

The effect of exposure measurement error (aka dose uncertainties) on hazard assessment and dose-response estimation in linear and non-linear models

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Impact of the dose uncertainties on what?

- Point estimate – shape/slope of dose-response curve
- Variance estimate – 95% confidence interval around dose-response curve?
Around relative risk at specified doses?

Impact of the dose uncertainties on what?

- REGRESSION CALIBRATION
 - Corrects for bias in point estimate from relative risk; if variance is correctly calculated, will also give valid confidence interval
- A single imputation of the dose will give an approximately unbiased estimate of the dose-response curve
 - If it is too difficult to write down the model to determine the expected value, the empirical distribution of true doses can be estimated; the average over these estimates should be used.
 - A single estimated relative risk is the result
- Bootstrap re-sampling from the empirical distribution of true doses and repeated re-estimation of the relative risk will give an empirical distribution of the distribution of the estimated regression calibration relative risk
 - The 5th and 95th percentile of this relative risk distribution will give the 95% confidence interval for the regression calibration relative risk, *under the assumption that the dosimetric model is completely known and correct*
- **The naïve variance estimation from the statistical software package will be underestimated unless the above step is followed**

Impact of the dose uncertainties on what?

- MULTIPLE IMPUTATION
 - Corrects for bias in point estimate *and* interval estimate of the relative risk, if imputation has been done properly, given the assumed dosimetric model is known, up to all of its parameters
- Sample x from its modeled or assumed conditional distribution given (z,y) for all study subjects, where x , is the true exposure, y is the outcome and z is the surrogate exposure and other covariates
 - **If the conditional distribution of imputed true exposure is not modeled conditional on the outcome, bias towards the null will result (**
Measurement error caused by spatial misalignment in environmental epidemiology.
Gryparis A, Paciorek CJ, Zeka A, Schwartz J, Coull BA. *Biostatistics*. 2009 Apr;10(2):258-74; Little RJA, *J Amer Statist Assoc* 1992; p. 1234).
- Estimate RR
- Repeat B times (e.g. B=1000)
- Average of the B RR's gives the final estimated RR
- Variance of this RR is the average over the B variance estimates + the sample variance of the B RRs
 - **The naïve variance estimation from the statistical software package will be underestimated unless the above step is followed**

Impact of the dose uncertainties on what?

- SENSITIVITY ANALYSIS for dosimetric model uncertainty
 - Explores the effect of departures from the assumed dosimetric model – either specified parameter values (e.g. values of variance components or their ratios) or the overall form of the model (e.g. normal, log-normal, gamma,...)
 - A range of RRs will be produced under the range of assumptions
- BAYESIAN SENSITIVITY ANALYSIS for dosimetric model uncertainty
 - Calculates a weighted average of RRs under different departures from the assumed model from the primary analysis, with weights determined by expert opinions.
 - A smooth function can be used instead of discrete weights for different departures
 - A multivariate collection of weights can be used to assess departures from assumptions on different axes
 - This has not been done yet as far as I can tell

Sensitivity analysis vs. empirical correction for measurement error

- In the absence of validation data, the relative risk is not identifiable
 - Validation data: augments the usual study design with more detailed information on exposure, through an assessment via the ‘gold standard’ or an unbiased estimate of the gold standard
- In the absence of validation data, sensitivity analysis can be conducted

Basic Strategies for Dealing with Measurement Error and Misclassification in Epidemiologic Research:

2. Design Phase

- re-design study to eliminate measurement error
 - costly
 - infeasible
 - unethical
- Personal samplers for 100,000 subjects in a prospective cohort over the full duration of follow-up to ascertain exposure
- Fat biopsies of 2,000 subjects in a longitudinal study to determine PCB and DDT concentrations in adipose tissue
- in some cases, fewer subjects with better measurements have more information than many poorly measured subjects
- replicate measurements
- prospective cohort vs. case-control: eliminate recall bias, retrospective exposure assessment

3. Design + Analysis Phase

A. Design Phase

- validation substudy: collect better measured data on a subsample (small) of subjects
- reliability substudy: collect R replicates on a small subsample of subjects

A. Analysis Phase

- use appropriate statistical methods to adjust point and interval measures of effect for measurement error

Some Examples

1. Keshaviah AP, Weller EA, Spiegelman D. Occupational exposure to methyl *tertiary*-butyl ether in relation to key health symptom prevalence: the effect of measurement error correction. *Environmetrics*, 2002; 14:573-582.

