LBL-34154

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The Association Between Cancers and Low Level Radiation: An Evaluation of the Epidemiological Evidence at the Hanford Nuclear Weapons Facility

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May 1993

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THE ASSOCIATION BETWEEN CANCERS AND LOW LEVEL RADIATION: AN EVALUATION OF THE EPIDEMIOLOGICAL EVIDENCE AT THE HANFORD NUCLEAR WEAPONS FACILITY

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This work was supported by the Director, Office of Epidemiology and Health Surveillance; Office of Health; Office of Environment, Safety and Health; U.S., Department of Energy under Contract No. DE-AC03-76SF00098

DISCLAIMER

This paper was written for a Graduate Seminar that is part of the master's program in Epidemiology/Biostatistics at the University of California at Berkeley. It is not intended to be an exhaustive review of the literature on the Hanford Nuclear Production Facility.

Cancer has traditionally been linked to exposure to high doses of radiation, but there is considerable controversy regarding the carcinogenicity of low doses of ionizing radiation in humans. Over the past 30 years there have been 14 studies conducted on employees at the Hanford nuclear weapons facility to investigate the relationship between exposure to low doses of radiation and mortality due to cancer (1-14). Interest in this issue was originally stimulated by the Atomic Energy Commission (AEC) which was trying to determine whether the linear extrapolation of health effects from high to low dose exposure was accurate (see Appendix for the occupational radiation protection standards in the United States). If the risk had been underestimated, then the maximum permissible occupational radiation exposure in the United States had been set too high. Because the health risk associated with low level radiation are unclear and controversial it seems appropriate to review the studies relating to Hanford at this time.

BACKGROUND INFORMATION

The Facility

Hanford, located in Richland, Washington, was established in 1942 as part of the Manhattan Project. Large quantities of radioactive material were manufactured, refined, and stored at Hanford. Originally, Hanford's main activity was to produce plutonium, which began on a large scale in 1944. Since Hanford opened, research involving radioactive substances, including power generation, has taken place. Over 40,000 people, predominantly white males, have been employed in occupations that are continuously monitored for external radiation. Some early employees, such as the construction workers, were not monitored. Workers in high risk jobs are periodically tested for internal depositions of radioactive substances. In fact, data on all workers since the facility opened has been thoroughly maintained, and it includes information on sex, date of birth, dates of entering and leaving the facility, annual external doses, internal doses for high risk occupations or following accidents, date of death, cause of death, and other factors. Due to the small number of women employed, and particularly the small number exposed to radiation, most Hanford studies are based on the male population. As a consequence, this review will focus on the results of analyses that pertain to men. The large work force, the systematic recording of occupational data on all employees, and the facility's long history (which spans cancer's long latency period) makes Hanford an ideal facility to study the relationship between low doses of radiation and cancer (7, 15).

At Hanford, radiation exposure was primarily gamma, but also included neutron, some of the higher X-ray radiations, and tritium exposures. To calculate the dose equivalent, the quality factors for fast neutrons, slow neutrons, tritium, and for all other types of radiation are 10, 3, 1.7, and 1, respectively (13, 16, 17). It should be noted that is unclear whether the dosimeters used to measure exposure were able to distinguish accurately between different types of radiation before 1972 (17). (This will be discussed in more detail after the results of the studies are presented.) In order to avoid confusion and ease valid comparisons, all units have been converted to sieverts, the current measurement system (see Appendix for radiological units).

Standard Analysis

Standardized mortality ratios (SMR) identify diseases that show excess mortality in the study population and determine whether the pattern of such diseases seems consistent with a causal association with occupational exposure. Most of the studies calculated SMRs by comparing the observed death rates among the cohort to the expected mortality rates for the United States population. The national rates were adjusted for age and calendar year of death. SMRs can be calculated for subgroups of the study population defined by age, length of employment, latency period of the disease, and quantitative measures of exposure (i.e. 0-5 mSv, 6-10 mSv, etc.) (7). In order to calculate the SMRs, several of the studies used a computer program developed in 1974 by Richard Monson, which provides SMRs for 23 categories of cancer and 34 other disease categories (7). Since the Monson program produces so many estimates regardless of multiple-testing power concerns, caution should be used when inferring significance from the results. In addition, the use of SMRs limits the analysis because it requires an external control group, and, as a result, adjustments can only be made for variables for which data exists from the control population.

The proportionate mortality ratio (PMR) contrasts the proportion of observed deaths from specific disease in the exposed population with the proportion of expected deaths from a non-exposed population. The cause-specific expected deaths are calculated by multiplying the total number of deaths in the study population by the rate of death for the specific disease in the reference population (18).

Bias introduced by using external control groups can be eliminated by comparing groups internally. Methods developed by Mantel-Haenszel, Mantel (trend test), and Cox (proportional hazards model) allow for direct comparisons while adjusting for specific confounders. In an attempt to standardize the trend tests and tests

for differences among subgroups performed in occupational studies, Buchanan developed the Mortality and Occupational exposure computer program (MOX) in 1979 (19). Most of the studies in this review were done before MOX was developed; however, some of the later studies did use this program.

For trend tests, workers are first grouped into exposure categories, which can be lagged to reflect latency assumptions about the cancer of interest. The expected deaths for each exposure category are then calculated based on the entire study population's mortality and finally the categories are analyzed for mortality trends associated with increasing exposure. The tests can be adjusted for a number of variables, including length of employment, calendar year, and age (7). In addition to the information gained by these statistical techniques, the use of an internal comparison group allows the investigators to compare workers who are as similar as possible in every respect except for their level of radiation exposure. Hence selection bias from the use of an inappropriate control group is alleviated (20).

The comparative mean dose method (CMD) is used to determine whether there is an association between cancer mortality and radiation exposure. In a CMD analysis, only workers within the facility are used. In the studies presented in this paper, cases and controls were either defined as cancer and non-cancer deaths, respectively or as deceased and living workers, respectively. The mean and variance of radiation doses for the two groups are calculated, and the null hypothesis -- that the two groups are the same with respect to cumulative mean dose -- is tested by a t-test (5).

Many studies attempted to determine the exposure dose needed to increase cancer mortality by calculating the doubling dose, which is defined as "the amount of radiation required to add a frequency of cancer equal to the spontaneous frequency, during a specified period (21, p.364)." In other words, it is the radiation dose just sufficient to double the normal risk of a cancer death. Based on the doubling dose the number of radiation-induced cause-specific deaths within the study population are calculated.

THE STUDIES

Conflicting results about the cancer mortality experience at Hanford have created considerable scientific, public and political controversy (22). The studies reviewed in this paper will be presented in chronological order to show both the development of the controversial findings as well as the results from newly obtained data.

Early Studies

Six of the original studies from the early '70s, five by Mancuso and one by Milham, were government publications or progress reports that were unavailable through public sources. All were discussed in later studies, and all appear to be of a preliminary nature. Mancuso's early studies led to the conclusion that the mean cumulative dose (MCD) of external penetrating radiation was lower for deceased than for living workers. Mancuso refused to publish (in journals) his early works because he felt his results could be misleading since a proper latency period for cancer had not yet passed (15). Milham's analysis consisted of calculating proportional mortality for men. He found that cancer of the pancreas and of the large intestine showed an elevated PMR; multiple myeloma had a slightly elevated PMR; and leukemia had a low PMR. However, his findings were considered preliminary due to his lack of information on more than one-half of the deaths (3).

