Beyond Dose and Response: Relating Radiation and Detriment

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Introduction

- Detriment (ICRP 60)
  - Expectation of harm
  - A comprehensive expression of risk
- Need to predict (i.e., model) detriment
  - For populations & individuals
  - Prospectively and retrospectively
- Relationship of detriment to radiation is *enormously* complicated
- Beyond new NCI "Probability of Causation" software

Goal:
Develop a Radiation-Detriment Model

- Modular
- Easily be updated or modified
- Incorporate *all* variables we know are important
- Ennumerate what must be measured or known
- Predict all effects of interest
- Faithfully carry uncertainty through
  - Especially when knowledge is absent
- Must include as *possibilities*
  - Thresholds (for particular cancers, e.g., bone, liver)
  - Hormesis (for some endpoints in some irradiation scenarios)
  - Adaptive response (*very* complicated time response)
  - Sensitive or susceptible sub-populations

Probabilistic Approach

- List all the organism-level outcomes of interest
  - Various kinds of cancer, stochastic non-cancer somatic effects, heritable ill-health, deterministic effects
- For each outcome, choose a risk measure
  - Relative or absolute risk
  - Severity
  - Frequency
  - …
- For each outcome, list all variables known to affect it
  - Species, sub-species, and sex
  - Space-and-time-course of irradiation
  - Space-and-time-course of modifying factors
  - Space-and-time-course of biological change and damage

Who's Irradiated?

- Species
  - Human, animal, plant, cells in vitro
- Sub-species (racial makeup, ethnicity)
  - Genetic predisposition
    - e.g., DNA repair
  - Susceptibility
- Sex
  - Thyroid CA $\propto$ # x-chromosomes
  - Breast CA $\propto$ (# x-chromosomes)^{10}
- Stage of development as a function of time (age)
  - Embryo, fetus, infant, child, adult, elderly adult
  - Reproductive status
  - Hormonal status

Space-and-Time-Course of Irradiation

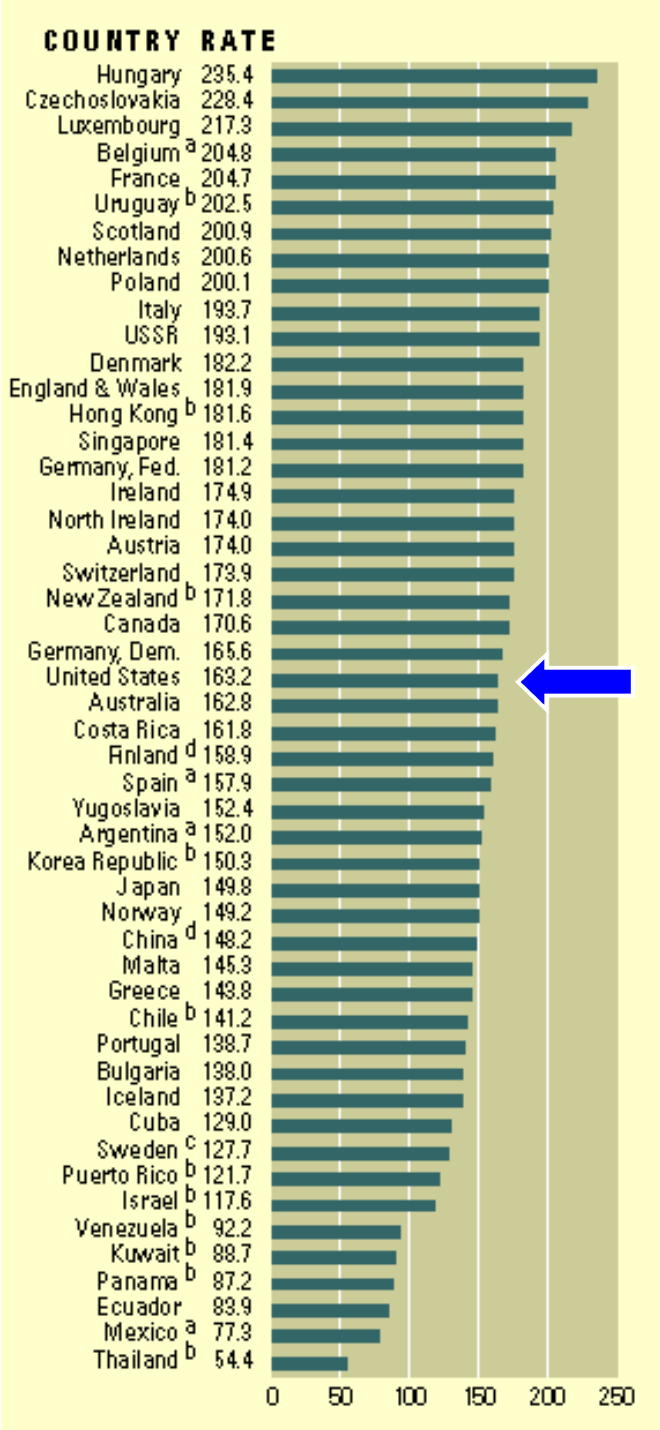
- Instantaneous spatial distributions of ionizations and excitations throughout existence of organism
  - Dose
  - Dose rate
  - Fractionation
  - “Quality” or LET or lineal energy
- As a function of time (age)
- As a function of tissue or body part