2. Thurston SW, Williams P, Hauser R, Hu H, Hernandez-Avila M, Spiegelman D. A comparison of regression calibration methods for measurement error in main study/internal validation study designs. *Journal of Statistical Planning and Inference*, 2005; 131:175-190.

Fetal lead exposure in relation to birth weight;
MS/IVS; bone lead vs. cord lead ($r=0.19$)

3. Weller EA, Milton DK, Eisen EA, Spiegelman D. Regression calibration for logistic regression with multiple surrogates for one exposure. *Journal of Statistical Planning and Inference*, 2007; 137:449-461 .

Metal working fluids exposure in relation to lung function; MS/EVS; job characteristics vs. personal monitors ($r=0.82$)

Some Examples

4. Horick N, Milton DK, Gold D, Weller E, Spiegelman D. Household dust endotoxin exposure and respiratory effects in infants: correction for measurement error bias. *Environmental Health Perspectives*, 2006; 114:135-140.
5. Li R, Weller EA, Dockery DW, Neas LM, Spiegelman D. Association of indoor nitrogen dioxide with respiratory symptoms in children: the effect of measurement error correction with multiple surrogates. *Journal of Exposure Analysis and Environmental Epidemiology*, 2006; 16:342-350.
6. Van Roosbroeck S, Li R, Hoek G, Lebret E, Brunekreef B, Spiegelman D. “Re-analysis of the relationship between respiratory symptoms and outdoor air pollution from traffic using exposure measurement error correction.” *Epidemiology*, 2008; 19:409-416.

Correcting for Measurement Error Bias In
Cumulative Exposure Variables: A Cox
Model For Lung Cancer Mortality In
Relation To Radon Progeny Exposure.

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Original Study:

Lung Cancer Mortality and Exposure to Radon Progeny In A Cohort Of New Mexico Underground Uranium Miners.

J. Samet, D. Pathak, M. Morgan, C. Key, A. Valdivia, J. Lubin.

Health Physics , vol 61, No. 6, 1991, pp745-752.

Types of Measurements

Source of exposure data	Years Spanned
1 Individual estimates (c)	1967–1985
2 Company-section Measurements (C)	1956–1976
3 Grants clinic	1942–1979
4 Colorado Plateau	1967–1985
5 Overrides	1959–1974

Hierarchy of data quality $1 > 2 > 3$.

Assume that the individual estimates are the gold standard, in the sense that the ‘ideal’ study would have used these measurements for everyone.

There are 8 years of overlap between c and C, between 1967–1976.