Sanders

In 1975, Sanders conducted an historical cohort study on Hanford employees hired between 1944 and 1971 who had been monitored for exposure (1). The cohort consisted of 17,600 males and 3,900 females. Analyses were performed on several different subsets of the study population. For all the male subsets, the MCD of radiation increased progressively over time, as determined by the near-perfect correlation between the MCD and time. The mean radiation dose went from 1.42 mSv in 1944 to 37.45 mSv in 1972. However, when the MCD for deaths from cancer was compared to the MCD for deaths from other causes, the results for each year (1944-72) were not statistically significantly different. In addition, when the MCD for all deaths was compared to the MCD for survivors for each year, the mean dose for deaths was almost always lower. If it was higher, it was not statistically significantly higher. Although there was a progressive increase in the mean dose level over time, the proportion of deaths from cancer over time did not increase significantly. Based on these results, Sanders concluded that there was no indication that radiation exposure within the standard occupational limits was the cause of the increase in male deaths at Hanford. The SMR for all cancer deaths among exposed males is 114 and it is statistically significant ($p = 0.03$).

Mancuso, Stewart, and Kneale

In 1977, Mancuso, Stewart, and Kneale (hereafter referred to as Mancuso et al.) conducted a facility-based case-control study on white employees of Hanford who worked there between 1944 and 1972 (2). There

were 670 cases of cancer mortality. These were compared to 2,850 controls with death from other causes. Based on an informal review of the data, they concluded that the cancer deaths contained a higher percentage of exposed workers and had a higher mean cumulative radiation dose in comparison to non-cancer deaths. No statistical tests were done to compare the two groups. The SMR for all cancers was 100. Mancuso et al. discussed in detail several factors which could have confounded their analyses, including calendar year of exposure, employment year of exposure, pre-death year of exposure, exposure age, and death age. By examining each factor individually, they concluded that when controlling for each variable the causal association between exposure to external radiation and cancer deaths was strengthened. They then proceeded with several statistical analyses without controlling for these variables separately or simultaneously. In fact, only pre-death year is controlled for in some of the analyses contained in their paper.

Mancuso et al. found a higher mean cumulative radiation dose at death for (i) reticuloendothelial system (RES) neoplasms, (ii) pancreatic cancer, and (iii) bone marrow cancer (which they defined as the combination of myeloid leukemia and multiple myeloma) when compared with all non-cancer deaths ($p < 0.05$). However, for all cancers as a group and for the category lung cancer a statistically significant elevated MCD for cancer deaths was found only when looking at MCDs in a variety of pre-death periods ($p < 0.05$).

The doubling dose for all cancers was 120 mSv. Mancuso et al. calculated the doubling dose using the observed doses cumulated up to the pre-death interval showing the maximum contrast between dose to cancer deaths and dose to non-cancer deaths. By using the maximum contrast the authors insured an unusually low doubling dose. The authors estimated that 25.8 cancer deaths out of 442 cancer deaths in the study population were induced by radiation.

Marks, Gilbert and Breitenstein

In 1978, Marks, Gilbert, and Breitenstein conducted an historical cohort study on white males hired before January 1, 1965 (3). Death ascertainment was compiled until April 1, 1974. SMRs were calculated for two groups separated by length of employment, defined as less than two years (<2) or two or more years (+2). Statistically significant, though low, SMRs were found for all causes, all malignant neoplasms, carcinoma of the lung, and leukemia ($p < 0.02$). The SMRs for all cancers were 88 and 85 for <2 and +2, respectively. The SMRs for all causes were 86 and 75 for <2 and +2, respectively.

For the trend test, the study population was further restricted to only those men employed for two or more years whose date of termination of employment was after January 1, 1960. In the statistical test for trend, neither cancer nor non-cancer mortality was found to be correlated with levels of radiation exposure ($p > 0.05$). However, both multiple myeloma ($p = 0.01$) and carcinoma of the pancreas ($p = 0.03$) were statistically significant in the trend test. The mortality rates for white males, aged 25-70, and for three exposure categories (0-20, 20-50, 50+ mSv) were calculated and compared with United States white male mortality rates. In all cases the rates were lower for the study participants, except for malignant neoplasms (20-50 mSv), where the rate was equal.

Kneale, Stewart and Mancuso

In 1978, Kneale, Stewart, and Mancuso (hereafter referred to as Kneale et al. (1978)) reanalyzed the Hanford data in a facility based case-control study, with follow-up information through 1977 (4). Certified death and exposure information was available on 3,742 men and 291 women. The mean radiation dose was higher for all cancers compared to non-cancers after simultaneously controlling for sex, age at death, death year, internal radiation, exposure period, and external exposure. Results of the controlled comparison of the mean doses were not actually presented in the paper. In a CMD analysis for the 16 years prior to death the mean cumulative dose was statistically significantly greater for cancers than non-cancers ($p < 0.05$). The radiosensitive tissues classified by ICRP as high sensitivity established and high sensitivity apparent account for this statistical significance (Table I). The doubling dose for men was 337 mSv with a 95% confidence interval of (153, 797) which infers that 35 of the 743 male cancers were radiation induced.

Hutchison, MacMahon, Jablon, and Land

In 1979, Hutchison et al. reviewed and reevaluated the study by Mancuso et al. (5, 2). The facility-based case-control study population consisted of 2,238 males with certified deaths and external exposure information through 1973. Hutchison was unable to explain the differences between the number of participants in his study and those of Mancuso et al. but cumulative doses at death were very similar except in 2 categories of disease that were not in question. In a trend test, using standardized PMRs, carcinoma of the pancreas ($p = 0.011$) and multiple myeloma ($p = 0.009$) were significant, hence there is a linear trend of proportionate mortality with cumulative dose at death. A third set of trend tests done on standardized PMRs at 5, 10, and 15 years prior

to death verified Mancuso et al.'s conclusions that a significant association between dose and proportionate mortality of all cancers was only found by looking at a series of intervals prior to death. At death ($p = 0.13$) and at 5 years prior to death ($p = 0.22$) the association was not significant but 10 years prior to death the association was significant ($p = 0.04$) and 15 years prior to death the association was close to significance ($p = 0.07$). The doubling dose for cancer, adjusted for year at death and age, was 120 mSv.

Gofman

In 1979, Gofman also reviewed and reanalyzed data from both of the Mancuso studies (2, 4, 6). The cohort for the facility-based case-control study consisted of deceased white males, monitored for external radiation, who survived 15 years beyond their respective dates of hire. Individuals that had internal depositions recorded were excluded from the analyses due to potential confounding from internal dose. After exclusions there were 3,193 subjects with exposure less than 100 mSv and 115 subjects with exposure greater than or equal to 100 mSv. In order to make the cancer and non-cancer groups comparable Gofman made corrections for age at hire, age at death, and total number of years worked by adding eight cancer cases before he began any statistical analyses. This is done instead of the standard technique of controlling for such variables. To test whether there was an association between radiation of 100+ mSv and cancer induction, Gofman performed a chi-square test to compare the ratio of the number of malignant deaths versus the number of non-malignant deaths for the low to high dose groups. The chi-square test was statistically significant ($p = 0.047$) confirming Mancuso's results of an association between radiation, accumulated at rates below the permissible dose, with cancer induction. Gofman felt that it was not appropriate to test for a dose-response relationship with this data since there were too few cases with doses in the 50-100 mSv range. The doubling dose for all cancers was 430 mSv but has extremely wide 95% confidence intervals $(180,\infty)$. Based on this doubling dose, 23 cancer deaths can be attributed to radiation.

