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An Overview of the Hanford Controversy

An Assessment of Health Studies of Hanford Workers

by

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Occupational Medicine:
State of the Art Review

The Nuclear Energy Industry

Introduction

As early as 1946 the US government decided to outlaw private possession of nuclear materials and thus put research and development of nuclear power beyond the reach of industrialists who were unable to conform with the safety regulations of a new agency - i.e., the Atomic Energy Commission, which was made responsible for all radiation protection rules and their implementation. This legislation created both an immediate need - for monitoring of radioactivity levels in all U.S. nuclear facilities - and a deferred need - for eventual assessment of the success of this monitoring in preventing radiogenic cancers.

In practice, all AEC regulations relating to permitted doses and monitoring procedures were channelled through an independent 'National Council on Radiation Protection' whose original recommendations came from a committee mainly concerned (in the 1930's) with the safe use of x-rays and radium in hospitals. These early guidelines of great use to the Manhattan Project in World War II and were later modified by NCRP to conform with safety recommendations of an International Commission on Radiological Protection. Several members of this Commission were also members of NCRP. Therefore, in practice, there was little difference between ICRP recommendations and AEC regulations.

The AEC originally accepted 36.5 rem per year (or the equivalent of 0.1 rem per diem) as an upper limit of dose rate for occupational exposures. But later decided to recognise two levels of "tolerance doses", namely, 0.3 rem per week for workers under 45 years and 0.6 rem per week for older workers. Meanwhile, ICRP had officially accepted the linear hypothesis with its assumption of no safe exposure. Therefore, in 1956,

the term 'tolerance dose' was dropped in favour of 'maximal permissible level of exposure'. The latter was loosely defined as the amount of radiation which would not be expected to cause appreciable bodily harm at any time after exposure. For external penetrating radiation the MPL recommended by ICRP was originally 7 rem per annum, but this was later changed to 5 rem (1960), and 2 rem (1990).

This progressive lowering of permitted doses was largely the result of geneticists discovering that even a minute dose of radiation may cause irreversible damage to germ cells. But it was also the result of physicians gradually realizing the disastrous consequences of allowing young women to lick radium contaminated paint brushes. The tragic experiences of these pre-war luminizers made for easy acceptance of extreme safety precautions during World War II. But when it became evident that a follow-up of A-bomb survivors was not finding any evidence of harmful effects at low dose levels, AEC contractors began to press for some relaxation of the stricter rules. This pressure was strongly resisted. However, in 1964, the AEC did agree to sponsor "a study of the lifetime health and mortality experiences of all employees of AEC contractors". They put in charge of this study a physician (Thomas Mancuso) who had recently shown how the US Social Security System could be used to identify the dates and causes of death of all insured workers. This was an important innovation since intervals between cancer induction and diagnosis may exceed 10 or even 30 years.

First Phase of the Mancuso Study

As director of the AEC project, Mancuso was at liberty to include any or all the post-war offshoots of the Manhattan Project. His master plan

included workers from Oak Ridge, Los Alamos and Hanford. But it soon became apparent that his attempts to link radiation exposures to subsequent events were proving more successful at Hanford than elsewhere.

The main activity at Hanford was the production of weapons grade plutonium. Large scale manufacture of this nuclide began in 1944 and, by 1964 more than 20,000 men had worked for several months or years on "reprocessing operations" or work which required constant monitoring of external gamma radiation (by film badges) and periodic tests for internal depositions of radioactive substances (by urine examination and other procedures which were known collectively as bioassay tests). Over 6,000 of these men were recruited in 1943 or 1944, and the Mancuso method of tracing dates and causes of death (by linking Social Security Death Benefit Claims with state death registrations) was operating smoothly. Therefore, it was possible that the experiences of Hanford workers would reveal any harmful effects of the 'permitted' exposures.

Essential data for this test included the following records from each and every worker: sex and date of birth, dates of entering and leaving the industry, and specifications of all intervening occupations, radiation exposures and bioassay tests. These records were readily available for Hanford workers and, by 1972, Mancuso had traced all the 1944-1969 SSDB claims and retrieved most of the death certificates.

Even before these early deaths had been included in any tests of radiation effects, it was obvious that the mean cumulative dose of external penetrating radiation was appreciably lower for dead than live workers. This was welcome news for the nuclear industry, but Mancuso refused to publish at this stage on the grounds that "*any analysis which did not meet the number of years required to induce the occupational cancer would lead*

to false negative findings that would be misleading and could be misused"(1).

Two years later Mancuso was about to embark on an analysis of 1944-72 deaths when Samuel Milham, who was conducting an occupational mortality study on behalf of the Washington State Health Department, reported the following findings direct to AEC: in a sample of 842 deaths of Hanford workers registered in three nearby counties there were more than the expected number of cancer deaths (i.e. 173 instead of 148) and considerably more than the expected number for deaths before 65 years of age (i.e. 118 instead of 93)(2).

The official who conveyed this news to Mancuso had prepared a press release which implied that the AEC project was in a position to refute the Milham conclusion that "*an occupational hazard exists for Hanford employees*". When asked to ratify this statement Dr. Mancuso refused saying that he could not legitimately make any statement either way until he had completed his own analysis. This action was naturally displeasing to AEC and a few months later Mancuso was told that they would not be renewing his research contract. Mancuso might have resigned there and then, but his contract still had two years to run, and he had just asked two epidemiologists from Britain (Stewart and Kneale) to help with his analysis of Hanford data.

This invitation was a direct consequence of Stewart being a member of Mancuso's steering committee. In this capacity she was sent a departmental report written in response to the Milham analysis. The author of this report, Barkov Sanders, had confirmed the Milham finding - of an unusually high proportion of cancer deaths - in a much larger sample of Hanford workers, but he insisted that radiation was unlikely to be the cause of the

extra deaths. Since no alternative explanation was offered Dr. Mancuso had invited comments from his steering committee.

The thrust of Sander's argument was that no harmful effects could be imputed to the radiation exposures since average annual doses were consistently higher for live than dead workers. His report was eventually published[3] but not before Mancuso had received the following commentary from Stewart and Kneale: the differences between the radiation doses of the live and dead workers are too consistent to be chance findings and too great to be a "hormesis" effect of the radiation. Furthermore, as between the cancer and non-cancer deaths, there are differences which are suggestive of harmful effects of the radiation. For example, from 1965 to 1972 there is only one year when the mean cumulative dose is not higher for the cancer than the non-cancer deaths. Therefore, in spite of the much bigger difference between live and dead workers, it is not possible to exclude a cancer effect of the radiation. On receipt of this commentary Dr. Mancuso promptly asked the authors "to come and take a closer look at the data".

Second Phase of the Mancuso Study

The first analysis of Hanford data by Mancuso, Stewart and Kneale (MSK) was mainly concerned with 2184 men whose deaths had followed 'positive' monitoring for external radiation[4]. For these 'exposed' workers there were 442 cancer deaths with a mean dose of 2.10 rem, and 1742 non-cancer deaths with a mean dose of 1.62 rem. Likewise for 112 exposed females there was a higher mean dose for 38 cancer deaths (1.33 rem) than for 74 deaths from other causes (0.68 rem). Since these differences were suggestive of a cancer effect of the radiation, they were followed by a

more detailed study of mean cumulative doses. Accordingly to this 'Comparative Mean Dose' or CMD analysis, the Sander's classification of radiation doses (by calendar years) was less informative than a classification which measured time either backwards from actual death or forwards from actual birth. Thus a grouping by 'pre-death intervals' showed that differences between cases and controls were largely the result of radiation received 10 or more years before death; and a grouping by 'exposure age' showed that they were largely the result of exposures after 40 years of age.

Division of the male deaths into 27 diagnostic groups produced 13 groups with more than 20 cases (table 1). In this series there were 7 cancer variants with mean cumulative doses ranging from 1.35 rem(other and unspecified sites) to 3.99 rem (pancreas), and 6 groups of non-cancer deaths with mean cumulative doses ranging from 1.33 rem (respiratory diseases) to 1.90 rem (digestive diseases). But much the highest mean dose (10.66 rem) was recorded by 8 men whose deaths were ascribed to myeloma, or a cancer which originates in plasma cells of red marrow (table 1).

These findings were indicative of some cancer effects of the radiation. Therefore, an attempt was made to estimate a) the proportion of extra 'radiogenic' cancers and b) the radiation dose needed to double the normal cancer risk. The risk model for these calculations made the usual assumption - of a constant or linear relationship between cancer risk and radiation dose - and had the following results: a) between 6 and 7 per cent of the cancer deaths were probably a direct result of the radiation exposures; b) under certain conditions 12 rem might be sufficient to double the normal cancer risk; c) the cancer risk was positively correlated with exposure age (and was greater for myeloma, pancreas and lung than for other neoplasms) and d) intervals between induction and death usually exceeded 10 years.

