FINAL REPORT

Measurement errors in occupational epidemiology

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Abstract: The specific aim of the project was the development of new measurement error methods which would be applicable to retrospective cohort and cross sectional studies typically found in occupational eqidemiology. The methods were to be easy to use and understand. The usefulness of the methods was demonstrated through an analysis of an important occupational data set, the ACE study of the relationship between health and occupational exposure to anticancer drugs. Work was also performed on developing a user friendly computer software system to implement these methods so as to encourage routine use by occupational epidemioligists. The major findings of the study were that exposure measurement error is often an important source of bias in occupational epidemiology and that methods are available to correct for these biases. The second significant finding was that the fully parametric maximum likelihood method is efficient and consistent if an empirically verified measurement error model is correctly specified.

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Significant Findings

1. Exposure measurement error is often an important source of bias in occupational epidemiology. Methods are available to correct for these biases, and investigators are encouraged to use them.

2. The fully parametric maximum likelihood method is efficient and consistent if an empirically verified measurement error model is correctly specified. Semi-parametric estimating equations which are locally semi-parametric efficient can be used to check for sensitivity of the results to measurement error model mis-specification.

3. Automatic differentiation is an easy-to-use indispensable tool for developing error-free code for finding the root of non-linear equations, such as semi-parametric estimating equations, or for finding the maximum of the log-likelihood.

Usefulness of the findings

Workplace diseases and injuries cannot be prevented until sound scientific research can justify appropriate policy for the prevention of exposure and the implementation of protective devices. Sound scientific research has been difficult, in part due to the difficulties in accurately measuring occupational exposures in occupational studies. Inaccurate exposure measurements produce biased estimates which can be spuriously heterogeneous from study to study, as the degree and type of measurement error varies with the particular features of each study design. Accessible statistical methods which make it possible for investigators to incorporate correction for bias due to measurement error in routine analysis is essential for this obstacle to the interpretation of the data to be overcome. Several methods for correction of point and interval estimates of relative risk for measurement error were developed and illustrated here. They vary in the restrictiveness of the assumptions required and in their computational complexity. The least computationally complex, *regression calibration*, makes the most restrictive assumptions, but these assumptions may be reasonable in some occupational settings. As long as exposure validation data are available, epidemiologists should use these methods whenever non-trivial exposure measurement error is observed. In occupational epidemiology, this will be almost always. The regression calibration method can be easily used by any investigator with validated exposure data, in cross-sectional studies of rare events and in cohort studies of rare events with baseline exposures. It will be difficult for investigators to apply less restrictive maximum likelihood methods without the assistance of a trained statistician.

Abstract

The purpose of this project was to develop new statistical methods to correct point and interval estimates of relative risk for exposure measurement error, that are appropriate for occupational epidemiology. The focus was on cross-sectional studies of symptom

prevalence in relation to occupational exposures. Regression calibration, fully parametric maximum likelihood methods, and semi-parametric estimating equations were developed and compared, using data from the ACE study of the health effects of occupational exposure to anti-neoplastics among hospital pharmacists. Automatic differentiation was an essential tool for software development for the maximum likelihood methods and semi-parametric estimating equations methods considered, obviating the need for algebraic differentiation and computer coding of the gradients and Hessians of the multi-parameter, non-linear functions needed.