Gilbert and Marks

In 1979, Gilbert and Marks conducted an historical cohort study on 20,842 white males, hired before 1965 (7). The analysis focused on 13,075 white males who had been employed for two or more years. Follow-up on exposure and mortality information was complete through April 1, 1974. For males the SMRs for all cancers were 88 and 85 for less than two (<2) and two or more (2+) years of employment, respectively, and

were statistically significant ($p < 0.02$). For males the SMRs for all causes were 86 and 75 for the <2 and 2+ years of employment, respectively, and were statistically significant ($p < 0.01$). When SMRs were stratified individually by length of employment, employment status, age, and occupation, none of them were elevated. For the exposure analyses the investigators included only male participants who survived until January 1, 1955, had exposure data, and had worked for 2+ years. This resulted in a cohort of 12,522 white males with 1,826 deaths. The tests for trend, lagged for two and 10 years, showed no evidence of a positive correlation of radiation exposure with death from all causes or all cancers ($p >> 0.05$). For the two year lag, both carcinoma of the pancreas and multiple myeloma showed evidence of a positive correlation with radiation exposure ($p = 0.07^*$ and $p = 0.006$, respectively). The evidence of a positive correlation for both of these cancers with exposure was probably due to small number of deaths in the highest exposure category. For multiple myeloma three deaths were observed and 0.5 deaths were expected and from cancer of the pancreas there were three deaths compared with one expected. In the trend test with a 10 year lag multiple myeloma remained statistically significant ($p = 0.0006$), but cancer of the pancreas was no longer significant ($p = 0.29$). Adjusted mortality rates, stratified by exposure levels (0-20, 20-50, 50+ mSv), for all causes and all malignant neoplasms were lower than the rates for United States white males.

Gilbert and Marks

In 1980, Gilbert and Marks updated their 1979 study with follow-up data through May 1, 1977 (7, 8). In this cohort study the same restrictions were placed on the study population as were used in the earlier study. An additional 390 deaths had occurred, 94 of these from cancer -- bringing the total number of male deaths to 2,216. A test for trend, lagged for two years, yielded evidence that carcinoma of the pancreas and multiple myeloma were significant ($p = 0.06^*$ and $p = 0.0006$, respectively), but that all causes and all cancers were not statistically significant ($p >> 0.05$). It is interesting to note that the p-value from the trend test for cancer of the stomach was reduced to 0.13 from 0.82. There were three new deaths in the 150+ mSv exposure group from cancer of the stomach.

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* This p-value is slightly underestimated. Due to the small number of cases the significance level can not be accurately determined from the chi-square or normal distribution.

Tolley, Marks, Buchanan, and Gilbert

In 1983, Tolley, Marks, Buchanan, and Gilbert updated their 1979 study with follow-up data through January 1, 1979 (7, 9). The cohort was extended to include all employees working for two or more years which resulted in a study population of 15,992 including 2,500 certified deaths. In the test for trend, lagged for two years, multiple myeloma was statistically significant ($p << 0.01$). However, the trend test for pancreatic cancer was no longer significant due to four additional deaths from cancer of the pancreas in the two lowest exposure categories ($p = 0.17$). In addition, all causes and all cancers were not statistically significant ($p >> 0.05$). Evidence of a positive correlation for cancer of the stomach and exposure is nearing statistically significance ($p = 0.08$).

Kneale, Mancuso, and Stewart

In 1981, Kneale, Mancuso, and Stewart (hereafter referred to as Kneale et al. (1981)) conducted an historical cohort study on the Hanford workers (10). The cohort consisted of monitored employees of the facility up until 1975. Mortality data was ascertained up until 1977. In many of the previous studies at Hanford living employees have higher MCDs than deceased employees. Kneale et al. (1981) have attributed this to the healthy worker effect within the work place (workers in higher exposure jobs are healthier prior to employment than workers in lower risk occupations). The healthy worker effect was controlled for in two ways: dangerousness of the work performed based on job specifications (hazard index) and by bioassay records. By controlling for the healthy worker effect, they hoped that the MCDs for dead workers would be higher than the MCDs for living workers. If the test statistic was positive than the mean dose for deaths was higher.

When controlling for sex, work cohort, hire age, employment period, and highest bioassay level reached by each worker, there was not a statistically significant difference in the MCD between living and dead workers due to all causes of death ($t = -0.48$, $p = 0.63$). For two groups of cancers of radiosensitive tissues, high sensitivity established plus RES neoplasms, all digestive cancers, and breast cancers (hereafter referred to as group A), and high sensitivity apparent (hereafter referred to as group B), there was a significant difference between the mean cumulative doses for living and dead workers (t-values 2.47 and -2.20, respectively and p-values 0.01 and 0.03, respectively) (Table I).

When sex, work cohort, hire age, and hazard index are controlled for the test statistics for all causes of

death and group A were both positive, but group B had a negative test statistic and was no longer significant (t-values were 0.12, 2,24, -1.88, respectively and p-values were >0.05, <0.05, >0.05, respectively). In addition, no explanation was given for not controlling for employment period in this series of tests.

Concerned over the negative findings in group B, Kneale et al. (1981) performed the test again excluding sudden deaths (myocardial infarctions and accidental deaths) and controlling for place of death in order to account for under-reporting of cancer deaths. For group A and group B the t-values were 2.07 and 0.14, respectively ($p = 0.05$ and $p > 0.05$). From the results of their final analysis the MCDs of radiation were statistically significantly higher for the dead individuals in group A. In group B the MCD was higher but not statistically significant. For this test the results for all causes were not presented.

The maximum likelihood estimate of the doubling dose was 150 mSv for the half-power model and 300 mSv for the linear model.

Darby and Reissland

In 1981, Darby and Reissland conducted an historical cohort analysis on 13,076 monitored, white males employed prior to 1965, who had worked for at least 2 years (11). Mortality data ascertainment was complete up until April 1, 1974. Of 2,089 deaths, 49 did not have a cause of death available. In the SMR analysis, which excluded deaths that occurred less than five years after commencing employment, the SMRs for all cancers, all causes, carcinoma of the pancreas, and leukemia were all lower than 100 -- only all causes was statistically significant ($p < 0.01$). Multiple myeloma showed an elevated, though not statistically significant, SMR of 114. Tests for trend, lagged for 10 years and between two and 10 years, further excluded individuals whose death occurred over the age of eighty or if all of their person years at risk were in a single dose category. For both trend tests the majority of the T-values were negative, including the values for all causes and for all cancers. However, multiple myeloma, cancer of the pancreas and cancer of the kidney had positive T-values for both trend analyses. In the 10 year lag multiple myeloma ($p << 0.01$), and kidney carcinoma ($p < 0.01$), were statistically significant and cancer of the pancreas was not ($p = 0.13$).

Gilbert, Fry, Wiggs, Voelz, Cragle, and Petersen

In 1989, Gilbert, Fry, Wiggs, Voelz, Cragle and Petersen (hereafter referred to as Gilbert et al. (1989)) conducted a combined analysis of Hanford, Oak Ridge National Laboratory (ORNL), and Rocky Flats Nuclear

Weapons Plant (12). The historical cohort study consisted of monitored white males who were employed for at least six months. The year for which follow-up was complete varied for individual sites: Hanford through 1981, ORNL through 1977, and Rocky Flats through 1979. The SMRs for all cancers were 82, 82, 66, for Hanford, ORNL, and Rocky Flats, respectively. In the trend tests for each of the facilities, as well as for the combined population, the relationship of cancer mortality and radiation exposure was in a negative direction, although never statistically significant. Except for Hanford the relationship between non-cancer mortality and radiation exposure was in a positive direction. Only for Rocky Flats was the trend statistically significant ($p < 0.01$). Multiple myeloma and radiation exposure showed a significant trend for Hanford and for the combined study ($p << 0.05$). Neither of the other facilities had deaths due to multiple myeloma. Pancreatic cancer was not significant for any of the facilities or for the combined study. For the study population the relative risk estimates for all cancer mortality from 50 mSv of exposure were 1.06, 1.23, 0.82, 1.06, for Hanford, ORNL, Rocky Flats, and the combined study, respectively. Using a linear relative risk model, the absolute risk estimate for the combined study and for Hanford were -30 with 95% confidence limits (<0,11), and -29 (<0,26), respectively.