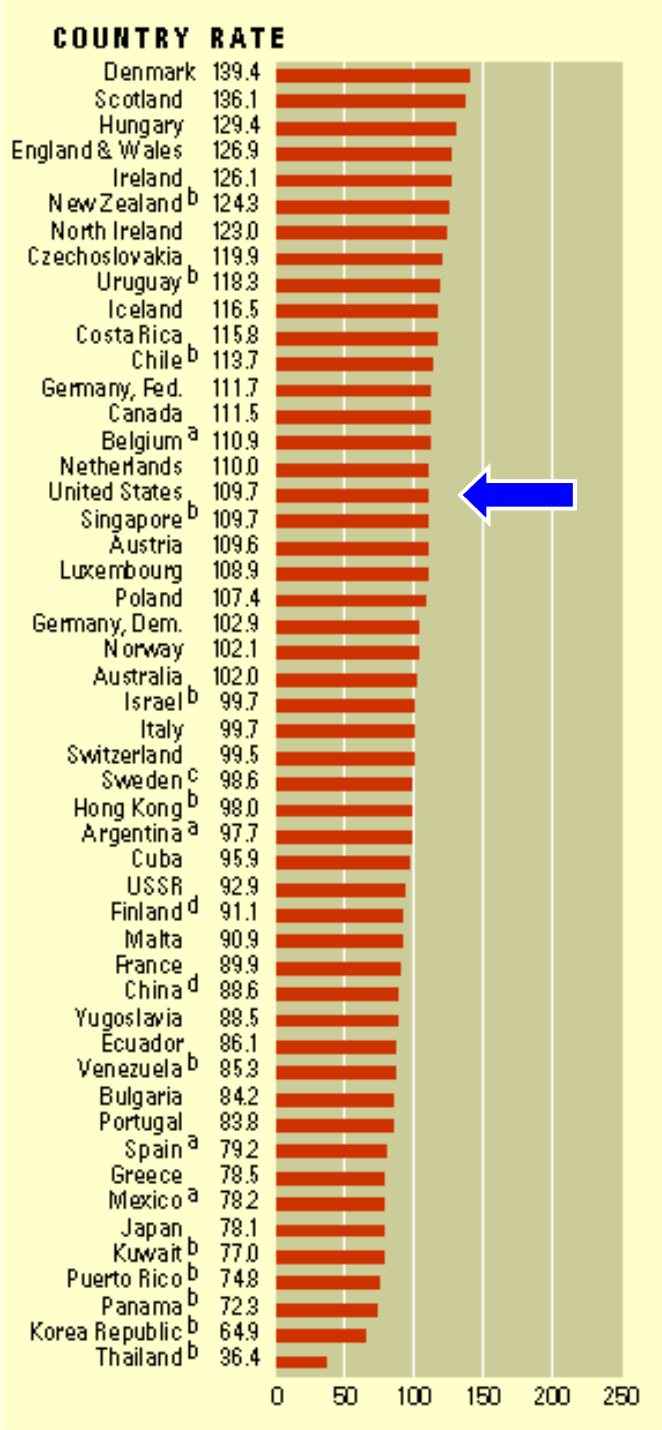
Space-and-Time-Course of Modifying Factors

- Modifying factors include
  - Diet
  - Temperature
  - Infectious agents
  - Combined injury: trauma, burns
  - State of organ function
  - State of adaptive response (e.g., DNA repair stimulation)
  - Other initiators, promoters, tumor progressors [smoking]
  - Oxygen
  - Dehydration
  - Exogenous hemicals [antioxidants, free radical scavengers], drugs
  - Medical interventions such as surgery
- As a function of time (age)

Cancer Death Rates by Country 1986-88

- Averaged over
  - All sites
  - All ages
  - Both sexes
- 4-fold range
- USA
  - Males: 24th
  - Females: 17th
- Some CA rates differ by ×100





Space-and-Time-Course of Biologic Change and Damage

- As a function of time (age)
- The input to building a radiation-detriment model
- The output from a completed radiation-detriment model is harm or expectation of harm