Background

Nearly all occupational studies face problems in measuring exposures. Other types of epidemiology are also faced with this problem; for example, in recent years, nutritional epidemiologists have made considerable progress in this area (Willett, 1990). The considerable cost, and in many cases, feasibility, of detailed personal exposure sampling makes this problem a particularly difficult attribute of occupational safety and health research. It is quite possible that many occupational studies which have been interpreted as negative have failed to detect important exposure-response relationships due to substantial exposure measurement error or misclassification. Inconsistency between a series of studies of the same exposure-disease relationship may also be due to degrees and types of measurement error and misclassification which vary from study to study. Statistical methods currently available are in many cases not appropriate for occupational data because, for example, they assume normality or at least homoscedasticity of the errors. Excellent non-technical reviews of the statistical issues which emerge when exposure variables have been measured with error have been given by Armstrong (1990), Clayton (1991), Hatch and Thomas (1993), Prentice and Thomas (1993), and Thomas, Stram and Dwyer (1993), and a textbook with good coverage of these topics has appeared (Armstrong, White and Saracci, 1992). Despite the existence of several excellent texts discussing general methods for occupational safety and health research (Monson, 1990; Checkoway et al, 1989), both of these give but the most cursory treatment of the topic of exposure misclassification and measurement error. There are a few published examples of explicit correction for exposure measurement error in the analysis of occupational data (Armstrong and Oakes, 1982; Heederik and Miller, 1988; Gilbert and Fix, 1995). Validation data were used in none of these -- rather, assumed values for the parameters of a simple, empirically unverified measurement error model were plugged in. Most recently, paper have begun to appear which demonstrate that under a variety of realistic circumstances with non-differential measurement error (error which is independent of disease status), bias can be away from the null value of no exposure-disease association (Dosemici et al., 1992; Flegal et al., 1991; Wacholder, 1995; Wacholder et al., 1991).

Specific Aims

The long-term objectives of the proposed research were to develop, implement and apply statistical methods for the correction of point and interval estimates of relative risk for

bias due to measurement error that are appropriate for data typically found in occupational studies. It was hoped that the strong emphasis on specific applications and computer software development will facilitate the introduction of measurement-error methods as a practical and useful form of statistical analysis in occupational epidemiology. The specific aims of this project were:

1. To develop new measurement error methods applicable to retrospective cohort studies as typically found in occupational epidemiology, which are simple to use and understand, and to study the properties of these methods. Emphasis will be placed on methods for which the measure of the effect is the relative risk from cumulative exposure on disease incidence or mortality. The properties of the new methods will be compared to methods previously proposed, to the extent that these exist and are appropriate for occupational data.

The work completed on this aim is described in the body of this report.

2. To develop new measurement error methods applicable to case-control studies as typically found in occupational epidemiology, which are simple to use and understand, and to study the properties of these methods. Emphasis will be placed on methods for which the measure of the effect is the relative risk from exposure on disease incidence or mortality. The properties of the new methods will be compared to methods previously proposed, to the extent that these exist and are appropriate for occupational data.

Due to lack of time, no work was done on this aim during the project period.

3. To develop new measurement error methods applicable to cross-sectional studies as typically found in occupational epidemiology, which are simple to use and understand, and to study the properties of these methods.

This aim was completed, and the work is contained in two manuscripts submitted for publication (Spiegelman and Casella; Spiegelman, Valanis, and Casella) which are included in this report.

4. To illustrate the use of these methods through the analysis of important occupational data sets including

a) the GM/UAW study of the relationship between respiratory and digestive cancer mortality and cumulative machining fluids exposure,

b) the New Mexico uranium miners' study (UNM) of the relationship between exposure to radon progeny and lung cancer mortality

c) the GM/UAW study of the relationship between acute respiratory effects and components of current machining fluids exposure, and

d) the ACE study of the relationship between health and occupational exposure to anti-cancer drugs

Specific Aim 4d) was completed in conjunction with Specific Aim 3, and is documented in the submitted manuscripts by Spiegelman and Casella, and Spiegelman, Valanis and Casella. Work on Specific Aim 4b) has begun but has not been completed. Progress is documented in the body of this report. Due to lack of time, no work was done on Specific Aims 4a) and 4c).

5. To develop user-friendly computer software to implement those methods which appear to be most useful in practical settings, in order that their more routine use by occupational epidemiologists may be facilitated.

Work on this aim is documented in the publication by Hovland, Bischof, Spiegelman and Casella. Automatic differentiation is an essential tool for non-standard maximum likelihood-based estimation and inference, as is necessary in occupational epidemiology with covariate measurement error. When regression calibration is appropriate, i.e. in cross-sectional studies with rare outcomes, a manuscript submitted for publication by Spiegelman, McDermott and Rosner, illustrates new, user-friendly software developments, in the form of SAS macros, which can be used. Since other funding supported this work, in particular programmer Aidan McDermott's effort on that project, the current grant was not acknowledged.