Gilbert, Petersen, and Buchanan

In 1989, Gilbert, Petersen and Buchanan updated their previous study to include an additional three years of data (1979-81) (13). In their historical cohort study all workers, other than construction workers, initially employed at the Hanford site during the years 1944-1978 were included. Cause of mortality information was complete through 1981. The cohort consisted of 31,500 males and 12,600 females. The SMRs for all cancers were 85 and 85 for all workers and males, respectively. In a trend test, controlled for age, calendar year, sex, and length of employment, with a 10 year lag the direction of the correlation of mortality with radiation exposure was negative for all causes of death and all cancers (males) ($p = 0.13$ and $p = 0.18$). Both multiple myeloma and female genital cancer were statistically significant ($p = 0.002$ and $p = 0.046$, respectively). It is interesting to note that cancer of the pancreas was not statistically significant ($p = 0.39$). Relative risks estimates were elevated for all cancers, and several subgroups of cancer, including lung cancer and leukemia, in some exposure categories, but all of the confidence intervals included unity. Multiple myeloma had elevated relative risks and 95% confidence intervals of 8.52 (1.9, 38) and 14.7 (3.6, 600) for the 50-149, and 150+ mSv exposure categories, respectively. Additional mortality information was available for Washington state for the years 1982-

5. There were 189 new deaths from cancer and 35 of those had doses exceeding 50 mSv. These doses are higher than doses characteristics of earlier workers. Statistical tests showed no change in association of radiation exposure with cancer mortality but these tests were preliminary. Using a linear model, the absolute excess risk at Hanford for all cancer except leukemia was -13 deaths per million person years per 10 mSv with 95% confidence interval (-59, 44).

Petersen, Gilbert, Buchanan, Stevens

In 1990, Petersen, Gilbert, Buchanan and Stevens conducted a case-cohort analysis of lung cancer deaths in the Hanford population (14). The study population consisted of white males monitored for external exposure for at least three years, and terminated employment after January 1, 1965. The control group, referred to as a sub-cohort, which was compared to the lung cancer cases was a random sample of the cohort with employment dates and age similar to the cases. Smoking information was obtained from medical records. There was no statistical evidence of a trend of increasing lung cancer risk with increasing cumulative dose, with or without adjustment for smoking status. Based on a linear relative risk model the excess relative risk when adjusting for smoking was -0.7 per 10 mSv (<0, 9.9).

CAUSAL INFERENCE

Quality of Exposure Records

At Hanford, surveillance of radiation exposure on employees was done for safety reasons. As a result, the amount of radiation received by each worker was overestimated, to err on the side of safety. The overestimation of exposure means that the risk for the exposures received by workers is potentially underestimated.

The accuracy of the recorded exposures was limited by the dosimeters used to measure exposure, though dosimeters improved over time. Between 1944-1956 a two-element film dosimeter was used and it generally resulted in an underestimation of recorded dose because it had problems in measuring plutonium X-rays and due to its inability to accurately distinguish neutron radiation from other types of radiation. Between 1957 and 1971 a multi-element film dosimeter was used because it was able to measure plutonium X-rays more efficiently. Between 1972-1989 a thermoluminescent dosimeter was employed due to its ability to accurately separate out and measure neutron radiation (17).

Another problem in the quality of exposure records was that Hanford's official records of doses were maintained in rems, implying the ability to separate different types of radiation (10). However, prior to 1957 it was difficult to distinguish between types of radiation with any real accuracy. Although measurement capabilities improved in 1957, it was not until 1972 that neutron doses were measured accurately. When all types of radiation are lumped together without any real ability to distinguish between the different types, a conversion from absorbed dose to dose equivalent can only be done based on the assumption that the quality factor is 1, or 1 rad = 1 rem. It is clear that at Hanford the quality factor was not always 1, as noted in the introduction different types of radiation have different quality factors. For example, roughly 2.3% of recorded dose in rem was due to neutrons, and prior to 1972 the neutron dose itself was underestimated (13).

The quality of exposures was also affected by the skewed distribution of annual and cumulative doses at Hanford (see histogram of cumulative exposure at Hanford). The majority of workers at Hanford received very little radiation. Between 1948-1978 there were 274,561 annual doses and of these 99% were less than or equal to 50 mSv. In fact, only 18 annual doses during this entire time period were greater than the annual effective dose equivalent of 50 mSv set in 1977. For cumulative exposure 32,955, or 91%, of the 36,259 monitored employees had doses that were less than or equal to 50 mSv by the end of 1978 (see histogram of cumulative exposures at Hanford <= 50 mSv).**

Consistency of Results

Healthy Worker Effect and Standardized Mortality Ratios

The SMRs for deaths from all causes and deaths from all cancers are all below 100, except for the Sanders study in which the expected values were based on white males in Washington State (Table II). However, the reduction in the SMRs should not be interpreted to mean that radiation exposure is protective. Instead, the SMRs should be looked at in conjunction with the healthy worker phenomena that is seen frequently in many occupational groups. Employees tend to be healthier due to a variety of things: health insurance, medical surveillance programs, and the socio-economic benefits of steady employment. The magnitude of the healthy worker effect varies with disease categories. It is generally accepted that the benefits of a job are less

**The data used to compute these statistics and create the histograms was obtained from the Comprehensive Epidemiologic Data Resource. The Hanford analysis file, called hanfrd1.d2 as of February, 1993, was used.

protective for most cancers than for other diseases (3). Also, the healthy worker effect on cancer as compared to other diseases is more visible over longer time periods. For instance, in Marks' 1978 study, the SMRs for all cancers are 88 for less than two years (<2) of exposure and 85 for two or more years (+2) of exposure. These are very similar values even though the time period of exposure differs. The SMRs for all causes are 86 and 75 for <2 and +2 years of exposure, respectively. In the short term, the SMRs for all cancers and all causes are close (88 and 86). However, over the long term the SMRs differ from each other (85 and 75) (3).

It should be noted that for some specific cancers the SMRs were statistically significant but in a decreased direction, i.e. lower than 100. Carcinoma of the pancreas and multiple myeloma often had elevated SMRs although they were never statistically significant and had wide confidence intervals (Table II).

Comparative Mean Dose Method

It is difficult to draw conclusions regarding the relationship between low levels of radiation and cancer induction from the CMD analyses, not only because of the discrepancies between the authors' results and methodologies but also due to faulty statistical procedures. In Sanders' study it was demonstrated that the MCD increased over time but that the proportion of cancer deaths did not increase over time. And when compared for each year of the study the MCD for cancer deaths was not statistically significantly different from the MCD for other causes. When the MCD for all deaths was compared to the MCD for survivors for each year, the mean dose for deaths was almost always lower. This evidence leads to the conclusion that radiation exposure at low levels does not cause an increase in cancer (1).

In the 1977 CMD analysis performed by Mancuso, Stewart and Kneale, they did not control for any variables. For all cancer deaths the MCD were only statistically significantly higher in certain pre-death years. A statistically significant difference in MCD between cancer and non-cancer deaths was found at death for RES neoplasms, pancreatic cancer, and bone marrow cancer. Mancuso et al. have been highly criticized for their grouping of myeloid leukemia and multiple myeloma into the category of bone marrow cancer, and in their later studies they switched to the ICRP categorization of cancers (2). Since myeloid leukemia as its own category did not show an effect in any of the other studies the significance for the bone marrow group has been accredited to multiple myeloma. In their 1978 CMD analysis in which there is simultaneous control for sex, age at death, date of death, internal radiation and exposure period, the same three investigators claim that the mean radiation doses

for cancers were higher than for non-cancers, but they do not say if it is statistically significant and they do not actually provide the results of tests in their paper (4).

