Brain Dosimetry and High-LET Exposure

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United States Transuranium and Uranium Registries, established 1968

College of Pharmacy and Pharmaceutical Sciences
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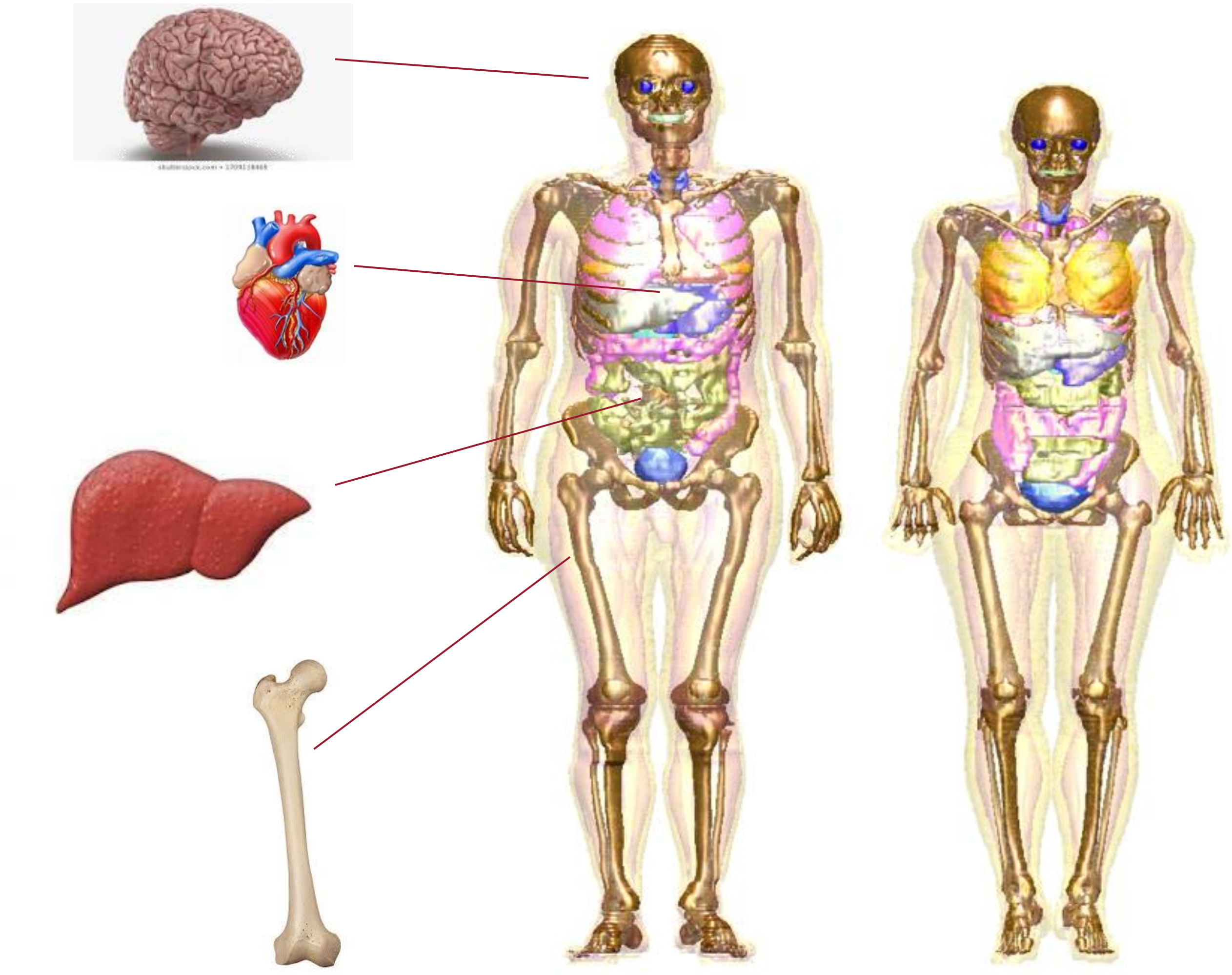
How Do We Do Brain Dosimetry for an Internally Deposited Radionuclide *R*?

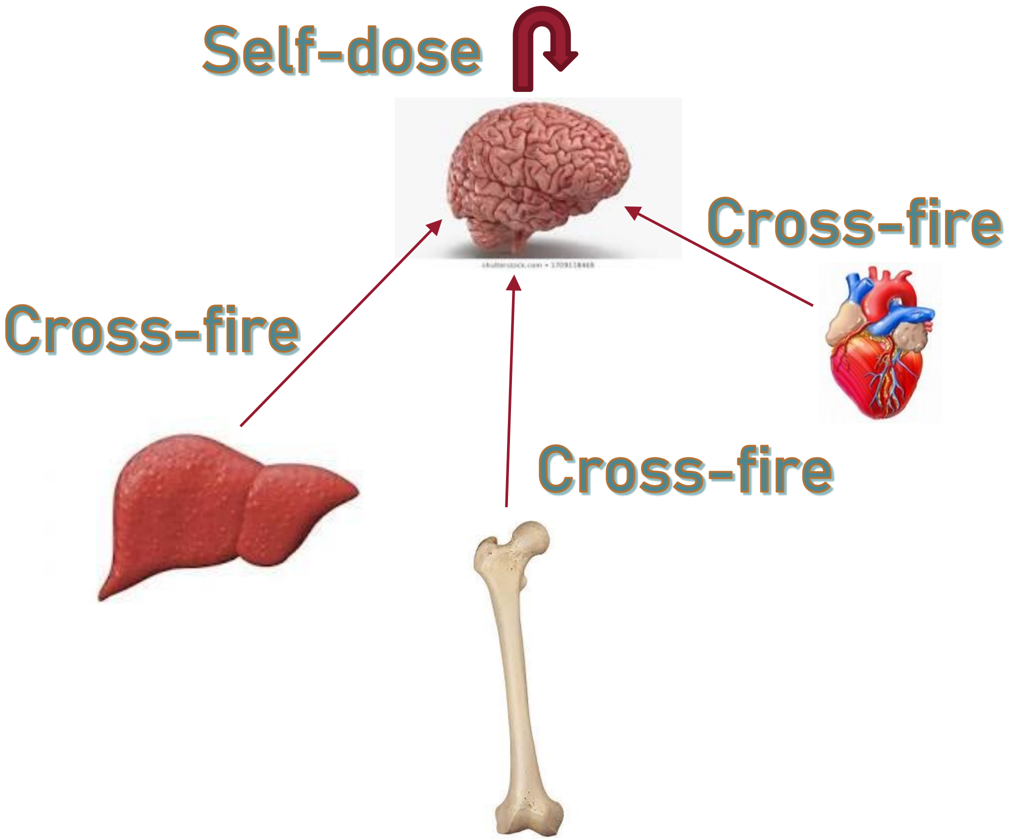
- Biokinetic models are used to describe the time-dependent distribution of activity in the body following intake of *R*
- The derived time-dependent activity includes that of *R*, plus any radioactive progeny produced in the body after intake of *R*
- Dosimetric models are used to estimate the absorbed dose (energy deposited per unit mass of tissue, J kg^{-1}) to each tissue of interest (e.g., brain) based on the time-dependent distribution of activity
- Radiation weighting factors may be used to modify the absorbed dose (Gy) estimates to reflect the relative effectiveness of different radiation types in producing the endpoint of interest (e.g., cancer)

Human Voxel Phantoms in Dosimetry



The basic dosimetric models currently used are realistic human phantoms made up of millions of voxels (volume pixels). Adult male and female phantoms derived from external imaging.

Calculating Radiation Dose to a Tissue



The dose to a tissue is the sum of "self-dose" from radiations emitted within that tissue and "cross-fire" doses from radiations emitted in other tissues (illustrated above for brain). Cross-fire dose estimators are derived from radiation transport models applied to dosimetric phantoms.

