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THE HANFORD STUDY -- A REVIEW OF ITS LIMITATIONS AND CONTROVERSIAL CONCLUSIONS

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ABSTRACT

The Hanford data set has attracted attention primarily because of analyses conducted by Mancuso, Stewart, and Kneale (MSK). These investigators claim that the Hanford data provide evidence that our current estimates of cancer mortality resulting from radiation exposure are too low, and advocate replacing estimates based on populations exposed at relatively high doses (such as the Japanese atomic bomb survivors) with estimates based on the Hanford data. In this paper, it is shown that the only evidence of association of radiation exposure and mortality provided by the Hanford data is a small excess of multiple myeloma, and that this data set is not adequate for reliable risk estimation. It is demonstrated that confidence limits for risk estimates are very wide, and that the data are not adequate to differentiate among models. The more recent MSK analyses, which claim to provide adequate models and risk estimates, are critiqued.

THE HANFORD DATA

The Hanford plant, located in southeastern Washington State, has employed many workers in jobs involving some exposure to radiation. The initial purpose of this plant was the manufacture, chemical separation, and purification of plutonium. In addition research of a diverse nature and, more recently, power generation have been conducted at the facility.

The Hanford data base includes demographic data and employment histories, which have been obtained from employment records, as well as mortality and radiation exposure data. Mortality data, which is obtained primarily from the Social Security Administration, includes date and cause of death, while the exposure data, which is obtained through the use of personal dosimeters, consists of annual estimates of external exposure to radiation. A more detailed description of the Hanford data base is found in Gilbert and Marks (1979).

Exposures of Hanford workers have been deliberately limited as a protection to the worker with the result that exposures are far lower than those received by the Japanese atomic bomb survivors and other populations currently providing the data that form the basis for risk estimation. The fact that exposures are low can be regarded as a strength in that exposures are at the levels of actual interest, thus providing a direct method of assessing risks from low level exposure to radiation for medical, occupational or other reasons. However, the limited exposure is also a weakness in that it severely limits the potential of the study. In fact, if current estimates of radiation effects are correct, it is highly unlikely that statistically detectable effects can be identified in a population such as Hanford, and such data are not adequate for reliable estimation of radiation effects. A principal rationale for studying groups that have been exposed occupationally and environmentally is the investigation of the hypothesis that effects might be many times larger than current estimates would suggest. That is, such studies serve as a rough check on estimates and models that have been developed from other sources.

The Hanford data has been analyzed by several investigators including Mancuso et al. (1978), Hutchison et al. (1979) and Darby and Reissland (1981). In this section we describe analyses that have been conducted at Pacific Northwest Laboratory (PNL). Additional detail regarding these analyses is given in Gilbert and Marks (1979) and Gilbert (1984*).

METHODS FOR ANALYZING THE HANFORD DATA

The procedures that have been used for PNL analyses of the Hanford data can be derived from the proportional hazards model of Cox (1972). Initially PNL analyses emphasized tests of the null hypothesis of no association of radiation exposure and mortality from several different causes, but more recently estimates and confidence limits have also been obtained.

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*"How Much Can Be Learned From Populations Exposed to Low Levels of Radiation?" To be published in The Statistician 34 (1985).

Both test and estimation procedures are based on comparing doses of workers dying from the cause of interest to the doses of comparable workers alive, and therefore, at risk of dying at that time. "Comparable" is used loosely to mean similar with respect to age, sex, calendar year and other specified variables. For example, suppose that worker i dies at age 56 in 1967 with cumulative dose z_{i56}. We might then compare z_{i56} with the cumulative doses (up to age 56) for workers who are alive and at risk of dying at age 56 in calendar years 1965-1969.

We will call the set of doses of those workers alive at age 56 in a similar calendar year period the risk set for worker i and denote this set by R_i. We will denote the mean of the doses in R_i by μ_i and the variance by σ_i^2. A test of the null hypothesis can be obtained by comparing the observed and expected scores defined, respectively, by $Z = \sum_{i=1}^{n} z_i$ and $MU = \sum_{i=1}^{n} \mu_i$ where i indexes deaths from a particular cause and z_i is a measure of dose for worker i at the time or age of death t_i. Asymptotically, the statistic $Y = (Z - MU)/[\sum_{i=1}^{n} \sigma_i^2]^{1/2}$ will have a standard normal distribution.