In their 1981 analysis the MCD for all causes of death and two cancer groups was compared for living and deceased workers (10). For the first cancer group, called high sensitivity established (which included some additional cancers), the MCD for deceased workers was statistically significantly greater than for living workers in all analyses done. But, in the second cancer group, called high sensitivity apparent, the MCD for the dead was greater than for the living only in the final analysis and even then it was not statistically significant. It also appears that the authors did several analyses, i.e. controlling for different variables in various combinations, until the MCD for deceased workers was higher than for living workers, or until their results fit their hypothesis. The CMD analyses of these three investigators are difficult to interpret due to comparison groups changing, lack of controls, lack of results, and also the fact that their methods and results were not presented in a straightforward manner.

The CMD analyses performed on the Hanford data have also been criticized on statistical grounds. The CMD method uses a t-test and one assumption of the t-test is that the population from which the data are sampled is assumed to be normally distributed. But at Hanford the distribution of exposures is highly skewed making the t-test inappropriate (7). Due to skewed distribution of exposure, the evasiveness of Mancuso, Stewart, and Kneale, and the discrepancy between their results and Sanders', it is not clear which groups truly have a higher MCD, let alone whether there is a relationship between low level radiation and cancer.

Trend Test

In all of the trend test analyses the investigators chose different exposure categories making it difficult to compare the results of the studies (for trend test results see Table III). Because the researchers measured exposure in discrete categories they lost information. The majority of individuals are always in the lowest categories due to the skewed exposure distribution. In addition, the researchers all controlled for different factors in their analyses (Table IV). The results for the tests for trend demonstrate that all causes and all cancers are never statistically significantly associated with radiation. In some cases the test statistic was negative, i.e. there was a decrease in mortality with increase in dose. The lack of an association is not surprising based on the studies of atomic bomb survivors and on the studies investigating patients exposed to high doses of radiation for

the treatment of ankylosing spondylitis. These studies demonstrate that there appears to be a relationship for specific cancer sites, but not to cancer or all causes as a whole (5).

For radiosensitive tissues, particularly multiple myeloma and leukemia, only multiple myeloma was consistently associated with low level radiation at Hanford (3, 5, 7-9, 11-13). In the trend tests multiple myeloma continually showed a positive trend, or increases in mortality with increased exposure. The evidence from other studies for a relationship between multiple myeloma and radiation is inconsistent. Some studies on American radiologists and Japanese survivors of atomic bombs show higher multiple myeloma mortality with radiation exposure, while others disagree with that relationship (3). Leukemia never showed an association with low level radiation, which is contrary to what is expected from high level radiation studies (3). The fact that leukemia does not demonstrate a statistically significant association disturbs many of the authors and many feel that the lack of a relationship between leukemia and low dose radiation is critical evidence that workers are not at increased risk. Since leukemia does not show an association in low dose studies the other associations between low dose radiation and cancer might not be valid. However, the different types of cancer that develop could be the result of how the dose is received. Chronic exposure to radiation might manifest itself differently from acute exposure (4, 7).

Evidence for the relationship between pancreatic cancer and low doses of radiation at Hanford has changed over time. In the early studies there was a statistically significant increasing trend between exposure and pancreatic cancer mortality (3, 5), but as time progressed the statistical association ceased to exist (12, 13). In other studies an excess of cancer of the pancreas was seen in patients heavily irradiated for the treatment of ankylosing spondylitis but not in studies on medical specialists or the Japanese survivors life-span study (3).

In some studies specific cancer sites, kidney (11) and female genital (13), showed that a statistically significant relationship exists with low dose radiation. In addition, carcinoma of the stomach appears to be approaching statistical significance (7-9). Although these relationships might be spurious, they caution against drawing the conclusion that there only exists a relationship between multiple myeloma and low doses of radiation. There clearly might be other cancers associated with low dose exposures that could be uncovered in time, as the latency period passes and more deaths occur. Based on trend analyses the relationship between low doses of radiation and multiple myeloma is extremely consistent but for other cancer sites there does not appear

to be concrete relationships at this time.

Confounders

In the statistical tests performed in these studies there are several factors not controlled for that could potentially be confounding the relationship between cancer and low level doses of radiation. The key confounders are:

1. Smoking. Smoking is known to be related to cancer, especially lung cancer. Data on smoking at Hanford is not readily available or complete. In the one study that obtained smoking information at Hanford, the association between lung cancer and radiation remained essentially the same with and without controlling for smoking habits (14). There was not a statistically significant trend.

2. Internal radiation. There were only three individuals with confirmed internal radiation depositions who subsequently died of cancer, one each from cancer of the brain, buccal, and lung (7). Internal radiation was not confirmed by depositions in cancer types that showed positive correlations with low doses of radiation (multiple myeloma and pancreatic cancer).

3. Other chemicals. For the workers dying from cancer of the pancreas and multiple myeloma there is no evidence to suggest that these individuals were involved in chemical exposure. However, records regarding chemical exposures and other hazards were incomplete and less reliable than records on radiation exposure (7).

These three variables are important potential confounders because in all likelihood they are differential among cases and controls. These confounders could have strongly influenced the relationship between low level doses of radiation and cancer, but there is not significant data available on these variables to confirm their effect.

Misclassification

In addition to confounding, misclassification of disease is a problem in all of these studies, particularly for cancer of the pancreas. Studies have looked at the discrepancies between clinical and autopsy diagnoses of pancreatic cancer. In the Atomic Bomb Casualty Commission study only 62% of diagnoses of cancer of the pancreas recorded on death certificates were confirmed at autopsy (7). Gilbert and Marks made an effort to check the validity of pancreatic cancer diagnoses but were never able to complete the task with any degree of certainty.

Extrapolation debates

The debate regarding the safety of workers exposed to low levels of radiation includes a smaller debate

over which extrapolation model best predicts low level risks from high dose exposures. Just as the issue of increased risk of cancer has not been completely resolved, neither has the issue regarding the extrapolation model. The domestic occupational standards are based on linear extrapolation. Some individuals, particularly Mancuso, Stewart, and Kneale, believe in a supralinear model because they feel that risk from low doses of radiation exposure are underestimated using a linear model. Others subscribe to the sublinear model, in which the effect of low dose exposure is even lower than what is estimated based on linear extrapolation.

Two statistical techniques used in the studies, absolute risk estimates and doubling dose, provide means of examining this issue. However, neither resolves the issue. The risk estimates based on linear models for all cancers were negative and the confidence intervals were fairly wide (12, 13). The span of the confidence intervals does not allow us to clearly distinguish whether the linear, supralinear, or sublinear model is appropriate for extrapolation.

Another interpretation of the risk estimates is that the Hanford data is useful in establishing the correctness of the ICRP estimates because the data rules out large departures from estimates. For instance, in Gilbert et al.'s (1989) study the absolute risk estimate derived from a linear models was -29 with 95% confidence intervals (<0,26). The upper confidence limit on this absolute risk estimate for Hanford is only six times greater than the ICRP estimate for all cancers except leukemia of four per 1,000,000 person years per 10 mSv (12).

