Allowing for Dose-Estimation Errors for the
A-Bomb Survivor Data

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Dose-errors/Cancer risk estimates/Errors-in-variables

Unless allowances are made, random errors in radiation dose estimates cause underestimation of linear risk
estimates and distort the shape of dose-response curves. These errors also result in spurious associations between
radiogenic endpoints, exaggerating possible, variation in individual sensitivity to radiation. Statistical methods have
been developed which reduce these biases, based on assumptions regarding the nature and magnitude of dose-
estimation errors. Some understanding of the underlying statistical basis for these methods is necessary to both
those interested in interpreting radiogenic effects and those interested in the dosimetry system. This paper discusses
the basic statistical issues and their implications, presents some statistical methods to deal with the problem,
and indicates the sensitivity of certain results to assumptions about the magnitude of the dose-estimation errors.

INTRODUCTION

In regard to the follow-up of A-bomb survivors by the Radiation Effects Research Foundation
(RERF), it has long been realized that imprecision of individual radiation dose estimates causes
systematic biases in estimation of dose-response relationships. In linear dose-response analyses
the slope will be underestimated, and moreover, the apparent shape of the dose-response will
be distorted. These statements are true even if dose estimates are unbiased in the ordinary sense
of this term. Consideration is given here only to what might be called “random” errors in dose
estimates, due largely to imprecise knowledge of survivor location and shielding, in contrast to
those of a more systematic nature such as in the yield of the bombs and in radiation transport.

As early as 1963, before there was a dosimetry system, RERF statisticians pointed out that
these biases would arise. In 1971 Jablon11 analyzed the probable form and magnitude of
estimation errors. His results remain useful for the recently-revised Dosimetry System 1986
(DS86) because they focussed on errors in basic inputs of survivor location and shielding. Gilbert21
subsequently provided further results on both the basic issues and methods to cope
with the problems. Pierce and Vaeth45 used these methods in analysis of the shape of the
A primary aim here is to encourage wider understanding of the basic statistical issues, including the distinction between biases in dose estimates and biases in risk estimates which results from dose errors. Dose estimates may be said to be unbiased if the average value of the estimates, for those with a given true dose, equals this true dose. Biases in risk estimates depend, though, on the average value of the true dose for those having a given estimated dose. This distinction is subtle and important.

Further, statistical methods developed in (3) are described, which can reduce the biases in both the estimated slope for linear risk models and the apparent shape of dose responses. Applying these methods also provides assessment of the extent of biases which are present when allowance for dose errors is not made.

These methods require assumptions regarding the nature and magnitude of dose-estimation errors. Although information about the errors is rather limited, and further assessment is important, analysis of sensitivity to these assumptions suggests that the proposed methods are currently useful. Perhaps equally important, better understanding of the rather subtle statistical issues is crucial to the task of further assessment of the dose-estimation errors.

Random errors in dose estimates have important effects in addition to the biases discussed above. For example, it has recently been observed that survivors reporting significant acute radiation effects have markedly higher response per unit (estimated) dose for both certain cancers and chromosome aberrations than other survivors; Neriishi, et al.6), Sposto, et al.7). Such effects are of interest as possible evidence of individual variation in sensitivity to radiation. It is clear, however, that imprecision of dose estimates causes spurious associations of this type and analysis of this issue is given in6,7), and by Stram and Sposto8) elsewhere in this volume.

Of the vast statistical literature on what is called the “errors-in-variables” problem, some particularly relevant references are Armstrong9), Clayton10), and Prentice11,12).

BASIC STATISTICAL ISSUES

A survivor's true dose will be denoted by x, and the estimated dose denoted by z. By Avg(z|x) is meant the average estimated dose for those at true dose x; this is a function of x. A dosimetry system is unbiased in the usual sense of this term if Avg(z|x) = x for all values of x. The expression Avg(x|z) will denote the average (unobserved) true dose among survivors with (approximately) the same estimated dose z; this is a function of z. Even though Avg(x|z) cannot be directly observed, it can be estimated as explained here, and consideration of this quantity is the key to understanding the biases in risk estimates arising from random errors in dose estimates.

