Joint Coordinating Committee for Radiation Effects Research (JCCRER): Shorter Term Direction 2 Projects

Project 2.1: Metabolism and dosimetry of plutonium industrial compounds

Project 2.3: Deterministic effects

Project 2.5: Plutonium microdosimetry in the lung

Project 2.6: Molecular markers of lung cancer in Mayak workers

Project 2.7: Radiation biomarkers

Project 2.9: Database integration

Scott C. Miller
University of Utah
Salt Lake City, USA
Scott.Miller@hsc.utah.edu

Project 2.1

Comparison of the Dosimetry-Autopsy Programs: Dosimetry Registry of the Mayak Industrial Association (DRIMA) and the United States Transuranium and Uranium Registries (USTUR)

Valentin Khokharyakov (Southern Urals Biophysics Institute [FIB-1, now SUBI], Ozersk, Russian Federation)

Ronald Filipy (United States Transuranium and Uranium Registries, [USTUR], Washington State University, USA)

Project dates: ≈ 1994 - 2004

Project 2.1 Objectives

- **To conduct a joint analysis of the data collected by the U.S. Transuranium and Uranium Registries (USTUR) and the Dosimetry Registry at Mayak (DRIMA) on deceased people with occupational exposure to radiation**
- **To determine the inter comparability of data from the USTUR and DRIMA**
- **The data were used to develop and improve dosimetry models**

Keith Eckerman
Valentine Khokhryakov

Project 2.1 Accomplishments

- **Compatibility for liver and skeletal measurements**
- **Uniform radiochemical methods, standards and equipment**
- **In vitro solubilities of industrial compounds were related to lung transportability**
- **Liver diseases altered plutonium biokinetics and excretion**
- **Contributed to an initial lung clearance model (later with Project 2.4)**

References:

Suslova et al. Rad. Prot. Dos. 67:13, 1996

Khokhryakov et al., J. Radioanal. Nuc. Chem. 234:293, 1998

Khokhryakov et al. Health Pays. 79:63, 2000

Khokhryakov et al., Health Phys. 82:425, 2002

Project 2.3

Non-Cancerous Effects of Radiation Exposures (Deterministic Effects)

Nadezha Okladnikova (Southern Urals Biophysics Institute, Ozersk, Russian Federation)

H. Gregg Claycamp (University of Pittsburg, USA)

Project Dates ≈ 1994 - 2004

Project 2.3 Objectives

- **To validate and analyze the data on acute and chronic effects of radiation, other than cancer, observed in a large number of workers at the Mayak facility.**

- **Test existing nuclear regulatory models for consequences of nuclear accidents using human health effects data from the study.**

Nadezha Okladnikova
Gregg Claycamp

Project 2.3 Accomplishments

- **Developed a cohort of about 600 workers (1948-1958) who had dosimetry (internal and external), work histories and medical records**
- **Detailed clinical and blood count records on workers diagnosed with ‘Acute Radiation Syndrome’ and/or ‘Chronic Radiation Syndrome’**
- **Plutonium pneumosclerosis**
- **Differential blood cell counts provided improved diagnostic classification**

References:

Claycamp et al., Health Phys. 79:48, 2000.

Claycamp et al., Health Phys. 81:522, 2001.

Azizova et al., J. Radiol. Prot. 39:890, 2019 (updated CRS registry)

Project 2.5

Improved Dosimetry and Risk Assessment for Plutonium-Induced Lung Disease Using a Microdosimetric Approach

Sergey Romanov (Southern Urals Biophysics Institute, Ozersk, Russian Federation)

Ray Guilmette (Lovelace Respiratory Research Institute, Albuquerque, NM, USA)

Project dates: 1999 – 2009

(Later merged with Project 2.4)

