USC Acct.# 53-5146-0501
Award No. R01/CCR11869-06
Title: Occupational Radiation and Energy Related Health Research Grants-
Measurement Error Methods for Underground Miner Studies
Principal Investigator: Daniel O. Stram
Period: 09-30-95 to 11-30-02

**FINAL REPORT**

This grant supported developments in statistical methodology for dealing with measurement-error related issues organized around the Colorado Plateau Uranium Miners Cohort Study. Work in the first cycle of the grant concentrated mainly upon reanalysis of those data, whereas work in the 2nd cycle was more focused upon a specific general statistical problem that the Colorado uranium miner cohort typified. This more general problem concerns the appropriate use of "complex dosimetry systems" in risk estimation for epidemiological studies. Complex dosimetry systems may be either based (as the Colorado dosimetry was) on limited measurements for a job/time exposure matrix or be based upon a dose-reconstruction system using few if any actual measurements of dose, e.g., the Centers for Disease Control (CDC)-supported Hanford Thyroid Disease Study. From our statistical perspective complex dosimetry systems are those for which dosimetry errors are shared from subject to subject. Shared dosimetry errors may occur as a result of the sharing of jobs by workers in an occupational study where the estimate of exposure for a job for a specific time interval (job-year) is based upon a limited number of measurements, or is interpolated or extrapolated from exposures in similar jobs or from exposures for the same job at different time periods. For environmental exposures the shared dosimetry errors may be due to the use of a limited set of environmental measurements, and/or the use of an imputation system that estimates doses based on (generally incomplete) knowledge of the physical processes by which exposure releases spread in the environment and food supply (e.g. weather, pasture conditions, uptake and concentration into cows milk, etc., for I-131 from Hanford).

Our initial work concentrated upon developing a model for mine-year exposures in the Colorado Plateau cohort (replacing the PHS system of dose interpolation from mine-years with measurements to mine-years without measurements with one based-upon a multilevel model for the dose-distribution in the mines of interest). A considerable amount of unplanned additional work was undertaken in order to incorporate into our analyses additional measurement data that Dr. Victor Archer, retired PHS researcher, made available to us from his personal files. This work lead to a lengthy technical report (12) some methodological work from one of us (Mark Huberman in the course of his Master's thesis, 13) and the 1999 reanalysis published in Health Physics (1). The results of the 1999 reanalysis of the Uranium Miner's cohort data helps to resolve a portion of the discrepancies that have been noted in this cohort relative to those of other underground miners, (Lubin et al 1994). In particular a lower dose-response (excess risk per unit radon dose) has been seen for this cohort compared to most others. In the reanalysis, corrections for dosimetry error using our multi-level model increased the apparent dose-response (at high dose) by approximately 60 percent. Since the lower-dose dose response was relatively unchanged in our reanalysis we explored in that and a subsequent paper (3) the impact upon apparent dose-rate effects, of the corrected dosimetry developed for the 1999 Health Physics paper. Generally speaking the evidence in the Colorado data, for an inverse dose-rate effect, was reduced by approximately half using either empirical models such as that of Lubin et al, 1994 (see also BEIR 6) or using more mechanistic models including the two stage clonal expansion models.

These papers did not deal directly with the problem of shared dosimetry errors, however the work did motivate our thinking on this subject that has been key not only to our continuing research uses methods similar to those for the Colorado Plateau (11, now being supported separately), but which also lead to important contributions by the PI of this grant (Stram) to three National Academy of Sciences reviews of dosimetry systems and/or epidemiological studies developed for the CDC (6-8).

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A treatment of the primary aspects of shared dosimetry error upon the statistical power and uncertainty of epidemiologic studies that use complex dosimetry systems has now been resubmitted, after an initial positive review, to Radiation Research (5). Basic results from that paper may be summarized as follows

1 Ignoring shared dosimetry error does not affect the asymptotic size of the test of the null hypothesis (of no radiation effects).

2 However samples sizes or power of a test calculated under a specific alternative hypothesis (of an effect) will be overstated if they ignore shared error.

3 Confidence intervals will also be affected. Ignoring shared dosimetry error while constructing confidence intervals based will result in confidence intervals that are too narrow, for the same reasons as point 2.

4 However, because of point 1 a naïve confidence interval ignoring dosimetry error that does not overlap the null hypothesis (of no effect of exposure) will not overlap the null once the shared errors in the dosimetry are properly handled. In this sense it is the often the upper bounds of the radiation dose response and not the lower bounds, that are most affected by shared dosimetry error.