Suppose the expected dose-response for some outcome y is linear in the true dose x, and written as \( \alpha + \beta x \) where \( \alpha \) and \( \beta \) are parameters to be estimated. Due to the linearity in x the expected response among those with estimated dose z is \( \alpha + \beta \text{Avg}(x|z) \). The numerical values of the parameters \( \alpha \) and \( \beta \) are the same in these two expressions. Dose-response analysis without allowance for errors in dose estimates consists of fitting models of form \( \alpha^* + \beta^*z \), and the parameters (\( \alpha^*, \beta^* \)) estimated in this way are numerically different from (\( \alpha, \beta \)). In this case
of linear dose response models the key to unbiased estimation of \((\alpha, \beta)\) is to replace the estimated doses \(z\) by estimates of \(\text{Avg}(x|z)\) when carrying out the dose response analysis.

It is easy to confuse the notion of \(\text{Avg}(x|z)\) with that of \(\text{Avg}(z|x)\). Although it is appropriate to make the working assumption that \(\text{Avg}(z|x) = x\), to a reasonable approximation, it is clear that \(\text{Avg}(x|z) < z\) over most of the dose range. This is because the relative numbers of survivors drops off very rapidly with increasing dose. Thus the parameter \(\beta^*\) introduced above, which is estimated by fitting models linear in \(z\), is smaller than the true value \(\beta\).

The artificial example developed in Table I helps to clarify why \(\text{Avg}(x|z) < z\). Rounding to the nearest gray, the numbers of survivors in true dose categories there are roughly those of the RERF Life Span Study (LSS) cohort. Consider a highly artificial statistical model for errors, such that with probability 0.5 the estimate is correct, with a probability of 0.25 of a one gray error in either direction. The table indicates the expected numbers of survivors in a cross-classification of true and estimated doses. Consideration of the rows of the table shows that, for each true dose, the average estimated dose is equal to that true dose and thus the estimates are unbiased in the sense of \(\text{Avg}(z|x) = x\). On the other hand, \(\text{Avg}(x|z)\) is computed by averaging true dose according to the frequencies in each column, and some selected values are given at the bottom of the table. The average true dose for those in an estimated dose category is less than the estimated dose. This is seen to result from far more survivors, in each column, being one Gy below the estimate than one Gy above the estimate. This, in turn, is due to the extreme skewness of the marginal distribution of true doses.

The error distribution in Table I was chosen largely for simplicity, but it illustrates some important points. It is often thought that a major part of the problem resulting from errors is that they are: (i) greater for large doses, and (ii) rather symmetric on a logarithmic scale, resulting in larger overestimates than underestimates. These two factors are relevant, but it is seen from the above table, having neither of these features, that the fundamental problem caused by the

| Estimated Dose \(z\) (Gy) | Number of Survivors |
|--------------------------|---------------------|
|                      1 2 3 4 5 6 |
| True Dose \(x\) (Gy) | 2 500 250 | 1000 |
| 3 75 75 75 75 75 | 300 |
| \(x\) | 4 33 66 33 132 |
| 5 15 30 15 60 |
| \(\text{Avg}(x|z)\) | 2.50 3.62 |
highly skewed distribution of true doses among survivors would exist even without them.

The precise relevance of $\text{Avg}(x|z)$ depends on the linearity in $x$ of the dose-response, and the focus here is on that case. However it can be generalized in various ways; extension to linear-quadratic models is discussed below. It is noted that if for each value of $z$ the nonlinearity in the expected value of $y$ given $x$ is not great in the restricted range of $x$-values relevant to those with estimated dose $z$, then a graph of $y$ versus $\text{Avg}(x|z)$ would still reflect the true shape of the dose-response. Corrections can be made to the approximation in this, but the point remains that the relationship between $z$ and $\text{Avg}(x|z)$ is generally important.

A reasonable aim of a dosimetry system is to achieve estimates without bias, i.e. $\text{Avg}(z|x) = x$ for all values of $x$. It is useful to think of this issue in terms of an idealized dosimetry system which would give exact estimates were it not for errors in input parameters such as the individual's location, shielding, etc. Then unbiased estimation of these input parameters would lead, to an approximation which might be improved by transforming to a log scale, to $\text{Avg}(z|x) = x$. We would say that dose estimates of this nature are essentially unbiased. It will be assumed in this paper that DS86 estimates are unbiased on a log scale; whether this is actually the case is not considered here. However, as indicated above, this does not imply that parameters estimates in dose response analyses are unbiased. In particular, these biases are directly related to the ratios $\text{Avg}(x|z)/z$.