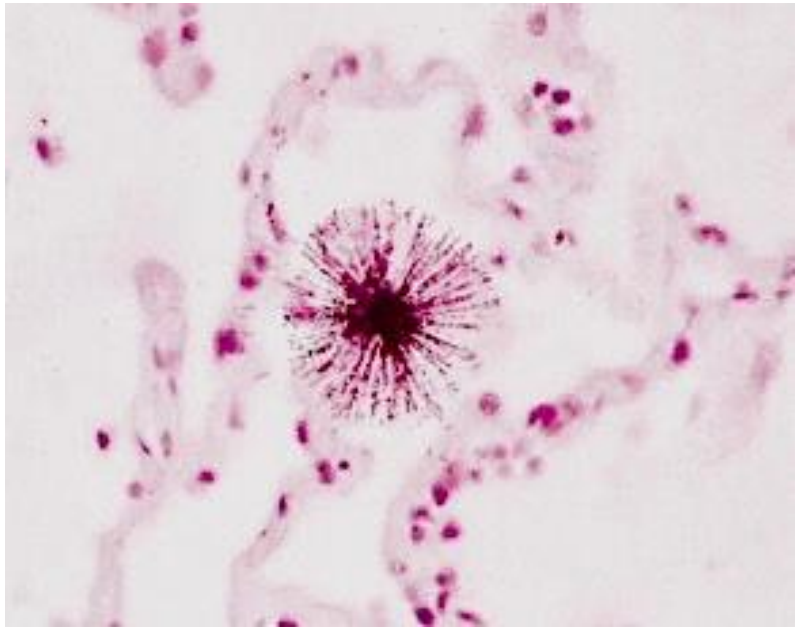
Project 2.5 Objectives

- **Use archival tissues to measure microscopic distribution of plutonium using stereological and quantitative autoradiography**
- **To quantify plutonium activity in different lung regions and tissues (e.g. conducting airways, parenchyma, pleura, scars, lymphatic tissue)**
- **How might non-uniform distributions influence dose-related lung cancer risks?**

Sergey Romanov

Project 2.5 Accomplishments

- **Plutonium in lung tissues is not uniformly distributed**
- **Over 40% of the Pu was found in parenchyma, most highly concentrated in scars and regions of fibrosis**
- **Longer-term sequestration of plutonium may reduce radiation exposures to critical target cells and tissues**
- **New Bayesian approaches for dosimetry modeling were developed**



References:

Romanov et al., Med. Rad. & Safety 40:58, 2001

Guilmette et al. Rad. Prot. Dosimetry 99:457, 2002

Romanov et al., Rad. Prot. Dosimetry 105:85, 2003

Hahn et al., Rad. Res. 161: 568, 2004

Miller et al., Rad. Prot. Dosimetry 131:316, 2008

Project 2.6

Molecular Markers of Lung Cancer

Vitaliy Telnov (Southern Urals Biophysics Institute, Ozersk, Russian Federation)

Steven Belinsky (Lovelace Respiratory Research Institute, Albuquerque, NM, USA)