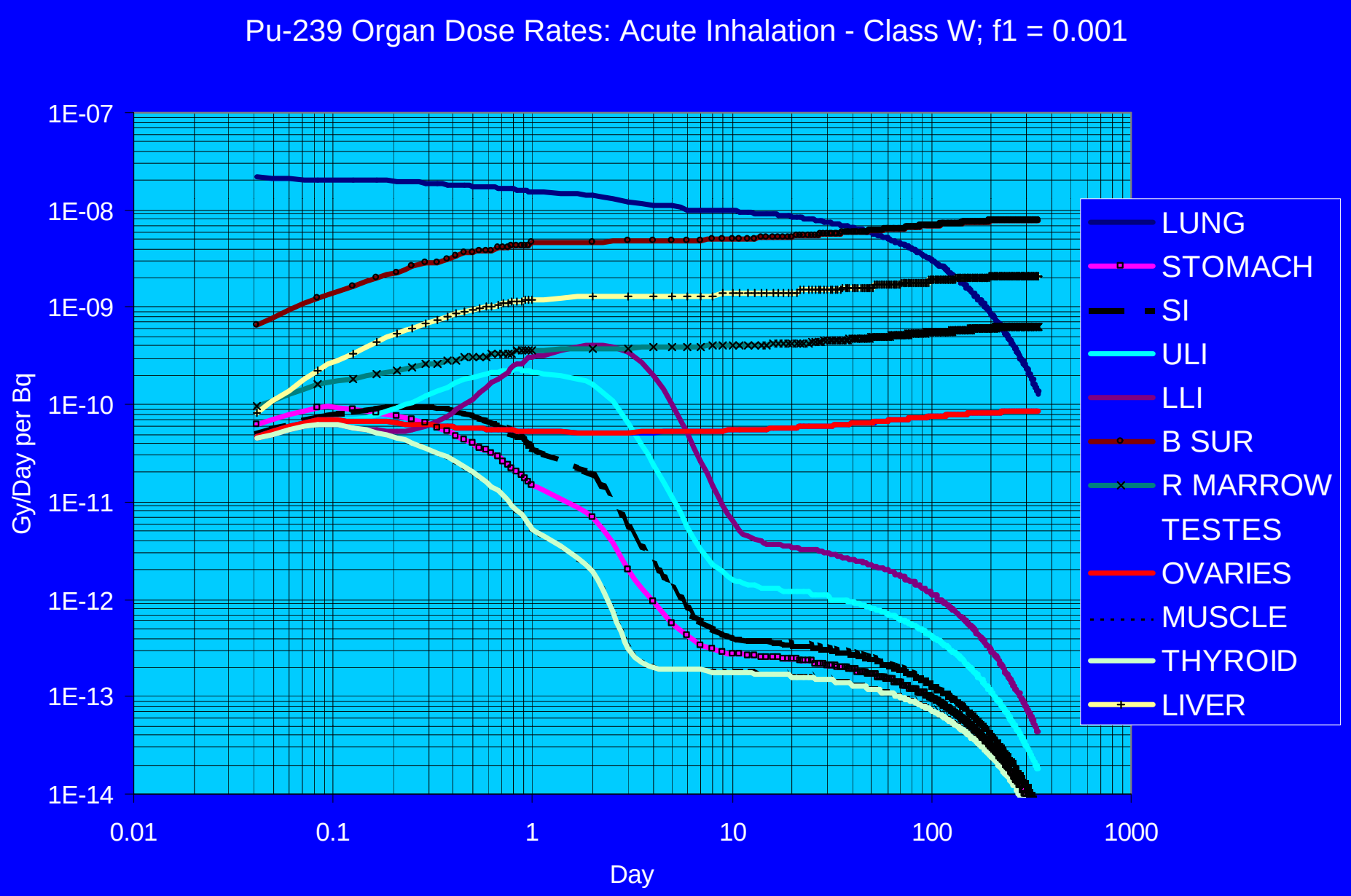
What Radiation Measurements Would Be Sufficiently Predictive?

- External
  - Tissue-equivalent proportional counters to record lineal energy spectra as a function of time for the entire body for the entire life, to *infer* what's going on inside the body
  - Is "dose" –imetry an example of the "lamp post effect?"
- Internal
  - Difficult to imagine precise enough *measurements* of emissions from radionuclides in the body to compare with external measurements
  - Must *model*

Example: Plutonium

- Human data suggest *dose* and *dose rate* thresholds
  - Osteosarcoma in Ra dial painters
  - Liver cancer in Thorotrast patients
- Internal Pu primarily irradiates bone and liver
- If thresholds exist, then only the irradiation that occurs above a certain *dose rate* matters
- Dose, especially committed dose, *alone* does not predict risk in this case
- Must model entire time course of irradiation in each tissue
- There's nothing "linear" about it

Example: Plutonium



Conclusions

- The notion of a “dose-response” relationship is hopelessly simplistic
  - Knowing “dose” is not enough to predict detriment
- Radiation measurements sufficient to predict detriment would be a challenge
  - External sources: measurements can be imagined
  - Internal sources: inference from models
- Risks to
  - Populations may be inferred from studies of populations only to a very limited extent
  - Individuals may be inferred only by exhaustive study of variables we already understand

Quantum Physics Approach

- In principle, if one knew enough physics, the biology could be predicted
- Let's see… If one knew the wave function of every particle in an organism from conception to death…
  - 70 kg ≈ 3E27 atoms
  - 6 degrees of freedom
  - about 20 particles (n, p, e) per atom
  - (4E29 variables × a lifetime) × (environment) = …
- Get real!