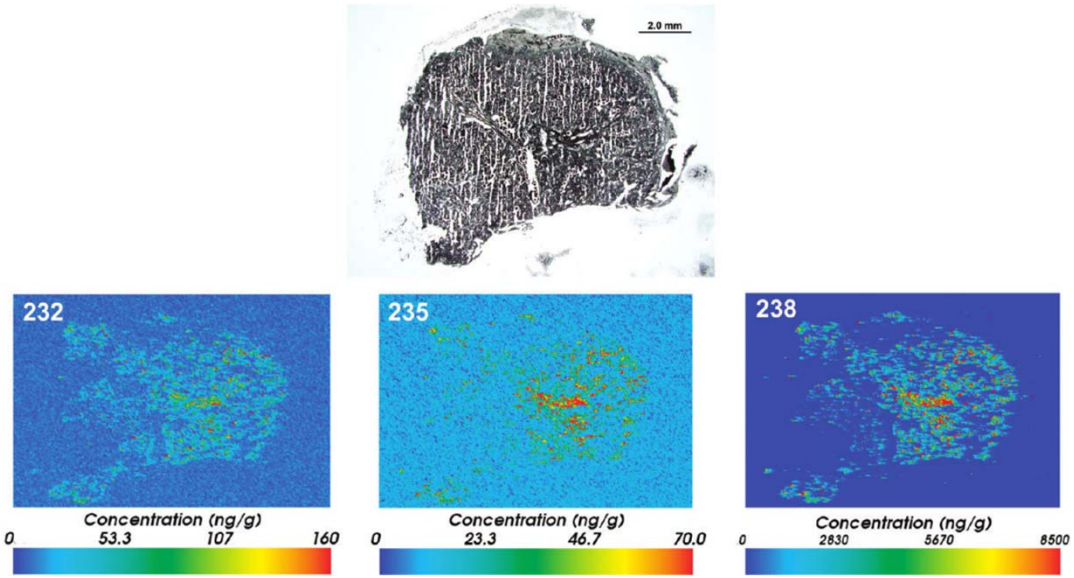
  Occupational exposure – ^{241}Am: 40 MBq (1,080 µCi)



G. Tabatadze, B. W. Miller, S. Y. Tolmachev. *Radionuclide distribution measurement within anatomical bone structures using digital autoradiography. (2015 in preparation)*

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).

Biodosimetry of Incorporated Radionuclides

- Pelger-Huët Anomaly (PHA) in blood cells

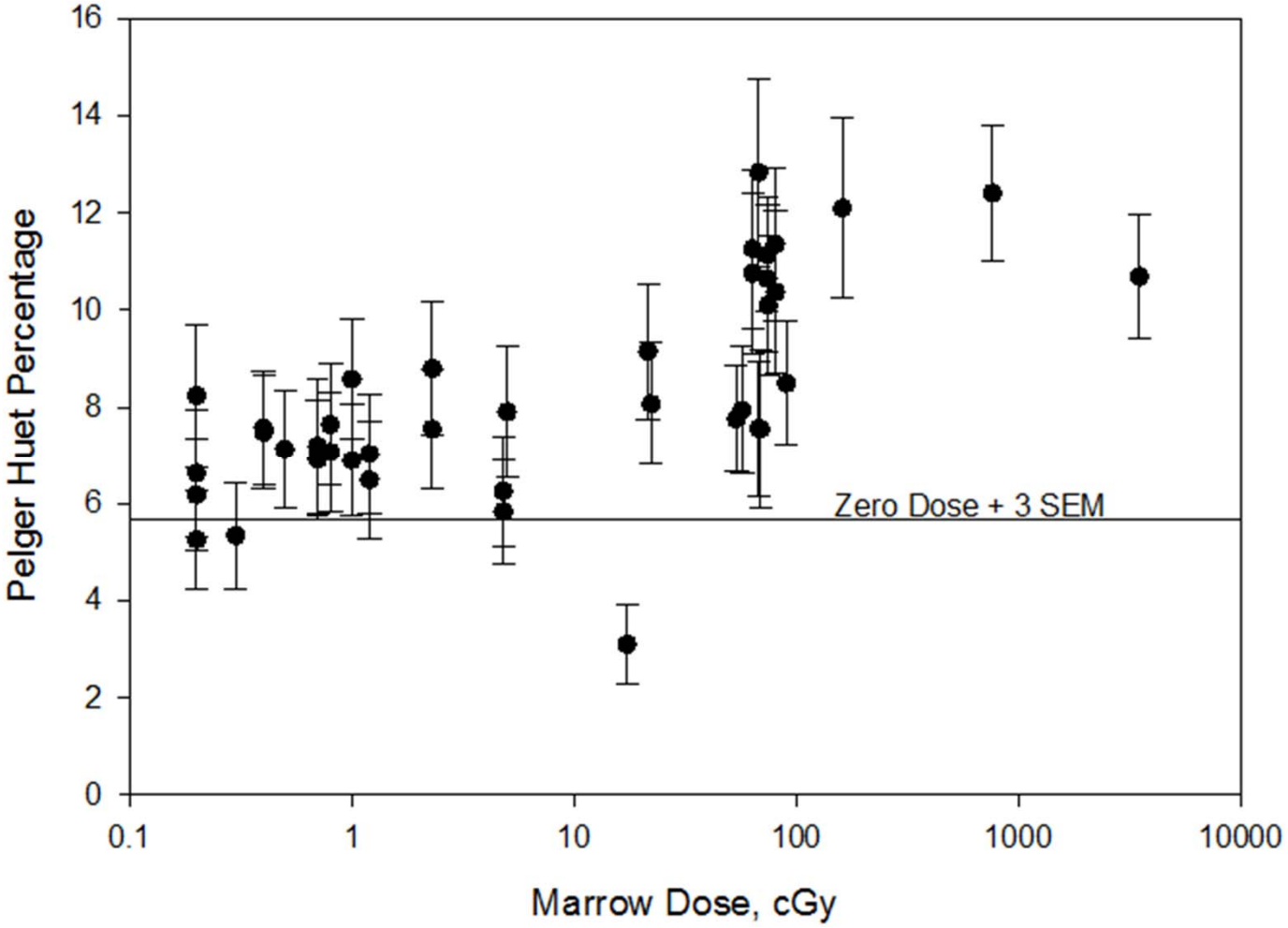
Goans, R. E., Iddins, C. J., Christensen, D., Wiley, A. and Dainiak, N. Appearance of pseudo-Pelger Huet anomaly after accidental exposure to ionizing radiation in vivo. Health Phys. 108, 303-7 (2015)

- Study of Radium Dial Painters
- Internal exposure to ^{226}Ra and ^{228}Ra
- Exposure in 1915 – 1925
- Exposure time 4 – 208 weeks
- Bone marrow dose 0.1 cGy – 3,400cGy
- Peripheral blood slides prepared in 1970 – 1975
- Available at the NHRTR in 2015

New, Permanent Radiation-induced Biomarker

Pelger-Huët Anomaly: RDP 09-064; Started 1916; Exposed for 9 weeks

PHA – Marrow Dose Correlation



Thank you!

Disclaimer

- *This presentation was prepared as an account of work sponsored by an agency of the United State Government. Neither the United States Government nor any agency thereof, nor any of their employees, make warranty, expressed or implied, or assumes any legal liability or responsibility for the accuracy, completeness, o 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 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.*