These findings were published in 1977 and were promptly refuted by all advisers to the agency which had replaced AEC (US Department of Energy or DOE). These experts dismissed the CMD analysis as useless and insisted that Mancuso was doing a great disservice to radiation protection by grossly exaggerating the cancer risks of nuclear workers. The National Radiological Protection Board of Britain, in an "An Assessment of the Mancuso Study", referenced all the criticisms and claimed that "*there is wide agreement that the Hanford study, as presented by MSK, does not represent a valid statistical interpretation of the actual data*"[5]. This report assumed (wrongly) that the only important finding of MSK was a higher proportion of exposed workers among cancer than non-cancer deaths, and concluded that "*MSK is basically a proportional mortality study which has the disadvantage that a decrease in one cause of death produces an apparent increase in another*".

Meanwhile, DOE had appointed Marks and Gilbert as principal investigator and chief scientist of the Hanford project, and sent samples of Hanford data to the National Cancer Institute and elsewhere for what was later described as "a federally sponsored re-analysis of Hanford data". From Marks and Gilbert came two analyses[6,7] which showed, among other things, that "*a statistically significant [dose] trend was obtained for multiple myeloma and carcinoma of the pancreas*"[6]. Even so, it was concluded that "*in view of the absence of such a correlation for diseases more commonly associated with radiation such as myeloid leukaemia, as well as the small number of deaths in the higher exposure group, the results cannot be considered definitive*"[6]. This opinion was largely the result of comparing the Hanford cohort with national statistics (standardized mortality ratio or SMR analysis) and finding a "*substantial 'healthy worker*

effect". Thus, the SMR for all causes of death was 75 and for all cancer deaths it was 85.

The data tape sent to NCI gave Hutchison *et al* an opportunity to compare the MSK findings with an analysis which computed (for all deaths and several diagnostic subgroups) ratios of observed to expected deaths for each dose level, and then used a standard trend statistic (based on the ratios for all deaths) to discover whether for any cause of death there were dose trends which differed significantly from the standard trend[8]. According to this analysis there was a) evidence of a radiation effect for myeloma and pancreatic cancer (but not for lung cancer) and b) evidence that these associations were strengthened by restricting the analysis to radiation received more than 10 years before death (so called "dose lagging"). Even so, Hutchison *et al* decided that "*the conclusion of Mancuso* et al *with regard to variations in sensitivity to radiation by age at exposure appears was untenable*" - giving as the reason that "*radiobiologic considerations, including the results of other studies, suggest that the excess of proportional mortality at doses above 10 rem for cancer of pancreas and multiple myeloma is likely to be explained in terms of dose rather than in terms of radiation*". They also concluded that "*a cohort analysis of the Hanford data will permit better understanding of the experience than the present proportional mortality analyses*".

One of the Hanford data tapes was sent to the NRPB in Britain where it was examined by Darby and Reissland who claimed that their method "*presents a more standard analysis of these data in which the observed death rates are examined for trends with increasing radiation dose, and also the total numbers of observed deaths are compared with those expected from United States national mortality data*"[9]. This analysis is chiefly remarkable

for the number of times that a summary dose trend statistic had a negative value. Thus, with doses lagged for 10 years there were 59 tests of dose trends for various causes of death, and with doses lagged for 5 years there were 64 tests. In the first series 85% of the trend statistics had negative values and in the second series 89%. These results evoked the following comments: first, "*there is some evidence of a deficit in the number of deaths from all causes in the high dose groups, particularly when the more recent doses are considered*", and second, "*a tendency towards a negative trend with dose is also apparent in deaths due to solid tumours whether or not those associated with smoking are excluded*".

In spite of the Darby and Reissland analysis revealing so much in the way of negative dose trends there was a positive dose trend for a group consisting of three types of cancer, i.e., myeloma, pancreatic cancer and renal neoplasms. With doses lagged for 10 years this group accounted for 5 deaths of men whose total dose exceeded 10 rem, when the expected number was only 0.5. At one point in their analysis Darby and Reissland admitted that "*when using an internal comparison there is some evidence of a tendency towards decreased overall mortality among those with higher recorded radiation doses*". But they finally decided that the only abnormal finding was an "*increased mortality from multiple myeloma in the higher dose categories*".

During the period covered by the federally sponsored re-analyses of Hanford data, MSK were trying to justify their methodology by a) comparing the relative efficiency of an SMR and a CMD analysis (given the size of the Hanford data base); b) observing the effects of simultaneous control of all the cancer related factors except radiation (Mantel Haenszel analysis), and c) using an ICRP classification of radiosensitive tissues[10] to obtain a

more compact classification of cancer than was possible with the international or W.H.O. classification of diseases and causes of death (table 2)[11,12]. They succeeded in showing that, in order to be equally efficient, an SMR analysis would require a much larger database than a CMD analysis[11]. They also used Mantel-Haenszel procedures to show that, in the 1977 version of the CMD analysis, there had been no confusion between radiation effects and other cancer related factors[11]. Finally, by using the ICRP classification in table 2 they showed that: a) the radiation effect was coming from cancers in tissues with high or apparent sensitivity to cancer induction by radiation' - so called A cancers which accounted for two thirds of the Hanford deaths; b) the different trends of dose with age for cancer and non-cancer deaths owed more to deaths before 56 than to later deaths, and c) this difference affected B cancers more than A cancers (fig. 1)[12]. MSK were intending to replace their analysis of dead workers with a full cohort analysis but only the CMD analysis was completed while Dr. Mancuso was still director of the research.

Final Stage of the MSK Analysis

When Stewart and Kneale returned to England they took with them copies of the Hanford data. They had neither funding nor access to new data but they were aware that the problem which had originally led to their involvement in a U.S. project - i.e., the higher radiation doses of live than dead workers - was still unresolved. In 1975 they had deliberately shelved this problem and concentrated on differences between cancer and non-cancer deaths. But before doing so they had discovered, first, that the proportion of workers with records of internal radiation monitoring

(IRM) was much higher for live workers (70%) than dead workers (25%) and, second, that within the group of dead workers the average dose for gamma radiation was much higher for the IRM subgroup (3.75 rem) than for the remaining cases (0.23 rem)[4].

Bioassay tests are usually reserved for workers actually performing or supervising nuclear operations. Therefore, a significant difference between live and dead workers in respect of IRM levels as well as gamma doses might be the result of an association between 'danger money' and the healthy worker effect (HWE). This was possible since the more dangerous the job the greater the need for two types of worker: i.e., experienced health physists and workers with the strength and the skill to perform difficult tasks while encased in air proof coveralls. Therefore, the problem facing MSK was how to distinguish not only between safe and dangerous jobs but also between workers with and without special skills.

For several years after July 1977, MSK continued to work on Hanford data. This later work was partly the result of Mancuso obtaining a grant from the National Institute of Safety and Health for the express purpose of updating his records of Hanford deaths. But in addition Kneale was devising new methods of statistical analysis and Stewart was trying to produce a rational classification of Hanford occupations.

As 'coded job titles' there were more than 8000 different occupations at Hanford, and when movements between the broad occupational categories in table 3a were examined, evidence was obtained of frequent interchanges between safe and dangerous jobs, as well as between professional and manual grades (table 3b). Therefore, in desperation, Stewart turned her attention to the IRM data.

Fortunately, Dr. Mancuso had seen fit to retrieve both the dates and the results of all the bioassay tests. This meticulous data collection made it possible for each worker to be given both a final position on an arbitrary IRM scale and a series of intermediate positions, based on annual tests (table 4). It also meant that all the job titles could be compacted into the 9 groups in table 5 preparatory to obtaining a set of differential mortality scores - based on annual death rates of workers who were free to move between the different groups - and adapting these scores for use as a controlling factor (so called 'job hazard index').

When this new factor was added to more usual controlling factors (e.g. age, sex and employment period) an otherwise negative dose trend for all causes of death was reduced to non-significance, and the same effect was obtained when the special controlling factor was each workers final position on the IRM scale (see below). Therefore, MSK assumed that the healthy worker effect was job related and that control of this internal bias required consideration of IRM data as well as the coded job titles.

The following excerpt from the first MSK analysis to make use of IRM data[13] reveals the main concerns of Kneale during this period.

> *"An ideal methodology [for Hanford data] should assume nothing about death rates in the absence of radiation. It should also be able to control statistically for any combination of relevant epidemiological variables, as a Mantel-Haenszel analysis can, and be able to include data on both live and dead workers. Ideally, it should also be able to estimate parameters of simple dose-effect models - for example, latent period, doubling dose linearity of dose response etc. - as well as testing the null hypothesis of no*

radiation effect.

