Recent Uses of Biological Data for the Evaluation of A-Bomb Radiation Dosimetry

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Random errors in the DS86 radiation dose estimates used in the analysis of A-bomb survivor data are recognized to have an important impact upon estimates of the risk of late effects such as cancer. Little however is known for certain concerning the distribution of such random errors. This paper gives an overview of recent work at the Radiation Effects Research Foundation (RERF) using multivariate analysis of biological data, including acute effects of radiation exposure, late effects (e.g., leukemia mortality) and stable chromosome aberrations, for the purpose of evaluating the extent of random error in the estimation of individual doses using DS86. The emphasis here is on analyses of apparent association between biological endpoints, in light of a dosimetry error model framework proposed recently by Pierce et al.1,3). Analyses performed to date appear to be consistent with the view that lognormal random dosimetry errors with a standard deviation of 40% or greater of true dose may exist in DS86.

Association between radiogenic outcomes in A-bomb survivors, after adjustment for DS86 estimated dose level, has been detected for such widely varying pairs of outcomes as mutant T-cell frequencies and chromosome aberrations3), epilation and leukemia mortality4), and epilation and chromosome aberrations5). The motivation for examining association between pairs of biological endpoints has usually been to determine the extent to which radiation sensitivity varies between individual survivors. Recognizing, however, that random error in dose estimates results in apparent association between biological outcomes is crucial to interpreting studies, such as these, which use data on multiple biological endpoints. To go one step further, in situations where there is a prior knowledge about the biological plausibility of such associations in outcome data the amount of association between radiogenic outcomes (remaining after adjustment for estimated dose), to the extent that they are greater than that assumed to be reasonable, is an important potential source of information concerning the magnitude of random errors in the DS86 dose estimates.

INTRODUCTION

The use of biological data to assess the degree of radiation exposure for the A-bomb survivors predates the development of physically based radiation dosimetry systems such as the DS86 system currently used by the Radiation Effects Research Foundation (RERF). Work by the Joint Commission, begun in Hiroshima and Nagasaki in the fall of 1945, included direct medical evaluation of acute radiation sickness and radiation injury status, data which is still maintained by RERF. Later data collected by interview on acute radiation sickness such as the occurrence of epilation, bleeding, nausea, and anorexia, was incorporated as a basic component of the
permanent files kept on each of the survivors who were entered into the Life Span Study (LSS) mortality follow-up cohort. These data were obtained over the period from 1950 to 1960, either previous to or concurrent with survivor location and shielding data, which serve as input to the DS86 radiation dosimetry system. At present more than 90% of the LSS cohort has computerized data in the RERF master file on the occurrence of at least one of three acute symptoms collected by interview: epilation, oropharyngeal lesions, and radiation induced bleeding.

That the acute symptoms were viewed early on as crucial in the assessment of degree of radiation exposure may be seen in the way that the four basic subcohorts of the Adult Health Study (AHS), the medical follow-up arm of RERF's research effort, were established. Begun in 1958, the AHS study was divided into proximal, distal, and not-in-city portions. The proximal group, defined as a sample of LSS members within 2 km of the hypocenters in Hiroshima and Nagasaki, was divided into those reporting and those not reporting at least one of the three radiation sickness symptoms coded on the master file. Thus in a sense the use of distance and acute symptoms categories was a crude radiation dosimetry system for the AHS, wherein proximally exposed individuals reporting acute symptoms could be taken as the high exposure group, proximally exposed but no acute symptoms as the medium, and distally exposed the low exposure group. Of course such crude methods were soon supplanted by the use of the early physical dosimetry, predecessors to the T65D and the current DS86 systems.

In recent years, analysis of the acute radiation sickness data began with the extensive evaluation, using the acute effects, of the T65D radiation dosimetry system (and certain modifications of this system) reported by Gilbert and Ohara. This report investigated inhomogeneities in the observed dose-response relationship between each of the three master file encoded acute effects, and estimated radiation dose. Analysis of inhomogeneities in radiation dose response represent one important way in which biological data may be utilized for the evaluation of radiation dose estimates. Despite the fact that the T65D dosimetry system has been replaced by the DS86 system, Gilbert and Ohara's analysis is still relevant, both from a practical and a more philosophical standpoint. Practically, because many of the inhomogeneities in acute effects dose response observable using T65D can still be found under DS86, as demonstrated in the analysis by Stram and Mizuno of severe epilation using both dosimetries. Philosophically, because Gilbert and Ohara identified the important issues in the use of acute effects data for assessing the DS86 dosimetry system used today. Notable among these is the recognition that random errors in physical dose estimates, as well as systematic errors, may be the cause of inhomogeneities of dose-response.