The 2003 Radiation Research paper goes on to give several methods to use for estimation of study power and the confidence intervals for dose-response parameters that adequately reflect the sharing of dosimetry errors, including an examination of Monte Carlo-based maximum likelihood methods.

There are a few loose ends remaining for this grant. For example, Stram is now collaborating with Drs. Leslie Stayner from NIOSH in Cincinnati, and Elisabeth Cardis of IARC in Lyon, on applying the methods of the 2003 Radiation Research paper to additional NIOSH supported work (9) specifically a reanalysis of the international nuclear workers study accounting for dosimetry error in badges used at the different facilities involved in the study. In addition Drs. Langholz and Gilliland are now finishing an update of the cancer mortality for the New Mexico cohort study. We anticipate that the relatively minor amount of work remaining on these papers will be easily supported from other available funding sources.

We list the output from this grant (both 3 year cycles) below.

## PUBLISHED PAPERS IN PEER REVIEWED JOURNALS

(1) Stram DO, Langholz B, Huberman M, Thomas DC. Correcting for exposure measurement error in a reanalysis of lung cancer mortality for the Colorado Plateau uranium miners cohort. Health Physics 77:265-275, 1999.

(2) Langholz B, Thomas DC, Xiang A, Stram DO. Latency analysis in epidemiologic studies of occupational exposures: Application to the Colorado Plateau uranium miners' cohort. American Journal of Industrial Medicine 35:246-256,1999.

(3) Stram DO, Huberman M, and Langholz B. Correcting for exposure measurement error in uranium miners studies: impact on inverse dose-rate effects. Radiation Research, 154:738-9;discussion 739-40, 2000.

(4) Stram DO. and Kopecky KJ. Power analysis of epidemiological studies of radiation-related disease risk when dose estimates are based on a complex dosimetry system with an application to the Hanford Thyroid Disease Study Radiation Research 158: 797-8, 2002.

(5) Stram DO, Kopecky KJ. Power and Uncertainty Analysis of Epidemiological Studies of Radiation-related Disease Risk where Dose Estimates are Based Upon a Complex Dosimetry System; Some Observations. In Press for Radiation Research, 2003.

**PEER-REVIEWED AND PUBLISHED NATIONAL ACADEMY OF SCIENCES COMMITTEE REPORTS CONTAINING SIGNIFICANT CONTRIBUTIONS BY D.O. STRAM MOTIVATED BY THE RESULTS OF THIS GRANT**

(6) Committee on Exposure of the American People to I-131 from the Nevada Atomic Bomb Tests and Committee on Thyroid Screening Related to Iodine-131 Exposure of the American People to I-131 from Nevada Atomic-Bomb Tests: Review of the National Cancer Institute Report and Public Health Implications. National Academy Press, Washington DC, 1999.

(7) Subcommittee to Review the Hanford Thyroid Disease Study Final Results and Report. Review of the Hanford Thyroid Disease Study Draft Final Report. National Academy Press, Washington, DC 2000

(8) Subcommittee to Review a Research Protocol Prepared by the University of Utah.
Letter Report: Review of a Research Protocol Prepared by the University of Utah.
Board on Radiation Effects Research, National Academy of Sciences, Washington, DC
2002

**STILL IN PREPARATION**

(9) Stayner L, Cardis E, Stram DO, Vriejheid M, Deltour I, Howe G. Monte Carlo methods for evaluating the impact of shared errors in exposure estimates on exposure-response models in cohort studies: Application to an international study of nuclear workers.

(10) Langholz B, Gilliland F. Update of lung cancer mortality for the New Mexico cohort study

(11) Stram DO, Kang T, Langholz B. Multi-level models for exposure measurement estimation in survival analysis.

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## UNPUBLISHED TECHNICAL REPORTS

(12) Stram DO, Langholz B, Thomas DC. Measurement Error Correction of Lung Cancer Risk Estimates in the Colorado Plateau Cohort. Part I: Dosimetry Analysis. Technical Report # 126, Division of Biostatistics, Los Angeles, CA., 1998.

(13) Master's Thesis in Biometry (University of Southern California, Preventive Medicine Department, 1998) Huberman M. Imputation of true exposure from a multi-level model with added measurement error.

## ADDITIONAL REFERENCES

Lubin J, Boice J, and Edling C, Radon and lung cancer risk: A joint analysis of 11 underground miners studies. NIH Publication no. 94-3644. 1994: Department of Health and Human Services, Public Health Service, National Institutes of Health.