ICRP's Biokinetic Treatment of Systemic (Absorbed) Radionuclides

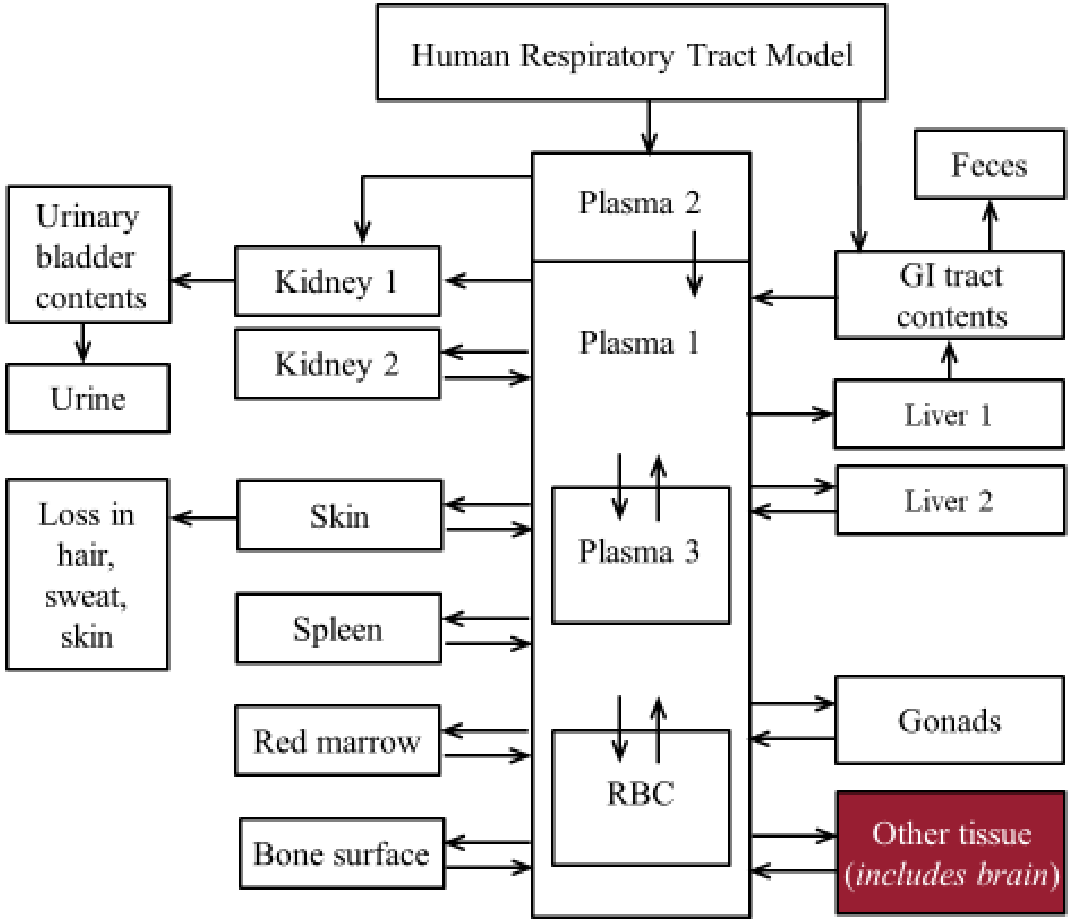
- Systemic biokinetic models, recommended by the International Commission on Radiological Protection (ICRP), generally are element specific
- Typically, the systemic biokinetic model for an element *explicitly* depicts only a small number of dosimetrically important tissues
- Remaining tissues and fluids are aggregated into a pool called *Other tissue*
- Activity in *Other tissue* is assumed to be uniformly distributed

ICRP's Treatment of Brain for Internal Emitters

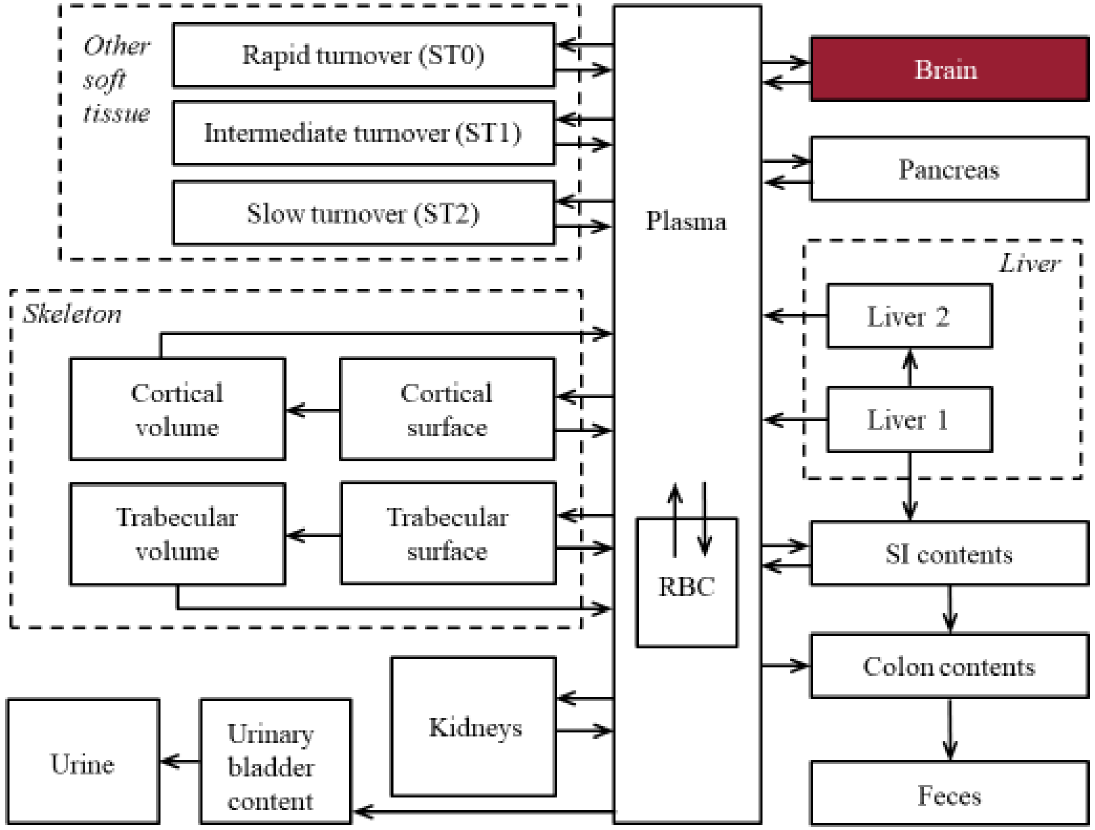
- Typically, brain is included in *Other tissue* because it is rarely a major repository for a radionuclide
- Brain is addressed *explicitly* in systemic biokinetic models for a few elements with elevated uptake by brain:
  - ✓ Nitrogen as ammonia (ICRP Publication 53)
  - ✓ Copper (ICRP Publication 30)
  - ✓ Manganese (ICRP Occupational Intakes of Radionuclides series)
  - ✓ Mercury (ICRP OIR series)

Example of Biokinetic Models with *Implicitly* (Polonium) and *Explicitly* Depicted Brain (Manganese)

Polonium (Po)



Manganese (Mn)



Growing Interest in Brain Dosimetry for Internal Emitters

- U.S. Million Person Study: estimating brain radiation doses and evaluating dementia, Alzheimer's, and other motor neuron diseases as possible adverse effects of radionuclide depositions in the brain
- National Aeronautics and Space Administration: interested in adverse effects of alpha dose on brain as a limited but perhaps informative analogy of behavioral and cognitive effects of galactic cosmic ray (high Z and high energy ions) exposure on astronauts
- National Council on Radiation Protection and Measurements: interested in improvements in brain dose estimates for internal emitters for radiation protection

National Council on Radiation Protection and Measurements (NCRP) Vision

- To examine ways to improve current biokinetic and dosimetric treatments of the brain that may result in improved dose estimates for brain tissue from internally deposited radionuclides
- To improve estimates of brain dose from internal emitters, emphasis is on dose from alpha emitters as a limited but possible surrogate for brain dose from high-energy radiations encountered on long space flights
- To provide guidance for epidemiologic studies as to the optimum way to characterize brain tissue dose from alpha-particle emitting radionuclides in relationship to the occurrence of dementia, Alzheimer's, Parkinson's, other motor neuron diseases and cognitive impairment

NCRP Scientific Committee 6-12

Development of Models for Brain Dosimetry for Internally Deposited Radionuclides (2018 – 2020):

- Richard Leggett (*Chair*, ORNL)
- Sergei Tolmachev (*Vice-chair*, USTUR)
- Maia Avtandilashvili (USTUR)
- Keith Eckerman (ORNL, *retired*)
- George Sgouros (Johns Hopkins University)
- Gayle Woloschak (Northwestern University)
- Helen Grogan (*Staff Consultant*, Cascade Scientific)

Task of Scientific Committee 6-12

To investigate potential improvements in brain dose estimates for internal emitters resulting from *explicit* rather than *implicit* biokinetic treatment of brain (and improved dosimetric treatment)

- *Explicit treatment:* systemic biokinetic model contains compartments and transfer rates specifically representing brain kinetics
- *Implicit treatment*: brain is considered as part of *Other tissue*

Study Design

- Several elements (Mn, Cs, Hg, Bi, Pb, Po, Ra, U, Pu, Am), for which brain kinetics can be modeled reasonably well, were selected. Further, Po, Ra, U, Pu, and Am are radionuclides being evaluated for adverse health effects within the Million Person Study
- For a selected radioisotope of each element, we compared two derived injection dose coefficients (Sv Bq^{-1}) for brain, using ICRP Publication 133 (2016) dosimetry and two versions of the latest ICRP systemic model for occupational intake of the radionuclide:
  1. with brain contained implicitly in *Other tissue* (A)
  2. with brain explicitly modeled (B)