The above approach can be regarded as a simple application of Cox's regression model in which the time variable is age, grouped in single year intervals (calendar year or follow-up time could also play this role), in which there is a single time-dependent regression variable, dose, and in which other variables such as calendar year are controlled through stratification. A variety of dose-response relationships can be investigated by varying the definition of dose. For example, to account for a latent period, exposures can be lagged by various intervals; that is, only exposure accumulated up to some specified period prior to t_i would be included both for the worker who dies and for those in his risk set R_i. Doses can also be replaced with scores for exposure categories resulting in analyses similar to those described by Mantel and Haenszel (1958) and by Mantel (1963). A computer program, MOX (Mortality and Occupational eXposure) (Buchanan and Gilbert 1984), is available for performing the needed computations for testing the null hypothesis for several different diseases.

Procedures for obtaining estimates and confidence limits require specification of the hazard or risk function. The model originally described by Cox (1972) was the "log-linear" model, in which the form of the dose response function is exponential, or of the form $\lambda_{kt} \exp(\beta z_{kt})$, where λ_{kt} is the spontaneous hazard for worker k at time t and z_{kt} is the cumulative dose for worker k at time t. However, risks due to radiation are usually expressed in terms of linear (or linear-quadratic) models, and such models cannot be expressed in the exponential form.

A linear form of the proportional hazards model is available and can be written $\lambda_{kt}(1 + \beta z_{kt})$. The partial log likelihood function based on this model can be written as indicated below:

$$\log L(\beta) = \sum_{i=1}^{n} \log \frac{(1 + \beta z_i)}{(1 + \beta \mu_i)}$$

where i indexes deaths and z_i and μ_i are defined as previously. This likelihood is a relatively simple function based only on the observed and expected doses associated with the workers who die of the cause of interest. Maximizing this likelihood thus requires iterating only on a relatively small set of data rather than on the several hundred thousand person-years in the full data set.

Confidence limits based on the likelihood ratio statistic can be obtained by making use of the fact that under the hypothesis that $\beta = \beta_0$, $-2 \log L(\beta_0)/L(\hat{\beta})$ will be asymptotically distributed as chi-square with one degree of freedom. This statistic tends to approach its asymptotic distribution more rapidly than the maximum likelihood estimate $\hat{\beta}$ and thus should provide more accurate confidence limits than the more direct approach using a normal approximation to $\hat{\beta}$. Because of the use of a linear model and the very skewed exposure distribution, the distribution of $\hat{\beta}$ can be expected to be quite skewed. By setting $\beta_0 = 0$, the likelihood ratio statistic can also be used as an alternative to the score statistic Y for assessing the p-values in tests of the null hypothesis of no effect.

RESULTS OF PNL ANALYSES OF THE HANFORD DATA

Until recently, PNL analyses have been aimed primarily at testing for associations of radiation exposure and and mortality from several causes. Results of these analyses have been described in detail in Gilbert and Marks (1979) and Tolley et al. (1983). Here it is noted only that of 17 cancer types tested, only multiple myeloma shows evidence of a significant correlation with radiation exposure. This correlation results from three deaths with relatively large exposures. Since the possibility that the correlation is a false positive finding cannot be ruled out, the appropriate interpretation of the multiple myeloma finding remains uncertain at this time.

Because of the limited magnitude of the exposures received by Hanford workers, estimates based on this data set are not likely to be very meaningful. However, confidence limits provide a useful way of quantifying the uncertainty in this data set. For example, it is possible for the Hanford data to show no evidence of positive correlations of radiation and various cancer types, yet be consistent with effects several times currently accepted estimates; large upper confidence limits will demonstrate this. On the other hand, claims are sometimes made that effects are magnitudes higher than standard estimates would indicate. Upper confidence limits that are less than such extreme claims serve to demonstrate that the Hanford data are inconsistent with such extreme claims.

In Table 1, estimates and 95% confidence limits are presented for several cancer types. With the exception of the estimate for leukemia, the study population upon which these estimates are based consists of 13,632 monitored male workers with at least three dosimeter readings who survived at least 10 years following their initial employment date. The analyses include deaths occurring over the period January 1, 1955 through December 31, 1978. The basic time variable is age (grouped in single year intervals) and the analyses are stratified by calendar year (five-year intervals except for the period 1975-1978 for which single year intervals are used). Exposures have been lagged for 10 years since this is thought to be the minimal latent period for most cancer types other than leukemia. The estimate for leukemia is based on

TABLE 1. Risk estimates and 95% confidence limits for several cancer types.