A methodology satisfying these criteria was developed during correspondence with interested scientists, but as was pointed out to us the method of Cox on the analysis of regression models in life-tables (originally supposed to be of use only in clinical trials) had simply been re-discovered. Therefore, the mathematical explanation (see appendix) is based on the paper by Cox.

The method divides into two parts: firstly, a relatively simple calculation to test the null hypothesis of no radiation effects and, secondly, a more complex calculation, based on a transformation of the dose to estimate parameters of a specific dose-effect model. In both calculations the data are first divided into a large number of subgroups by levels of controlling variables. In each subgroup a life-table is constructed, giving for each year of follow-up the total number at risk, the number of deaths from cancer in that year, and the mean doses (transformed dose in the second calculation) of these two categories, cumulated to the year of follow-up or death. Summary variables are then obtained for each subgroup by certain summations over years of follow-up and finally a grand summary by all subgroups. The result is, in the first case, a t-statistic with an approximately normal distribution if the null hypothesis is true and, in the second case, a log-likelihood that measure the goodness of fit of the specific dose-effect model according to which the dose transformation was calculated. By varying the

parameters of the dose-effect model the maximum likelihood estimates may be calculated in the usual way".

These deliberations were followed by inclusion of all workers in table 6 in several tests of the null hypothesis. The "typical" life table in table 7 shows the nature of these tests and the summary statistics (or t values) in table 8 show the results of having 5 sets of controlling factors and 3 sets of test factors or causes of death.

With 'all deaths' as the test factor and no 'special' controlling factors, there was a strong impression of a beneficial effect of radiation (see first and second tests in table 8). This amounted to confirmation of the earlier work by Sanders[3]. However, when Kneale calculated the strength of the association, he found that it was equivalent to a dose of 50 rem being more than sufficient to halve the normal risk of dying from any cause! This was absurd, so Kneale proceeded to show the results of inserting 'extra' controls in tests of the null hypothesis.

The third test in table 8 shows that the negative dose trend for all deaths was much reduced by having annual positions on the IRM scale as an extra controlling factor, and the later tests show that this trend ceased to exist when the extra controls were the final position of each worker on the IRM scale (fourth test) or the job hazard index (fifth test). Under these conditions there was firm rejection of the null hypothesis by the A cancers despite the fact that for B cancers there was still a negative dose trend.

In pursuit of the idea that the findings for B cancers in table 8 and fig. 1 might be the result of competing causes of death, the 1981 analysis of Hanford data by MSK shows the effects of a) equating violent deaths and

myocardial infarction with sudden deaths and b) distinguishing between two age groups (under and over 56 years), two dose levels (under and over 2.5 rad) and two death registration areas (Washington State and elsewhere). According to this test the proportion of high doses was consistently higher for the sudden deaths than from other non-cancers, and in the older age group the proportion was higher for sudden deaths than for B cancers. Therefore, MSK were inclined to suspect that latency deaths were masking the frequency of radiogenic cancers and having a selective effect on B cancers.

Having obtained evidence of a radiation effect for the group of radiosensitive cancers, Kneale proceeded to estimate the parameters of two dose effect models. The first model only allowed for variation of the doubling dose (D) and for possible non-linearity of dose response (i.e., the exponent of change with dose (E) might be greater or less than 1.0). This simple model sufficed to show that the highest log-likelihood value (relative to no radiation effect) was obtained when D = 15 rem and E = 0.5 (table 10). With these approximate values for D and E it was possible to observe both the effects of varying the interval between cancer induction and death (cancer latency or L), and the effects of sensitivity to cancer induction being age related (S) (table 11). These results were summarised in the following terms: For A cancers there is 1) Non-linearity of dose-response with a maximum likelihood estimate for E of 0.5 (with E = 1.0 rejected at the 1% level); 2) a maximum likelihood estimate for D of 15 rads (with a 95% confidence interval of 2 to 150 rads); 3) a maximum likelihood estimate for L of 25 years, and 4) a maximum likelihood estimate for S of 8 years (where S is as the time needed to double the risk between two consecutive years of adult life).

The results of this analysis of 1944-77 deaths of Hanford workers was published in 1981 with the following abstract[13]:

"This paper reports on results from the study initiated by Mancuso into the health risks from low-level radiation in workers engaged in plutonium manufacture at Hanford Works, Washington State, USA, and attempt to answer criticisms of previous reports by an in-depth study. Previous reports have aroused much controversy because the reported risk per unit radiation dose for cancers of radiosensitive tissues was much greater than the risk generally accepted on the basis of other studies and widely used in setting safety levels for exposure to low-level radiation. The method of regression model in life-tables isolates the effect of radiation after statistically controlling for a wide range of possible interfering factors. Like the risk of lung cancer for uranium miners the dose-response relation showed a significant downward curve at about 10 rem. There may, therefore, be better agreement with other studies, conducted at higher doses, that is widely assumed. The findings on cancer latency (of about 25 years) and the effect of exposure age (increasing age increases the risk) are in general agreement with other studies. An unexplained finding is a significantly higher dose for all workers than for workers who developed cancers in tissues that are supposed to have low sensitivity to cancer induction by radiation".

ICRP was firmly of the opinion that linear extrapolation of high dose effects tends to exaggerate the cancer risks of occupational exposures. Therefore, the analysis of Hanford data by MSK was no more acceptable to the nuclear establishment than was the earlier CMD analysis. For example, according to ICRP 26, "*the dose response curve for LET radiation will generally increase in slope with increasing dose*"[14]. Such upward curvature would imply an E value greater than 1.0 (see fig. 2). Therefore, in 1984, MSK repeated their analysis in circumstances which allowed for the possibility that an 'internal healthy worker bias' had somehow given E (i.e., the exponent of change with dose) too low a value. This repeat analysis also provided an opportunity to describe the components of the 'job hazard index'[15] and to observe the effects of a) lagging doses by 10 years and b) equating their age sensitivity effect with a 10% increase in risk for each year of adult life[16].

The results of this analysis are summarised in table 12. Once again there were striking differences between A cancers and other causes of death, also evidence that control for age, sex and duration of employment was not sufficient to prevent a (false) impression of beneficial effect of the radiation exposures. Replacing maximum likelihood estimates of E, L and S with other estimates made little difference to the results which were summed up in the following terms: "*For tissues which are sensitive to cancer induction by radiation there is a risk of cancer for Hanford exposures whose dose response is curvilinear, with long latency and an increasing effect with increasing exposure age*"[16].

Gilbert Analyses of Hanford Data

Dr. Mancuso's contract with DOE was finally terminated in July 1977. Since then, Ethel Gilbert, who has always been extremely critical of the uses made by MSK of the IRM data (and the ICRP classification in table 2) has been the principle analyst of Hanford data. Regarding 'A Cancers' she once had this to say: "*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 analysed 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*"[17]. She further claimed that, in the 1981 analysis , the IRM data are "*used inappropriately in that workers are classified as being in their final category throughout the follow-up period*" and that "*MSK obtain a significant correlation of radiation exposure and cancer mortality only by restricting the analysis to 'radiosensitive cancers' and by including the final level of internal monitoring as a control variable*".

The point that Gilbert was trying to make was that risk estimates based on Hanford data are so unstable (and so dependent on the risk model) that "*we cannot hope to address such issues as the shape of the dose-response function, the effect of such variables as age at exposure or the manner in which radiation risks are related to spontaneous risks. Thus we must continue to place strong reliance on estimates and models derived from populations exposed as relatively high levels*". She clearly had in mind the life span study population of A-bomb survivors and the fact that "*the high-level Japanese data give far greater precision than do the low-level Hanford data*"[17].

There has already been occasion to mention the 1979 analysis of Hanford data by Gilbert and Marks[7]. Included in this analysis were 12,522 badge monitored men who were employed for at least 2 years. For these workers there were several comparisons of cancer death rates by exposure status which showed that, with doses lagged for 2 years, there were positive findings for myelomas and pancreatic cancers. But with doses lagged for 10 years, the myelomas (with only 6 deaths) were alone in showing a significant dose trend.

In 1985 Gilbert and Petersen[18] produced what they regarded as evidence that MSK were mistaken when they a) assumed that control for IRM levels was essential to prevent a (false) negative correlation with dose for all deaths[13], and b) claimed that risk coefficients based on A bomb survivors were underestimating the cancer risks of occupational exposures[12]. For this purpose Gilbert and Petersen distributed the 1944-78 deaths of Hanford workers according to the same log scale of dose as in table 6. After adjustment for exposure age, hire year, sex and duration of employment they summed all the strata risk estimates (to obtain, for each dose level, an expected number of deaths for comparison with an observed number for all deaths, A cancers and B cancers) and finally obtained a single 'trend test statistic' (comparable to the t values in table 8) for each of the test factors included in the MSK analysis (table 13). According to this analysis all three dose trends retained their original directions (i.e., they remained positive for A cancers and negative for all deaths and B cancers), but there was no longer a statistically significant finding for A cancers. Therefore, Gilbert and Petersen concluded that there was no "*compelling reason to believe that the Hanford data are inconsistent with current estimates of radiation risks*"[18].