Radionuclides in Brain: What Do We Know

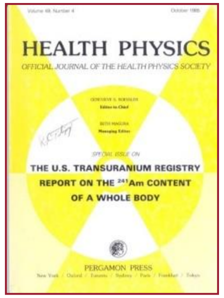
- Human and animal studies show that radioactive elements can accumulate in the brain, despite the presence of a blood-brain barrier that serves to shield the brain from foreign substances and regulates entry of nutrients and xenobiotics
- Best available data for the human brain usually come from autopsy studies of occupationally and environmentally exposed individuals. The autopsy data provide insights into the long-term retention and concentration of the element in the brain compared with other tissues, which is useful for modeling brain kinetics

Radionuclides in Brain: Potential Pathways of Entry

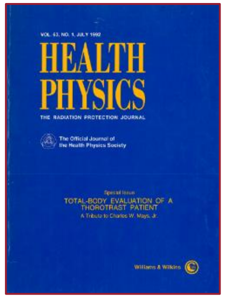
- Some elements are essential to brain function, e.g., S, K, Ca, Zn, Fe, Cu. Radioisotopes of such elements follow the same pathway as the stable element
- Some essential elements have physiological analogues ('biological twins') that gain access *via* the essential element channel, e.g., Rb, Cs, and Tl generally follow K into tissues to some extent; and Sr, Ra, and Pb follow Ca
- The transport systems for some essential elements have binding sites that attract elements with very limited similarities, e.g., Pu competes with Fe for a specific binding site on the iron-transport protein transferrin, apparently due to a similar charge-to-radius ratio

“Best Available Data”: United States Transuranium and Uranium Registries (USTUR)

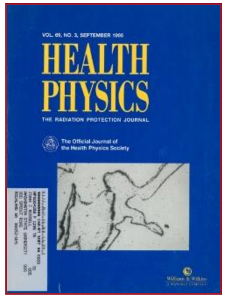
- federal-grant program funded by U.S. Department of Energy
- since 1968, focuses on actinide (Pu, Am, U) biokinetics for radiation protection and dosimetry
- is not an epidemiological study
- supports radiation epidemiology through the improvement of biokinetic models for more accurate dose reconstruction



1985 49(4)



1992 63(1)



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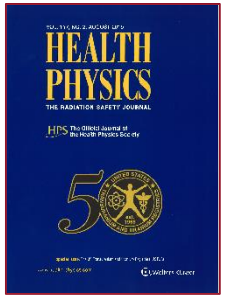


2019 117(2)

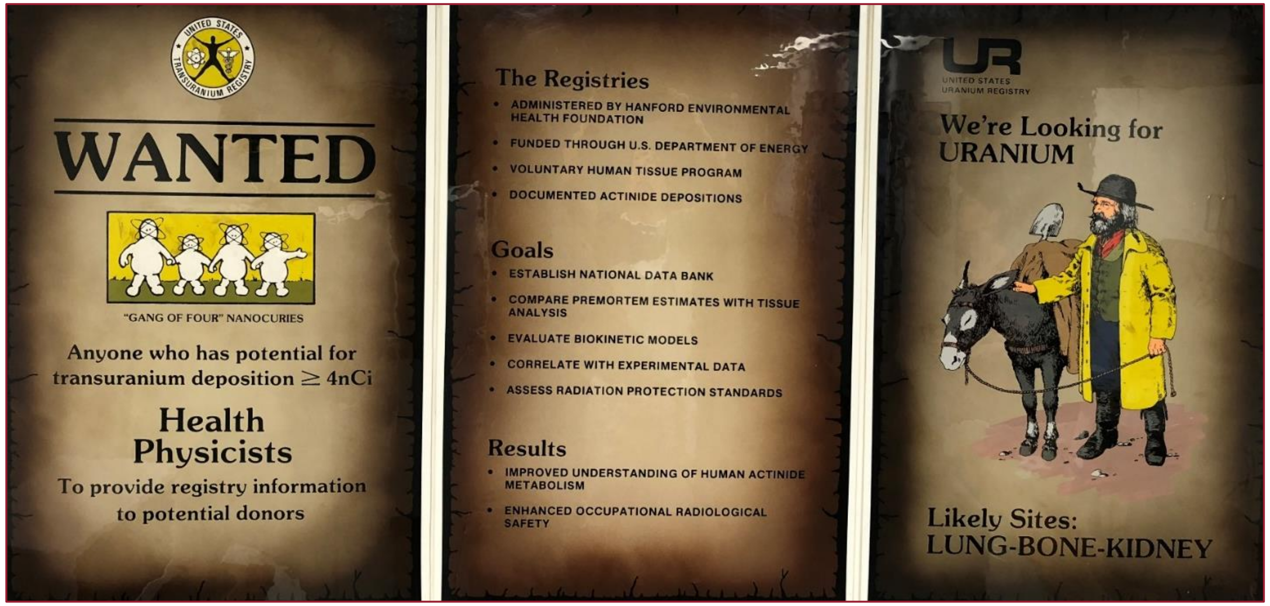
Kathren RL, Tolmachev SY. (2019): *The United States Transuranium and Uranium Registries (USTUR): A five-decade follow-up of plutonium and uranium workers.* Health Physics. 117(2):118–132.

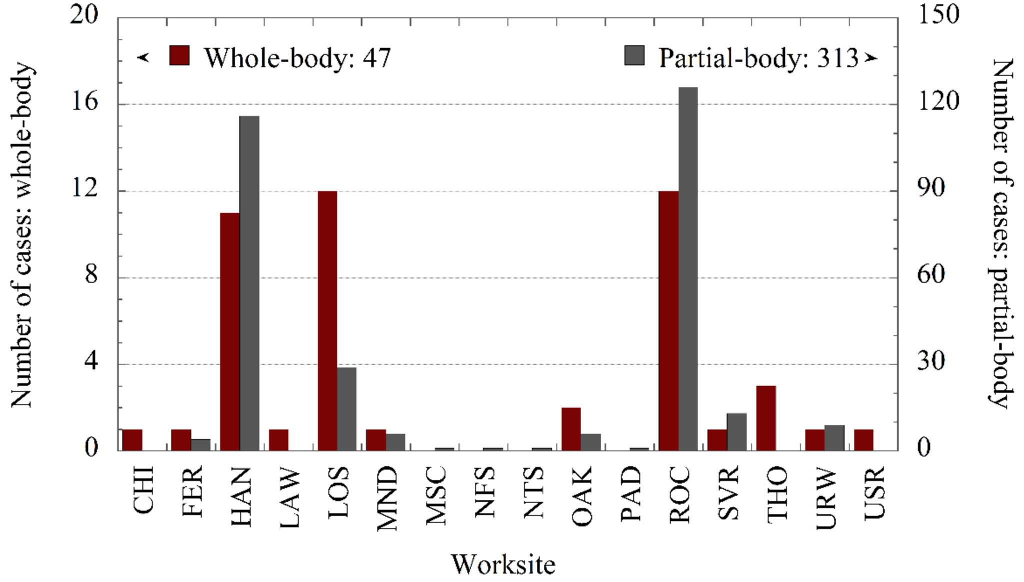
USTUR Registrants

- Voluntary tissue donors (posthumous):

whole- (47) and/or partial-body (313) donations

- Former nuclear workers mainly from U.S. DOE worksites
- Actinide intake ≥ 2 nCi (74 Bq)





Unique Data Resource

USTUR data

- Work history
- Medical records
- Smoking history†
- Chemical exposure records†
- Radiation exposure records
- Bioassay measurements
- Tissue analysis results (Pu, Am, U)

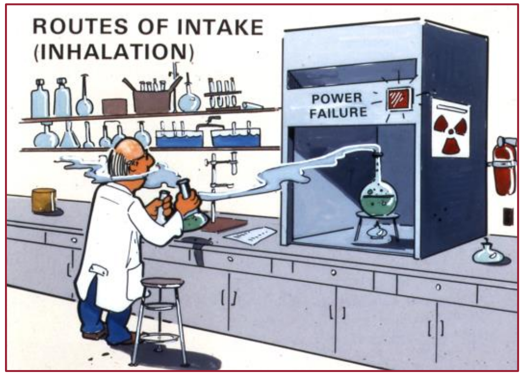
† - self-reported data

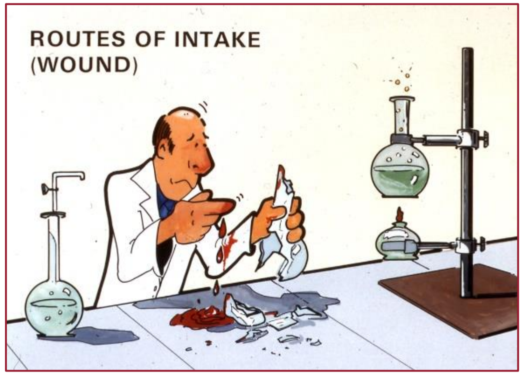
National Human Radiobiology Tissue Repository (NHRTR) at the USTUR

