



National Human Radiobiology Tissue Repository

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*“Learning from Plutonium
and Uranium Workers”*





What is the NHRTR?

- The National Human Radiobiology Tissue Repository (NHRTR) is a tissue collection associated with the Registries
- Created in 1992 when the USTUR acquired tissues and related materials from Argonne National Laboratory
 - ✓ Radium dial painters
 - ✓ Plutonium injection studies

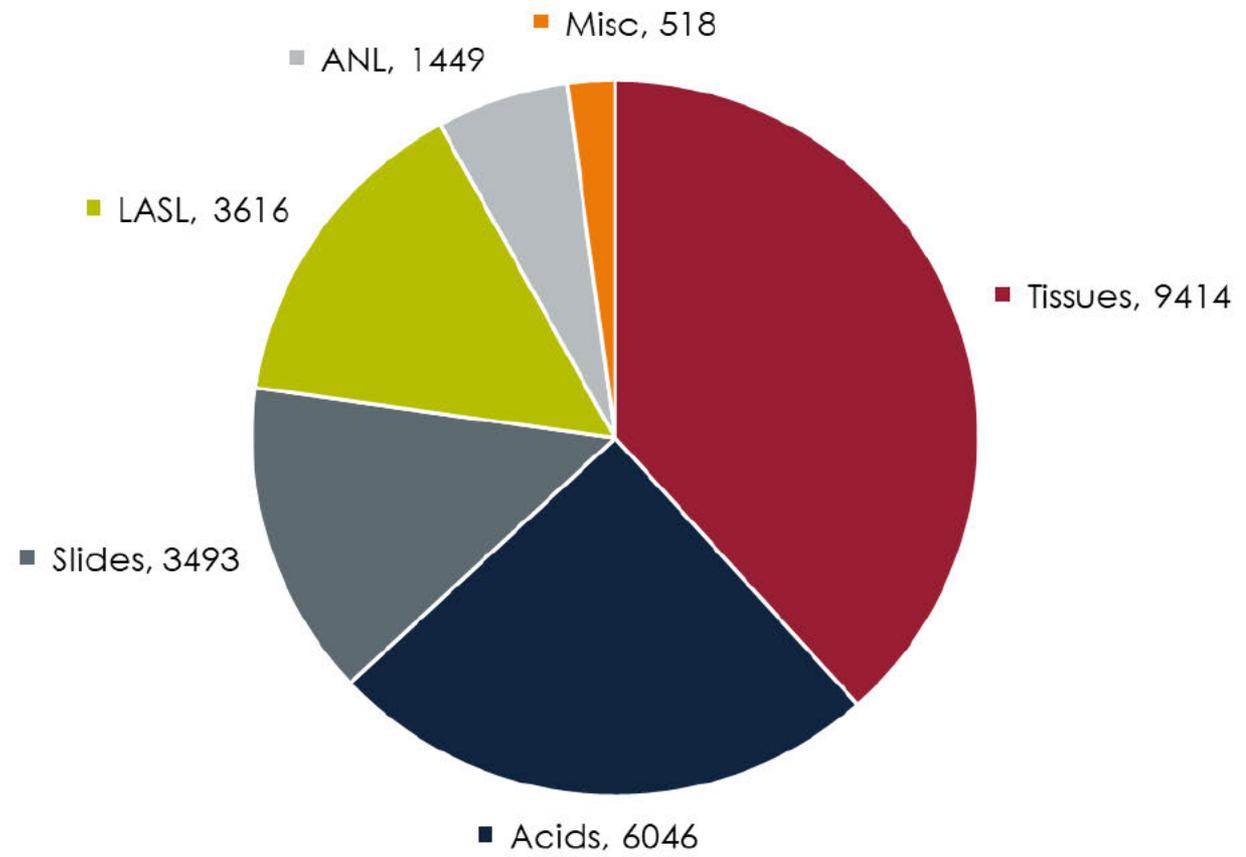


Materials at the NHRTR

- USTUR tissue donations
 - ✓ Frozen and formalin-fixed tissues
 - ✓ Acid-digested tissues
 - ✓ Histological slides and tissue blocks
- Argonne National Laboratory (ANL) historical samples
 - ✓ Frozen tissues
 - ✓ Dried bones
 - ✓ Histological slides and tissue blocks
- Los Alamos National Laboratory (LANL) population studies
 - ✓ Acid-digested tissues