An important step in the biological assessment of radiation exposure was taken in the mid 1960's with the first establishment, in Hiroshima and subsequently Nagasaki, of laboratory facilities for measuring stable chromosome aberrations in circulating lymphocytes, for members of the Adult Health Study. A primary limitation of these data, for the assessment of dose, compared to the physical dosimetry systems, which produce dose estimates for a very large fraction of survivors in the LSS, is the restriction of these new methods to those members of the AHS who were alive at least into the mid 1960's. To characterize the chromosome aberration program at RERF as being solely devoted to biological dosimetry, even within the AHS, is at least partially a misnomer; the assignment of dose estimates entirely from chromosome counts would require;
an a priori knowledge of the dose-response relationship of chromosome aberrations. Such a priori
dose-response information is not available. Rather, given the uniqueness of the A-bomb survivor
cohort, a principal motivation of the chromosome program at RERF is to use the physical
dosimetry in order to estimate a dose-response relationship for chromosome aberration in humans.

Application of other potentially useful biological dosimetry methods are in earlier stages
of utilization at RERF, eg. in vivo mutant T-cell frequency\(^3\) and the frequency of variant
erythrocytes\(^1\)\(^1\). For the above reason, however, it may be safely said that all useful work with
biological assessment of radiation dose for the A-bomb survivors must be in conjunction with,
rather than in lieu of, the physical dosimetry system.

This paper discusses some results of recent analyses which have used biological outcome
variables, including early effects data, late effects such as cancer mortality, and the chromosome
aberration data, on joint analyses to investigate associations between biological outcome variables
which have been shown to be evident in the Hiroshima-Nagasaki data after adjustment for DS86
estimated radiation exposure. One of the most striking findings is the report by Neriishi et al.\(^4\)
that the slope of a model for the dose response of mortality due to leukemia is 2.4 times higher
among subjects reporting severe epilation than those not reporting this degree of epilation. Similar
association have been reported between in vivo mutant t-cell frequencies and chromosome
aberrations in a small number of subjects\(^3\), and between frequency of chromosome aberration
and epilation\(^5\). Such findings have bearing on the radiobiologically important question of the
degree of variation among individuals in their sensitivity to a given dose of radiation. Central
to the proper analysis of data of this type, as discussed in Pierce et al.\(^1\)\(^,\(^2\)) and Neriishi et al.\(^3\),
is a recognition that dosimetry imprecision is at least partially confounded with individual variation
in radiosensitivity as competing explanations for associations between endpoints.

A crucial step enabling sophisticated analysis of associations between biological outcomes
was the proposal by Pierce et al.\(^1\)\(^,\(^3\)) of a class of dosimetry error models for use in epidemiological
analysis using DS86. These models combine a Weibull distribution for true dose with a lognormal
measurement error distribution. In this framework the magnitude of the random errors in dose
estimates are described by a single parameter, \(\sigma\), which is approximately the coefficient of
variation (CV) of estimated dose given true dose. As discussed by Pierce et al.\(^1\) the size of \(\sigma\)
in the dosimetry error model has an important impact on estimates of risk of radiation-caused
excess cancer mortality obtained from the Hiroshima-Nagasaki data set. While Pierce et al.\(^1\)
made a recommendation for choosing a size of \(\sigma\) for routine use (\(\sigma = .35\) \(\text{ie the "35\%" error}
model) this recommendation was only tentative and not based on firm knowledge of the actual
extent of errors in the dosimetry system.

One potential source of data concerning the variability of DS86 dose estimates is an
appropriate biological dosimetry. For example, if the dose-response function for chromosome
aberrations was known a priori, and was known to be subject to only limited variations from
individual to individual, then a direct comparison of estimated DS86 dose to the expected amount
of chromosome aberrations in individuals from the AHS subcohort would give information about
the variability (ie the size of \(\sigma\)) of DS86 dose directly, which could be extrapolated to the doses
for the entire Hiroshima-Nagasaki study population. Such a direct evaluation of DS86 dose is
not possible, however, first because the true chromosome aberration dose response function in
the AHS cohort is unknown, and even more importantly because the extent of individual variation in dose response is also unknown.