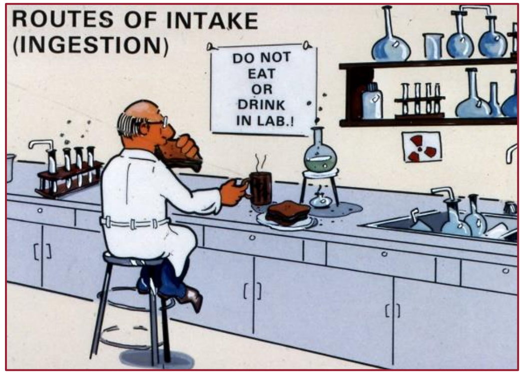
NHRTR materials

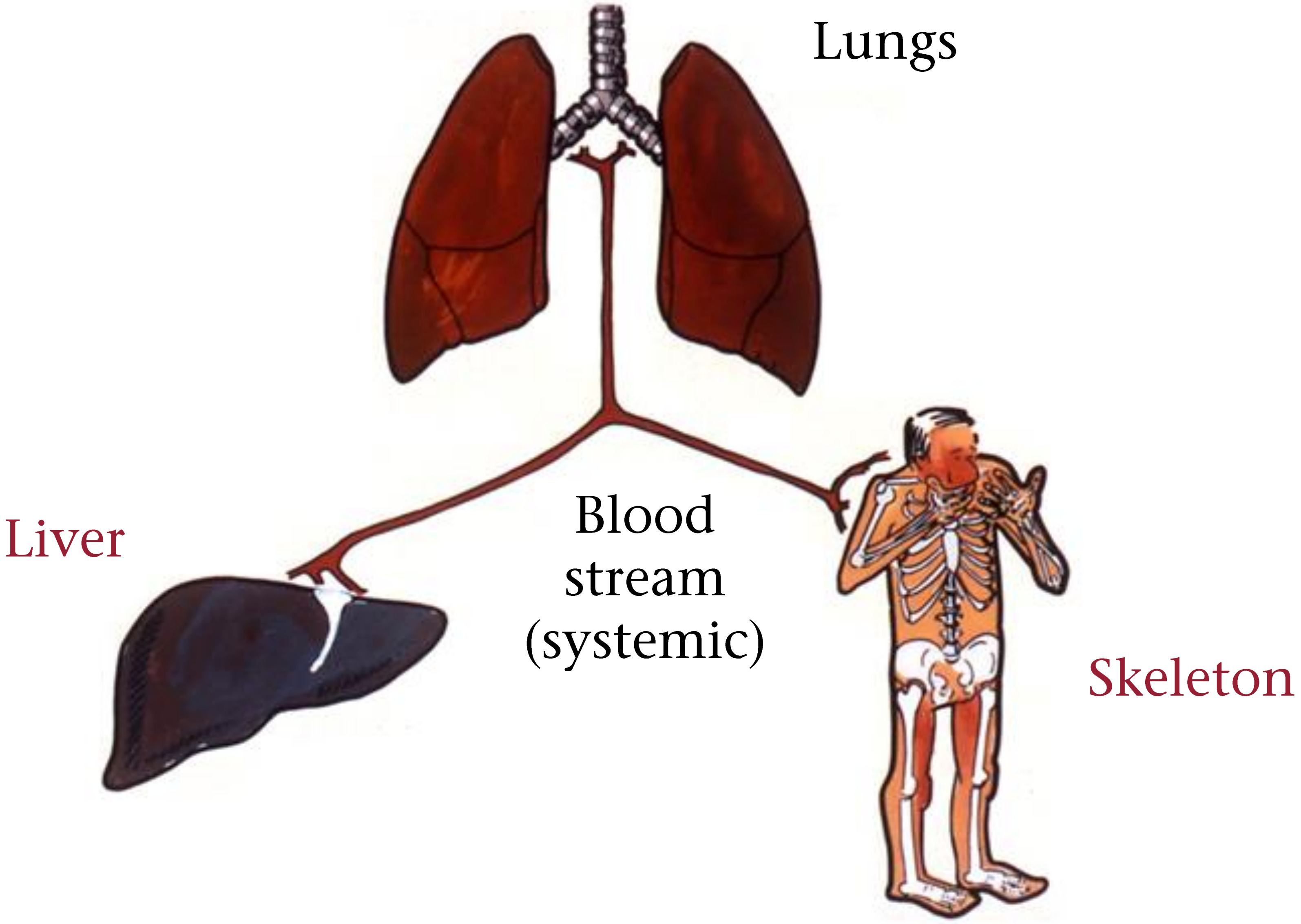
- USTUR research: *frozen and acid-digested tissues (acid solutions)*
- Radium Dial Painter study: *frozen and dry tissues*
- Los Alamos Environmental study: *acid solutions*
- Plutonium Injection study: *plastic-embedded bones*