Body of the report

The body of this report will summarize the work on Specific Aims 1 and 4b, regarding the development of methods to correct point and interval estimates of relative risk obtained from failure-time regression models for exposure measurement error (Aim 1), and applying these methods to the UNM data (Aim 4b). Much of the necessary data were transferred to us by our consultant, Dr. Jonathan Samet, and his colleagues at the University of New Mexico in Albuquerque, NM, during Dr. Spiegelman's visit there in 1993. Additional data was transferred via the internet when the need became apparent in subsequent analyses. In collaboration with Dr. Samet, we determined that we could reproduce the analyses published in Samet et al. (1991). This analysis is, of course, uncorrected for measurement error, and was presented as relative risks for categories of cumulative exposure in working level months (WLM). Before commencing with measurement-error corrected analysis, we felt it was important to understand some of the basic features of the model as it fit the data and proceeded with this analysis first. Of course, since fitting the models to the data in the usual way, ignoring exposure measurement error, is biased, these results are to be considered preliminary and will need to be reconfirmed once a valid model is obtained.

We fit a multiplicative relative risk model using Cox regression and assuming log-linearity of the lung cancer mortality rates to the data, and obtained results very similar to those given in the original publication. We tested the sensitivity of the analyses to underlying time scales upon which the Cox model was based: age (which involves left-truncation) and

time from entry into the study (years worked), since more detailed modelling of the data involves making this choice. Adjusting for all significant covariates, the deviances were 754.25 and 789.94 when age and years worked, respectively, were used as the time scale variables -- this implies that age is a much better choice of time scale from the point of view of empirical fit. Next we wished to identify what covariates were associated with improved fit of the Cox model to the data, using age as the time scale. We used stepwise regression methods, and allowed the following variables as candidates for selection into the model: calendar year, smoking status (ever/never), Hispanic, Native American, age at entry into the cohort, coal mining experience (yes/no), other non-coal, non-uranium mining experience (yes/no), the interactions of each of these variables with cumulative exposure at each time t, and squared terms for calendar year and cumulative exposure at time t. Cumulative exposure, as a time-varying covariate, was forced into the model. The variables which were selected at the $p=0.05$ significance level to be associated with lung cancer mortality were smoking status [RR (p-value) 3.7 (0.01)], Hispanic [RR (p-value) 0.40 (0.02)], age at entry into the uranium mines [RR (p-value) 0.60 for each 10-year increase in age (0.02)]. No significant interactions were found between cumulative exposure and other covariates, nor were either squared terms found to be significant. The original publication considered the use of a time-lagged cumulative exposure variable, with cumulative exposure lagged by 5 years at each risk set. Because lung cancer is believed to be a slowly developing, chronic disease, only exposures in the more distant past can be considered relevant to the growth of a clinically detectable tumor. The results from this analysis, compared to the one which did not lag exposure, were identical, both with respect to goodness-of-fit and with respect to the estimated value of the effect of exposure on lung cancer mortality rates.

These exercises were repeated for the analysis of death from all causes, as this endpoint was also the subject of some consideration in the original manuscript (Samet et al., 1991). There was again a big improvement in fit seen when age was used as the time metameter in the Cox model, compared with time since entry into the work force. The same variables and functions of the variables were used as candidates for stepwise selection into the model for all-cause mortality and smoking status, Native American (vs. white), and years since last worked were associated with significant, increased risk of death, while Hispanics were at a significantly decreased risk of death, compared with whites. In addition, the dose-response curve for Native Americans was significantly higher than that of whites and Hispanics -- 50% higher at every WLM ($p=0.006$). An appreciable improvement in fit was seen when the 5-year lag on exposure was implemented, compared to when it was not, as judged by a larger log-likelihood, and the estimate of the effect of radon progeny was greater when 5-year lagged exposure was used. It would be of interest in future analyses to estimate the optimal lag, using a profile likelihood method.