22,798 Parent Samples*



*Pie chart includes 2,096 slide subsamples



Inventory Status

An inventory status has been assigned to each project:

- ✓ **Maintenance:** Inventory of existing samples is complete; new samples are inventoried as they are received or generated
- ✓ **Active:** Inventory of existing samples is ongoing
- ✓ **Future:** Inventory not yet initiated



Inventory Status: USTUR Samples



Tissues

Status: Maintenance
9,414 parent samples
(233 during FY2018)



Acid Solutions

Status: Maintenance
6,404 parent samples



Planchets

Status: Active
New stand-alone
database designed
by Elizabeth Thomas

Contains detailed
information such as
isotopic activities

THEMIS continues to
track sample
locations



Slides & Blocks

Slides: Maintenance
3,493 samples

Blocks: Future work



Inventory Status: LANL Samples

- Acid-dissolved tissues from population studies carried out by Los Alamos Scientific Laboratory



Status: Active

3,616 parent samples
(445 during FY2018)



Inventory Status: ANL Samples

- Tissues received from ANL in 1992
- Primarily radium worker studies: MIT, NJRRP, ANL
- Plutonium injection studies – Chicago (1), Rochester (4)
- No further progress toward this task



Frozen Tissues: Active
979 parent samples

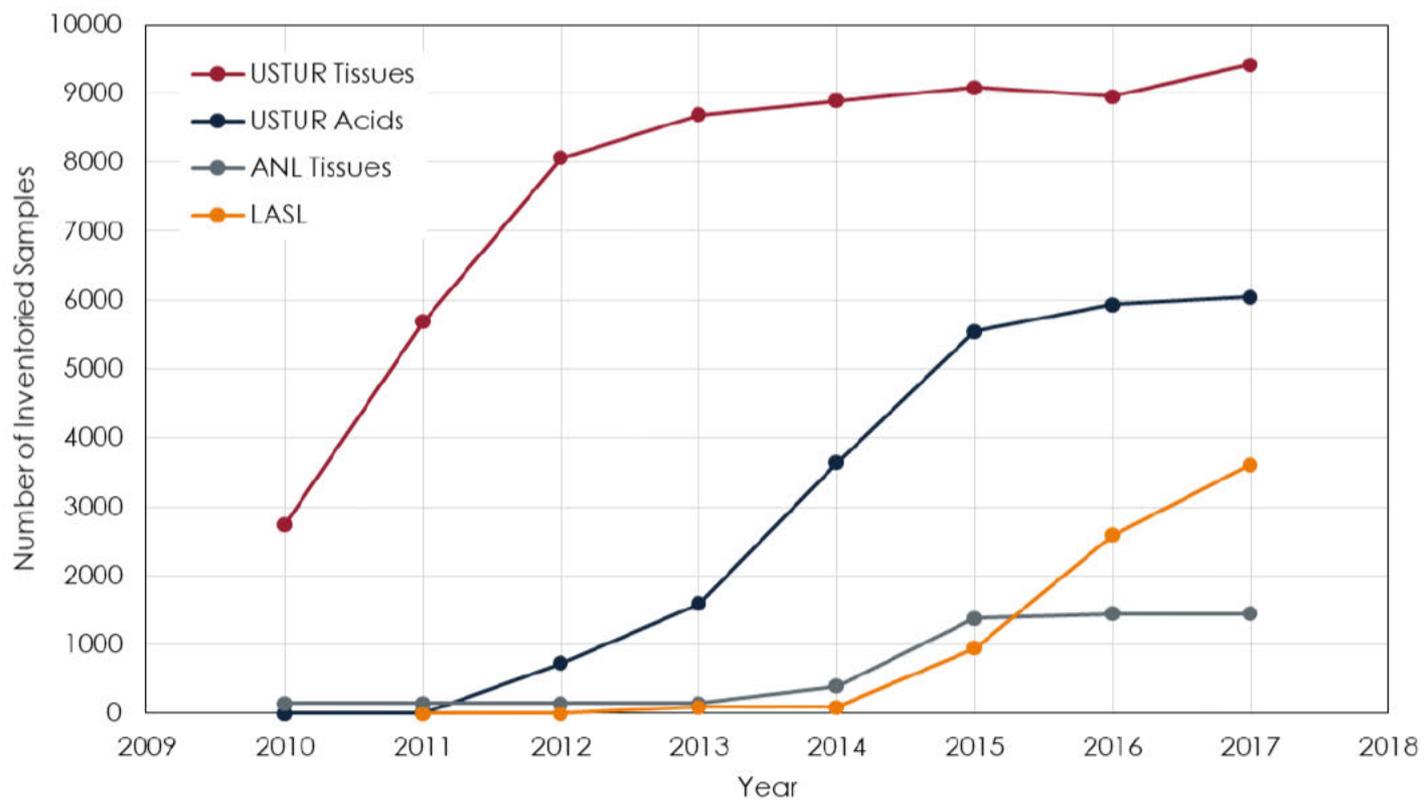
Slides: Active
470 blood smears

Dried Bones: Future

Plastic embedded: Future



Data Trends



Big Picture

Health Protection Character 2017, Vol 18, No 12, pp 20–30
doi:10.1093/heap/ckx019

THE MAYAK WORKER DOSIMETRY SYSTEM (MWDS) 2013: A RE-ANALYSIS OF USTUR CASE 0269 TO DETERMINE WHETHER PLUTONIUM BINDS TO THE LUNGS

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Radionuclides in particulate form can become chemically bound to the alveoli of the lungs following dissolution of inhaled particulates in lung fluid. The presence of long-term binding can greatly increase lung doses from inhaled plutonium, particularly if it occurs in the bronchial and bronchiolar regions. However, the only published evidence that plutonium binding occurs in humans comes from an analysis of the autopsy and biopsy data of United States Transuranium and Uranium Registries Case 0269, a plutonium worker who experienced a very high (50 LBi) acute inhalation of plutonium nitrate. This analysis suggested a bound fraction of around 8%, inferred from an unexpected low ratio of estimated total thoracic lymph node activity to total lung activity, at the time of death. However, there