The next contribution made by Gilbert and her associates to the Hanford controversy was an analysis of 1945-81 deaths which was published in 1989[18]. On this occasion a conventional SMR analysis was used to show that Hanford workers have unusually low death rates, and that this healthy worker effect owed more to exposed than non-exposed workers. For all workers the SMR was higher for cancer (85) than for other causes of death (78) but it was below the general average for leukaemia (71) and thyroid cancer (47), and even for myeloma the observed number of deaths (14) was smaller than the expected number (16.2).

These comparisons with national statistics were followed by comparisons between workers with different causes of death and different levels of radiation dose after lagging for 2, 10 or 15 years. Thus, the proportional hazards method of Cox was used to compare dose trends for 24 causes of death with doses lagged for 2 and 10 years (table 14); a modified Mantel-Haenszel analysis was used to obtain relative risk (RR) estimates for 10 causes of death at 4 dose levels (table 15) and, a Cox analysis of all cancer deaths was repeated with different controlling factors and dose restrictions (table 16).

For 31 of the 48 tests in table 14 the summary trend statistic had a negative value. But it was only among exceptions to this rule that there was any approach to levels of statistical significance (see myeloma, female genital cancers and all female cancers). For most of the groups in table 15 the RR was below unity in the highest of 4 dose groups (over 150 mSV), but for 10 cases of lung cancer in this dose group the RR was 1.21 and one case of myeloma it was 14.7. Finally, In table 16, one can see the effects of adding "main occupation" to the other controlling factors, also the effects of varying intervals between discharge and death and excluding

either employment periods or workers with confirmed internal radiation. In all there were 12 tests of excess relative risk for all cancers and they all had RR values of less than 1.0.

In concluding stages of the 1989 analysis Gilbert *et al* show the results of adding an extra 189 cancer deaths (all from 1982-85 registrations in Washington State) and include a list of cumulative doses for 21 cases of myeloma. These additions made little difference to a report which was given the following summary:

> *"Analyses of mortality of workers at the Hanford Site were updated to include an additional three years of data (1979-81). Deaths occurring in the state of Washington in the years 1982-85 were also evaluated. Hanford workers continued to exhibit a strong healthy worker effect with death rates substantially below those of the general US population. Comparisons by level of radiation exposure within the Hanford worker population provided no evidence of a positive correlation of radiation exposure and mortality from all cancers combined or of mortality from leukaemia. Estimates of cancer risk due to radiation were negative, but confidence intervals were wide, indicating that the data were consistent with no risk and with risks several times larger than estimates provided by major groups concerned with risk assessment. Of 18 categories of cancer analyzed, a correlation of borderline statistical significance was identified for female genital cancers (p=0.05), but was interpreted as probably spurious. The previously identified correlation for multiple myeloma persisted (p = 0.002)".*

According to Gilbert there are several reasons why the myeloma correlations are unlikely to be artifacts of the type that are liable to be caused by a multitude of statistical tests[20]. Nevertheless, she warns that, since Hanford estimates are based on small numbers, they have wide margins of error. For example, although her (Hanford based) estimate for all cancers except leukaemia had a negative value (-.04) and the corresponding estimate for A-bomb survivors had a positive value (+0.17), the 90% confidence limits estimate were so wide (-1.7 to +1.25) that there was considerable overlap with the equivalent LSS estimates (+0.13 to +0.21)[21].

These findings reinforced the need for much firmer estimates for occupational exposures. Therefore, the 1989 analysis of all Hanford workers was repeated with a study population consisting of men who had worked for at least 6 months either at Hanford (23,704), Oak Ridge (6332) or Rocky Flats (5897) and the combined series (35,933). This analysis still left 12 cases of myeloma (all from Hanford) as "*the only cancer to exhibit a statistically significant correlation with radiation exposure*"[21]. However, for all cancers there were now four estimates of relative risk and absolute risk (with 90% confidence limits) for comparison with LSS estimates for A-bomb survivors (table 17). Each of the worker based estimates of relative and absolute risk had a negative value, and each of the LSS estimates had a positive value. However, the upper limits of the 90% confidence limits for the combined series (with 1036 cancer deaths) were sufficiently close to the upper limits of the LSS estimates to conclude that "*estimates obtained through extrapolation for high dose data do not seriously underestimate risks for low-dose exposure*"[21]

In short, all the 1989 analyses of DOE data supported a conclusion of Gilbert that "*a major objective of studying populations exposed to low levels of radiation is provision of direct assessment of the adequacy of estimates of health risks obtained by extrapolation of data on populations exposed at high levels*". They were also in line with a contention of Land, namely, that "*there is more to be learnt about cancer risks associated with low doses of radiation by studying populations with high and intermediate levels than by studying populations only exposed to low doses*"[22].

Future Prospects

Though several years have elapsed since the last MSK publication, work has been going on behind the scenes. From correspondence with Gilbert - which led to exchange of computer programmes and notes on these programmes - Kneale discovered that whereas he was using the basic ideas of Cox[23] to extend the concept of a Mantel-Haenszel analysis, Gilbert was using the same ideas to extend the concept of an SMR analysis. As a result of this difference there was much finer stratification of hire years than years of birth in the MSK analysis, and much finer stratification of years of birth than hire years in the Gilbert analysis. Furthermore, until recently, only third generation computers were available. Therefore, neither party had been able to play for safety by having equally fine stratification of both variables.

Each of the two adaptions of the Cox method was equally legitimate, but the one requiring fine stratification of hire years made it much easier to see that the healthy worker effect was dose related than the one

requiring fine stratification of birth years. Also, recent work by Kneale (with data released by DOE to the Three Mile Island Public Health Fund) has shown that, even after standardization for all usual and special factors, the cancer risk estimate remains significantly higher for men who were born before 1900 (and hired before 1950) than for other workers. This statistical difference must be an artifact. But it could be caused either by ratios of actual to recorded doses of external radiation being exceptionally high for the atypical group (biased recording of radiation doses), or by there being less involvement of these men in situations which prevent full recognition of the cancer risk (failure to recognise a confounding variable). The first effect would reduce the MSK risk estimates and the second effect would increase them. Therefore, a critical point in the Hanford controversy has been reached and, as yet, there is no indication whether there will be narrowing or widening of the present gap between rival estimates.

References

1. Caufield C: Multiple exposures: chronicles of the radiation age. Ed. Secker and Warburg. London, 1989.

22. Cox DR: Regression models in life-tables. J R Statist Soc 34:187-220, 1972.

9. Darby SC, Reissland JA. Low levels of ionizing radiation and cancer - are we underestimating the risk? J R Statist Soc 144:298-331, 1981.

17. Gilbert ES. The Hanford study - a review of its limitations and controversial conclusions. in Proceedings of the 1984 Statistical Symposium on National Energy Issues, 1984, pp16-18.

20. Gilbert ES. Issues in analysing the effects of occupational exposure to low levels of radiation. Statistics in Med 8:173-187, 1989.

21. Gilbert ES, Fry S, Wiggs L, *et al*. Analyses of combined mortality data on workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Nuclear Weapons Plant. Rad Res 120, 1989.

6. Gilbert ES, Marks S. An analysis of the mortality of workers in a nuclear facility. Rad Res 79:122-148, 1979.

18. Gilbert ES, Petersen GR. A note on "Job related mortality risks of Hanford workers and their relation to cancer effects of measured doses of external radiation". Brit J Indust Med 42:137-139, 1985.

19. Gilbert ES, Petersen GR, Buchanan A. Mortality of workers at the Hanford Site: 1945-1981. Health Physics 56:11-25, 1989.

8. Hutchison GB, MacMahon B, Jablon S, *et al*. Review of report by Mancuso, Stewart and Kneale of radiation exposure of Hanford workers. Health Physics 37:207-220, 1979.

References cont.

10. ICRP 14. Radiosensitivity and spatial distribution of dose. Pergammon Press, Oxford, 1969.

14. ICRP 26. Recommendations of the commission adopted January 1977. Pergammon Press, Oxford, 1977.

11. Kneale GW, Mancuso TF, Stewart AM. Hanford IIA: re-analysis of data relating to the Hanford study of the cancer risks of radiation workers. in Late Biological Effects of Ionizing Radiation, IAEA, Vienna, 1:387-410, 1978.