The remainder of this paper will examine some recently described indirect methods for evaluating the magnitude of random errors in DS86 dose estimates. As emphasized in the next section of this paper, such measurement error calibration is possible under the assumption that no true association in biological outcome exists, for individuals exposed to a single true dose of radiation. This underlying biological assumption, as it relates to the outcomes considered below, may require careful future examination.

**RADIOSENSITIVITY OR DOSIMETRY ERROR? ASSOCIATIONS BETWEEN OUTCOMES**

Figure 1, from Sposto et al.⁵, gives a graphical depiction of chromosome aberration dose response for 1,028 survivors divided into two groups, those who reported severe epilation (loss of 2/3 of hair on head) and those who reported less severe or no epilation, within 60 days of the time of the bomb. Here chromosome aberration data is summarized for each survivor as the proportion of cultured circulating lymphocytes examined, having at least one stable aberration (out of 100 cells typically). As can be seen in the figure, the apparent dose response for chromosome

![Figure 1](image_url)

**Fig. 1.** Chromosome aberration rates for 1028 A-bomb survivors plotted by estimated DS86 dose. Shown separately are the dose-responses of survivors reporting and not reporting the occurrence of severe epilation.
aberrations among those survivors who reported severe epilation is estimated to be about twice as steep as for the remainder of the population. Neriishi et al. reports a similar finding for leukemia mortality over a follow-up period beginning ten years after the bomb, using excess relative risk regression models. In that study, survivors who reported severe epilation were estimated to have, at any given level of DS86 dose, approximately 2.4 times as great an excess relative risk of dying from radiation-induced leukemia over the follow-up period from 1950–1985, compared to those estimated to have received the same radiation dose but not reporting severe epilation. Both of these associations were strongly statistically significant, and both raise exactly the same question; are survivors who reported severe epilation more radiosensitive than those who did not, since at a given value of DS86 dose, they showed both higher chromosome aberration rates and greater risk of leukemia mortality than those who did not report severe epilation?

This issue of the existence of differential radiation sensitivity between survivors reporting epilation needs to be distinguished from the more general question of whether and to what degree variation in individual radiosensitivity in biological outcomes exists. It may well be that there are unknown or unmeasured factors responsible for variation in individual dose response to a variety of radiogenic outcome variables, although the evidence is incomplete and in some cases conflicting. What is at issue in Figure 1 is whether there exists association between two or more outcomes observed on the same individual, and not just simply whether there is individual variation in one or the other outcome. To date there has been little in vitro evidence of either variation or differences in radiosensitivity in cell types relevant to these three endpoints (epilation, leukemia, and chromosome aberrations), but further work in this area would again appear to be required.

Irrespective of whether association between radiogenic outcomes is biologically plausible, it is crucial to recognize that random dosimetry errors are a major cause of observed associations between outcomes such as that depicted in Figure 1. To see why this is true, consider two individuals with the same estimated dose, one of whom suffered severe epilation, while the other did not. Given that the DS86 dose estimates are subject to considerable imprecision, it is, speaking probabilistically, more likely that the survivor who experienced epilation was also the survivor who experienced the higher true dose and who will therefore have the larger probability of suffering other effects of radiation exposure. The statistical models discussed below for dosimetry error have been used to estimate the level of dosimetry error (value of $\sigma$) which explains the observed association between outcomes as due to the effect of random dose errors alone. These models are presented initially in terms of the analyses given by Neriishi et al. and Sposto et al., who specifically examined severe epilation occurrence and the two other radiation effects, leukemic mortality, and chromosome aberrations. Later, adaptations to other settings will be mentioned.