The statistical methods suggested for linear risk models involve the replacement, in dose-response analyses, of the estimated doses $z$ by adjusted estimates $\text{Avg}(x|z)$. Correct values of $\text{Avg}(x|z)$ are not known, but these may be approximated as explained below. For some types of data additional modifications are required to allow for excess variation in the response which is introduced by errors in dose estimates; for the cancer data this is generally not necessary. Additional, or sometimes different, adjustments are required for nonlinear models.

It is emphasized that this adjustment of estimated doses is not intended to correct any fault in the dosimetry system. When the distribution of true doses is very skewed, the two conditions $\text{Avg}(z|x) = x$ for all $x$ and $\text{Avg}(x|z) = z$ for all $z$ are simply incompatible. Coping with the fact that $\text{Avg}(x|z)$ is less than $z$ for large dose estimates falls more within the realm of dose-response analysis than that of the dosimetry system.

FURTHER DETAILS OF STATISTICAL MODELS AND METHODS

This section is divided into several subsections, each dealing with a major aspect of the statistical methods.

Statistical Models for Dose Errors

An appealing model for errors in dose estimates $z$ is the lognormal distribution; that is, for any given true dose $x$, $\log(z)$ is normally distributed with mean $\log(x)$ and standard deviation independent of $x$. In this lognormal model the standard deviation of $z$ is proportional to $x$, which seems essential for any reasonable error model. Precise normality of $\log(z)$ is less well justified, but it is more reasonable to assume approximate symmetry of the distribution of $\log(z)$ than
of z itself. Some investigation of consequences of using models other than the lognormal has been made\(^3\). In particular, a model was considered for which log(z) is symmetrically distributed but with "heavier tails" than the normal distribution. The following results were not sensitive to this departure from the lognormal model.

In the lognormal model with standard deviation \(\sigma\) for log(z), the standard deviation of z is approximately 100\(\%\) of x, and this relative standard deviation of z is called the coefficient of variation (CV) of z. There is limited information about the actual CV of dose estimates. Jablon\(^1\), considering mainly errors due to imprecise knowledge of survivor location and shielding, suggested use of a CV of 30\(\%\) or somewhat greater; he also gave support for use of a lognormal model. The report of the DS86 development\(^13\), Ch.\(^9\) contains some preliminary analysis of DS86 errors, suggesting CV’s in the range 25\(\%\)–35\(\%\). Sposto, et al.\(^7\) have found that CV’s in the range 45\(\%\)–50\(\%\) are required to explain completely apparent associations between chromosome aberration rates and presence of acute effects. Estimates of the CV obtained in this manner would require assumption of no individual variation in radiation sensitivity — these results are discussed further in Stram and Sposto\(^8\). In this paper results are given for CV’s of 30\(\%\), 35\(\%\), and 40\(\%\); providing some analysis of sensitivity to this assumption.

**Estimation of \(\text{Avg}(x|z)\)**

The desired quantity \(\text{Avg}(x|z)\) is the mean of the distribution \(f(x|z)\) of true doses x given estimated dose z. This distribution is interpreted here as the actual, but unobserved, distributions of the true doses x, in groups of the RERF cohort having approximately the same estimated doses z. The density function \(f(x|z)\) satisfies

\[
f(x|z) \propto f(x) f(z|x)
\]

where \(f(x)\) is the distribution of true doses for the cohort, \(f(z|x)\) is the distribution of estimated dose z among those at true dose x, and the proportionality is with respect to x. Lognormal models as discussed above are used here for \(f(z|x)\). The distribution \(f(x)\) is of course not observable, but can be estimated by making some adjustment to the observed distribution of z’s. In particular, \(f(x)\) is taken so that, in conjunction with an assumed distribution \(f(z|x)\), the induced theoretical distribution of z agrees closely with the observed distribution for the cohort. This is discussed in more detail in (3).