Cancer Type	Estimate ($\hat{\beta}$)	95% Confidence Limits	Number of Deaths
Leukemia[a] (205-7)	-3.3% per rem	(Negative, 8.7% per rem)	12
All M.N. except[b] leukemia, bone, skin, prostate	-0.0% per rem	(Negative, 3.0% per rem)	433
M.N. of digestive system (150-159)	-0.5% per rem	(Negative, 5.3% per rem)	147
M.N. of stomach (151)	5.3% per rem	(Negative, 37% per rem)	25
M.N. of colon (153)	-7.8% per rem	(Negative, 0.5% per rem)	50
M.N. of pancreas (157)	3.5% per rem	(Negative, 28% per rem)	35
M.N. of lung (162)	0.2% pre rem	(Negative, 6.1% per rem)	153
M.N. of lymphatic and hematopoietic tissue except leukemia (200-202, 209)	4.0% per rem	(Negative, 25% per rem)	38
Multiple Myeloma (203)	96% per rem	(6.4% per rem, ∞)	8

[a]Exposures lagged for two years.

[b]For all cancer types other than leukemia, exposures are lagged for 10 years.

a lag of two years, includes deaths occurring over the period January 1, 1947 through December 31, 1978, and the study population includes monitored male workers with at least three dosimeter readings who survived at least 2 years. Because the estimates are based on a model in which the radiation risk is assumed to be proportional to spontaneous risk, these estimates are expressed as a per cent increase per rem.

The estimate for leukemia is negative, but the upper 95% confidence limit of 8.7% is several times standard estimates. Documents such as BEIR III (1980) do not usually present estimates in this form, but it is possible to determine that the BEIR III linear estimate for leukemia is about 2 to 3% per rem. Thus the upper confidence limit for leukemia is approximately 3 or 4 times the BEIR III linear estimate. The other cancer grouping for which BEIR III presents lifetime risk estimates is all cancer except leukemia, bone, prostate and skin, and here it can be determined that the BEIR III linear estimate is

approximately 0.3% per rem. The estimate for this cancer grouping based on the Hanford data is negative with an upper 95% confidence limit of 3.0%, 10 times the BEIR III estimate.

Estimates for other cancer types are also presented in Table 1 including an estimate for multiple myeloma, the one cancer type showing evidence of a significant correlation with radiation among Hanford workers. The estimate for multiple myeloma is 96% per rem, with an infinite upper 95% confidence limit (the log likelihood function approaches an asymptote). Even the lower confidence limit of 6.4% per rem is larger than the standard linear estimate for leukemia, the cause of death that has been most strongly linked with radiation in other studies. The large estimate and large lower limit reflect in part the fact that this cause of death was selected as the cancer type showing the strongest correlation in the Hanford data. If, for example, one accounted for the fact that 17 cancer types were being considered by calculating a $1 - 0.05/17 = 0.997$ level confidence interval, the lower limit would be negative. Also the normal approximation may not be entirely adequate for obtaining confidence limits for an effect that results from three deaths with relatively large doses.

The analyses described above demonstrate that estimates based on the Hanford data are very unstable. Additional analyses, which are not presented here, indicate that such estimates may also be highly dependent on the model upon which the estimates are based. Furthermore, we cannot hope to address such issues as the shape of the dose-response function, the effect of variables such as age at exposure, or the manner in which radiation risks are related to spontaneous risks. Thus we must continue to place a strong degree of reliance on estimates and models derived from populations exposed at relatively high levels. However, data on populations exposed at low levels can serve as a valuable check on such estimates and models.

RECENT ANALYSES BY MANCUSO, STEWART, AND KNEALE (MSK)

Early analyses of the Hanford data by Mancuso, Stewart, and Kneale (1977) resulted in claims that Hanford workers were experiencing cancer risks due to

radiation that were far greater than would be predicted based on estimates such as found in BEIR III (1980). These analyses have been criticized by many scientists including Hutchison et al. (1979), Anderson (1978), Reissland (1978) and Gilbert and Marks (1979). Several problems with the early Mancuso, Stewart, and Kneale (MSK) analyses have been identified. Analyses of the Hanford data by other investigators (Hutchison et al. 1979, Gilbert and Marks 1979, and Darby and Reissland 1981) have failed to confirm the conclusions of MSK.

In the more recent MSK analyses, which are described in Kneale et al. (1981, 1984), the methodology has been revised considerably. Although these recent analyses avoid most of the problems for which the early papers were criticized, a number a new problems have been introduced. These recent analyses have not attracted the attention of the earlier ones, but risk estimates based on the 1981 paper have been used in workman's compensation hearings. Although there is not space here for a complete critique of these analyses, an attempt is made below to describe some of the difficulties.