Validation Study

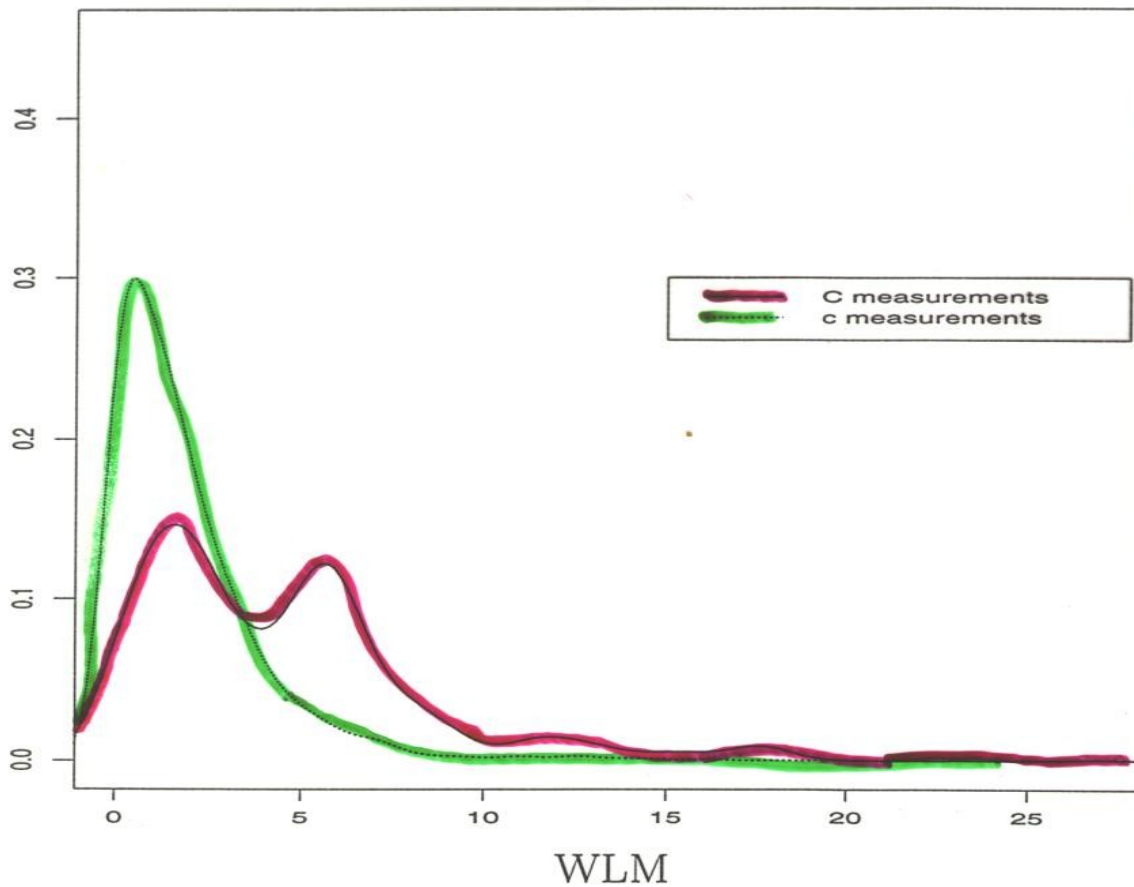
The validation study consists of 2833 pairs of individual annual measurements and annual section/company samples (c and C measurements).

