Kazakhstan – Possible Improvements

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Workshop on Impact of Dose Uncertainties on the Dose Response
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Background

- Population exposed as juveniles to fallout from nuclear test explosions at the Semipalatinsk Test Site in NW Kazakhstan during 1949-1962

- Study cohort established in 1960's, monitored by Soviet govt & then by Kazakhstan govt institutes

Rationale

- Use thyroid nodule prevalence as outcome variable, based on ultrasound screening during August 1998
- Reconstruct external and internal doses
- Evaluate dose response for external and internal radiation, estimate RBE

Dose reconstruction crucial

- Outcome variable: Ultrasound-detected thyroid nodule prevalence
- Outcome reasonably secure: We did the determination ourselves
- External dose depends mostly on place of exposure
- Internal dose depends additionally on pasture-milk pathway

Possible improvements: Better dose estimates, better uncertainty information

- New information on residential histories of individual study cohort members
  - Eligibility for new govt. compensation program depends upon confirmed residential history

- Focus group data on customary nutrition practices among ethnic Europeans and Kazakhs

Berkson Error (Grouping Error)

- Error is independent of observed dose
- Error that results when single dose used to represent group
- Variance of true doses larger than variance of measured doses
- Little distortion in linear dose-response

Examples of Berkson Error

- Error that results when single dose used to represent group
  - Example: Same exposure assigned to all underground miners in particular location/time period. Exposure of individual miner is likely to depart from the assigned exposure.

- Error that results when model is used to estimate doses for a group

Some important distinctions

- Classical errors versus Berkson errors
- Shared errors versus Errors that are independent for different subjects
- Impact on dose-response analyses depends on these distinctions

Examples of Shared Errors

- Errors in the yields of the Hiroshima or Nagasaki bombs

- Error in parameters of models used to convert measurements to doses

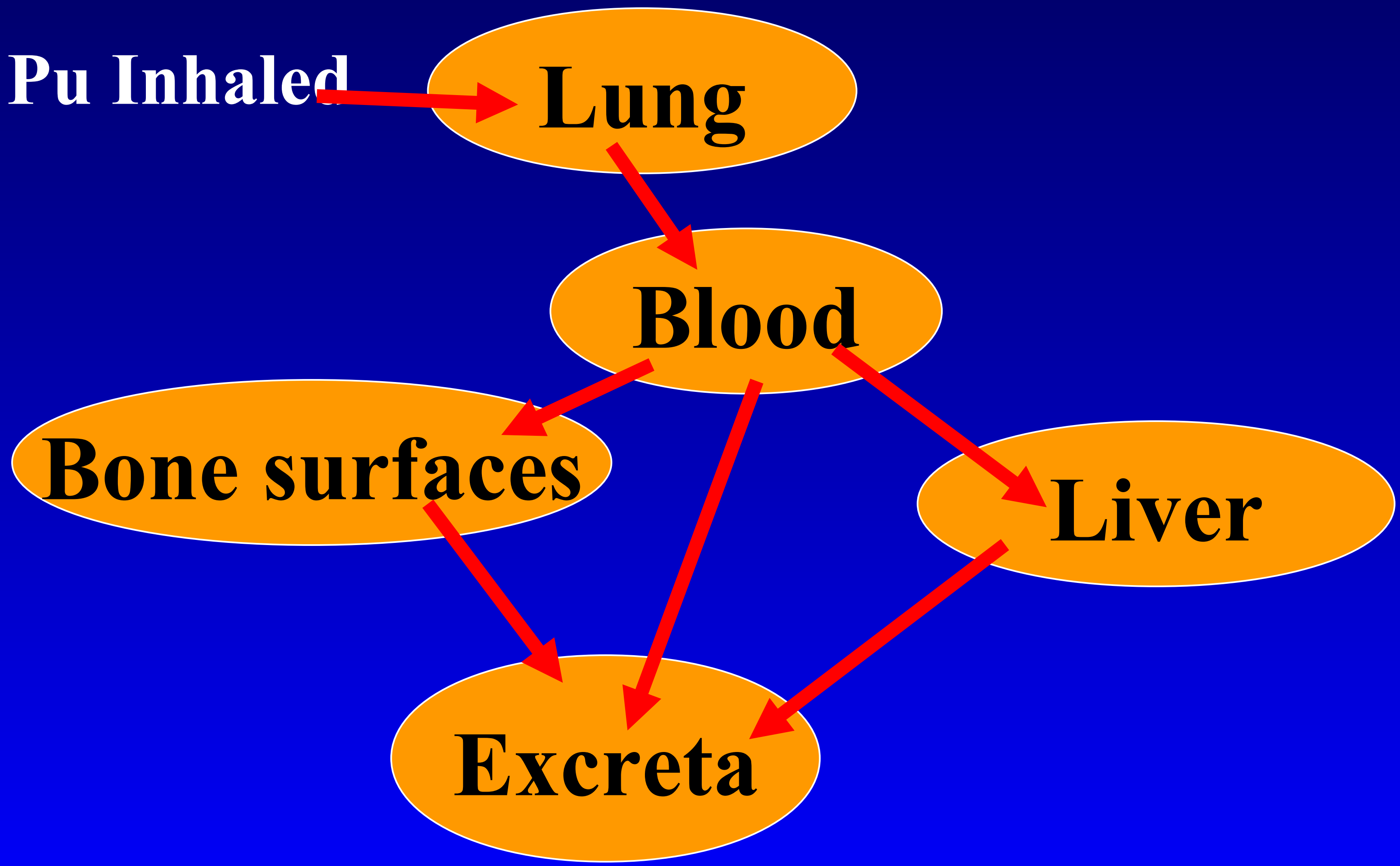
Example: Nuclear workers exposed to plutonium