We will start with a discussion of Kneale et al. (1981), since this is the paper upon which the estimates used in recent hearings have been based. The analyses in this paper are based on the Cox model with initial efforts directed toward testing the null hypothesis of no effect. Conclusions based on these analyses differ from our own (which are also based on the Cox model) primarily because of differences in the cancer categories chosen for analysis, and differences in the control variables included.

The only disease groupings selected for analysis are all causes of death combined, a group of cancers identified as "radiosensitive" cancers (pharynx, most digestive cancers, breast, lung, thyroid, lymphatic and hematopoietic), and a group including all remaining cancer types (which will be referred to here as "non-radiosensitive" cancers). MSK claim that this grouping of cancers was obtained independently of any analyses of the Hanford data since it is similar to that found in ICRP 14 (1969). However, many of the cancers that are excluded from the "radiosensitive" group are those that show negative associations with radiation exposure in the Hanford population. Thus analyses based on the "radiosensitive" group show stronger evidence of association with

radiation exposure and also lead to higher estimates than would an analysis based on all cancers.

Although the group of cancers chosen does not seem entirely unreasonable, it is not one that would be universally accepted by all scientists as appropriate. Also since MSK had analyzed the Hanford data before arriving at this choice, the possibility that results of these early analyses may have subtly influenced this choice cannot be ruled out. Finally, Darby, Nakashima, and Kato (1984) have used data on the Japanese A-bomb survivors to investigate whether the "radiosensitive" cancers showed stronger evidence of association with radiation exposure than the "non-radiosensitive" cancers. They found that the relative risk estimate based on the "non-radiosensitive" cancers was actually slightly higher (although not significantly so) than the estimate based on the "radiosensitive" cancers.

We turn now to a discussion of the control variables used in the recent MSK analyses. The control variables used in the initial analyses presented in Kneale et al. (1981) are a group of variables described as "obvious factors", and which include sex, hire age, hire date, and duration of employment, with follow-up time serving as the time variable. No evidence of a significant positive correlation of radiation exposure and death from the "radiosensitive" cancers was identified, but a significant negative correlation was identified for all causes of death combined. Based on this negative correlation, MSK argue that there is evidence of selective bias in the Hanford population, and that it is therefore necessary to introduce an additional control variable to eliminate this bias.

Their choice for this task is the level of internal monitoring. In addition to being monitored for external radiation exposure, Hanford workers are also monitored for internal exposure through urinalysis (bioassay) and whole body counts. MSK define four levels of monitoring for internal depositions as follows: 1) no record of bioassays or whole body counts, 2) records of these tests but all with negative findings, 3) no record of whole body counts or internal deposition but at least one of the bioassays recorded some radioactivity (positive bioassays), and 4) either definite

evidence of internal deposition or a combination of positive bioassays and whole body counts.

There are several points to be made with regard to the use of this variable. First, there is always the possibility of bias in an epidemiological study, and the general idea of trying to minimize such bias is a laudable one. However, it does not follow, that just because the inclusion of a particular control variable results in a flat dose response curve for all causes of death combined, it is therefore appropriate to include the variable. (One could for example control for survival itself and achieve an absolutely flat response curve.) A part of the explanation for the negative correlation observed in the Hanford data is that workers who die will frequently be ill for some period preceding their deaths, and thus will not be reporting to work and having their dosimeters read. We have found that the relatively straightforward procedure of lagging exposures for ten years greatly reduces the negative correlation observed for all causes of death. Also the use of age and calendar year as control variables (as well as sex and length of employment in analyses including females and short term workers) seem to result in less negative correlation than the use of the "obvious" factors identified by MSK.

Perhaps the most important point with regard to the use of the bioassay variable is that it is used inappropriately in that workers are classified as being in their final category throughout the follow-up period. It is evident that when workers initiate employment at Hanford, they will be in category 1 (never bioassayed). After some period of time, they may progress to category 2 (bioassayed but with no positive results), and so forth. In a correct application of the Cox model, they should not be considered to be in the higher level categories until they actually get there. This incorrect application by MSK leads to an artificial bias toward a positive correlation of radiation exposure and mortality.