$$\text{corr}(c,C) = 0.33, n= 2833.$$

$$\text{corr}(x(t),X(t)) = 0.64, n= 862,$$

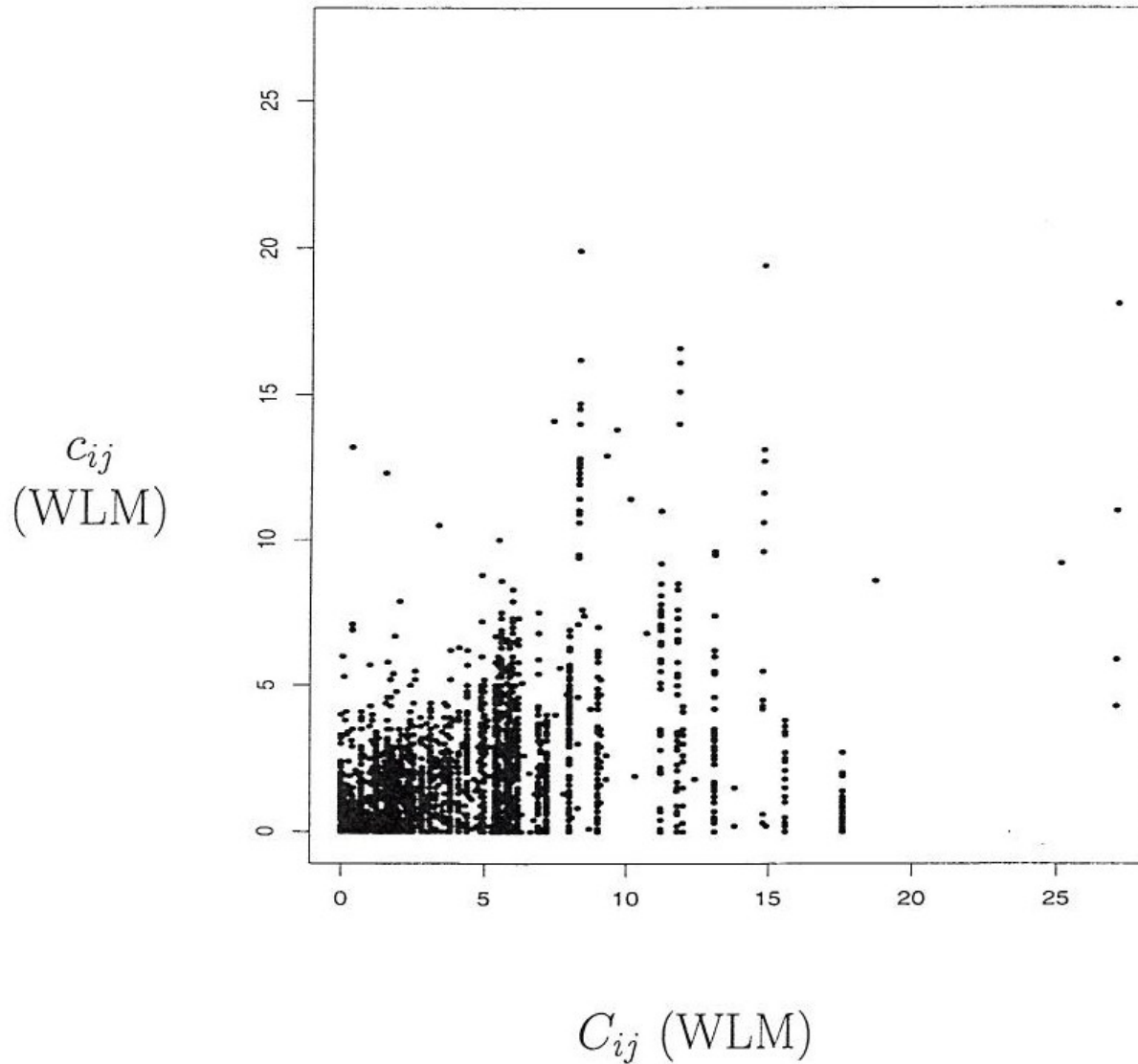
where $x(t)$ and $X(t)$ are the longest available cumulative exposure measurements for the 862 miners in the validation study.

Empirical density functions of individual annual exposure intensity estimates (c) and area samples (C).



radon, New Mexico Uranium miners,
Samet et al.

Scatter plot of c_{ij} vs C_{ij} in the validation study



Effect of radon exposure on lung cancer mortality rates:

UNM uranium miners

	$\hat{\beta}_1 (SE) \times 10^{-3}$	Mortality RR(95% CI)	
		$\Delta = 100$ WLM	500 WLM
Uncorrected	3.52 (0.658)	1.4 (1.3, 1.6)	5.8 (3.1, 11)
EPL	5.00 (1.00)	1.7 (1.4, 2.0)	12 (4.6, 32)

- > 30% attenuation in $\hat{\beta}_1$
- policy implications for risk assessment

A few additional points

- $E(z|y)$ can be estimated directly as needed for regression calibration when $f(Z)$ is similar in the main study and validation study
- If the disease isn't rare (cumulative incidence greater than 5-10%), risk set regression calibration should be used for survival analysis (Xie et al., JRSS B, 2001)
 - When risk set regression calibration is needed but not used, spurious flattening of the dose-response curve may appear

Closing comments

- Further research should investigate how much bias towards the null results from dropping outcome from the dosimetric model
 - In simulations, Gryparis et al. show that bias towards the null is substantial
 - Better yet, do it the right way and move on!
- Sensitivity analysis to departures from the assumed functional form and parameter values of the dosimetric model should be high priority
- Variance of the regression calibration estimator should be properly calculated, or further research conducted to investigate when this is important
- Dosimetric models should be empirically validated if at all possible; validation could be accomplished in new studies external to the epidemiologic ones; instrumental variables models using biomarkers can be further explored.