13. Kneale GW, Mancuso TF, Stewart AM. Hanford radiation study III: a cohort study of the cancer risks from radiation to workers at Hanford (1944-77 deaths) by the method of regression models in life-tables. Brit J Indust Med 16:156-166, 1981.

15. Kneale GW, Mancuso TF, Stewart AM. Identification of occupational mortality risks for Hanford workers. Brit J Indust Med 41:6-8, 1984.

16. Kneale GW, Mancuso TF, Stewart AM. Job related mortality risks of Hanford workers and their relation to cancer effects of measured doses of external radiation. Brit J Indust Med 41:9-14, 1984.

4. Mancuso TF, Stewart AM, Kneale GW. Hanford I: radiation exposures of Hanford workers dying from cancer and other causes. Health Physics 33:369-384, 1977.

7. Marks S, Gilbert ES, Breitenstien. Cancer mortality in Hanford workers. in Late Biological Effects of Ionizing Radiation, IAEA Vienna, 1:369-386, 1978.

2. Milham S. Occupational mortality in Washington State, 1950-79. Contract No. CDC-99-74-26, 1975.

References cont.

5. Reissland JA. An assessment of the Mancuso study.
National Radiological Protection Board (NRPB) - R79, Harwell, 1978.

3. Sanders, Barkov S. Low level radiation and cancer deaths.
Health Physics 34:521-538, 1975.

12. Stewart AM, Mancuso TF, Kneale GW. Hanford IIB: the Hanford data - a reply to recent criticisms. Ambio 9:66-73, 1980.

Table 1

Radiation Doses of Exposed Workers with Certified Deaths[1]

Certified Causes of Death (ICD Nos.)	Exposed Workers (Nos.)	Cumulative Radiation Dose (centirads)	Mean R Dose (centirads)
Non Cancers:			
Infective (000-136)	16	1,258	79
Benign neoplasms (210-39)	4	155	39
Endocr. & blood (244-89)	34	5,199	153
C.N.S. (290-389)	20	3,389	169
C.V.S. (390-458)	1,149	191,987	167
Respiratory (460-519)	108	14,330	133
Digestive (520-577)	83	15,807	190
Accidents (800-999)	271	42,244	156
Residue (580-796)	57	8,592	151
RES Neoplasms:			
* Lymphomas (200-2)	28	4,049	145
* Myelomas (203)	8	8,530	1,066
* Lymphatic Lk (204)	2	57	29
* Myeloid leukaemia (205)	6	1,337	223
* Residue (206-9)	3	58	19
Solid Tumours:			
Mouth & pharynx (140-9)	14	2,134	152
* Stomach (151)	26	2,227	86
* Large intestine (153)	48	8,222	171
* Rectum (154)	16	1,887	118
* Other intestinal (150;152)	10	581	58
* Liver & gall bl. (155-6)	10	557	56
* Pancreas (157)	31	12,377	399
* Lung (162-3)	130	32,384	249
Prostate (185)	21	1,817	87
Kidney (189)	14	3,935	281
Other G.U. (186-8)	10	1,225	123
Brain (191)	11	3,967	361
Residue	54	7,313	135
Totals:			
Non-cancers	1,742	282,961	162
RES neoplasms	47	14,031	299
Solid Tumours	395	78,626	199

(1) from Mancuso *et al* 1977[4]

* A cancers (see text and table 2)

Table 2

Alternative Classifications of Adult Cancers

Authority		Groups	ICD Nos.
WHO	1	Mouth & Pharynx	140-149
International Classification of Diseases and Causes of Death	2	Digestive & Peritoneum	150-159
	3	Respiratory	160-163
	4	Bone, Skin, Connective Tissue (incl. Breast)	170-174
(8th Revision)	5	Genito-Urinary	180-189
	6	Other Solid Tumours	190-199
	7	Lymphatic & Haemopoietic	200-209
ICRP 14 Table 3 "*Tentative classification of relative sensitivity of organs and tissues to cancer induction by radiation in adult life*"	A 1	High Sensitivity[2]	193;203
	A 2	Apparent Sensitivity	151;153;157;162; 163;174;200-202; 205-209
	B 1	Low Sensitivity	140-145;150;152; 155;156;160;161; 170-173;186;187; 189;191;192:194
	B 2	Unclassified	Residue

Table 3a

Classification of Hanford Occupations

Code	Census Code Nos.	Description	Man Years	Mean Dose per Man Year (rad)
1	001-280	Nuclear Specific Professional	71,229	0.35
2	401-698	Nuclear Specific Craftsmen	38,355	0.68
3	001-280	Other Professional	17,002	0.13
4	301-395	Clerical	28,795	0.06
5	401-580	Other Craftsmen	28,947	0.22
6	601-695	Other Operatives	5,895	0.15
7	740-986	Services and Unclassified	47,824	0.17

Table 3b

Hanford Occupations. Year by Year Movements of Workers(1)

Occupations*	Man Years						
1	62,594	955	2,143	631	556	131	215
2	1,375	34,522	154	231	1,423	163	220
3	2,003	93	15,326	457	55	23	62
4	1,023	234	668	39,347	127	173	175
5	539	930	83	94	26,836	121	134
6	214	184	49	135	211	5,324	389
7	447	584	87	347	465	479	30,142
Principal Job Type (nos.)	9,888	3,780	3,234	8,467	2,800	1,094	5,584

(1) Workers who were hired and discharged in the same calendar year are not included in this table. Workers who left the following year have one position which shows whether the first year job (vertical axis) was the same or different from the second year job (horizontal axis). For workers who spanned three calendar years there are two positions which show the relative positions of sequent jobs, and so on. Therefore, the diagonal axis shows the main occupations of all workers who spanned more than one year.

* see table 3a.

Table 4

Classification of Internal Radiation Monitoring (IRM Levels)

IRM Levels		Final IRM position of each worker	Man years of work	Mean Dose per Man Year (rad)
1	No IRM monitoring	14,873	40,500	0.10
2	Urine tests (all negative)	5,402	72,436	0.15
3	Urine tests (transient radioactivity)	3,448	60,351	0.36
4	One or more whole body counts (WBC)	10,701	59,959	0.48
5	Confirmed internal deposition of Pu etc.	421	4,801	1.04

Note: Individuals can only move up the IRM scale (which records tests not exposures).

Table 5

Method of Scoring IRM Data and the Job Hazard Index[1]

(A) IRM Scoring System

Danger Levels	Types of Monitoring for internal radiation	IRM Levels	
		Individual Workers	Occupations
1	Film badge only	1	1.0-2.4
2	Film badge and routine urine tests	2	2.5-2.8
3	Repeat urine tests	3	2.9-3.0
4	Repeat urine tests and whole body counts	4	3.1-4.0

(B) Hanford Occupations. Combination of 3 Work Grades and IRM Levels.

Work Grade	Census code	IRM Levels	Man-years No.	Man-years %
Professional	001-245	1	26,861	2.83
		2	27,208	2.86
		3	25,584	2.69
		4	23,754	2.50
Clerical	301-395	1	47,598	5.01
Manual	401-964	1	34,529	3.63
		2	27,001	2.84
		3	23,167	2.44
		4	33,828	3.56
Totals	Hanford working years		269,530	28.36
	Post Hanford years		680,990	71.64
	Both		950,520	100.00

(C) Job Hazard Index or Differential Mortality Score

Hanford Occupations Work Grade	Danger Levels	IRM Mean Scores	External Radiation mean annual dose in millirems	Job Hazard Index or Differential Mortality Score Index	(Rank)
Professional	1	1.92	87	- 288	(1)
	2	2.74	168	- 210	(3)
	3	3.08	260	- 222	(2)
	4	3.69	639	- 29	(6)
Clerical	1	2.03	37	+ 92	(9)
Manual	1	2.28	61	+ 65	(7)
	2	2.76	126	+ 82	(8)
	3	3.20	166	- 43	(4)
	4	3.60	831	- 35	(5)

(1) from Kneale *et al* 1984[15]

Table 6

Hanford Workers Included in the 1981 Cohort Analysis by MSK[1]
(1) External Radiation Doses for Four IRM Levels