MODELS FOR ASSOCIATION BETWEEN SEVERE EPILATION AND OTHER RADIATION RELATED EFFECTS

Pierce et al. discuss the selection of two components (herein termed submodels) which in conjunction form a dosimetry error framework which is then recommended for epidemiological
analysis of the Hiroshima and Nagasaki A-bomb survivor data. The model development described here amounts to an addition of a submodel (ie a model for epilation occurrence as a function of true dose) to that framework. Briefly, the two components discussed by Pierce et al. were 1) The marginal distribution, g(x), of true dose, x, in the population, and 2) the measurement error model, f(z|x), describing the probability distribution of estimate dose, z, given true dose x. The form of g(x) suggested by Pierce et al. was Weibull,

\[ g(x) = \theta_1 \theta_2 x^{\theta_2-1} e^{-\theta_2 x^\theta_1} \]

with scale parameter \( \theta_1 \) equal to 0.5 and shape parameter \( \theta_2 \) taken as 2.84 for Hiroshima and 2.33 for Nagasaki. The distribution f(z|x) is taken as lognormal so that log(z) has a gaussian distribution with mean log(x) and standard deviation, \( \sigma \), generally taken in the range from .3 to .4 corresponding to a coefficient of variation of approximately 30–40%. As discussed in more detail in Pierce et al. the analysis of outcome data which has a dose-response function which is linear in true dose, x, can be performed by using the expected value of true dose given estimated dose, \( \text{Avg}(x|z) \), as the dose variable in the regression. This calculation of an expected true dose for use in regression analysis is termed the dose-adjustment procedure, since the value of estimated dose, z, is being adjusted to take account of both the measurement error, f(z|x), and the distribution, g(x), of true dose.

Dose-adjustment can be extended to include covariates, such as severe epilation, the occurrence of which also depends upon true dose. In their analysis of the association between leukemia occurrence and severe epilation, Neriishi et al.4), extended the dose-adjustment procedure to include severe epilation by adding a third submodel, p(e|x), for the occurrence of epilation (denoted herein as \( e = + \) for severe epilation and \( e = - \) for less severe or no epilation) as a function of true dose x.

The model (it’s justification is discussed further below) for epilation used by Neriishi et al.4) was to take

\[
p(e = + |x) = \begin{cases} 
0.01 & 0.01 < x < 0.75 \text{ Sv} \\
0.287x + 0.01 & 0.75 < x < 3.5 \text{ Sv} \\
0.80 & x > 3.5 \text{ Sv} 
\end{cases} \tag{1}
\]

This allowed Neriishi et al.4) to numerically integrate the combined joint distribution of epilation, estimated dose, and true dose

\[ k(e,z,x) = p(e|x)f(z|x)g(x) \]

to calculate the expected value of true dose given both estimated dose and the presence \( (e = +) \) or absence \( (e = -) \) of severe epilation, ie

\[ \text{Avg}(x|z,e) = \int xk(e,z,x) \, dx / \int k(e,z,x) \, dx \]
In order to see the relevance of $\text{Avg}(x|z,e)$ for epidemiological analysis of the association of severe epilation and other late effects, consider Figure 2 which plots (for Hiroshima) $\text{Avg}(x|z,e)$ against $z$ for both $e = +$, and $e = -$, assuming in the measurement error model either 35\% or 50\% errors (i.e. $\sigma = .35$ or .50). For outcomes with a dose response which is strictly linear in true dose Figure 2 illustrates both the cause and degree, and suggests a solution for, the existence of dosimetry-error induced association between epilation and the outcome of interest. If both the epilation model, $p(e|x)$, and the 35\% (or 50\%) dosimetry error model, $f(x|z)$ and $g(x)$, is correct, and making the key biological assumption that there is no true difference in radiosensitivity between those survivors reporting severe epilation and those not, then for such linear outcomes the apparent dose-response for the $e = +$ group will track (i.e. be roughly proportional to) the upper line in Figure 2, while the apparent dose-response for $e = -$ will track the lower line.

Figure 2 also illustrates that a regression analysis of a linear outcome on both estimated DS86 dose and epilation status will give a biased assessment of the true biological effect of epilation as a predictor of the linear outcome. Dosimetry error alone will introduce a separation in the dose-response relationships for the two epilation groups which is in addition to any such effect due to true biological differences between the epilation groups in radiosensitivity. This figure illustrates the general principal that there exists an important confounding in these types of analyses of the A-bomb survivor data, between effects due to dosimetry error and effects due to variations from individual to individual in their radiosensitivity.