Due to different distributions of the location of survivors in Hiroshima and Nagasaki relative to the location of the bombs, the distribution \(f(x)\) differs between the two cities. Thus \(f(x)\) and the distribution \(f(x|z)\) are estimated separately for each city. The calculation of \(\text{Avg}(x|z)\) from Eq.(1) corresponds essentially to the illustrative calculations in Table 1. Numerical integration has been used to avoid artificial constraints, for mathematical convenience, on the choice of models. Note that \(\text{Avg}(x|z)\) is a function of z and does not involve a particular value of x; for a given survivor with estimated dose z, the adjusted dose to be used in dose response analysis will be written as \(\text{Avg}(x|z)\).

Table 2 illustrates some resulting values of \(\text{Avg}(x|z)\), for each city and three values of the CV of z. The term dose for purposes of this table refers to tissue kerma, i.e. kerma in air at
Table 2. Adjusted dose estimates for three assumed levels of error

| Error CV: Estimated Dose (Gy) | Average Adjusted Dose Estimates (Gy) | Hiroshima | Nagasaki |
|-------------------------------|--------------------------------------|-----------|----------|
|                               |                                      | 30%       | 35%      | 40%      | 30%       | 35%      | 40%      |
| 0.5                           |                                      | 0.50      | 0.50     | 0.50     | 0.50      | 0.50     | 0.50     |
| 1.0                           |                                      | 0.95      | 0.94     |          | 0.98      | 0.98     | 0.97     |
| 2.0                           |                                      | 1.84      | 1.79     | 1.73     | 1.89      | 1.86     | 1.82     |
| 3.0                           |                                      | 2.66      | 2.56     | 2.45     | 2.75      | 2.68     | 2.59     |
| 4.0                           |                                      | 3.44      | 3.28     | 3.12     | 3.58      | 3.46     | 3.32     |
| 5.0                           |                                      | 4.20      | 3.98     | 3.75     | 4.38      | 4.20     | 4.01     |
| 6.0                           |                                      | 4.93      | 4.64     | 4.35     | 5.16      | 4.92     | 4.67     |

the location of the survivor adjusted for external shielding. Adjustments for organ doses are discussed later.

As indicated in the previous section, the values of \( \text{Avg}(x|z) \) are less than \( z \) because for any given \( z \) and \( \Delta \), there are far more survivors with \( x = z - \Delta \) than with \( x = z + \Delta \). The reduction factors \( R(z) = \frac{z - \text{Avg}(x|z)}{z} \) are somewhat greater for Hiroshima than Nagasaki, because the relative numbers of survivors in the cohort decrease more rapidly with increasing dose in Hiroshima. Note that this difference in reduction factors implies that analyses without allowance for dose errors will produce biased estimates of city-specific differences in dose-response.

Because it is difficult to describe the relative importance of various parts of the dose range in fitting linear dose-response models, the results of replacing \( z \) by \( \text{Avg}(x|z) \) in dose-response analyses, and the sensitivity of these to the choice of error model, is not very clear from Table 2. In the next section some results of applying these adjustments are given.

Simple formulas for \( \text{Avg}(x|z) \) for the error models of Table 2, which agree within 0.01 Gy on the range 0–6 Gy to results of the numerical integration, are given in (3). These are in terms of the reduction factors \( R(z) \) defined above. For simplicity, it is recommended that adjusted doses for specific organs be obtained by applying these reduction factors, computed in terms of tissue kerma, to estimated organ doses. In choosing a CV value it should be realized that estimated organ doses have greater errors than estimated kerma, since true organ doses depend on additional factors. For analysis of grouped data it is recommended that fairly narrow dose categories be used, and that the adjustment be applied to the mean estimated dose for the category. Gilbert\(^3\) has pointed out that use of wider dose categories does not alleviate effects of errors in dose estimates, and the decisions about the number of dose categories to use should depend only on other issues.

Dose Response Analysis

Although the methods to adjust for dose-estimation errors basically consist of replacement of \( z \) by \( \text{Avg}(x|z) \), one should not think of the estimates \( \text{Avg}(x|z) \) as being equivalent to the true doses \( x \). Consideration is now given to further allowances that may be required in statistical
methods.

The need for allowances beyond replacement of $z$ by $\text{Avg}(x|z)$ depends on the nature of the response data to be analyzed. Consideration will be given below to the case of cancer incidence or mortality data, where no further allowances are needed; and to the case of data on chromosome aberrations, where the situation is different in this respect.

