National Cancer Institute

Point of View of the Statistician

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Workshop on Impact of Dose Uncertainties on the Dose Response
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National

Point of View of the Statistician

- Characterize different types of dosimetry uncertainties
- Indicate how dosimetry uncertainties distort dose-response analyses
- Discuss methods for correcting the distorting effects of dosimetry uncertainties

Some preliminaries

- Most work addressing dosimetry uncertainties based on the assumption that errors are independent of disease status (non-differential)

- Linear dose-response function plays important role in radiation epidemiology

- Relative risk = 1 + β dose where β is excess relative risk per unit of dose

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

Classical Error (Measurement Error)

- Error is independent of true dose
- Can be thought of as error that arises from an imprecise measuring device
- Variance of estimated doses larger than variance of true doses
- Adjustment needed to avoid attenuation of the true dose-response

Examples of Classical Errors

- Errors in readings of film badge dosimeters
- Errors in questionnaire data used in estimating doses

Berkson Error (Grouping Error)

- Error is independent of observed dose
- Error that results when
  - Single mean dose used to represent group
  - Same model is used to estimate doses for a group
- Variance of true doses larger than variance of measured doses
- Little distortion in linear dose-response

Shared Errors

- Also known as systematic errors

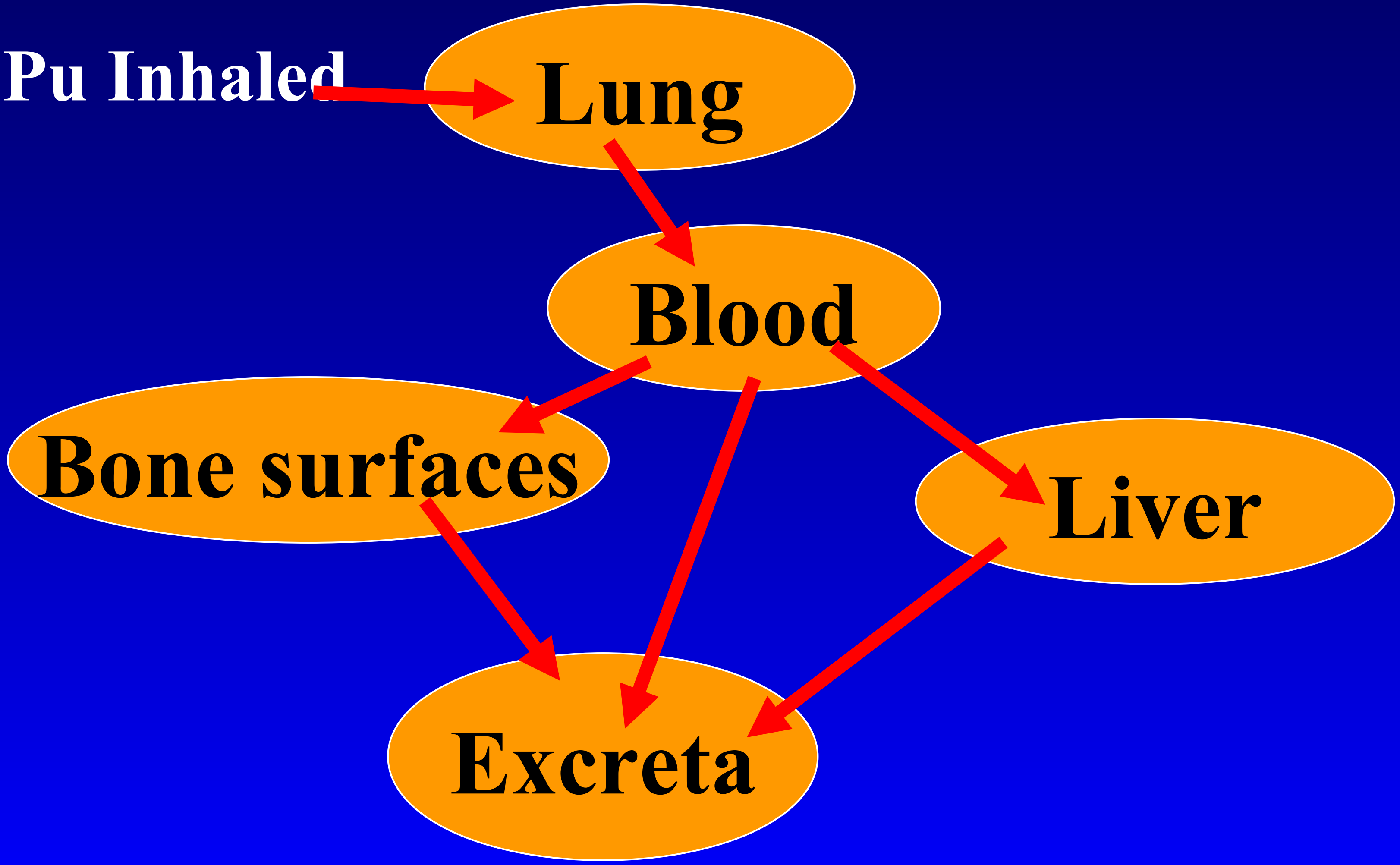
- Examples
  - Errors in the source term for an environmental exposure
  - Errors in doses assigned to groups of subjects
  - Errors in parameters of models used to convert measurements to doses