![Fig. 2. Plot of $\text{AVG}(X:Z,E = +)$ and $\text{AVG}(X:Z,E = -)$ for 35 and 50\% Error models.](image-url)
Going even further it is evident that the epidemiological data itself can support either one of two approaches. One approach involves making assumptions about the degree of imprecision due to random error in the dosimetry system and then using the data to estimate the true biological association between two endpoints, after taking account of the assumed level of dosimetry imprecision. The other opposite approach involves assuming that the true level of biological association between radiogenic outcomes is known and trying to estimate the level of dosimetry error required to explain the observed association between the pair of outcomes beyond that implied by the biological assumption. In the first approach the goal is to measure biological association, whereas in the second it is to assess the degree of dosimetry error. Although the distinction between the two approaches is mainly a matter of emphasis, it seems evident that an analysis of an association between a single pair of radiogenic outcomes cannot, by itself, untangle the two aspects of the problem.

Assessing biological association between severe epilation and other outcomes

The first approach described above takes an assumed level of dosimetry error, or more precisely, in terms of work done to date, assumes a value for $\sigma$ in the dosimetry error model $f(z|x)$ above and postulates a model for the occurrence of severe epilation. The solution for eliminating dosimetry error induced association between the occurrence of severe epilation and such linear outcomes is to use $\text{Avg}(x|z,e)$ as the dose variable in any regression analysis for which severe epilation is also to be considered as a covariate. If the assumptions used in calculating $\text{Avg}(x|z,e)$ are correct, including the model for epilation occurrence, then for an outcome variable, $y$, with a dose response which is linear in true dose, $x$, regressing $y$ on $\text{Avg}(x|z,e)$ and including epilation status ($e = +$ or $e = -$) as a further covariate in the regression ought to yield consistent estimates of the true effect of $e$ as a modifier of the dose-response of $y$.

| Adjustment for random dose errors |  |  |  |
|----------------------------------|--|--|--|
| none                            |  |  |  |
| Ratio of risk                   |  |  |  |
| 95%CI                            |  |  |  |
| Leukemia (cubic model)          |  |  |  |
| 2.4**                           | 1.2–4.7 | 1.8** | .91–3.4 | 1.6 | .78–3.2 |

sug (p 0.10) * (p 0.05) ** (p 0.005) *** (p 0.001)

95%CI: 95% confidence interval calculated from the ratio in log and its standard error
This approach, using the model for epilation occurrence stated above, is the path taken by Neriishi et al., in their joint analysis of severe epilation and leukemia mortality. Table 1, abstracted from their report, shows the results of estimating a multiplicative epilation effect in the leukemia data for two assumed levels, $\sigma$, of random dosimetry error. The values of $\sigma$ chosen are, as in Figures 2, .35 and .5, which correspond to a coefficient of variation of dose estimates of roughly 35 and 50% respectively. The 35% model is the same dosimetry error model tentatively suggested by Pierce et al.) whereas the 50% error model is used purposely to examine the effect of assuming considerably larger errors than that thought to be reasonable by Pierce et al.1). As discussed in greater length in their report, Neriishi et al.4) find the association between epilation and leukemia to be still marginally significant when an adjustment for the effect of 35% dosimetry errors was performed but found the association no longer to be significant (though the estimate of the association remained positive) when 50% errors in doses were assumed.

Assessing the level of dosimetry error required to explain the association between epilation and chromosome aberrations

The second of the two approaches to these data is exemplified by Sposto et al.'s5) analysis of the apparent association between epilation and chromosome aberrations illustrated in Figure 1. These authors explicitly made the assumption that there is no true biological association between

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Fig. 3. Plot of chi-square test for difference in chromosome aberration dose response between epilation groups, against values of the dose error parameter.
the occurrence of epilation and chromosome aberrations, and attempted to estimate the level of dosimetry error, \( \sigma \), which alone explains the difference in dose-response between the \( e^+ \) and \( e^- \) groups. For the purpose of performing this estimation a one degree of freedom \( \chi^2 \) test of a multiplicative difference between the dose response for the \( e^+ \) and \( e^- \) group was constructed and \( \sigma \) was chosen as the value which set this \( \chi^2 \) test statistic to zero. Figures 3 and 4, also taken from that report, provide a summary of the results. Figure 3 plots the \( \chi^2 \) statistic's value against the assumed value of \( \sigma \) using two somewhat different methods (labeled method 1 and method 2) for performing dose adjustment (the differences in method 1 and method 2 are not discussed here). Figure 4 plots the proportion of cells with chromosome aberrations in the same survivors as in Figure 1 but where estimated dose \( z \) has been replaced with \( \text{Avg}(x|z,e) \) with \( \sigma \) chosen as .45 (45% error model) which was approximately the best fitting value for the level of dosimetry error from Figure 3.