At first glance the doubling dose for all cancers implies that a linear extrapolation model greatly underestimates the risk of exposure to low doses of radiation. The doubling dose estimates range from 120-430 mSv and are much lower than those estimated from a linear extrapolation from high dose studies, which would mean that the risk for individuals exposed to low levels of radiation is higher than previously thought (2, 5, 6, 10). However, when confidence intervals are presented for the doubling doses they are extremely wide (4, 6). Based on these doubling dose estimates there are between 20-35 radiation induced cancer deaths at Hanford. Once again, according to ICRP absolute risk estimates there should only be four cancer deaths other than leukemia per 1,000,000 person years per 10 mSv. In Gilbert et al.'s (1989) combined analysis, restricted to white males employees working at least six months, there were only 492,326 person years at Hanford (12). According to the ICRPs' numbers, the Hanford cohort does not have enough statistical power to detect excess

cancers.

CONCLUSION

Based on the Hanford studies, small carcinogenic effects, especially multiple myeloma, are frequently associated with low levels of radiation. However, the increase in risk is not unequivocal due both to the constraints of the studies mentioned in this paper, as well as the limited knowledge regarding the etiology of radiation induced cancers. The risk of developing cancer from ionizing radiation depends on many factors: the type of cancer, the size of the dose to a particular organ, the age and sex of the individual, the type of radiation, exposure to other carcinogens that may interact with radiation, the time of exposure -- acute or chronic exposure, and individual susceptibility.

Even though the etiology of radiation induced cancers is complex and the epidemiological studies on the Hanford facility are hindered with limitations, the studies do provide a means to evaluate whether risk estimates based on data from higher doses and at higher rates underestimate the effects of low level radiation on human health. Studies reviewed in this paper, as well as re-evaluations of high dose data raise doubts about occupational standards. Because of the underestimate of the risk, occupational standards may be set too high to protect workers from cancer mortality associated with low levels of radiation. Based on a reassessment of A-bomb dosimetry the Committee on the Biological Effects of Ionizing Radiation concluded that "the average dose equivalent [was] smaller than estimated heretofore; furthermore, the neutron component of the dose no longer appears to be of major importance.... As a result, lifetime risk of cancer attributable to a given dose of gamma radiation now appears somewhat larger than formerly estimated (23, p. 5)." Recall that the radiation exposure at Hanford is primarily gamma.

Nuclear weapons production is declining, but there are many ways in which people are exposed to low doses of radiation, including but not limited to development and use of nuclear power and clean-up of nuclear waste. In order to validate the risk associated with low level radiation and to establish safe occupational radiation standards additional research is necessary. Further research on the employees at Hanford should not only include subsequent years of follow-up but should encompass additional factors, such as other exposures (chemical and smoking), internal doses, and types of radiation. There may not be information readily available on these variables but given time and money they could be obtained. Although more research is warranted,

without additional information, merely performing the same statistical tests over and over again will not in all likelihood produce any significant advances.

APPENDIX

The Radiological Units

Because the standard radiological units and terms have changed over the years it is essential to define precisely the measures of radiation exposure. The current system of units is the *systeme d'unites international* (SI). Under the old system, *exposure,* which applies to the production of ions in the air by electromagnetic radiation, was expressed in units called roentgen. In SI, it is expressed in units of coulombs per kilogram. *Dose*, more often referred to as *absorbed dose*, is the energy deposited by an ionizing radiation per unit mass of an absorbing material. In the old system, the unit for dose was the rad; in SI it is the Grey. The roentgen and rad were often considered to be equal, which generally resulted in an overestimation of the absorbed dose (when converting units from roentgen to rad) due to the fact that one rad is slightly more than one roentgen. *Dose equivalent* combines the absorbed dose with the ability of the particular radiation to produce biological damage. Defined mathematically: H=DQN, where H is the dose equivalent, D is the absorbed dose, Q is the quality factor for the radiation in question (i.e. gamma versus neutron), and N is the product of all other factors that may modify or affect the biological response. Under the old system the unit for dose equivalent was the rem and in SI the unit is the sievert (Sv), where 1 rem is equivalent to 0.01 Sv, or 10 millisievert (mSv). Because the quality factor is designed to insure that any errors will be on the side of safety, it is not an exact adjustment of the observed effectiveness of the radiation at causing biological damage. Hence the recorded exposure or potential risk to workers is overestimated. However, because the quality factor is inflated, the risk of actual exposure is underestimated. In the past, N was equal to 1 for external exposures, and in the current system it is either 1 or dropped altogether (24).

Radiation Exposure Protection Standards

The studies done on Hanford workers all investigated whether the maximum allowable radiation exposure for workers was low enough to prevent excess cancers in the population. A quick history of the recommended external dose limits that were used by the AEC, which was responsible for establishing protection standards for all domestic nuclear facilities, provides background on the limits investigated at Hanford. The AEC based its standards on those recommended by the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection (NCRP) (15). In 1934, the ICRP established a "tolerance dose," which was not by any means considered a harmless dose, though it generally inferred no visible effects. This dose of 2 mSv per day corresponds to an annual exposure of approximately 500 mSv (16).

During World War II, more workers were being exposed to radiation, so a reevaluation of the standards was necessary. At that time, the prevention of hereditary effects and leukemia was the dominant concern (25). By 1950, both the NCRP and ICRP had developed a new concept known as maximal permissible level of exposure (MPL). The permissible dose as defined by the NCRP is "the dose of ionizing radiation that, in the light of present knowledge, is not expected to cause appreciable bodily injury to a person at any time during his lifetime (16, p. 134)." The MPL recommended at that time was 3 mSv per week, which corresponds to an annual absorbed dose of 156 mSv (16, 25). A reexamination of standards occurred once again in the late 1950's when somatic effects (effects which occur within the exposed individual as opposed to hereditary effects which occur in later generations), particularly cancer, became the primary concern in the evaluation of health risks from exposure to radiation. At that point, both organizations decreased the annual MPL to 50 mSv (25). In the 70's technology made it possible to combine the measurement of internal and external radiation to determine the dose equivalent. In 1977, the annual effective dose equivalent (external and internal) was set at 50 mSv (25). Prior to 1977, separate limits were set for external and internal dose. In 1990, the ICRP once again lowered the annual MPL (external radiation only) to 20 mSv (15). This paper is based only on the portion of studies referring to external dose.

Quantitative risk factors (i.e. the risk per unit dose) were developed, based primarily on data from Japanese atomic bomb survivors, and were used to derive dose limits from an assumed limit of acceptable risk.

The ICRP set a nominal risk factor for all cancer mortality at 1 X 10^{-2} per sievert, which they felt was appropriate for the radiological protection of workers (26). Based on the nominal risk factor the absolute risk estimate for cancers was 5 per 1,000,000 person years per 10 mSv and for all cancers except leukemia the absolute risk estimate was 4 per 1,000,000 person years per 10 mSv (12). Note that in order to derive these numbers the nominal risk factors used in the calculation had to be divided by 20. No explanation of the 20 was provided and it is assumed that it is either related to the follow-up period or to a plateau period.