Simplified Pathways for Plutonium

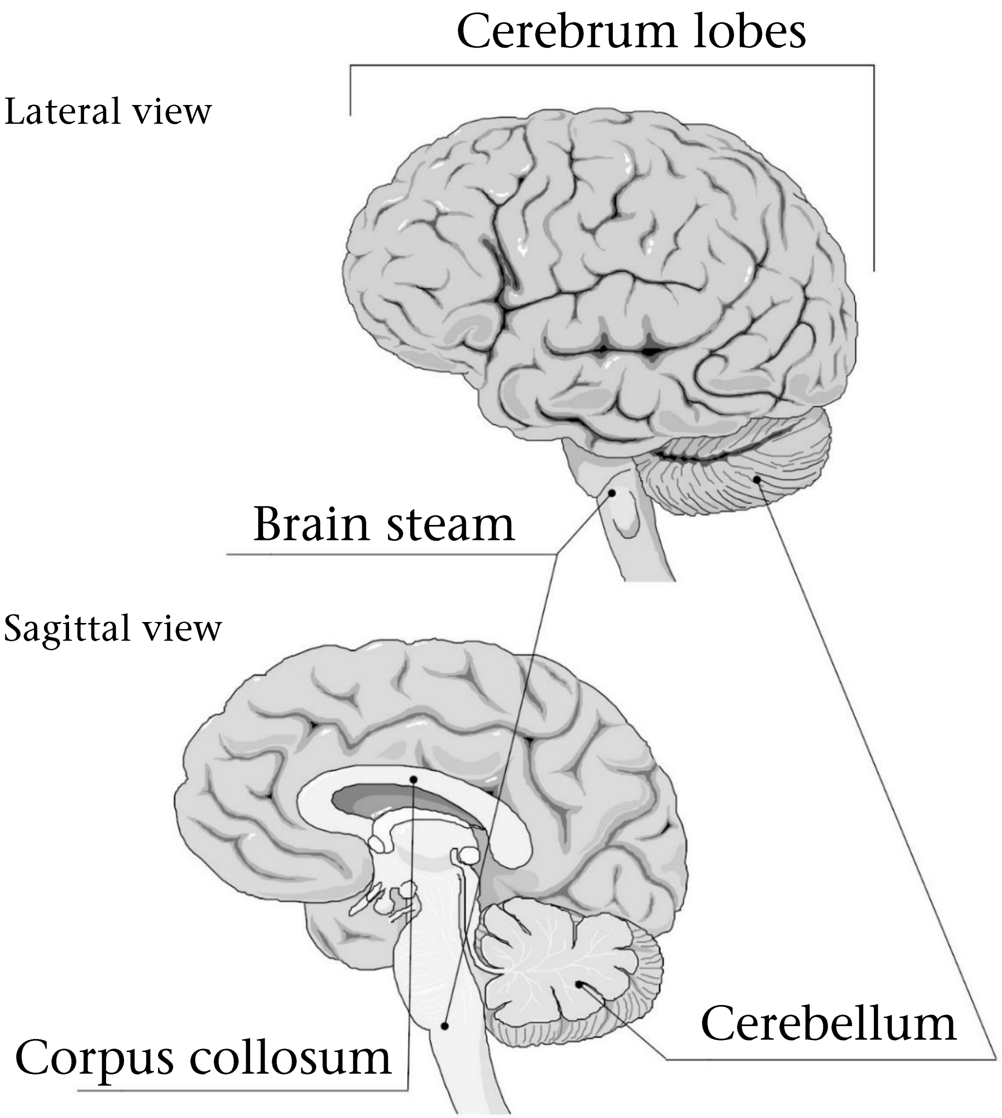






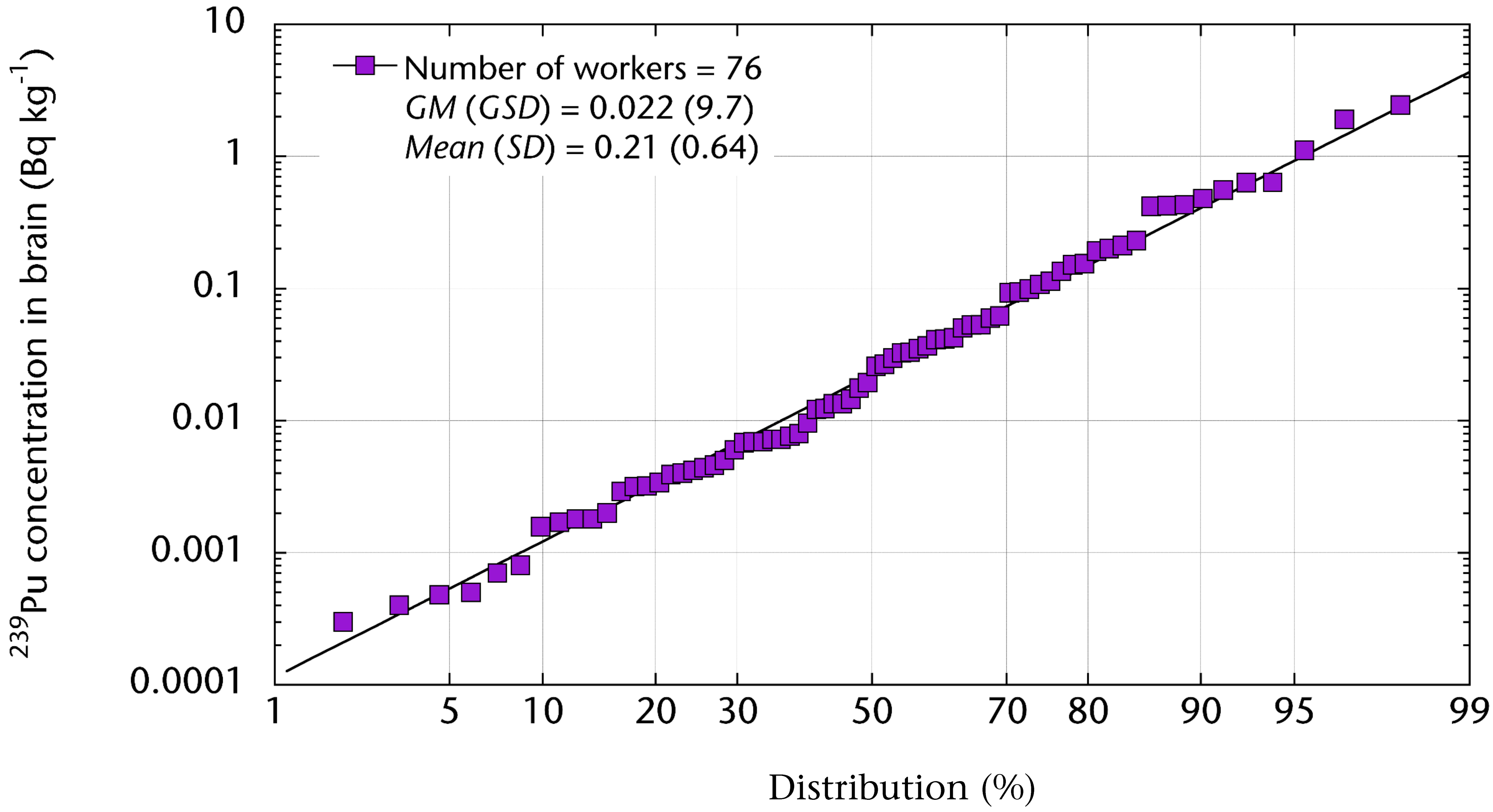


Radiochemical Tissue Analysis at the USTUR



- *Autopsy:* tissue collection
- *Tissues:* ashing, acid digestion and dissolution
- *Actinides (Pu/Am/U):* radiochemical separation
- *Measurements:* alpha-spectrometry
- *Results:* Pu/Am/U concentration in tissues

U.S. Transuranium and Uranium Registries: Plutonium in Brain of Occupationally Exposed Individuals



Plutonium Accumulation in Brain

Fraction of systemic activity: $f = A(\text{Brain})/A(\text{Systemic})$

- Data from dogs indicate a central tendency of

  $f \sim 0.0013$ at 2 – 4 weeks post intravenous injection

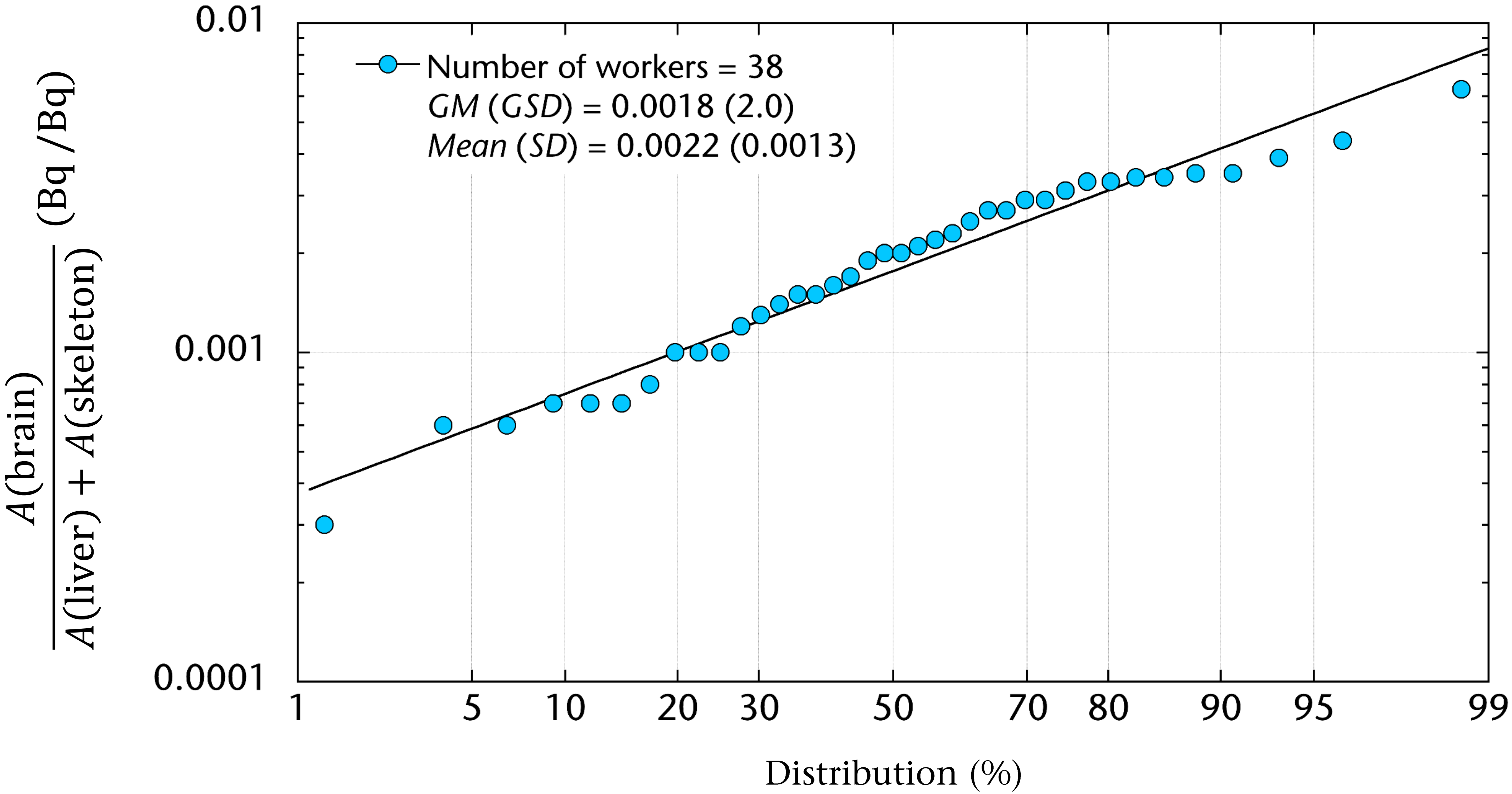
- Mayak Production Association (in Russia) data for plutonium workers indicate a central tendency of

  $f \sim 0.002$ (0.0010 – 0.0032) at 4 – 44 years post intake

- USTUR data for plutonium workers indicate a central tendency of

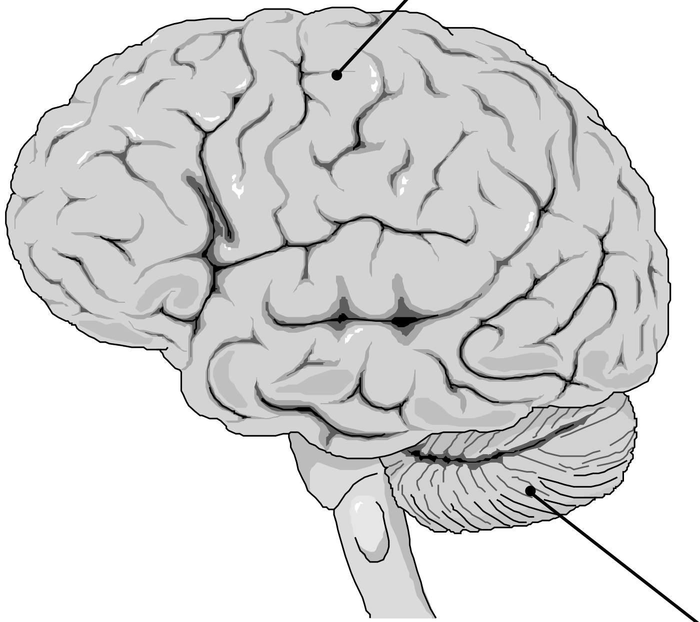
  $f \sim 0.002$ (0.0003 – 0.0063) at 18 – 64 years post intake

Plutonium: How Much is in the Brain?