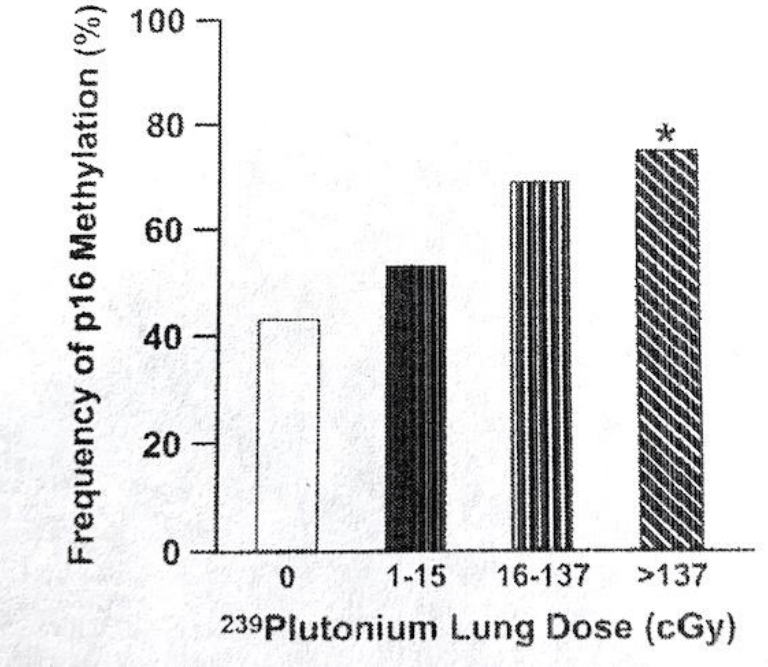
Project Dates: 2000 - 2008

Project 2.6 Objectives

- **Understand molecular mechanisms and identify biomarkers of lung cancer risk.**
- **Determine prevalence for promoter hypermethylation in silencing genes linked with the development of lung cancers (adenocarcinoma and squamous cell carcinoma).**
- **Identify new biomarkers, based on prevalence of gene methylation, using a cross-sectional study of cancer-free workers exposed to plutonium and an unexposed population.**

Project 2.6 Accomplishments

- **Dose response for methylation of the p16 gene (cell cycle regulation) in plutonium workers.**
- **Greater methylation of the GATA5, a tumor suppressor gene, in adenocarcinomas from male Mayak workers compared to controls. Similar, but limited, observations in females.**
- **Conclude that inactivation of genes by methylation is important in cell transformation and could be important in the development of adenocarcinoma after plutonium exposures.**



References
Telnov et al., Med. Radiol. & Rad. Safety 48:94, 2001.
Telnov et al., Rad. Hum. Health 575.2:616, 2002.
Belinsky et al., Carcinogenesis 25:1063, 2004.
Lyon et al., Rad. Res. 168:409, 2007.

Project 2.7

Radiation Biomarkers

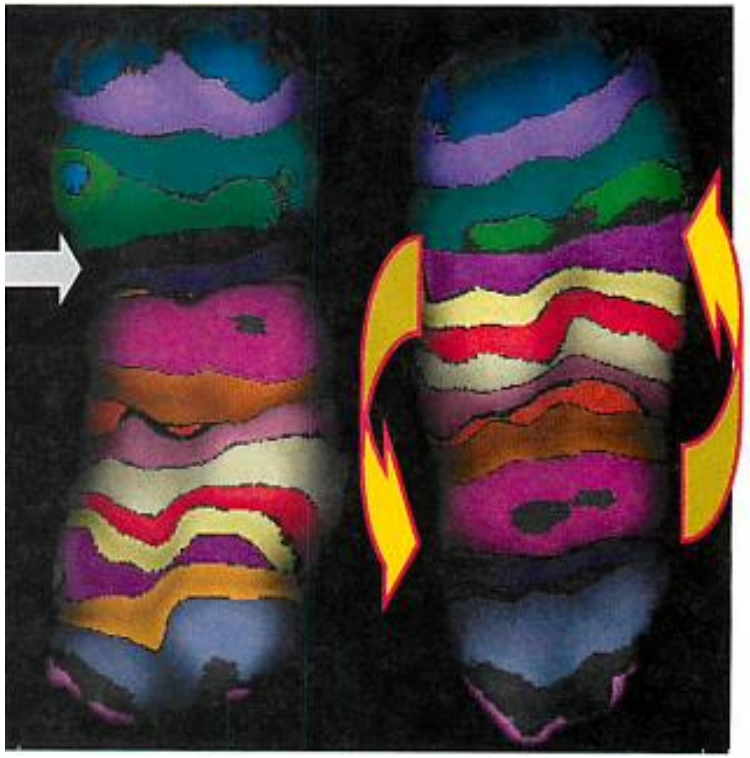
Tamara Azizova (Southern Urals Biophysics Institute, Ozersk, Russian Federation)

David Brenner (Columbia University, New York, USA)

Project Dates: 2001 - 2008

Project 2.7 Objectives

- **Develop a biomarker-based dosimetry system for plutonium (≥ 0.3 kBq) and separately for gamma (≥ 30 cGy) exposures.**
- **Identify stable biomarkers for past radiation exposures.**
- **Identify and compare intra- and inter-chromosomal aberrations in plutonium and gamma ray exposed workers.**



Project 2.7 Accomplishments

- **Chromosome painting techniques (mFISH, mBAND) identified stable intrachromosomal rearrangements in plutonium exposed workers.**