**FURTHER ASPECTS OF THE DOSIMETRY ERROR ANALYSIS**

Despite their somewhat different emphasis, the analyses of leukemia mortality and stable chromosome aberrations give roughly similar results. That is, assumptions of the existence of
random dosimetry error with a coefficient of variation somewhere around 40–50% (σ from .4 to .5) would appear to simultaneously explain the association between either of these endpoints and severe epilation. The statistically astute reader may recognize that the analysis performed by Sposto et al. is a type of instrumental variables or more properly, structural equations, analysis, with the occurrence of epilation being treated as an exogenous variable used for obtaining information about the measurement process. The statistical models being used however lie very far outside the multivariate normal theory setting in which these methods are typically discussed.

Particularly relevant to the differences between this analysis and more standard structural equations approaches are; 1) the Weibull distribution assumed for true dose, 2) the multiplicative measurement error model assumed, 3) the allowance for nonlinearity in the dose-response functions used to model leukemia mortality and chromosome aberrations, and 4) the use of a dichotomous variable, epilation occurrence, rather than a continuous one as the exogenous variable. The last two of these deserve some further comment.

**Nonlinearity in dose-response functions**

Although described above in terms of an outcome variable for which the dose-response, given true dose, is linear, in fact a crucial aspect of the analyses performed by both Neriishi et al. and Sposto et al. is that the models assumed for leukemia occurrence and chromosome aberrations, are nonlinear in dose. Sposto et al. used a linear-quadratic model (LQ) to analyze chromosome aberration dose response while Neriishi et al. described the risk of leukemia mortality with a relative risk model that included polynomial terms up to the cubic (an LQC model). As noted by Pierce et al., an approach to fitting LQ or other polynomial dose-response models, in the presence of dosimetry error, is to perform the regression using as the dose variables in the analysis the average values of the moments of x given z, Avg(x'i|z), i = 1, 2, etc. This approach can be extended to the situation where a covariate such as epilation occurrence is also included as a dependent variable in the analysis so that the values Avg(x i |z,e = +) and Avg(x i |z,e = -) are used in the regression, which can be done numerically using the dosimetry error framework above, given a model for epilation occurrence.

Allowing for a nonlinear dose response in these analyses is important for two reasons. One is that the dose adjustment procedure arising out of the dosimetry error model given above is a nonlinear one, and the strength of the nonlinearity of the adjustment depends on the value assumed for σ. Thus, if at one value assumed for σ, the dose response function of leukemia, for example, is linear in adjusted dose, at other, larger or smaller, values of σ, linearity will no longer hold. Second, epilation occurrence, being more common at higher estimated doses, will tend to be confounded with curvature remaining in the residuals of the regression after fitting a linear dose response function. To see most vividly what can happen, consider an outcome which is independent of epilation occurrence, but for which the dose response contains a strong positive quadratic component. Suppose that a linear model is fit to such data. Forgetting about dose errors at all for the moment, a plot of the residuals of the regression against dose would show many positive values at the upper end of the dose range. Since epilation is also more common at the higher doses, a test for epilation as an explanatory variable to be entered in the analysis might
be very strongly significant. This significant "epilation effect", might go away completely, if the better fitting LQ model was used instead. While this admittedly is a difficult issue to deal with adequately here it seems important enough to mention if only to serve as a caution to future investigators looking at association in biological outcomes in the Hiroshima-Nagasaki data.