First consider in general response data $y$ where the datum on each individual survivor is of the form

$$y_i = \alpha + \beta x_i + \text{error}_i \quad (2)$$

in terms of true doses, where $\text{error}_i$ represents ordinary sampling variation. The ideal analysis in terms of true doses would be done by using iterative weighed least squares for the model of Eq.(2). Weights are required because the variance $\text{Var(}\text{error}_i)$ depends on $(\alpha, \beta, x_i)$, and iteration is required because these depend on the parameters to be estimated. For the usual types of data arising at RERF this iterative weighed least squares method is equivalent to maximum likelihood fitting. These estimates would be essentially unbiased because the expected value of $\text{error}_i$, conditionally upon $x_i$ is zero.

A model expressing the expected value of $y_i$ for a survivor with given $z_i$ can be formulated by reexpressing Eq.(2) in the form

$$y_i = \alpha + \beta \text{Avg}(x|z_i) + \beta [x_i - \text{Avg}(x|z_i)] + \text{error}_i \quad (3)$$

In Eq.(3) the quantity $\beta [x_i - \text{Avg}(x|z_i)]$ is an additional random error term, representing the unknown deviation of a survivor’s true dose from the adjusted value $\text{Avg}(x|z_i)$ to be used in the dose-response analysis. Thus for statistical analysis the appropriate model is of the form

$$y_i = \alpha + \beta \text{Avg}(x|z_i) + \text{error}_i^* \quad (4)$$

where $\text{error}_i^*$ represents both aspects of the error in Eq.(3). The expectation of $\text{error}_i^*$, conditionally on $z_i$, is zero in the sense of averaging over survivors with the same estimated dose. This implies that parameter estimates based on fitting Eq.(4) will be essentially unbiased.

The proposed method is to apply iterative weighed least squares methods to the model of Eq.(4), similarly to the methods discussed above that would be used if the true does not known. The weights are determined by the variance of $\text{error}_i^*$, which is given by the expression

$$\text{Var}(\text{error}_i^*) = \beta^2 \text{Var}(x|z_i) + \text{Avg}[\text{Var}(\text{error}_i)]. \quad (5)$$

The first term in Eq.(5) reflects the additional variation in the data due to dose-estimation errors; the quantity $\text{Var}(x|z_i)$ is the variance of the distribution $f(x|z)$, and this can be computed from Eq.(1) similarly to the calculation of $\text{Avg}(x|z)$. The second term in Eq.(5) is the average of $\text{Var}(\text{error}_i)$ in the model of Eq.(2) with respect to the distribution $f(x|z)$.

For statistical models used to analyze the cancer data, calculations in (3) show that the first
term in Eq.(5) is very small in relation to the second term which, along with the nature of $\text{Avg}[\text{Var} \text{error}_i]$, implies that the only required modification to standard methods is to replace the $z_i$ by $\text{Avg}(x|z_i)$. That the second term is relatively large is mostly due to the fact that the datum on each individual is essentially binary. As will be clarified in a following paragraph, this results in relatively large sampling error, aside from errors in doses.

On the other hand, for the chromosome aberration setting the datum for each individual is the proportion of about 100 sampled cells which exhibit an aberration. The relevant model for Eq.(1) is the binomial distribution, in which the variance of the error term is inversely proportional to the number of cells sampled. Consequently, as shown in (3), the first term in Eq.(5) is not negligible in relation to the second term and methods suitable for analysis of binomial data require more modification than replacement of the $z_i$ by $\text{Avg}(x|z_i)$.

However, it has been apparent for many years that the chromosome aberration data exhibit much more variation than is consistent with the binomial model. Special methods of analysis to allow for this have been developed; see Preston, et al.\(^{14}\). These methods are based on an empirically-determined variance function for the data $y_i$, which is remarkably similar to that given by Eq.(5). Provided that this special method of analysis is used, rather than methods suitable for binomial data, the only additional modification required is the replacement of the $z_i$ by $\text{Avg}(x|z_i)$.

The points raised in the above paragraphs are considered in more detail in an Appendix to (3). Careful treatment of the case for the cancer data is somewhat more complicated than indicated here, since the datum on each individual is not really binary but consists of whether or not cancer appears during the follow-up to date, along with the time at which it appears. In addition to the discussion of this in (3), the papers by Prentice\(^{11,12}\) consider in more detail aspects of the modelling for the cancer data.