External Radiation in rads	Levels of monitoring for internal radiation* 1	2	3	4	Total
Men					
< 0.01	2609	494	87	21	3211
0.01- 0.07	1326	611	149	96	2182
0.08- 0.31	1586	1366	376	216	3544
0.32- 0.63	894	1019	338	209	2460
0.64- 1.27	707	822	523	670	2722
1.28- 2.55	321	686	801	1266	3074
2.56- 5.11	76	269	325	1064	1734
5.12-10.23	38	96	173	910	1217
10.24-20.47	27	37	69	686	819
20.48-40.95	3	8	33	675	719
40.96-99.99	2	2	1	193	198
Total	**7589**	**5410**	**2875**	**6006**	**21880**
Women					
< 0.01	1391	352	58	8	1809
0.01- 0.07	574	321	81	17	993
0.08- 0.31	829	532	128	43	1532
0.32- 0.63	315	243	71	39	668
0.64- 1.27	138	204	102	103	547
1.28- 2.55	54	84	77	103	318
2.56- 5.11	6	20	21	53	100
5.12-10.23	-	8	16	31	55
10.24-20.47	-	2	8	39	49
20.48-40.95	-	-	3	8	11
40.96-99.99	-	-	-	-	-
Total	**3307**	**1766**	**565**	**444**	**6082**

* see table 4

(1) from Kneale *et al* 1981[13]

Table 7

Hanford Workers Included in the 1981 Cohort Analysis by MSK
(2) Life Tables for Typical Cohort*

Years of Follow-up	Survivors to Beginning of Year (Rig) No.	Mean dose	Cancer of Radiosensitive Tissues Dying in Year (Aig) No.	Mean dose	Deviation (rads)	Variance (square rads)	t value
1-11	414	1.68	-	-	-	-	-
12	414	1.99	-	-	-	-	-
13	414	2.34	-	-	-	-	-
14	414	2.75	-	-	-	-	-
15	414	3.17	-	-	-	-	-
16	413	3.61	-	-	-	-	-
17	413	4.09	-	-	-	-	-
18	410	4.66	-	-	-	-	-
19	409	5.17	1	29.30	+24.13	61.00	+3.09
20	407	5.60	-	-	-	-	-
21	406	6.15	-	-	-	-	-
22	402	6.62	-	-	-	-	-
23	397	6.93	-	-	-	-	-
24	392	7.13	1	0.79	- 6.34	106.8	-0.61
25	387	7.42	2	15.28	+15.69	228.6	+1.04
26	378	7.63	1	4.76	- 2.87	121.0	-0.26
27	374	7.73	1	6.96	- 0.77	127.4	-0.07
28	267	7.50	1	2.17	- 5.33	115.1	-0.50
29	162	7.90	-	-	-	-	-
30	134	8.21	4	3.98	-16.92	404.8	-0.84
31	5	8.39	1	12.83	+ 4.44	27.3	+0.85
32	3	8.60	-	-	-	-	-
33	1	2.21	-	-	-	-	-
Total	11543 man years	3.50	12	8.60	+12.03	1192.0	+0.34

* Men from 1945-9 cohorts who were: (a) aged 25-34 when hired; (b) employed for more than eight years; and (c) had 4th grade of monitoring for internal radiation.

Table 8

Hanford Workers Included in the 1981 Cohort Analysis by MSK
(3) Tests of the Null Hypothesis of No Radiation Effects

Sequence of Tests	Controlling Factors	Summary Trend Statistic (t values)		
		All Deaths	A Cancers	B Cancers
1st	1 + 2 + 3	-4.64*	-	-
2nd	1 + 2 + 3 + 4	-3.60*	-	-
3rd	1 + 2 + 3 + 4 + 5	-2.15*	+1.65	-2.58*
4th	1 + 2 + 3 + 4 + 6	-0.48	+2.47*	-2.20*
5th	1 + 2 + 3 + 4 + 7	+0.12	+2.24*	-1.88

Controlling Factors (and levels)

1. Sex (2)
2. Hire age (5)
3. Hire year or work cohort (4) — usual controlling factors
4. Employment period (3)
5. Intermediate positions on the IRM scale (4)
6. Final position on the IRM scale (4) — special controlling factors
7. Job hazard index (5)

* significant dose trend

For Job Hazard Index see table 5.

Table 9

Hanford Workers Included in the 1981 Cohort Analysis by MSK
(4) Proportion of High Dose Workers by Cause of Death and Place of Death

Age in Years	Cause	Place of Death: Washington State Nos.	Washington State %HD[1]	Elsewhere Nos.	Elsewhere %HD	Total Nos.	Total %HD
under 56	Sudden deaths[2]	433	*12.2*	427	*3.5*	860	*7.9*
	Other non-cancers	242	*10.7*	282	*1.8*	524	*5.9*
	A cancers	112	*16.1*	125	*2.4*	237	*8.9*
	B cancers	54	*13.0*	54	*3.7*	108	*8.9*
	All causes	841	*12.4*	888	*2.8*	729	*7.5*
over 56	Sudden deaths	576	*16.8*	575	*4.2*	1151	*10.5*
	Other non-cancers	738	*16.1*	944	*3.1*	1682	*8.8*
	A cancers	266	*25.9*	250	*2.4*	516	*14.5*
	B cancers	131	*10.6*	127	*0.8*	258	*5.8*
	All causes	1771	*17.5*	1896	*3.2*	3607	*10.0*
All Ages	All Causes	2552	*15.8*	2784	*3.1*	5336	*9.1*

(1) HD = high doses (over 2.5 rad)

(2) Sudden deaths = trauma and myocardial infarction (see text)

Table 10

Fitting of Simple Model. Let X_j = dose in follow-up year j, and let the relative risk in follow-up year i be given by $R_i = 1 + \sum_{j=1}^{i}(X_j/D)^E$ where D is the assumed doubling dose and E is the exponent for non-linearity (E = 1.0 gives a linear dose-response relationship)

Model No.	E	D rads	Log-likelihood relative to no radiation risk
1	1.0	infinity	0.0000
2	1.0	100	1.7046
3	1.0	50	2.5307
4	1.0	25	2.8818
5	1.0	15	2.1187
6	1.0	10	0.3942
7	2.0		0.0000
8	2.0	50	1.1697
9	2.0	25	-0.6964
10	2.0	15	-9.7484
11	0.5		0.0000
12	0.5	50	3.8979
13	0.5	25	4.3815
14	0.5	15	4.5278
15	0.5	10	4.4394
16	0.3333		0.0000
17	0.3333	25	3.9659
18	0.3333	15	3.9173
19	0.3333	10	3.7579

Table 11

Fitting of More Complex Model. Let radiation received k years before death have to be multiplied by a factor W_k to give the effective dose, where W_k = (k/L) exp [1-(k/L)] and L is the optimum latent period in years (W_k is less than 1.0 for all k except k equal to L). Let radiation received at age a have to be multiplied by a factor U_a to give the effect of age at exposure, where U_a = exp [(a - 40)/S] and S is the amount in years by which age at exposure must increase to increase sensitivity by a factor e (2.7183). U_a is standardised to give a sensitivity of 1.0 at exposure age 40. Let the radiation received in follow-up year j be X_j and let the cumulative effective dose by follow-up year i be Z_i,

where $Z_i = \sum_{j=1}^{i} W_{(i-j)} U_{(h+j)} X_j$ and h is the hire age in years.

Let the relative risk in follow-up year i be given by R_i where $R_i = 1 + (Z_i/D)^E$ and E is the exponent for non-linearity and D is the assumed doubling dose for radiation received at age 40 and death after the optimum latent period (L years).

Model No.	L years	S years	E	D rads	Log-likelihood
1	any	any	any	infinity	0.0000
2	10	*	0.5	15	4.8748
3	20	*	0.5	15	5.0972
4	30	*	0.5	15	5.0483
5	25	20	0.5	30	6.4304
6	25	-20	0.5	30	2.6846
7	20	20	0.5	30	6.4806
8	20	15	0.5	30	7.0649
9	20	10	0.5	30	8.0644
10	20	5	0.5	30	7.3960
11	20	2	0.5	30	0.8342
12	20	8	0.5	30	8.5601
13	15	8	0.5	30	8.3384
14	25	8	0.5	30	8.6314
15	25	8	1.0	30	1.6531
16	25	8	0.3333	30	8.0394
17	25	8	0.5	20	8.8489
18	25	8	0.5	50	8.0931
19	25	8	0.5	100	7.0663
20	25	8	0.5	10	8.6104
21	25	8	0.5	15	8.8558

* = U_a is constant

Table 12

Results of the 1984 Cohort Analysis by MSK*

Sequence	End Points	Controlling Factors(1)	Summary Trend Statistic		E(2)
			Rank Weighted	Dose Weighted	
1st	All Deaths	1 + 2 + 3 + 4	-5.95*	-3.04	under 1.0
2nd	"	1 + 2 + 3 + 4 + 7	-3.68*	-1.94*	under 1.0
3rd	B cancers	1 + 2 + 3 + 4 + 7	-2.33*	-2.69*	over 1.0
4th	A cancers	1 + 2 + 3 + 4 + 7	+0.95	+0.77	under 1.0
5th	"	1 + 2 + 3 + 4 + 7 with L allowance	+1.76	+0.76	under 1.0
6th	"	1 + 2 + 3 + 4 + 7 with L and S allowance	+2.44*	+1.88	under 1.0

(1) see footnote to table 8 and text L = latency factor or doses lagged for 10 years
S = age sensitivity increasing by 10% per annum after 40 years.