are some limitations with this study, the most significant being that measurements of the regional distribution of plutonium activity in the lungs, which provide more direct evidence of binding, were not available when the analysis was performed. The present work describes the analysis of new data, which includes measurements of plutonium activity in the alveolar-interstitial (AI), bronchial (BR) and bronchiolar (Br) regions, and extra-thoracic (ET) regions, at the time of death. A Bayesian approach is used that accounts for uncertainties in model parameter values, including particle transport clearance, which were not considered in the original analysis. The results indicate that a long-term bound fraction between 0.4 and 6.7% is required to explain this data, largely because plutonium activity is present in the extra-thoracic (ET), bronchial and bronchiolar airways at the time of death.

INTRODUCTION

In the International Commission on Radiological Protection (ICRP) Publication 66 human respiratory tract model (HRTM) (1) and in the revised HRTM (2) the absorption to blood of material deposited in extra-thoracic region (ET) and the thoracic airways is assumed to occur by dissolution of the inhaled material, followed by uptake to blood. This latter is assumed to be instantaneous unless the dissolved ions of the radionuclide become chemically bound within lung epithelia. The proportion of material that becomes bound after material has dissolved is determined by the bound fraction, f_b . Because it occurs after dissolution, binding is dependent on the ionic form of the radionuclide and so is independent of the previous chemical form of the inhaled material. Hence, the value of f_b is assumed to be the same for plutonium dioxide (PuO₂) and nitrate (Pu(NO₃)₃). Uptake of material to blood from the bound state is assumed to occur at a rate k_b .

The presence of long-term binding can greatly increase lung doses from inhaled plutonium, particularly if it occurs in the bronchial and bronchiolar regions of the lung (3–6). However, evidence that it actually

occurs for plutonium is unclear. To ensure the reliability of ongoing radiation protection of plutonium workers and the accuracy of retrospective dose reconstruction for epidemiology, it is important to:

- Determine whether binding of plutonium actually occurs in the extra-thoracic (ET) and thoracic airways;
- If it does, to estimate values of the bound-state parameters f_b and k_b .