TABLE I. ICRP CLASSIFICATIONS OF CANCERS

HIGH SENSITIVITY ESTABLISHED	HIGH SENSITIVITY APPARENT	LOW SENSITIVITY	UNCLASSIFIED
Bone Marrow	Lymph nodes	Mouth and salivary	Rectum
Thyroid	Reticular tissue	Oesophagus	Other digestive
	Pharynx	Small intestine	Breast
	Lung	Liver & gall bladder	Uterus and ovaries
	Pancreas	Nose and larynx	Prostate
	Stomach	Bone, C.T. and skin	Bladder
	Large intestine	Testis and penis	Lymphatic leukemia
		Kidney	Other haemopoetic
		Eye and CNS	Ill-defined
		Other endocrine	

TABLE II. STANDARDIZED MORTALITY RATIOS*

STUDY	ALL CANCER SMR†	P-VALUE‡	ALL CAUSES SMR	P-VALUE	PANCREATIC CANCER SMR	P-VALUE	MULTIPLE MYELOMA	P-VALUE
Sanders (1975)	114 (101,129)	.03						
Mancuso et al. (1977)	100 (93,108)	1.00			131 (97,174)	.06		
Marks et al. (1978)	88 (78,98)	.02	86 (82,90)	.00	130 (86,190)	.17	160 (43,410)	.34
(SMRs for <2 and +2 years of employment)	85 (77,93)	.00	75 (72,78)	.00	100 (66,144)	.98	132 (42,307)	.54
Gilbert et al. (1979)	88 (78,98)	.02	86 (82,90)	.00	130 (86,190)	.17	160 (43,410)	.34
(SMR for <2 and +2 years of employment)	85 (77,93)	.00	75 (72,78)	.00	100 (66,144)	.98	132 (42,307)	.54
Darby et al. (1981)	80 (72,88)	.00	76 (72,79)	.00	98 (65,142)	.93	115 (46,236)	.72
Gilbert et al. (1989)§	82 (77,88)		74 (72,77)		89 (70,120)		90 (50,150)	
Gilbert et al. (1989)	85		78		97			

*Information was not available for blank cells.

†Standardized Mortality Ratios. Compared to U.S. white male mortality rates except in Sanders study which used white male mortality rates from the state of Washington. The 95% confidence intervals were calculated using formulas 5.7 and 5.8 of Checkoway et al. (18).

‡The p-values were based on a chi-square test with 1 degree of freedom. (see formula 5.9 in Checkoway et al. (18).)

§The combined study.

TABLE III. TREND TESTS*

STUDY	EXPOSURE INTERVALS†	LAG	SCORE	ALL CAUSES	ALL CANCERS	MULTIPLE MYELOMA	PANCREATIC CANCER	OTHER CANCERS OF INTEREST
Marks et al. (1978)	0-, 20-, 50-, >150		median	> 0.5	> 0.5	0.01	0.03	
Hutchison et al. (1979)	0.1-, 2.5-, 6.5-, 10.5-, 40.5-, >100.5		mean		0.13	0.009	0.011	
Gilbert et al. (1979)	0-, 20-, 50-, >150	2	mean	0.88	0.76	0.006	0.07‡	stomach: 0.82
		10	mean	0.91	0.57	0.0006	0.29	stomach: 0.81
Gilbert et al. (1980)	0-, 20-, 50-, >150	2	mean	0.88	0.81	0.0006	0.06‡	stomach: 0.13
Tolley et al. (1983)	0-, 20-, 50-, >150	2	mean	0.66	0.75	<< 0.01	0.17	stomach: 0.08
Darby et al. (1981)	0-, 10-, 50-, 100-, 150-, 200-, 250-, 300-, 350-, 400-, 450-, >500	2-10	median	0.009		0.0002	0.006	kidney: 0.19
		10	median	0.08		<< 0.01	0.13	kidney: 0.0004
Gilbert et al. (1989) (Hanford & Combined)		10§	indiv.		0.18	<< 0.05	0.35	
		10§	indiv.		0.10	<< 0.05	0.40	
Gilbert et al. (1989)		2	indiv.	0.06	0.25	<< 0.01	0.12	female genital: 0.048
		10	indiv.	0.13	0.18	<< 0.01	0.35	female genital: 0.046

*P-values from the trend tests are presented in chart. The expected values were calculated using the Mantel-Haenzel method in all of the studies except for the Hutchison study, which calculated the expected values to form proportional mortality ratios.

†Exposure intervals are in mSv.

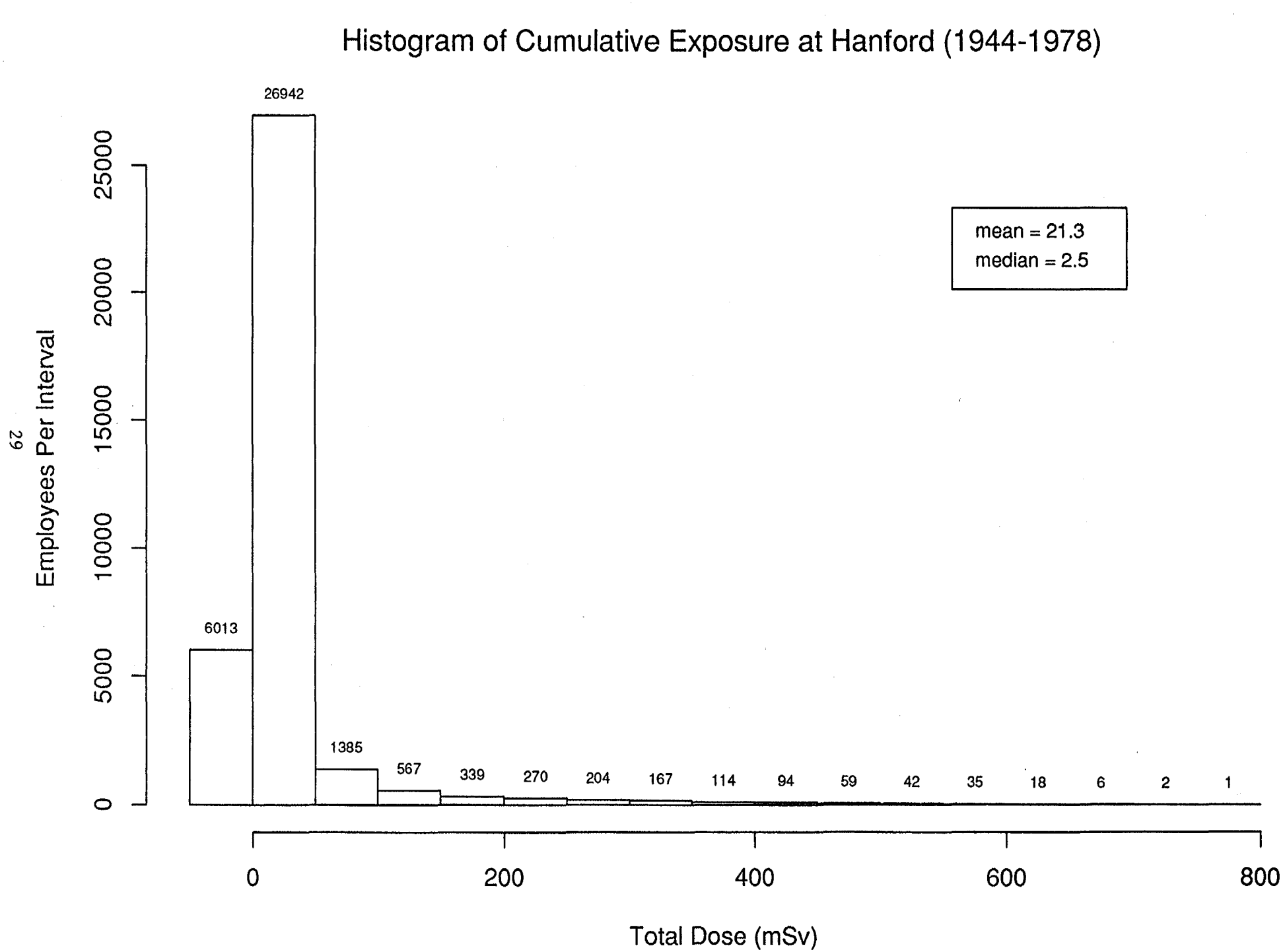
‡This p-value is slightly underestimated, see footnote in text.