(2) E = exponent of non-linearity of dose response (see Fig. 2).

* from Kneale *et al* 1984(16)

Table 13

Observed and Expected Numbers of all Deaths, Cancers, and B Cancers with Doses Lagged for 10 Years[1]

Dose (rem)	All Deaths Obs/Exp*	A-cancers Obs/Exp*	B-cancers Obs/Exp*
0.00	870/*835.5*	123/*125.0*	63/*49.2*
0.01-	499/*493.4*	79/*75.5*	21/*29.9*
0.08-	783/*777.0*	117/*119.1*	43/*45.8*
0.32-	615/*593.7*	94/*89.1*	29/*35.3*
0.64-	533/*570.2*	84/*87.9*	38/*35.0*
1.28-	307/*331.0*	48/*55.6*	23/*20.5*
2.56-	142/*149.3*	31/*25.7*	9/*9.4*
5.12-	93/*91.9*	16/*16.4*	5/*5.9*
10.24-	65/*65.7*	15/*11.4*	4/*4.4*
20.48-	33/*34.2*	5/*6.2*	2/*2.4*
Totals	3942	612	237
Trend test statistic	-0.67	+0.28	-0.43
Probability of trend arising due to chance[a]	0.75	0.39	0.67

* Expected deaths are calculated from experience of all monitored workers (including survivors) allowing for age, calendar year, sex, and duration of employment.

a Significance levels are for a one tailed test and are calculated using a normal approximation.

(1) from Gilbert and Petersen, 1984[18]

Table 14

(1) Results of analyses of external exposures in monitored Hanford Site Workers. Includes deaths 1955-1981 for analyses based on a 10-y lag and deaths 1947-181 for analyses based on a two-year lag[1]

Cause of death (8th revision ICD[a] code)	Trend test statistic[b]		Observed and expected deaths by exposure category in mSv (Based on 10-y lag)			
	Exposure lagged for 10 y	2 y	0- Obs./Exp.[c]	20- Obs./Exp.	50- Obs./Exp.	150+ Obs./Exp
All causes[e]	-1.15	-1.59	4234/4216.7	319/333.0	195/191.7	98/104.5
No certificate	-0.33	-0.08	48/45.8	0/1.6	0/1.1	1/0.5
All non-cancers	-0.94	-1.60	3259/3237.0	237/254.9	147/145.1	73/79.0
All cancers (140-209)	-0.65	-0.40	927/933.9	82/76.5	48/45.6	24/25.1
Male	-0.93	-0.67	808/808.4	74/72.6	42/42.4	24/24.6
Female	1.67[d]	1.76	119/125.5	8/3.8	6/3.2	0/0.5
Buccal (140-9)	-0.77	-1.14	27/24.8	1/2.3	1/1.2	0/0.8
Stomach (151)	-0.17	-0.07	43/42.1	2/3.4	2/2.2	2/1.3
Colon (153)	-0.80	-1.07	88/89.3	9/6.1	4/3.6	0/2.0
Rectum (154)	-0.90	-0.25	23/21.4	1/1.9	1/1.1	0/0.7
Pancreas (157)	0.27	1.24	58/58.7	5/5.1	3/2.7	2/1.5
Other digestive (150, 152, 155-6,158-9)	0.60	0.52	50/47.3	1/3.0	0/1.9	2/0.9
Lung (162)	0.11	0.36	272/282.5	32/26.1	20/16.0	10/9.3
Female breast (174)	-0.09	1.09	35/35.2	1/1.0	1/0.8	0/0.07
Female genital (180-3)	2.19[d]	1.66	9/11.3	2/0.3	1/0.3	0/0.06
Prostate (185)	-1.05	-1.29	69/66.5	4/5.4	4/3.1	0/2.0
Bladder and kidney (188-9)	-0.49	-0.53	40/38.7	2/3.3	2/1.9	1/1.1
Brain (191)	-0.91	-0.66	25/25.8	5/2.2	0/1.4	0/0.6
Other solid tumors (160-1, 163,170-3 190,192-9)	-0.49	-1.16	104/103.6	10/9.2	4/5.4	3/2.8
All lymphatic and haematopoietic cancer (200-9)	0.86	1.20	82/84.7	7/7.2	5/4.1	4/2.0
Lymphoma (200-2)	0.60	0.65	37/38.7	4/3.6	2/1.6	1/0.7
Multiple myeloma (203)	4.40[d]	3.60	11/12.7	0/0.9	2/0.4	1/0.1
Chronic lymphatic leukemia (204)	-0.96	-0.97	8/6.7	0/0.6	0/0.5	0/0.2
Leukemia[e] (205-7)	-0.69	-0.84	24/24.0	3/2.5	1/1.5	1/0.9
Leukemia[e] (Based on 2-y lag)			28/27.4	3/3.3	2/1.9	1/1.4
Person-years (Based on 10-y lag)			361,017	28,531	15,867	6,979

[a] ICD, International Classification of Diseases, Eighth Revision

[b] The trend test statistic was calculated from individual doses, not the four exposure categories. It may be compared with a standard normal distribution to assess statistical significance. However, statistical significance may be exaggerated for diseases with a small number of deaths. See footnote d.

[c] Expected deaths were calculated from the experience of all workers in the study population, allowing for age, calendar year, sex and length of employment.

[d] Based on computer simulations, the one-tailed p-values associated with the trend test with a 10-y lag were estimated to be 0.061 for all cancers in females, 0.046 for female genital cancer, and 0.002 for multiple myeloma.

[e] Excluding chronic lymphatic leukemia.

(1) From Gilbert *et al*, 1989[19]

Table 15

(2) Relative risk* estimates (with 90% confidence limits) by exposure category for all monitored Hanford Site workers. Exposures lagged for 10-y except where noted[1]

Cause of death (8th revision ICD[b] code)	Exposure category (in mSv)			
	0-	20-	50-	150+
All causes	1.00	0.95 (0.9,1.1)	1.00 (0.9,1.1)	0.92 (0.8,1.1)
All non-cancers	1.00	0.92 (0.8,1.0)	0.98 (0.8,1.1)	0.91 (0.7,1.1)
All cancers (140-209)	1.00	1.05 (0.9,1.3)	1.08 (0.8,1.4)	0.93 (0.7,1.3)
All digestive cancer (150-9)	1.00	0.89 (0.6,1.4)	0.83 (0.5,1.4)	0.88 (0.4,1.8)
Lung cancer (162)	1.00	1.37 (1.0,1.9)	1.44 (1.0,2.2)	1.21 (0.7,2.1)
Prostate cancer (185)	1.00	0.65 (0.3,1.6)	1.15 (0.5,2.9)	0.00
All lymphatic and haematopoietic (200-9)	1.00	0.97 (0.5,1.9)	1.29 (0.6,2.8)	1.65 (0.7,4.1)
Multiple myeloma (203)	1.00	0.00	8.52 (1.9,38)	14.7 (3.6,600)
Leukemia[c] (205-7)	1.00	1.12 (0.4,3.3)	0.73 (0.1,3.8)	0.92 (0.1,5.6)
Leukemia[c] (based on 2-y lag)	1.00	0.77 (0.3,2.2)	0.96 (0.3,3.2)	0.47 (0.1,2.8)

[a] The relative risks are the ratio of the risk for the indicated category relative to that of the 0-19.9 mSv category.

[b] ICD, International Classification of Diseases, Eighth Revision

[c] Excluding chronic lymphatic leukemia.

(1) From Gilbert *et al*, 1989[19]

Table 16

(3) Relative excess risk estimates (with 90% confidence limits) for all cancer based on alternative choices for lag period and for controlling factors. Expressed as percent increase per 10 mSv[1]

Analysis Number	Lag period in years	Additional controlling factors[a]	Relative excess risk estimate (with 90% confidence limits)
1.	10	None	-0.6% (-1.8%, 0.9%)
2.	10	No control for number of years monitored	-1.5% (-2.0%,-0.4%)
3.	10	Number of years monitored (1-4, 5-9, 10-19, 20+)	-0.6% (-1.8%, 1.0%)
4.	10	Job category[b]	-0.2% (-1.5%, 1.5%)
5.	10	Job category[c]	-0.8% (-2.0%, 0.8%)
6.	10	Years since termination of employment (0-9, 10+)	-0.3% (-1.6%, 1.5%)
7.	10	Years since termination of employment (0-9, 10+) plus job category[c]	-0.3% (-1.7%, 1.7%)
8.	10	Year of initial monitoring (1944-45, 46-49, 50+)	-0.7% (-1.9%, 0.7%)
9.	10	Workers with confirmed internal depositions excluded	-0.6% (-1.9%, 1.0%)
10.	2	None	-0.2% (-1.0%, 0.7%)
11.	2	Years since termination of employment (0-1, 2+) plus job category[c,d]	-0.1% (-0.9%, 1.0%)
12.	15	None	-1.3% (-2.0%, 1.1%)

[a] All analyses were controlled for age, calendar year, and sex, and, except for analyses numbers 2 and 3, for number of years monitored (1-4 versus 5+).