Since our intention in the measurement-error corrected analysis is to model the relationship between lung cancer mortality rates and cumulative exposure to radon as a continuous variable, we wished to investigate the consistency of the data with an assumption of linearity on the log scale of incidence rates. Using restricted cubic splines, we fit the data with several numbers and locations of knots, and graphic inspection of these plots indicated little sensitivity to these choices (Figure 1). There appears to be a consistent increase in the rates after 100 WLM (possibly beginning at 50 WLM) with a plateau occurring between 200-

300 WLM. In addition, these appears to be a decrease in rates, relative to the unexposed, between 0 and 50 WLM or so. It is known that exposure measurement error is a possible explanation for an apparent plateau in an underlying dose-response relationship which is actually log-linear, but it is currently unknown to us whether exposure measurement error can induce the observed dip in the 0-50 WLM range. Clearly, this figure indicates that we will need to explore departures from the assumption of linearity in our continuous exposure variable models.

We next turned to construction of preliminary exposure measurement error models. Data files given to us by Dr. Samet and colleagues provide a yearly exposure estimate for each year of work since entry into the study for each study participant. These yearly exposure estimates came from 4 sources, plus an override code: 0.073% of the total cumulative exposure came from Colorado plateau estimates (denoted C) spanning 1967-1985; 57% of the total cumulative exposure came from Grants clinic estimates (G), spanning 1942-1979, 33% of the total cumulative exposure came from direct company/section estimates (E), spanning 1956-1967; and 9% of the total cumulative exposure came from individual estimates (W), spanning 1967-1985. The remainder (0.2%) were 'overrides'. The investigators ranked the quality of measurements as follows: W > E > G -- thus, for the purposes of our analysis, we will regard W measurements as the 'gold standard'. Later, we will explore the impact of realistic violations of that assumption. Under the assumption that W measurements are the gold standard, we need to model the relationship between W and E measurements and W and G measurements to construct the likelihood (or partial likelihood) conditional upon the observed cumulative exposure variable. Data that has been provided to us thus far has allowed us to develop a preliminary measurement error model for the relationship between the W and E measurements. There are 3162 miner-years in which W and E data overlap, within 978 miners. The Pearson correlation between these 3162 measurements is 0.31, indicating substantial measurement error. However, a maximum cumulative exposure variable can be constructed for each of these 978 miners, based upon the maximum number of years of overlap of W and E measurements. The Pearson correlation between these 978 measurements is 0.64. In our analyses, we assume that the employment histories are correct and the same history is used to construct cumulative exposure based on either W or E measurements. Thus, it is not surprising that the correlation between the cumulative exposure variables is higher than the correlation between the annual measurements. We modelled the mean $E(W_{ij})$ as a function of E_{ij} and other variables, where $i=1,\ldots,978$, $j=1,\ldots,J_i$, and J_i is the number of years for miner i in which E and W measurements overlap. In the simplest model,