The above development depends strongly on the assumption of a linear dose response model as in Eq.(2). In fitting models where the expected response is not linear in $x$ it is generally not correct simply to replace the $z_i$ by $\text{Avg}(x|z_i)$ and carry out the analysis in the usual way. The most important nonlinear models for the RERF data are of the linear-quadratic (LQ) form

$$y_i = \alpha + \beta x_i + \gamma x_i^2 + \text{error}_i,$$

(6)

and the approach taken here leads directly to the generalization of fitting the response data using covariables $\text{Avg}(x|z_i)$ and $\text{Avg}(x^2|z_i)$. The required values of $\text{Avg}(x^2|z)$ can be obtained similarly to $\text{Avg}(x|z)$. For the LSS cohort data and error models considered here it is shown in (3) that the ratio $\text{Avg}(x^2|z)/[\text{Avg}(x|z)]^2$ is nearly constant in $z$; values of this are about 1.09, 1.11, and 1.14, respectively, for the error models of Table 2. This implies that simply using $\text{Avg}(x|z_j)$ and $[\text{Avg}(x|z_j)]^2$ as the covariables will provide essentially the correct fitted dose response curve and tests for linearity. The fitted coefficient of $[\text{Avg}(x|z_j)]^2$ will require adjustment by the reciprocal of the ratio discussed above. Analysis of the shape of the dose response curve by these methods has been made by Pierce and Vaeth\(^{4,5}\).
Additional Covariables

Risk models for the A-bomb survivor data ordinarily involve covariables in addition to dose. For the cancer data other primary covariables are city, sex, and age-at-exposure. Consideration must be given to how inclusion of additional covariables, measured without error, affect the above development.

If the model for the response data is extended to the form

\[ y_i = \alpha + \beta x_i + \gamma w_i + \text{error}_i, \]

where \( w_i \) represents values of another covariable, measured without error, then no further changes are required for inclusion of this in the analysis if \( f(x|z,w) \) does not depend on \( w \). Otherwise the method suggested above should, at least in principle, be modified by replacing \( \text{Avg}(x|z) \) by \( \text{Avg}(x|z, w) \).

Whether \( f(x|z,w) \) depends upon \( w \) is best considered by asking, in view of Eq. (1), whether \( f(x|w) \) or \( f(z|x,w) \) depend on \( w \). For the case that \( w \) denotes city this has already been implicitly considered, and since the marginal distribution of \( x \) does depend on city the computation of \( \text{Avg}(x|z) \) has been done separately for each city. On the other hand, it seems unlikely that either the distribution of \( x \) or the error model should depend substantially upon sex or age-at-exposure, and no further modification have been made when including these covariables. Some further consideration of these issues may be worthwhile.

A related matter is perhaps more important. Consider a covariable \( w \) which is not in the risk model but which does affect \( f(x|w) \) or \( f(z|x,w) \). A primary example of this is shielding category, which undoubtedly affects the magnitude of dose-estimation errors. In this case one should consider replacing \( \text{Avg}(x|z) \) by \( \text{Avg}(x|z, w) \). It can be seen that whether this is done has no effect on the bias of risk estimates, but that using \( \text{Avg}(x|z, w) \) could improve the precision of risk estimates. How much might be gained by this has not been investigated. This line of argument may suggest, however, that obtaining information on dose-estimation errors by shielding category is less important than previously considered.

Analysis of Subcohort Data

The data on chromosome aberrations raises an important point which has sometimes been overlooked. This issue arises in considering data which is available only for a subset of the RERF LSS cohort, whose selection has depended substantially on estimated dose. This is the case both for the chromosome aberration study and for the Adult Health Study involving a subset of the LSS followed up by clinical examinations.

A critical step in the statistical methods outlined here is estimation of the distribution \( f(x) \) of true doses for the cohort by adjustment of the observed distribution of estimated doses. In considering analyses of data on a subcohort of the LSS whose selection depends substantially on estimated dose, it would be wrong to use this same approach, based on the observed distribution of estimated doses for the subcohort. The problem is that selection of a subcohort based largely on the \( z \)-values results in substantial change in the error model \( f(z|x) \), and this change is difficult to assess. The error model used in this paper is that which corresponds to the dosimetry system.
per se, applying for all survivors or to a subset selected in some way which does not depend on $z$. The LSS cohort was not selected based on estimated doses, although there may be some insignificant selection related to this in the subcohort for which DS86 dose estimates are currently available.