- **Significant excess of intrachromosomal aberrations in chromosomes 1,2 and 5 in plutonium workers compared to high gamma ray exposed reactor operators and non-Mayak workers not exposed to plutonium.**

- **Conclusion: "..stable complex chromosome translocations represent a sensitive, specific, long-lived, quantitative, low-background biomarker of densely ionizing radiation exposure in human populations exposed many years ago."**

References
Hande et al., Am. J. Hum. Genet. 7:1162, 2003.
Mitchell et al., Rad. Res. 162:257, 2004.
Hande et al., Genes Chromosomes Cancer 44:1, 2005.

Project 2.9

Database Integration

Mikhail Sokolnikov (Southern Urals Biophysics Institute, Ozersk, Russia)

Mikhail Gorelov (Mayak Production Association, Ozersk, Russia)

Dale Preston (RERF, Japan; Hirosoft International, Eureka, USA)

Project Dates: 2001 – 2005

(Database integration and updates are ongoing)

Project 2.9 Objectives

- **Develop a “master” database and associated infrastructure linking Mayak records (dosimetry, occupational histories) and SUBI records (clinical, internal dosimetry, epidemiology, tissue archive).**
- **Documentation.**
- **Mechanism for access.**
- **Adapt over time for different platforms and research uses.**

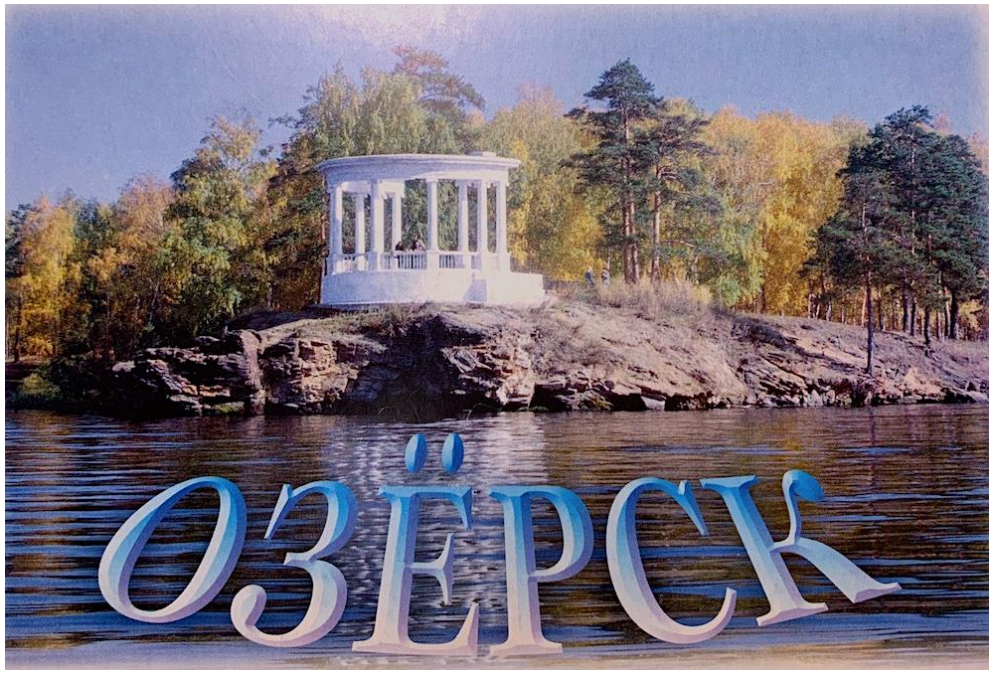
Project 2.9 Accomplishments

- **Data preservation and conversion to digital**
- **Continued upgrade of digital and database resources**
- **Common linking identifiers for databases**
- **Ability to migrate to different platforms for analyses**

Reference
Melamed, Health Phys 79:11, 2000.

JCCRER Direction 2

Many thanks to the many scientists, technicians, advisors, collaborators, administrators and funding agencies for their support in these extraordinary scientific projects



- **References for publications relating to these specific projects? Contact: Scott.Miller@hsc.utah.edu**