- **Workers in the US (Los Alamos, Rocky Flats), the UK (Sellafield) and Russia (Mayak) have been exposed to plutonium**

- **Mayak workers have by far the largest doses**

- **Main route of plutonium exposure is inhalation**

Inhaled Plutonium Dynamics



Plutonium Dosimetry

- Dose estimates based on
  - measurements of radioactivity in urine
  - autopsy data
  - occupational histories
- Use models for rates of clearance and transfer to estimate initial body burden at time of exposure

Uncertainties in Plutonium Dosimetry

- Imprecision in urine measurements
  - Unshared classical error

- Uncertainties in biokinetic models and parameter values used to estimate deposition and clearance in organs of the body
  - Shared classical error

- Models can only approximate behavior of plutonium in a given individual
  - Berkson error

Possible Effects of Errors in Dose Estimates

- Bias in estimates of risk per unit of dose
- Distortion of the shape of the dose-response function
- Underestimation of uncertainty
- Reduction in statistical power for detecting dose-response relationships

Statistical approaches for accounting for dosimetry uncertainties

What they can't do

- Improve power and precision of estimated risk coefficients

What they can do

- Avoid misleading results
- Correct biases in risk coefficients
- Widen confidence intervals to reflect dosimetry uncertainties

Error Structure

- Identify sources of error

- Nature of the error from each source
  - Classical or Berkson?
  - Shared or unshared?

- Describe the magnitude and distribution error from each source
  - Subjective judgments usually required
  - !

Tools for accounting for dosimetry uncertainties

- Sensitivity analyses
- Regression calibration
- Full maximum likelihood
- Multiple imputations
- Monte Carlo maximum likelihood

Sensitivity Analyses

Examples:

- Restrict analyses to subjects with higher quality dose estimates
- Conduct analyses based on doses calculated from alternative model(s)

Regression Calibration

- Replace the estimated doses with
  E (true dose|estimated dose)
  $= E(\xi \mid x)$

- Easy to apply once have the $E(\xi \mid x)$

- Limitations
  - An approximation for non-linear models
  - Uncertainty in risk estimates may be underestimated

Regression Calibration

- Replace the estimated doses with
  E (true dose|estimated dose)
  $= E(\xi \mid x)$

- Need information on --
  - distribution of x conditional on ξ
  - distribution of the true doses ξ

    (Can be a challenging task)

Regression Calibration

Let ξ =true dose; x=estimated dose

Errors ($x-\xi$) are independent of x (classical errors)

Special case 1:

$$\xi \sim N(\mu, \sigma^2); \; x | \xi \sim N(\xi, \kappa^2)$$

Then $x \sim N(\mu, \sigma^2 + \kappa^2)$

$$E(\xi | x) = (1-c)\,\mu + c\,x$$

where $c = \sigma^2 / (\sigma^2 + \kappa^2)$ **Cochran 1968**

Regression Calibration

Special case 2:

$\log \xi \sim N(\mu, \sigma^2)$; $\log x|\xi \sim N(\log \xi, \kappa^2)$

Then $\log x \sim N(\log \mu, \sigma^2 + \kappa^2)$

$$E(\xi|x) = [E(\log \xi)]^{(1-c)}\, x^c$$

where $c = \sigma^2 / (\sigma^2 + \kappa^2)$

[Likely will omit this slide]

Regression Calibration Examples

- A-bomb survivors (Pierce et al. 1990; 2009)
  - Increased slope by 10%
- European radon case-contol studies (Reeves et al. 1998; Darby et al. 1998)
  - Increased slope by 100%
- Colorado uranium miners (Stram et al. 1999)
  - Decreased magnitude of inverse exposure-rate effect

Full maximum likelihood

- **Regression model** : Relates disease to true dose
  - Linear relative risk model a common choice

- **Measurement model**: Relates estimated doses (x) to true doses (ξ)

- **Exposure model**: Specifies distribution of true doses (ξ)

Clayton 1990

Study of leukemia and thyroid cancer in relation to Utah fallout (Thomas et al. 1999)

- Lognormal distribution for classical (measurement) errors
- Non-parametric distribution for true doses
- Used Markov chain Monte Carlo (MCMC) methods to implement
- Shared errors not addressed

Study of leukemia and thyroid cancer in relation to Utah fallout (Thomas et al. 1999)

- Results
- [To be completed]

Multiple imputations

- Specify error structure
- Use Monte Carlo methods to generate N replications of the doses based on the error structure
  - Challenging to set up simulations appropriately
  - Assume unshared classical error has been addressed
- Estimate β of for each sample and calculate mean over all samples
- Estimate variances due to
  - dosimetry uncertainties
  - sampling

Monte Carlo Maximum Likelihood

- **Specify error structure**
- **Use Monte Carlo methods to generate N replications of the doses based on the error structure**
- **Estimate the likelihood function for each data set and average over samples**
- **Use average likelihood to estimate parameter and uncertainties**

Monte Carlo Maximum Likelihood: ORNL nuclear worker study (Stayner et al. 2007)

- Applied to Oak Ridge National Laboratory workers exposed to external radiation and monitored with personal dosimeters (~5000 workers)

- Uncertainty in factors used to convert recorded doses to organ dose
  - Shared error since same factor applied to all workers in a given time period

Monte Carlo Simulations: ORNL nuclear worker study (Stayner et al. 2007)

Parameters of the Log-normal Distribution of Bias Factors Developed for ORNL and Summary of the Annual Recorded Dose Distributions by Period

	Parameters of the distribution		Summary statistics of annual dose (mSv)		
Year(s)	Geometric mean (β)	Uncertainty (κ)	Median	Mean	90th percentile
1943	2.048	1.601	0.50	1.33	3.51
1944–1952	1.353	1.698	1.30	3.04	7.50
1953–1979	1.201	2.464	0.96	1.78	3.94
1980–1997	1.137	1.708	0.75	1.03	2.00

Monte Carlo Simulations: ORNL nuclear worker study (Stayner et al. 2007)

Estimated excess relative risk (ERR) per Gy for solid cancers

- **Conventional analysis estimate:**
  5.38 (90% CI: 0.54 to 12.58)

- **Based on Monte Carlo maximum likelihood**
  4.82 (90% CI: 0.41 to 13.31)

Examples where dose estimation errors have been taken into account

- A-bomb survivors (Pierce et al. 1996)
- Residential radon exposure (Reeves et al. 1998)
- Utah fallout study (Thomas et al. 1999)
- Underground miners (Stram et al. 1999)

- ORNL nuclear workers (Stayner et al. 2007)
- Hanford fallout study (Stram and Kopecky 2003)
- Tinea capitis patients (Schafer et al. 2001; Lubin et al. 2004)

Summary

- Methods for adjusting for dosimetry error are available
- Require detailed understanding of error structure
  - Lots of communication between dosimetrists and statisticians
- Methods are often computationally intensive
- Increasingly, errors are being evaluated and considered in radiation dose-response analyses