Plutonium Distribution in Brain

Cerebrum lobe (R): 0.034 – 0.95 Bq kg^{-1} (n=6)
grey + white matter



Cerebellum: 0.011 – 0.36 Bq kg^{-1} (n=6)
grey matter

- Concentration ratio in tissue

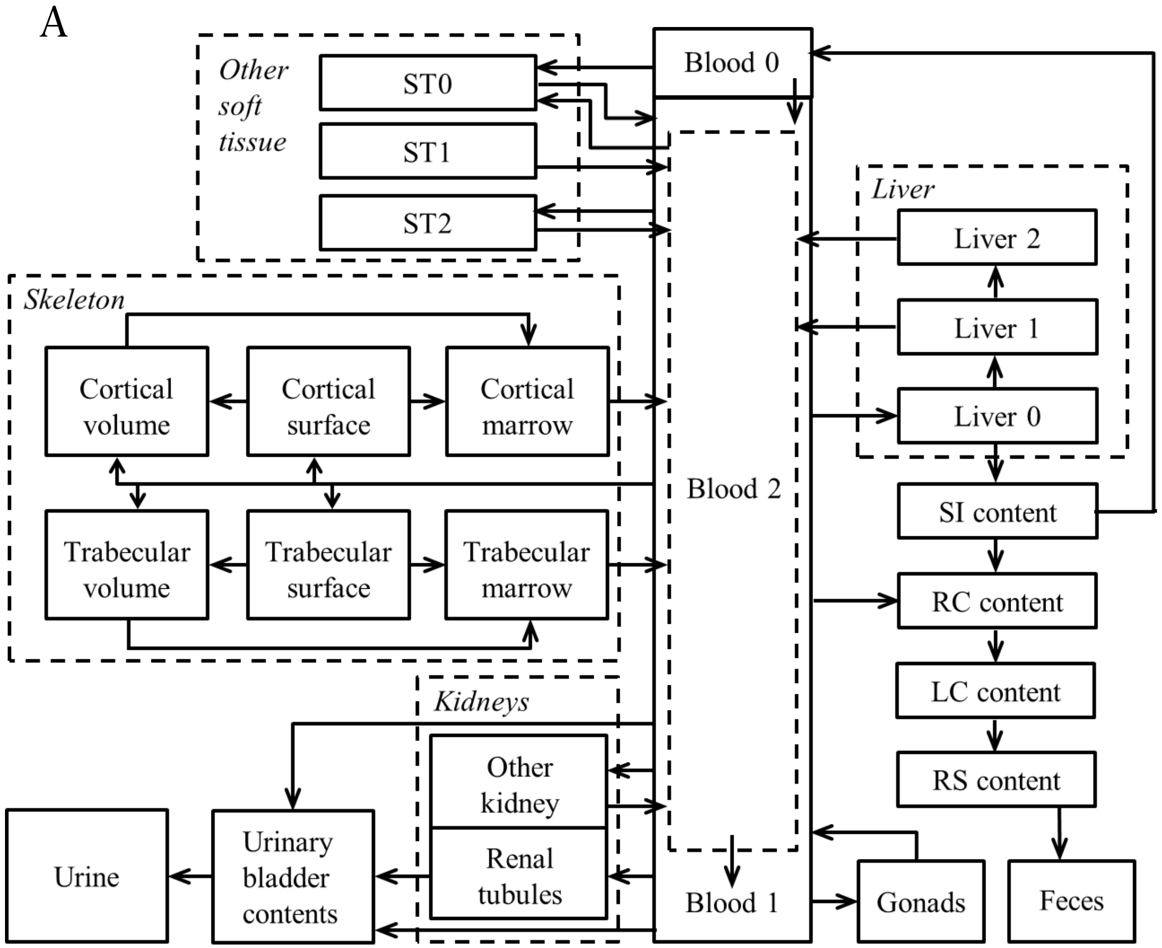
Cerebellum/cerebrum lobe = 2.3±0.7

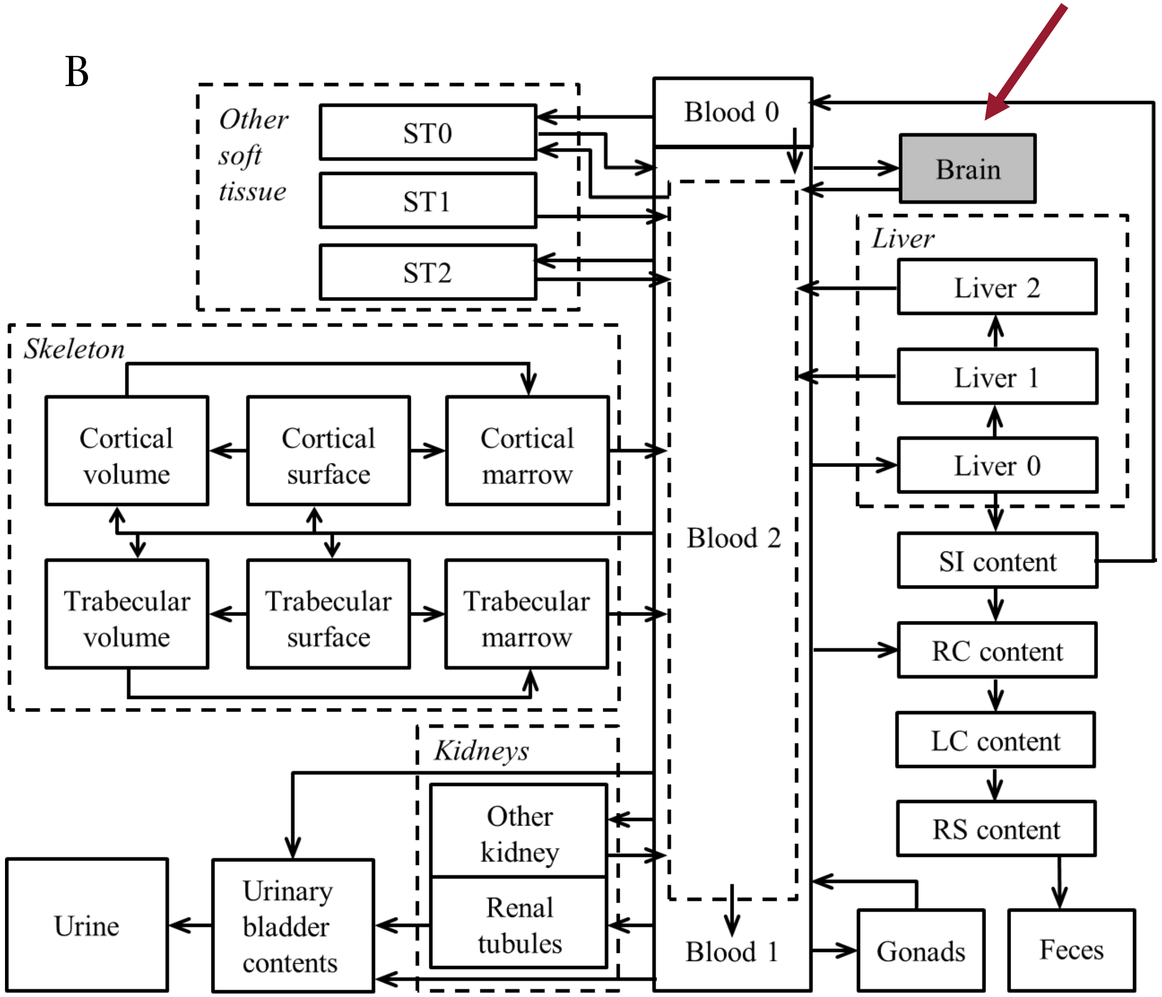
- Non-uniform distribution

Example (I): Modeling Plutonium Biokinetics

- The ICRP's biokinetic model for systemic plutonium is recently updated in ICRP Publication 141 (2019)
- As in previous ICRP models for plutonium, brain is included *implicitly* in *Other tissue*
- In the plutonium model, *Other tissue* consists of three compartments representing *fast* (ST0), *moderate* (ST1), and *slow* (ST2) removal of plutonium back to blood with brain belongs to ST2

Current (A) *vs* Alternate Biokinetic Model for Systemic Plutonium with Explicitly Depicted Brain (B)