With respect to Point (a), the only published evidence for binding, according to the ICRP definition, derives from an analysis of United States Transuranium and Uranium Registries (USTUR) Case 0269 by Jones *et al.* (7). This worker suffered a large acute inhalation of acidic plutonium nitrate (m3) whilst working at a nuclear defence facility. In an attempt to ameliorate the plutonium burden, Ca-diethylenetriaminepentaacetic acid (DTPA) and Ca-ethylenediaminetetraacetic acid (EDTA) were administered intravenously immediately and again intermittently over the next 2 y. Extensive measurements of plutonium (239, 240) Pu activity in urine and faeces were made following exposure until the individual's death. An initial estimate of

Paper

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

Ronald E. Goms¹, Richard E. Toohy², Carol J. Iddins³, Stacey L. McComish⁴, Sergei Y. Tolmachov² and Nicholas Dainiak^{2,5}

INTRODUCTION

Analysis of peripheral blood streams 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 radium dose, pseudo-Pelger Huet anomaly (PHA). The radium dial painter cohort is a well-characterized group of predominantly young women who incidentally ingested ²²⁶Ra and ²²⁸Ra as they painted luminous watch dials in the first half of the twentieth century (Booby et al. 1982; Rowland 1994, 1996). In the present study, we evaluate present the dose response of the pseudo-Pelger Huet anomaly in a large cohort of former dial painters. PHA has been recently described as a novel, permanent, radiation-induced biomarker in circulating neutrophils (Goms et al. 2015, 2017), and it appears to be a surrogate for the estimation of radiation dose to bone marrow. Peripheral blood smears 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 (DISTRU).

PHA was initially described by Karl Pelger (Pelger 1928) and later defined by G. J. Huet (Huet 1931) as a mutation with autosomal dominant inheritance. PHA is characterized in myelocytes by bi- or dumbbell-shaped, symmetric, bilobed nuclei whose lobes are joined by a thin nuclear bridge (Fig. 1). In peripheral blood smears, PHA is observed in myeloid elements, predominantly in neutrophils and rarely in eosinophils. PHA is caused by a decreased amount of the lamin B receptor (LBR).

Lamins are intermediate filaments that form a fibillary network on the inner surface of the nuclear membrane, together with membrane-associated proteins. This network provides both nuclear stability and chromatin organization within the nucleus. The B-type lamins are believed to play an important role in cell differentiation and embryonic development. The LBR is bound to the lamina where it is integral to the inner nuclear membrane. The gene that encodes the LBR is now known to be located on the long arm of chromosome 1, 1q42.12 (Cobbili and Hellensson 2012; Mitalovics

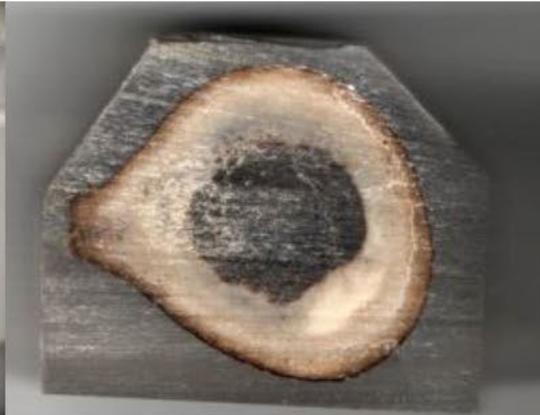
Abstract—Recently, the pseudo-Pelger Huet anomaly in peripheral blood neutrophils has been described as a new radiation-induced, stable biomarker. In this study, pseudo-Pelger Huet anomaly was examined in peripheral blood slides from a cohort of 164 former radium dial painters and ancillary personnel in the radium dial industry, 28 of whom had a marrow dose of or above background. Members of the radium dial painter cohort ingested ²²⁶Ra and ²²⁸Ra at an early age (average age: 20.6 ± 5.4 yr; range: 13–41 yr) during the years 1914–1955. Exposure duration ranged from 1–1820 wk with marrow dose 1.5–4,750 mSv. Pseudo-Pelger Huet anomaly, expressed as a percentage of total neutrophils in this cohort, rises to a significant level over five decades if not marrow dose. Six subjects in this cohort eventually developed malignancies: five osteosarcomas and one myeloid cell carcinoma. The pseudo-Pelger Huet anomaly percentage in these cases of neoplasia increases with marrow dose and is best fit with a sigmoid function, suggestive of a threshold effect. No marrow dose was seen for marrow doses under 2 Gy. These results indicate that pseudo-Pelger Huet anomaly in peripheral blood is a reasonable surrogate for the estimation of alpha dose to bone marrow in historical radiation cases. Hypotheses are discussed to explain the anomaly by cyclic, acute (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 ligands, and on cytokinesis through chromatin bridge fragmentation. *Health Phys.* 102(6):2016–2026, 2016
Key words: biomarker; dial painter; dosimetry; biomarkers; cell biology

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Questions?