MSK justify classifying workers according to the highest level of internal monitoring throughout the analysis by stating that "...although a worker might take some time to reach this level, he could easily be doing dangerous work for several years before personally reaching the level for the job" (Kneale et al. 1981). The problem with this argument is that workers who

die relatively early in their follow-up will never have the opportunity to be appropriately classified, and this is where the bias comes in. Suppose for the moment we accept the idea that at least for workers who stay at Hanford long enough, the final bioassay state is an appropriate measure of the "dangerousness" of their work. Also, for simplicity, suppose that there are two types of workers, those doing "dangerous" work and destinied for the higher bioassay levels (Group I), and those not doing "dangerous" work and who will never attain the higher bioassay levels (Group II). Because potential for internal exposure is correlated with external exposure, workers in Group I will tend to have higher levels of external exposure than those in Group II. Bias results because workers in Group I who die early are classified according to the low bioassay categories associated with Group II, and thus their relatively high external doses are inappropriately compared with the lower doses in Group II, resulting in a spurious positive correlation. This artifact explains at least in part why including control for level of internal monitoring removes the negative correlation initially observed for all causes of death combined, and pushes the correlation for "radiosensitive" cancers in the positive direction. In an analysis presented by MSK in which workers are allowed to progress through the four bioassay levels as they are followed through time, the negative correlation for all causes was not removed.

To summarize, MSK obtain a significant correlation of radiation exposure and cancer mortality only be restricting the analysis to "radiosensitive" cancers and by including the final level of internal monitoring as a control variable. Once MSK have obtained significant results, they then go on to fit a model upon which risk estimates can be based. They determine that the shape of the dose response function is non-linear and is best described by the square root function. It is claimed that linearity can be rejected. In PNL attempts to investigate the shape of the dose response function, we have found that linear and square root functions were basically indistinguishable although the square root function did fit slightly better than the linear one. MSK estimate that the doubling dose is 15 rad, or that the dose response function is of the form $\lambda(1 + \sqrt{z/15})$ where λ is the spontaneous risk. This estimate of 15 rad was obtained from an analysis of "radiosensitive" cancers

with control for the final internal monitoring level so that biases resulting from these choices will affect the estimate obtained.

MSK also estimate parameters describing the latency relationship and the effect of age at exposure. We will not comment on the latency parameter since it is not that unreasonable (although the Hanford data is hardly strong enough to effectively investigate latency), but we will comment on the results for age exposure. In the model determined by MSK, the relative risk of a worker with a given exposure is to be calculated by multiplying each annual radiation exposure by an exponential function of the age at which the exposure occurs. According to this model, an exposure received at age 60 is estimated to be about 12 times as effective at producing cancer as an exposure received at age 40, and nearly 150 times as effective as an exposure received at age 20.

First, we note that the age at exposure effect determined by MSK contradicts findings based on the Japanese A-bomb survivors (Kato and Schull 1982) and other populations (Boice et al. 1977) that suggest that relative risks decrease rather than increase with increasing age at exposure. Second, it is noted that the application of the age at exposure factor in workman's compensation hearings involving workers exposed relatively late in life can result in very large risk estimates. Finally, the main reason that MSK obtain their result for age at exposure is that analyses are controlled for age only in fairly broad categories (<25, 25-34, 35-34, 35-44, 45-54, and 55+). Spontaneous rates for cancer mortality increase markedly with age, and to a large extent MSK are simply picking up this increase within the broad ten-year intervals, and calling it an effect of age at exposure.

Even if none of the specific problems discussed above were present, there would be tremendous statistical uncertainty in risk estimates based on the Hanford data. In the first part of this paper, it was demonstrated that even under the assumption of a fairly simple model with only one parameter to be estimated, confidence limits were very broad. In the MSK model, several parameters are estimated. It is difficult to assess the full uncertainty resulting from simultaneous estimation of the parameters defined by MSK, but it is clear that the risk estimates obtained would have extremely large confidence regions. In summary, risk estimates based exclusively on the

Hanford data are far too unreliable to provide an adequate basis for setting radiation protection standards and for estimating the "probability of causation" in court cases involving persons exposed to radiation. At most the role of the Hanford data must be to supplement information obtained through extrapolation from populations exposed at high levels.

Early this year, Kneale et al. (1984) updated their analyses of the Hanford data to include recent deaths, and introduced a new job hazard variable. These recent papers have been critiqued by Gilbert and Petersen (1985*). Here we note only that it is evident from some of the findings presented in this most recent analysis that the updating has substantially reduced the correlation of radiation exposure and mortality from "radiosensitive" cancers. No estimates are presented in this recent analysis, but it is clear that they would be quite different from those presented in the 1981 paper.

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