$$E(W) = 1.104 + 0.176\ E,$$

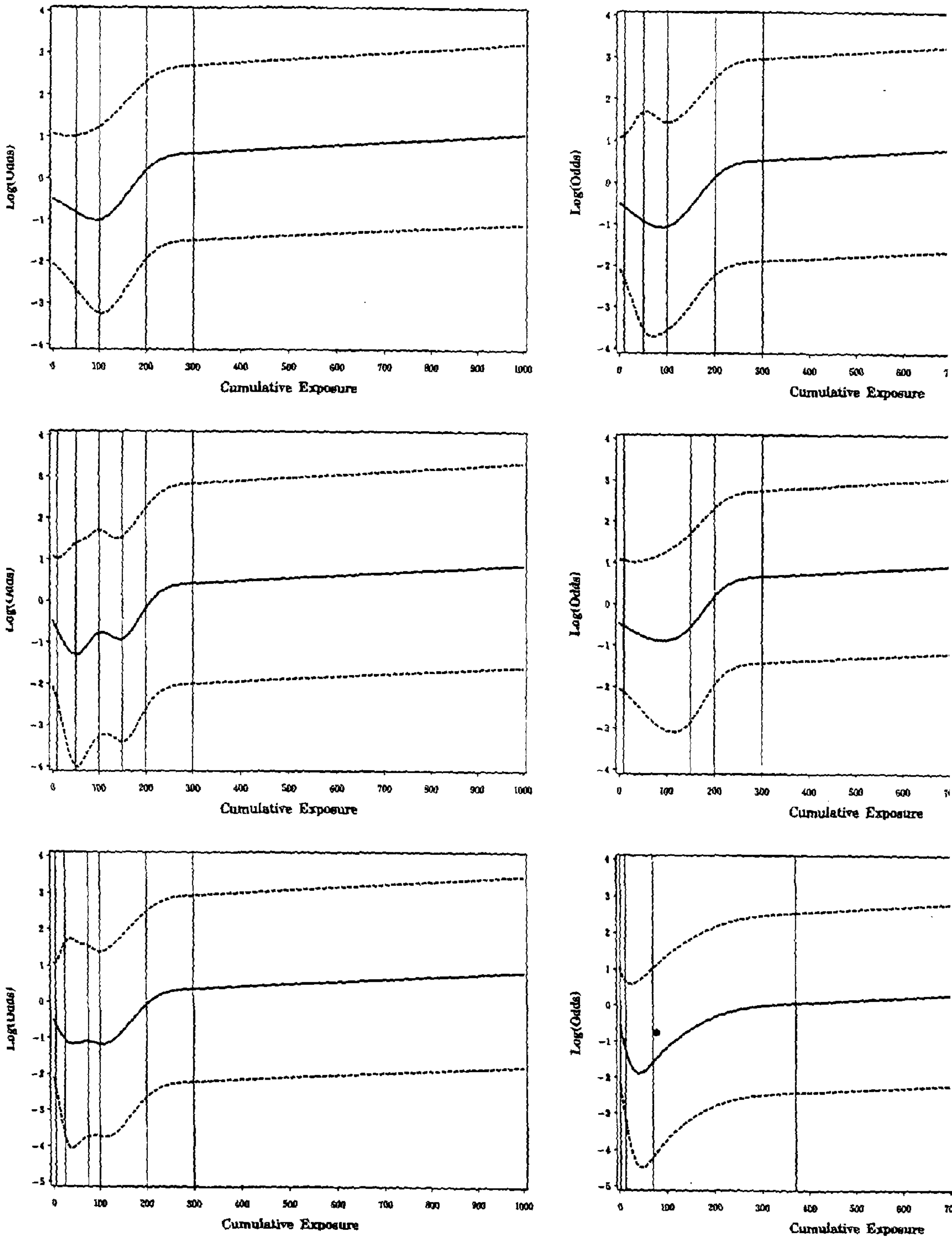
and the *p*-value for the coefficient corresponding to the E measurements was less than 0.0001. The R^2 of this model was 0.10. We then used stepwise variable selection procedures with calendar year, race, age, smoking status, and company as candidate variables, and year, age, hispanic, smoking status and both of the two available indicator variables for company were selected at the $p=0.05$ level, according to the model

$$E(W) = 30.0 + 0.10\ E - 0.39\ year + 0.01\ age + 0.37\ Hispanic + 0.25\ SMOKE - 1.26\ Company\_5 - 2.43\ Company\_6.$$

The R^2 of this model was 0.30. We then allowed squared terms for exposure (E), year, age,

and all two-way interactions between exposure and the other possible variables as candidates for the stepwise variable selection procedure. Two-way interactions between exposure and year and age were selected; in addition, age*year, exposure^2, company_5, company_6, year, smoking status, and age were selected. The R^2 of this model was 0.33 -- not a big improvement over the previous model. Graphical examination of the plot of the squared residuals on the predicted W exposures had a characteristic fan shape, indicating a strong dependency of the error variance on the observed exposure value. The correlation of these quantities was 0.22.