However, selection based on $z$ does not change the distribution $f(x|z)$. Thus estimates of these distributions made as in this paper, and corresponding values of $\text{Avg}(x|z)$, can be used for analysis of subcohorts such as that for chromosome aberrations or the Adult Health Study.

**APPLICATION TO CANCER DATA**

It was noted above that inspection of Table 2 does not give a clear idea of either the extent of bias removed by using adjusted doses, or the sensitivity of results to assumptions about the magnitude of the dose-estimation errors. Some effects on estimation of linear dose-response models are presented here for these purposes. Pierce and Vaeth\(^4,5\) have presented similar results on effects of adjustment for dose errors on conclusions about the shape of the dose response.

The RERF cancer mortality data have been reanalyzed using the data and models of Preston and Pierce\(^15\). Table 3 shows the resulting increase in their linear risk estimates, for all cancers except leukemia and for leukemia. These pertain to excess relative risk for nonleukemia, and excess absolute risk for leukemia. The risk depends on sex and age-at-exposure, and the summary measure of their paper is used, averaging over sex and three categories of age-at-exposure. Estimates are given for linear risk models fitted to both the 0–6 Gy and 0–4 Gy dose ranges. These two ranges refer to tissue kerma, but the increases in risk estimates are in terms of organ dose, using that to the large intestine for nonleukemia. Preston and Pierce (op cit) gave results for both ranges because of an apparent nonlinear plateau in excess risk above 4 Gy. Here we have the additional motivation of examining how restricting the dose range affects biases due to dose-estimation errors.

Reasons for the greater increase for nonleukemia than leukemia have not been investigated carefully. This may in part be due to greater biases from dose errors in estimating relative risk.

| Range of Analysis: | 0–6 Gy | 0–4 Gy |
|-------------------|--------|--------|
| **Percentage Error (CV)** | **Increase in Risk Estimate** |
| **All Cancer** | 30% | 10.0% | 6.8% |
| Except Leukemia | 35% | 13.3% | 9.0% |
| | 40% | 16.7% | 11.0% |
| **Leukemia** | 30% | 6.1% | 4.3% |
| | 35% | 8.1% | 5.6% |
| | 40% | 10.2% | 7.2% |

Table 3. Increases in linear cancer risk estimates for three assumed levels of error
than absolute risk. This is because in some generality dose errors result in underestimation of the slope, but overestimation of the intercept. However, the size of the unexposed portion of the cohort is very large, making it unlikely that this effect would be so great as seen here. There may also be differences due to leukemia being much more radiosensitive, so that information from lower doses plays a greater role than for nonleukemia.

If dose estimates were reduced by a constant factor, the increase in slope would be approximately \( \frac{z}{\text{Avg}(x|z)} \). This is not the case, but for the nonleukemia data the increases in risk for the 0–6 Gy analysis correspond roughly to ratios \( \frac{z}{\text{Avg}(x|z)} \) in the 2.5–3 Gy range for \( z \). For the 0–4 Gy analysis the increases reflect these ratios in the range just under 2 Gy. This may aid in interpreting results such as given in Table 2.

Restriction to 0–6 Gy, more precisely reduction of estimates above 6 Gy to that level, has been standard practice for many years. the primary motivation for this is the likelihood that estimates above that level have large errors. Although it could be argued that with more formal allowance for dose-estimation errors such an arbitrary practice could be discontinued, it does not seem advisable to do so because of uncertainties in the error model. In the current DS86 cohort there are only about 75 survivors with estimates above 6 Gy. It is becoming increasingly common to base estimation of risks on analyses restricted to a lower range similar to 0–4 Gy. All analyses in the recent BEIR V report[16] are restricted to 0–4 Sv organ dose equivalent.

For the cancer data the standard errors of the parameter estimates relative to the magnitude of the estimates, i.e. the coefficients of variation, are essentially unchanged by the allowance for dose-estimation errors. This reflects the fact discussed above that the additional variation in the data due to dose-estimation errors, beyond ordinary sampling variation, is negligible for that case. For the chromosome data, on the other hand, allowing for dose-estimation errors will result in substantially larger standard errors than those following from a binomial model. However, as discussed earlier, special methods allowing for overdispersion relative to binomial error have been used for some time, and the standard errors under the proposed method will be similar to those given by current methods.