**Choice of the Epilation Model**

Central to the results for both the leukemia and chromosome aberration analyses is the choice made of a model for severe epilation occurrence as a function of the exposure \( x \). The model given above, equation (1), which was used in the analysis of leukemia occurrence was designed to broadly reflect the overall results of Stram and Mizuno's\(^8\) analysis of the dose-response of severe epilation using DS86. Nevertheless important issues concerning the epilation model were left unresolved. For example it is known that the epilation data dose response exhibits a number of important inhomogeneities and oddities which are not reflected in Neriishi et al.'s\(^4\) epilation model shown in equation\(^1\). Some of these aspects of the epilation data are described in Stram and Mizuno\(^8\), and still more are described in the earlier report by Gilbert and Ohara\(^7\). Other remaining questions include the general issue of how to estimate epilation response given that doses are observed with error, and lastly what impact errors in the reporting of epilation occurrence, in addition to errors in dose estimation, might have on the results.

The last of these issues is probably the least important, although it is worthwhile to reiterate that the epilation data was collected by interview from 5 to more than 15 years after the bombings and can be expected to have inaccuracies. Nevertheless, for the analyses described above, what is required of the epilation data is less than full accuracy. So long as reports of epilation are assumed to be independent of estimated dose conditional on true dose then errors in epilation reporting are not themselves of primary concern here. Although it is possible to conceive of violations, as discussed briefly by Sposto et al.\(^5\), this assumption seems, relatively speaking, to be a rather modest requirement of the data. It is recommended, however, that future work attempt to judge the importance, in the epilation-based findings discussed here, of the failure of the epilation model given in equation\(^1\) to fully portray the details of epilation dose response.

**DISCUSSION AND FINAL REMARKS**

This paper has described the results of two analyses of biological outcome data which are in agreement that DS86 dose estimates may be subject to random errors with a coefficient of variation of 40% or even greater. Pierce et al.\(^1,2\) indicates that correcting for random errors of this size ( \( \sigma = 0.40 \) ) would raise estimates of excess relative risk of cancer mortality, at a given level of dose, by approximately 10% for leukemia and 17% for all cancers except leukemia, compared to estimates given with no dosimetry error correction. The method by which such an estimate of \( \sigma \) has been arrived at is a fairly complex statistical one, and in addition requires assumptions about individual radiosensitivities which are supported by only a limited amount of scientific evidence from in vitro laboratory work\(^13,14\). Nevertheless, given a wide interest at
RERF and elsewhere in the possibilities of using biological dosimetry for the evaluation of radiation exposure, and given the collection of multiple biological endpoints for A-bomb survivors, the expectation is that work along the lines described here for epilation, leukemia, and chromosome aberrations will continue in the future.

So far the joint analysis of biological outcome data was centered on the division of the LSS population into two halves based upon reports of early epilation occurrence for the purpose of comparing apparent dose response of other radiogenic outcomes by epilation group. The framework discussed above, however, for these epilation-based analyses may be extended to encompass other potential covariates. For example, Hakoda et al.\textsuperscript{2} reported the existence of apparent association between measurements of mutant T-cell frequencies and chromosome aberrations in A-bomb survivors, even after adjustment for level of estimated dose. These authors noted the difficulty that random errors in dosimetry estimates impose in interpreting such findings as due to differences between individuals in radiosensitivity. However they did not attempt to pursue the problem to the degree that either Neriishi et al.\textsuperscript{4} or Sposto et al.\textsuperscript{5} did for leukemia or chromosome aberrations.

A general approach by which this particular example of association between endpoints might be more carefully analyzed would be to add models (presumably LQ in dose) for the occurrence of chromosome aberrations into the Pierce et al.\textsuperscript{1} dosimetry error framework, so that such functionals as

\[
\text{Avg}(x|z, \text{prop of cells with chromosome aberrations})
\]

may be approximated, for a given level of dosimetry error, \(\sigma\), over a range of values for both \(z\) and aberration rate. These calculations would allow the use of polynomial models in dose for the analysis of T-cell mutation frequencies to explicitly account for random error induced association between T-cell mutations and chromosome aberrations. Such an analysis, carried out along the lines suggested above of the analysis of association between epilation and chromosome aberrations to estimate \(\sigma\), might provide one more potential source of information concerning the variability of DS86 dose. The choice in this example, of T-cell mutant frequencies, as another variable of interest, may of course be expanded to the many other biologic endpoints and biologic dosimeters which either are now, or may in the future, part of the A-bomb survivor data.