[b] Strata for job category were white collar and nuclear workers combined, craftsmen, and service workers.

[c] Strata for job category were white collar, nuclear workers and craftsmen combined, and service workers.

[d] Based on the same stratification variables as analyses presented in the appendix. The analysis in the appendix included only monitored males who were employed at Hanford for at least 2 y.

(1) From Gilbert *et al*, 1989[19]

Table 17

(4) Risk estimates* with 90% confidence limits for all cancer. Based on monitored white males employed at least 6 months at the Hanford Site (WA), Oak Ridge National Laboratory (TN), or Rocky Flats Nuclear Weapons Plant (CO)[1]

	Excess relative risk (per 10 mSv)	*Absolute risk (per 10^4 person-years per 10 mSv)*
Hanford	−0.9% (<0, 0.9%)	−29 (<0, 26)
ORNL	−0.7% (<0, 3.2%)	−16 (<0, 65)
Rocky Flats	<0[b] (<0, 2.8%)	<0[b] (<0, 48)
Combined	−1.0% (<0, 0.4%)	−30 (<0, 11)
A-bomb survivors[c]		
All with DS86 doses	0.41% (0.32%, 0.52%)	10.1 (8.0, 12.4)
Males only	0.25%	
Exposed over age 20	0.34%	
1950–1970 only	0.27%	

Note. Doses lagged for 10 years.

[a] Based a linear relative risk model with confidence limits based on the score statistic.

[b] Likelihood maximized at a value that would have led to negative relative risks.

[c] As presented in Shimizu *et al.* (*18*) for all cancer except leukemia, for the period 1950–1985, based on DS86 estimated dose to the large intestine.

(1) From Gilbert *et al*, 1989[19]

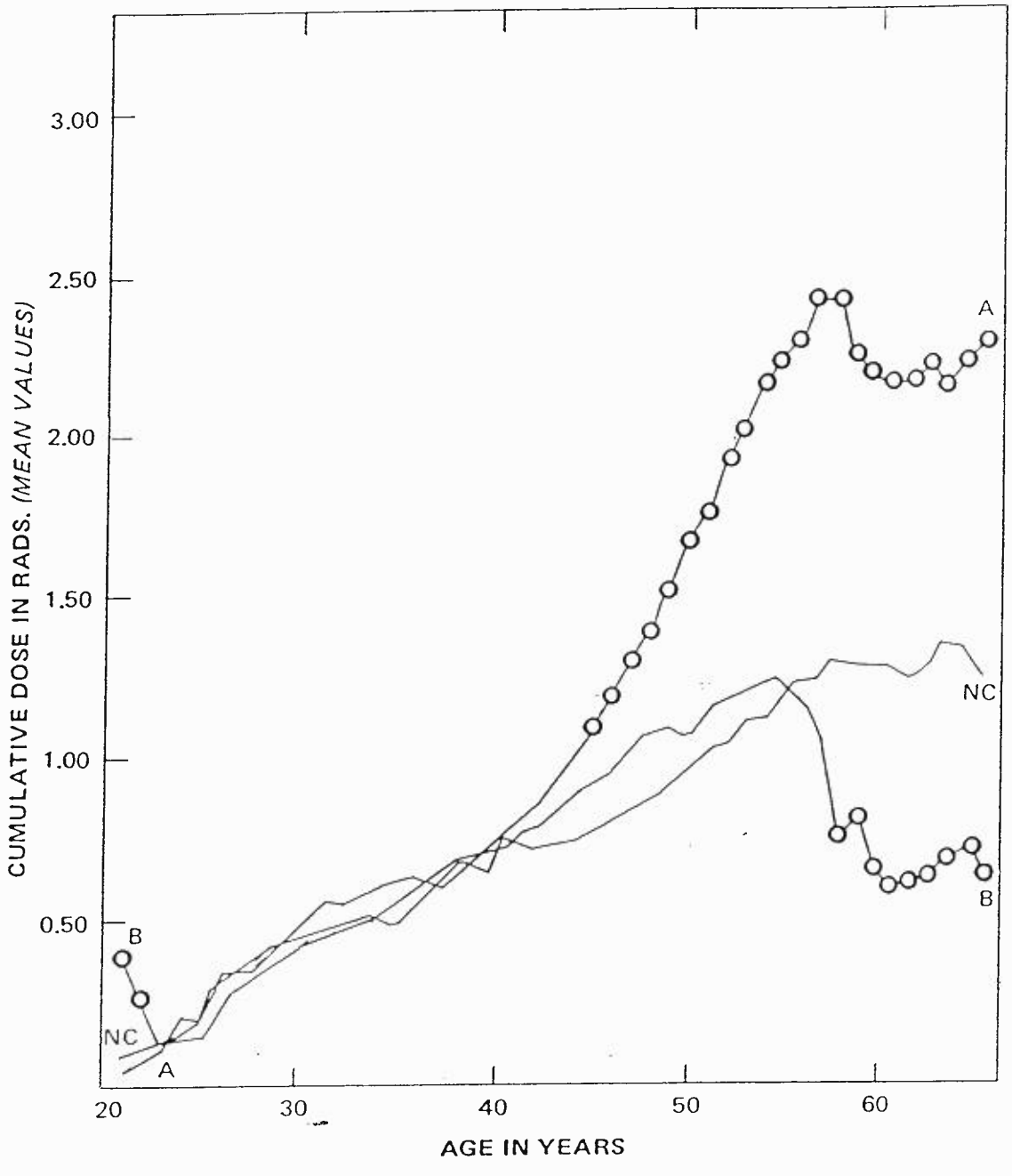

Figure 1

Age trend of cumulative radiation for the groups of male workers. (NC) Noncancers; (A) sensitive cancers; (B) other cancers; (o) any cancer dose that differs by a significant amount from the corresponding dose for noncancers.

From Stewart *et al* , 1980[12]

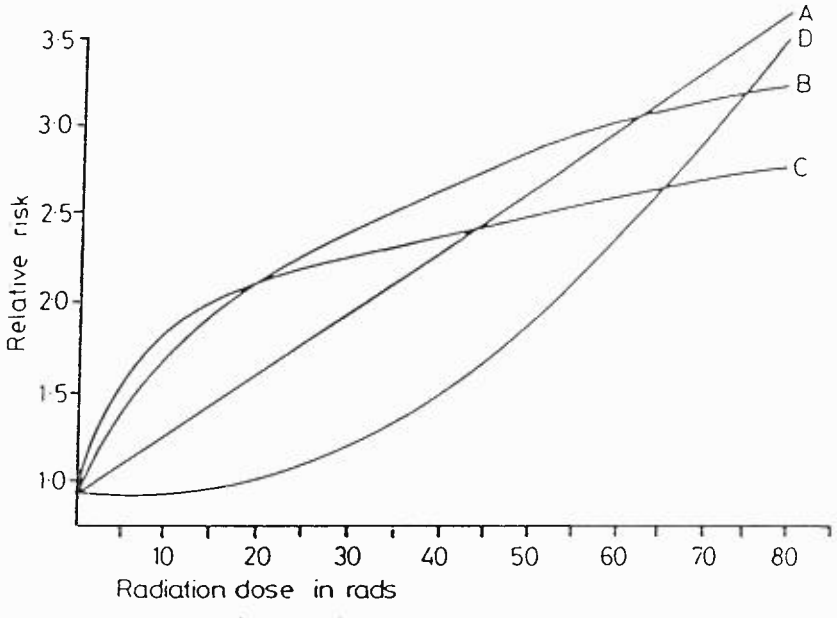

Fig 2 *Typical dose-response curves of relative risk (R) against cumulative dose (Σx) for various values of the parameters (D and E) in the simple model: $R = 1 + (\Sigma x/D)^E$. Curve A: D = 30 rads, E = 1·0 (linear law). Curve B: D = 15 rads, E = 0·5 (square-root law). Curve C: D = 15 rads, E = 0·3333 (cube-root law). Curve D: D = 50 rads, E = 2·0 (quadratic law).*

From Kneale *et al*, 1981[13]