Considerable work on this project remains to be done, and is ongoing with the assistance of Harvard School of Public Health biostatistics doctoral student Helen Parise and Masters level mathematician Mario Casella. Because of the heterscedasticity and other features of our preliminary measurement error model, we do not believe that the Gaussian distribution is a good model choice. We would like to explore variants of the gamma distribution, the log-normal distribution, and, possibly, mixture models which allow for more than one model family to be fitted over different regions of the data. We need to investigate the validity and other features of constructing a measurement error model in the cumulative exposure variable, as compared to modelling error in the individual measurements. We need to derive the full and possibly partial likelihood of the data, and fit this to obtain a point and interval estimate of the effect of radon exposure to lung cancer mortality. All of this is quite complex, and has been described in detail in a new grant application, submitted to the NIH on October 1, 1995, entitled "Measurement error in occupational cancer studies" (R01 OH03416-01). This grant was submitted in collaboration with Dr. Jonathan Samet and others.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Publications

1. Spiegelman D, Casella M. Explicit correction for exposure measurement error increases log relative risk estimates more than threefold: a case study of health effects of chemotherapeutics exposure in hospital pharmacists. Am J Epidemiol 1994; 139:S80.

2. Spiegelman D, Casella M. Explicit correction for exposure measurement error increases log relative risk estimates more than threefold: a case study of health effects of chemotherapeutics exposure in hospital pharmacists. Epidemiology 1995; 6:S41.

> *The above two publications fully address Specific Aim #3 and Specific Aim #4d.* The first publication is written for a general audience and illustrates two methods which can be used to correct cross-sectional studies for measurement error. The second publication is technical, and develops in detail fully parametric and semi-parametric methods to correct for exposure measurement error in cross-sectional studies, where the rare disease assumption is usually violated.

3. Hovland P, Bischof C, Spiegelman D, Casella M. Efficient derivative codes through automatic differentiation and interface contraction and an application to biostatistics. In press, SIAM Journal of Scientific Computing, 1995.

> *The above publication addresses Specific Aim #5. The scientific computing methods developed in this manuscript were used for calculations in the fully parametric methods developed by Spiegelman and Casella (1995). Automatic differentiation is an indispensable software tool when non-standard likelihood functions are to be maximized or used as the basis for statistical inference.*

Submitted for publication

4. Spiegelman D, Casella M. "Fully parametric and semi-parametric regression models for common events with covariate measurement error, in main study/validation study designs". Submitted for publication, Biometrics, 1995.

5. Spiegelman D, Valanis B, Casella M. "Correction for exposure measurement error increases relative risk estimates: a case study of occupational exposure to antineoplastics in pharmacists". Submitted for publication, *Journal of the American Public Health Association*, 1995.

The above two manuscripts fully address Specific Aims #3 and #4d, as they develop new methods for point and interval estimation of prevalence ratios in cross-sectional studies with possibly common events. In addition, they compare these new methods to another popular method in epidemiology which is strictly not appropriate for cross-sectional studies of common events, and highlight the advantages of the new method. The ACE study of the relationship between health and occupational exposure to anti-cancer drugs is used extensively as the example in both papers.

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15. Supplementary Notes

16. Abstract (Limit: 200 words) The specific aim of this project was the development of new measurement error methods which would be applicable to retrospective cohort and cross sectional studies typically found in occupational epidemiology. The methods were to be easy to use and understand. The usefulness of the methods was demonstrated through an analysis of an important occupational data set, the ACE study of the relationship between health and occupational exposure to anticancer drugs. Work was also performed on developing a user friendly computer software system to implement these methods so as to encourage routine use by occupational epidemiologists. The major findings of the study were that exposure measurement error is often an important source of bias in occupational epidemiology and that methods are available to correct for these biases. The second significant finding was that the fully parametric maximum likelihood method is efficient and consistent if an empirically verified measurement error model is correctly specified. Semiparametric estimating equations are locally efficient and can be used to check for sensitivity of the results to measurement error model misspecification. Thirdly, it was determined that automatic differentiation is an easy to use indispensable tool for developing an error free code for finding the root of nonlinear equations, such as parametric estimating equations, or for finding the maximum of the log likelihood.

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