**DISCUSSION**

In spite of the limited information about the actual magnitude of dose-estimation errors, it is better to begin making adjustments under some assumptions than to make none at all. The authors recommend that, until evidence emerges for improved assumptions, the lognormal 35% error model be used.

Use of this adjustment increases cancer risk estimates based on linear analyses on 0–4 Gy kerma by about 5–10%. This is a relatively small change in relation to other uncertainties in interpretations of these data, but it is a good policy to reduce any identifiable biases. The variation in results for linear risk estimation for the range of error models considered here is very small in relation to other uncertainties. Thus it seems unlikely that further information about the magnitude of errors will have substantial effect on this type of analysis.

This is not meant to imply that further work in this area is unimportant. There are numerous
reasons why it is important to learn more about both the true nature of the errors, including their relation to aspects such as survivor shielding situation, and the statistical methods needed to deal with them. Linear risk analyses are only one aspect of interpretation of the data, and results of other analyses may be more sensitive to assumptions and methods. Errors in dose estimates have affects on data interpretation beyond biases in risk estimates and distortion of the shape of dose-response curves. It is hoped that the results thus far will help to focus further work, both on assessing the nature of errors and development of statistical methods, towards the most important and productive directions.

Pierce and Vaeth\(^5\) have analyzed the sensitivity of inference about the shape of the cancer dose-response curves to assumptions about dose-estimation errors. In particular they have indicated effects on conclusions about factors to be used in extrapolation to low doses. These are more sensitive than linear risk estimates to assumptions about the magnitude of the errors.

That dose-estimation errors cause apparent variation in individual sensitivity to radiation is an important issue. For example, Nerishii, et al.\(^6\) show that the linear dose-response for leukemia in the RERF LSS is 2.5 times greater for those reporting severe epilation than for others. Errors in dose estimates result in spurious positive association between radiogenic effects, among those at the same estimated dose, caused by variation in true dose within such a group of survivors. This must of course be accounted for when the aim is investigating possible variation in sensitivity to radiation. Alternatively, if it is assumed that such variation in sensitivity is small, then some assessment of the magnitude of dose-estimation errors can be made in this way. These issues are discussed by Stram and Sposto\(^8\).

There is another interesting way of looking at the adjustments to dose-response analyses discussed in this paper. The dosimetry system estimates \(z\) take no account of the information provided by the survival of the individuals in the study cohort. That is, the estimates depend only on the location and shielding of the survivor, and physical calculations involving radiation transport and related matters. If a model for the probability of surviving as a function of true dose were available, it would be possible to make dose estimates incorporating the information provided by survival. It is not suggested that this be done. The way that the estimated distribution \(f(x)\) of true doses in the surviving cohort is used in this paper essentially incorporates the information provided by survival in a more feasible way.

This alternative view of the problem is raised for two reasons. First, it may reinforce the statistical reasoning that, except for those at very small doses, the true dose is more likely than not to be less than the estimated dose. In addition, there has long been interest in the important question of whether substantial biases may result in drawing inference about cancer risks for a general population from a study population which has been highly selected by surviving a situation with high mortality rates. The above comment makes clear that this issue is not unrelated to errors in dose estimates. Although it is very difficult to actually assess whether the selection bias has important effects, it is believed that progress can be made on more careful formulation of the essence of the problem.

Particularly when considered in a wide sense, the issues involving random errors in dose estimates are very interesting. The importance of the problem goes well beyond questions of bias in linear cancer risk estimates. It is hoped that the discussion here will motivate and facilitate
further progress in understanding the general problem.

ACKNOWLEDGMENTS

The Radiation Effects Research Foundation is equally supported by the Japanese Ministry of Health and the U.S. Department of Energy through the National Academy of Sciences. Much of the work of all of the authors was done while they were employed by the RERF. The first author's work was also supported by grants from the U.S. National Cancer Institute and National Institute of Environmental Health Sciences. The authors are grateful for contributions to this research by Seymour Jablon, Ethel Gilbert, and Daniel Schafer; and thank the Editor of Radiation Research for permission to base parts of this paper on one to appear in that journal.

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