In fairness the final remarks of this paper ought to include several additional caveats. It has been stressed repeatedly here that using apparent association in biological endpoints for obtaining information about dosimetry error is only possible under assumptions about the biological plausibility of true association in these endpoints. Beyond this point, however, the dosimetry error framework given by Pierce et al.\textsuperscript{1} involves other assumptions which perhaps are even less verifiable than this one. Even taking Pierce et al.'s\textsuperscript{11} Weibull-lognormal model as a reasonable one, several important technical issues have been neglected in work performed to date. For example the variability in calculating such quantities as \(\text{Avg}(x|z)\) or \(\text{Avg}(x|z,e)\) due to statistical uncertainty in estimating either the Weibull parameters in \(g(x)\) or the model used for epilation occurrence has been completely ignored in work to date. It is possible that after taking account of these omissions, confidence intervals for \(\sigma\), given using the chromosome aberration
data, for example, might become considerably wider than those nominally shown in Figure 3.

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REFERENCES

1. Pierce, D.A., Stram, D.O. and Vaeth, M. (1989) Allowing for random errors in radiation exposure estimates for the atomic bomb survivor data. RERF TR 2-89. (in press for Radiat Res)
2. Pierce, D.A., Stram, D.O., Vaeth, M. and Shaheffer (1990). This issue.
3. Hakoda, M., Akiyama, M., Hirai, Y, et al. (1988) In vivo mutant T cell frequency within assigned dose groups in Atomic bomb survivors carrying extreme dose-specific values of chromosome aberration frequency. Mutat. Res. 202: 203-208. [RERF TR 19-88]
4. Neriishi, K., Stram, D.O., Vaeth, M., et al. (1989) The observed relationship between the occurrence of acute radiation sickness and subsequent cancer mortality among A-bomb survivors in Hiroshima and Nagasaki. RERF TR 18-89.
5. Sposto, R., Stram, D.O. and Awa, A.A. (1990) An investigation of random errors in the DS86 dosimetry using data on chromosome aberrations and severe epilation. RERF TR 7-90.
6. Ishida, M. and Beebe, G.W. (1959) Research plan for joint NIH-ABCC study of life-span of A-bomb survivors. ABCC TR 4-59.
7. Gilbert, E.S. and Ohara, J.L. (1984) Analysis of atomic bomb radiation dose estimation at RERF using data on acute radiation symptoms. Radiat. Res. 100: 124-138. [RERF TR 9-83]
8. Stram, D.O. and Mizuno, S. (1989) Analysis of the DS86 atomic bomb radiation dosimetry methods using data on severe epilation. Radiat. Res. 117: 93-113. [RERF TR 1-88]
9. Awa, A.A., Sofuni, T., Honda, T., Itoh, M., Neriishi, S. and Otake, M. (1978) Relationship between radiation dose and chromosome aberrations in Atomic Bomb survivors in Hiroshima and Nagasaki. J. Radiat. Res. 19: 126-140. [RERF TR 12-77]
10. Preston, D.L., McConney, M.E., Awa, A.A., Ohtaki, K., Itoh, M. and Honda, T. (1988) Comparisons of the dose-response relationship for chromosome aberrations frequencies between the T65D and DS86 dosimetries. RERF TR 7-88.
11. Nakamura, M., Akiyama, M., Kyoizumi, S., Langlois, R.G., Bigbee, W.L., Jensen, R.H. and Bean, M.A. (1987) Frequency of somatic cell mutations at the glycoporphin A locus in erythrocytes of atomic bomb survivors. Science 236: 445-448. [RERF TR 1-87]
12. Lewis, P.D. (1987) Variation in individual sensitivity to ionizing radiation. In: Radiation and health: the biological effects of low-level exposure to ionizing radiation. Jones RR and Southwood R eds. John Wiley and Sons, Ltd. p.167-177.
13. Nakamura, N., Kushiro, J., Sposto, R. and Akiyama, M. (1989) Is variation in human radiosensitivity real or artificial? A study by colony formation method using peripheral blood T-lymphocytes. RERF TR 15-89.
14. Kushiro, J., Nakamura, N., Kyoizumi, S., et al. (1989) Absence of correlations between the radiosensitivity of human T-lymphocytes at G0 and skin fibroblasts at log phase from the same individuals. RERF TR 17-89.
15. Fuller, W.A. (1987) Measurement Error Models, New York: Wiley & Sons.
16. Bollen, K.A. (1989) Structural equations with latent variables, New York: Wiley & Sons.