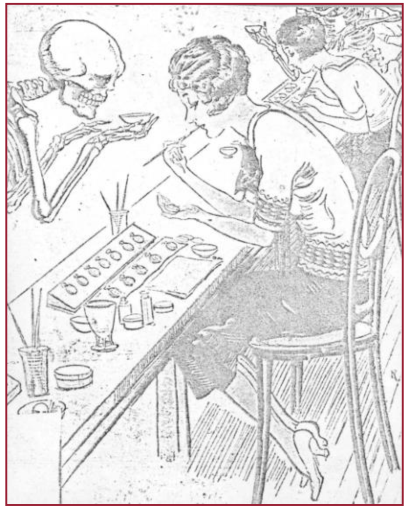


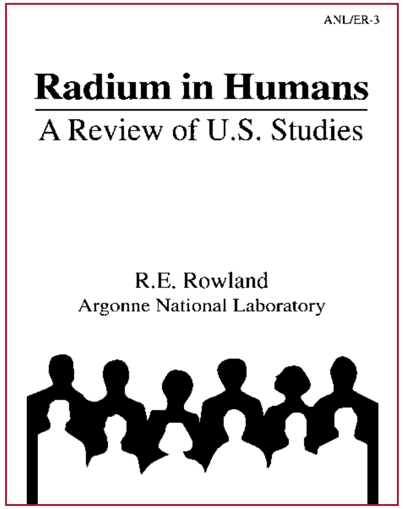


Example (II): Modeling Radium Biokinetics

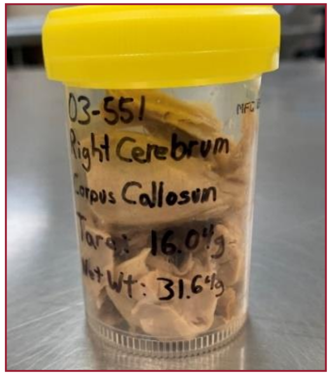
- The ICRP's biokinetic model for systemic radium is updated in ICRP Publication 137 (2017)
- Brain is included *implicitly* in *Other tissue*
- In the model, *Other tissue* consists of three compartments representing *rapid, intermediate,* and *slow* removal of radium back to blood

"Best Available Data": Radium Dial Painter Study





Microfiche



Brain tissue

- Arguably, the most important study on the adverse health outcomes from intakes of radionuclides
- Exposures were as early as 1912 among young women who painted dials, tipping brushes orally
- Active research began in the 1910s and continued through the 1980s at Argonne National Laboratory (ANL)
- In 1992, the USTUR received from ANL the detailed health and dosimetry records and biological tissues of radium dial painters
- The MPS recently re-activated the study of 3,276 radium dial painters, in part to evaluate dementia and other possible indicators of cognitive function

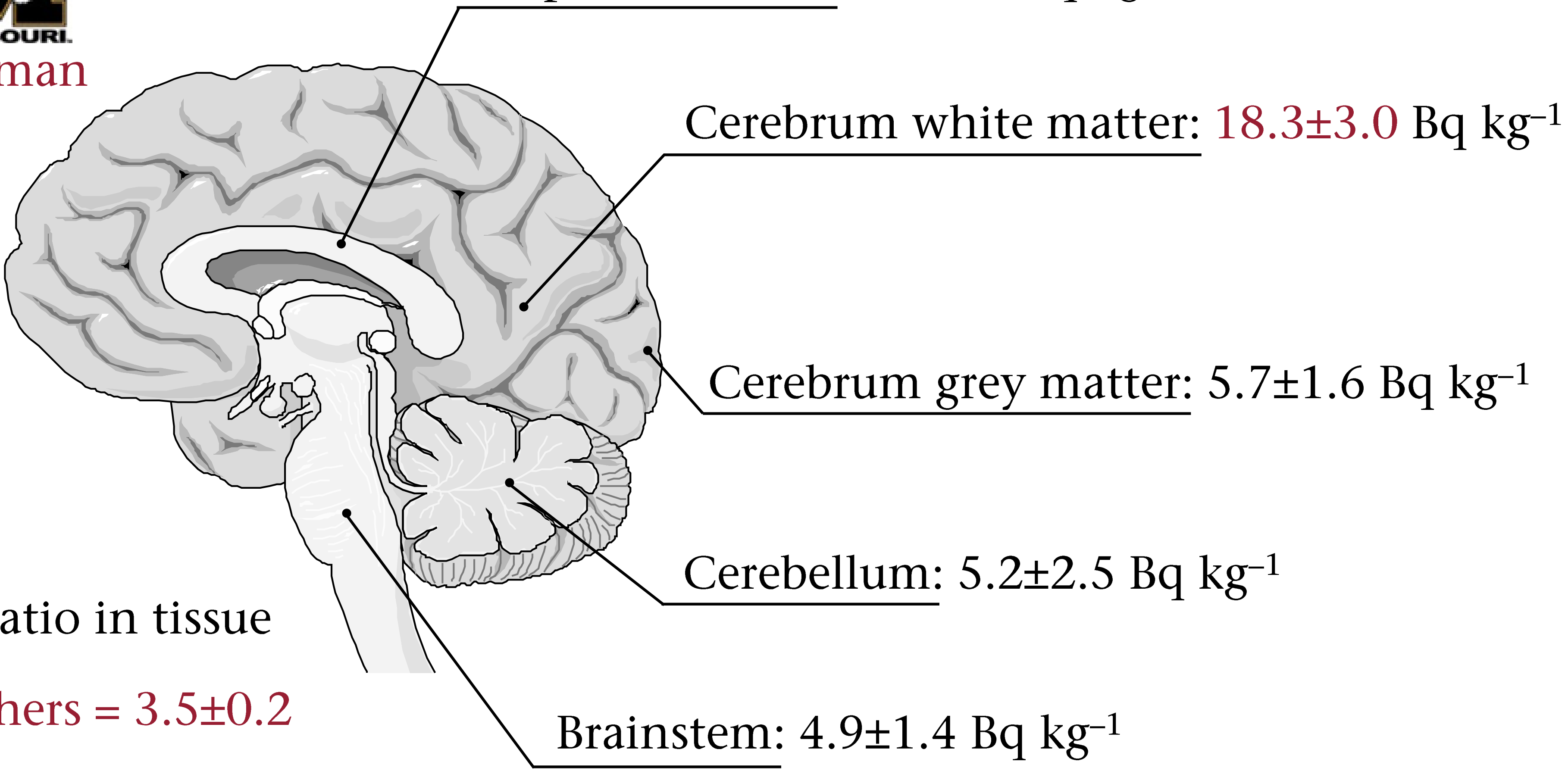
Radium Dial Painter Case

- ^{226}Ra intake = 261.7 µCi (µg)
- ^{226}Ra total body activity = 1.077 µCi (µg)