Error Structure

- For many epidemiological studies, error structure is a complicated mixture of different types of errors

- Illustration: Plutonium dosimetry used in nuclear worker studies exposed to inhaled plutonium
  - Example: Mayak plant

Inhaled Plutonium Dynamics



Pu Inhaled

Lung

Blood

Bone surfaces

Liver

Excreta

Plutonium Dosimetry

- Dose estimates based on
  - measurements of radioactivity in urine
  - occupational histories

- Use models for rates of clearance and transfer to estimate initial body burden and doses to lung, liver, bone surfaces and other organs

Some 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 linear risk coefficients
- 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

Simple approaches that may help

- **Restrict analyses to subjects with higher quality dose estimates**

- **Conduct analyses based on doses calculated from alternative models**

Statistical approaches for accounting for dosimetry uncertainties

- Regression calibration
- Full maximum likelihood
- Multiple imputations
- Likelihood averaging

Regression Calibration

- Replace the estimated doses with
  E (true dose|estimated dose) = E(x|z)
- Easy to apply once have the E(x|z)
- Leads to unbiased estimates of linear risk coefficients.
- Limitations
  - An approximation for non-linear models
  - Uncertainty in risk estimates may be underestimated

Regression Calibration

- How do we obtain E(x|z) ?

$$E(x|z) = \frac{\int x f(z|x) f(x)\, dx}{\int f(z|x) f(x)\, dx}.$$

- Need information on
  - distribution of estimated doses z conditional on the true doses x: f(z|x)
  - distribution of the true doses x: f(x)

(Can be a challenging task)

Regression Calibration

Let x =true dose; z=estimated dose

Errors (z–x) are independent of x (classical errors)

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

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

$E(x|z) = (1-c)\mu + cz$

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

Cochran 1968

Regression Calibration

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

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

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

Regression Calibration Examples

- A-bomb survivors (Pierce et al. 1990; 2009)
  - Increased slope by 10%
- European residential radon case-control 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 (z) to true doses (x)
- **Exposure model**: Specifies distribution of true doses (x)

Clayton 1990

Study of leukemia and thyroid cancer in relation to Utah fallout

- Lognormal distribution for classical (measurement) errors
- Non-parametric distribution for true doses
- Used Markov chain Monte Carlo (MCMC) methods to implement
- Increased estimates for leukemia and thyroid neoplasms
- Increased uncertainty in both estimates

Thomas et al. 1999

Study of leukemia and thyroid cancer in relation to Utah fallout

- Uncertainty information consisted of standard error for each subject
  - Included both unshared classical error and shared error
  - Thomas et al. assumed all was unshared classical error
  - Shared error later considered by Mallick et al. 2002
- Study revisited with dosimetry (and other) improvements
  - Lyon et al. 2006; Li et al. Biometrics 2007

Multiple imputations

- Use Monte Carlo methods to generate N replications of the doses based on the error structure
- Challenging to set up simulations appropriately
- Take account of correlations (shared errors)
- Assume unshared classical error has been addressed
  - Stram and Kopecky (2003)
  - Stayner et al. (2008)

    “We take as our starting point a Berkson model …”

Multiple imputations

How do we use the N samples?

A simple approach:

- Estimate β and its variance for each sample
- Average over samples
- Estimate total variance as sum of sampling variance and variance due to dosimetry uncertainties

A better approach: Likelihood averaging

Likelihood Averaging
(Monte Carlo Maximum Likelihood)

- 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

Likelihood Averaging: ORNL nuclear worker study

- ~ 5345 Oak Ridge National Laboratory workers exposed to external radiation and monitored with personal dosimeters
- Addressed uncertainty in factors used to convert recorded doses to organ dose
  - Same factor used for all dosimeter readings in a given time period (1943, 1944-52, 1953-79, 1980-97)
  - Shared error

Stayner et al. 2007

ORNL nuclear worker study

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

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

- Based on likelihood averaging
  4.82 (90% CI: 0.41 to 13.31)

Stayner et al. 2007

Examples where dose estimation errors have been taken into account

- **A-bomb survivors** (Pierce et al. 1996; 2008)
- **Residential radon exposure** (Reeves et al. 1998)
- **Utah fallout study** (Thomas et al. 1999; Mallick et al. 2002; Li et al. 2007)
- **Underground miners** (Stram et al. 1999)
- **ORNL nuclear workers** (Stayner et al. 2007)
- **Hanford fallout study** (Stram and Kopecky 2003; Hoffman et al. 2007)
- **Tinea capitis patients** (Schafer et al. 2001; Lubin et al. 2004)
- **Chornobyl thyroid study** (Kopecky et al. 2006)

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