Study of ^{226}Ra Distribution in Brain

ICP-MS measurements at

by John D. Brockman

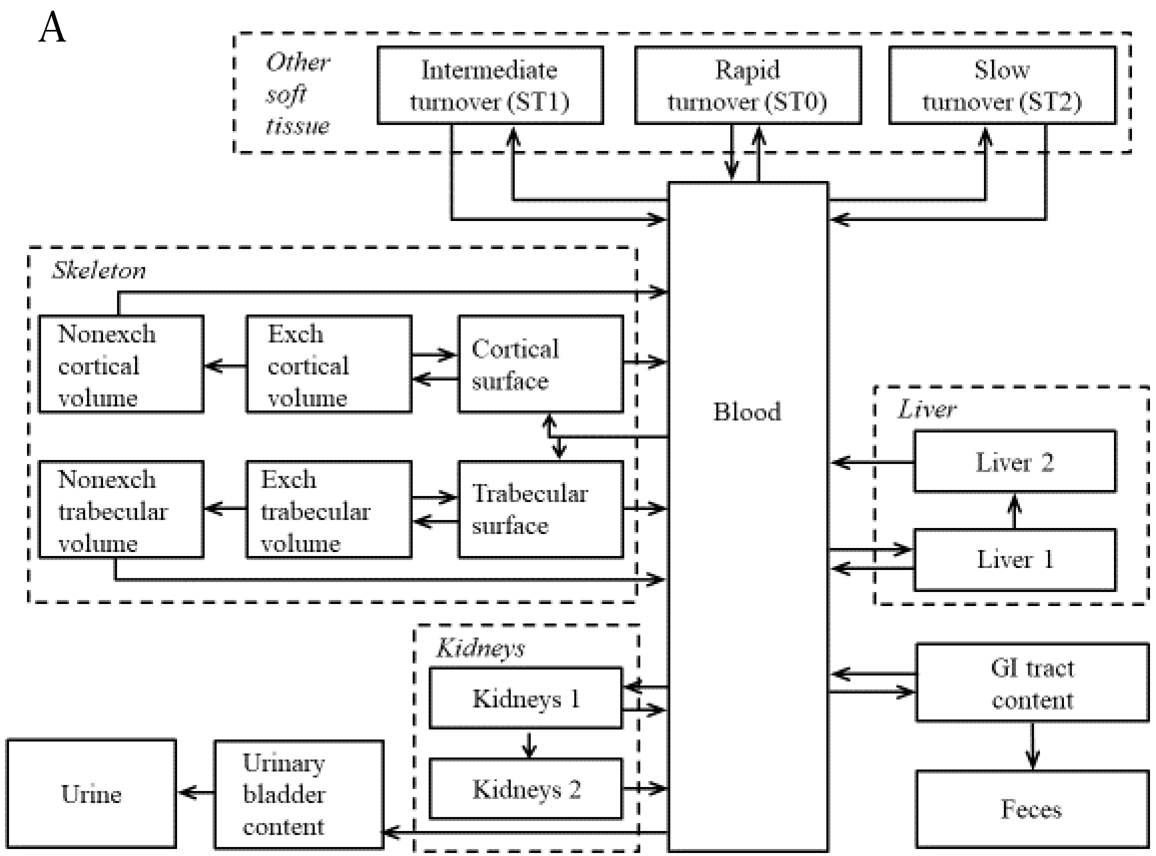


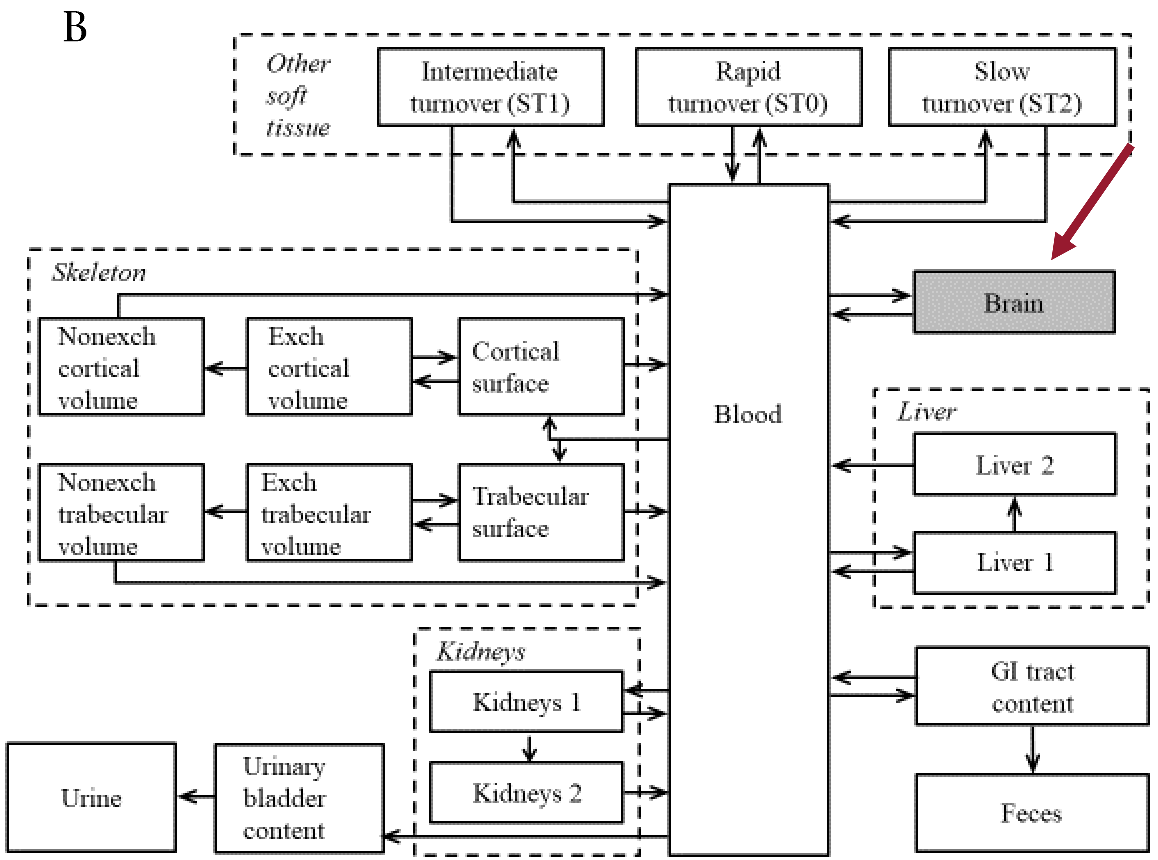
- Concentration ratio in tissue

Cerebrum white/Others = 3.5±0.2

- Non-uniform distribution

ICRP Current (A) *vs* Alternate Biokinetic Model for Systemic Radium with Explicitly Depicted Brain (B)





Ratio of Dose Coefficient (Sv Bq^{-1}) for Brain

Nuclide	Biokinetic model with *Implicit* brain (A)	Biokinetic model with *Explicit* brain (B)	Ratio B:A
Americium-241	2.80×10^{-5}	3.62×10^{-6}	0.13
Bismuth-207	2.20×10^{-9}	1.25×10^{-9}	0.57
Uranium-234	1.38×10^{-6}	1.11×10^{-6}	0.81
Plutonium-239	2.56×10^{-5}	2.45×10^{-5}	0.96
Mercury-203 (vapor)	5.25×10^{-10}	7.32×10^{-10}	1.4
Cesium-134	5.22×10^{-9}	7.63×10^{-9}	1.5
Manganese-54	1.39×10^{-9}	2.41×10^{-9}	1.7
Polonium-210	3.12×10^{-7}	5.22×10^{-7} (†)	1.7(†)
Radium-226	1.87×10^{-7}	3.62×10^{-7}	1.9
Lead-210	1.37×10^{-7}	4.45×10^{-7} (†)	3.3(†)

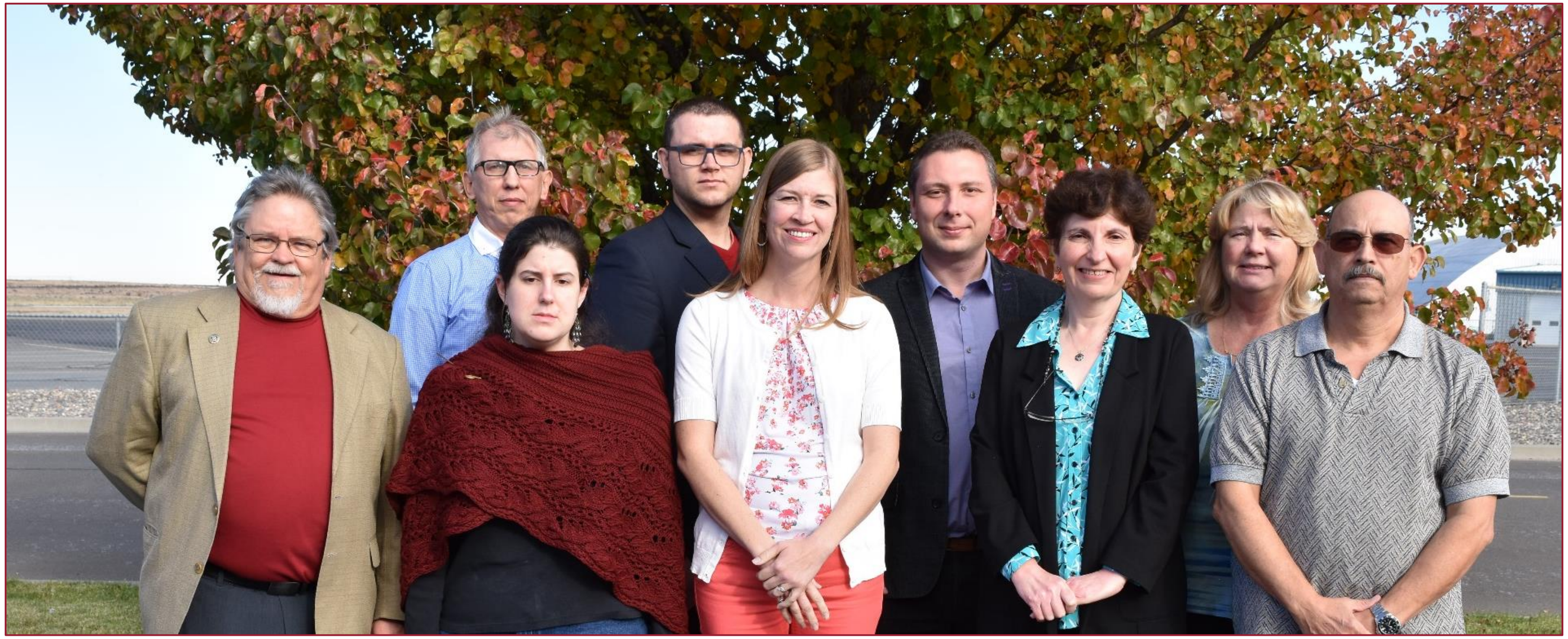
† - average value

Conclusions

- Where feasible, the brain should be depicted explicitly in biokinetic models used in epidemiological studies addressing adverse effects of ionizing radiation
- For *nine* radionuclides, the ratios of *explicit-to-implicit* (B:A) brain dose ranged from 0.13 to 3.3 and from 1.5 to 3.3 for *six* radionuclides, suggesting that treatment of brain, as a part of *Other tissue,* often results in an underestimate of radiation dose to the brain. For *two* radionuclides (^{234}U and ^{239}Pu), B:A ratios were slightly less than 1.0. For only *one* radionuclide (^{241}Am) B:A ratio was substantially lower than 1.0

Leggett RW, Tolmachev SY, Boice JD. (2018): Potential improvements in brain dose estimates for internal emitters. International Journal of Radiation Biology, Published online. DOI: 10.1080/09553002.2018.1554923

Acknowledgment



Questions?

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