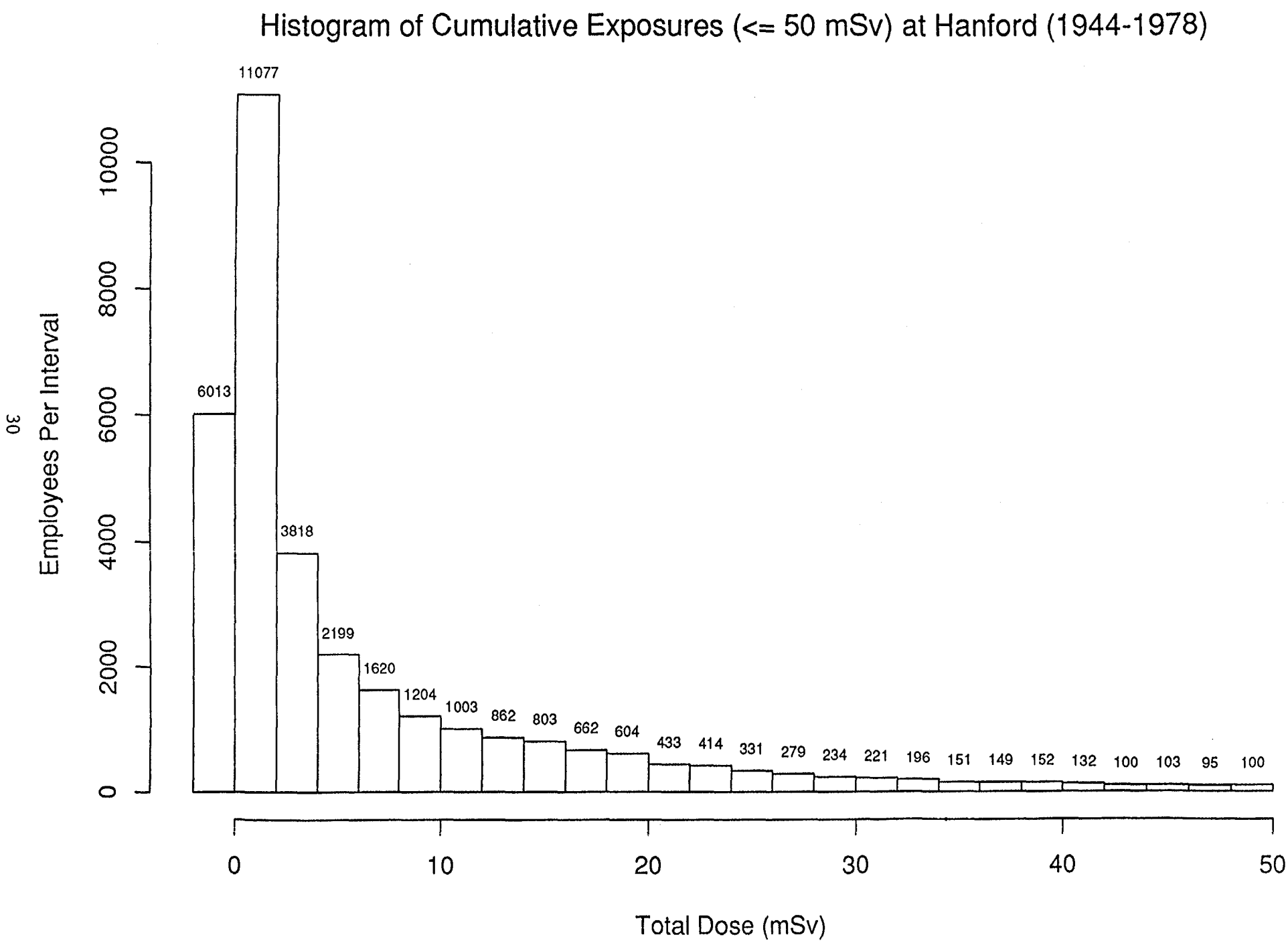
§10 year lag for all cancers except leukemia which is lagged for 2 years.

TABLE IV. CONTROLS FOR TREND ANALYSES

STUDY	CONTROLS
Marks et al. (1978)	*Age (5 year intervals) *Occupational catagory (Craftsmen and Operators vs Others) *Calendar year combined with employment status in 3 strata: -stratum 1: employed 2 years and working January 1, 1960 -stratum 2: stratum 1 individuals still living but no longer working on January 1, 1965 -stratum 3: employed 2 years and working on January 1, 1965
Hutchison et al. (1979)	*Age at death (20-49, 50-64, 64+ years) *Year at death (1943-60, 1961-67, 1968-73)
Gilbert et al. (1979) Gilbert et al. (1980) Tolley et al. (1983)	*Age (5 year intervals) *Occupational catagory (Craftsmen and Operators vs Others) *Calendar year (single year intervals) *Employment status (employed vs. teminated)
Darby et al.. (1981)	*Age (5 year intervals) *Calendar year *Length of time since commencement of employment (2-, 5-, 10-, 15-, 20+ years)
Gilbert et al. (1989)*	*Age (25-29, 30-34, single year intervals for ages 35-80, 80-84, and 85+ years) *Calendar year (1945-49, 1950-54, 1955-59, 1960-64, 1965-69, 1970-74, 1975-79, 1980-81) *Number of years monitored (1-4, 5+ years)
Gilbert et al. (1989)	*Age (25-29, 30-34, single year intervals for ages 35-80, 80-84, and 85+ years) *Calendar year (1945-49, 1950-54, 1955-59, 1960-64, 1965-69, 1970-74, 1975-79, 1980-81) *Number of years monitored (1-4, 5+ years) *Gender

* The combined study.


Histogram of Cumulative Exposure at Hanford (1944-1978)
mean = 21.3
median = 2.5
Employees Per Interval
0
5000
10000
15000
20000
25000
6013
26942
1385
567
339
270
204
167
114
94
59
42
35
18
6
2
1
0
200
400
600
800
Total Dose (mSv)


Histogram of Cumulative Exposures (<= 50 mSv) at Hanford (1944-1978)
Employees Per Interval
0
2000
4000
6000
8000
10000
11077
6013
3818
2199
1620
1204
1003
862
803
662
604
433
414
331
279
234
221
196
151
149
152
132
100
103
95
100
0
10
20
30
40
50
Total Dose (mSv)

ACKNOWLEDGMENTS

I would like to thank Mark Durst, Steve Selvin and Michael Mohr for their statistical guidance. In addition, I would like to thank Mark Durst for sharing his knowledge on both radiation and the Hanford facility.

The data used to compute the statistics and create the histograms were obtained from the Department of Energy (DOE), Comprehensive Epidemiologic Data Resource (CEDR). CEDR is a repository that contains the datasets for the majority of the published studies on DOE workers. For more information on CEDR please refer to the data catalog.

This work was supported by the Director, Office of Epidemiology and Health Surveillance; Office of Health; Office of Environment, Safety and Health; U.S. Department of Energy under Contract No. DE-AC03-76SF00098.

REFERENCES

1. Sanders BS. Low-level radiation and cancer deaths. Health Phys 1975;34:521-538.

2. Mancuso TF, Stewart A, Kneale G. Radiation exposures of Hanford workers dying from cancer and other causes. Health Phys 1977;33:369-385.

3. Marks S, Gilbert ES, Breitenstein BD. Cancer mortality in Hanford workers. In: Late biological effects of ionizing radiation. Vol 1. International Atomic Energy Authority report IAEA-SM-224/509 1978;369-386.

4. Kneale GW, Stewart AM, Mancuso TF. Re-analysis of data relating to the Hanford study of the cancer risks of radiation workers. In: Late biological effects of ionizing radiation. Vol 1. Internaltional Atomic Energy Authority report IAEA-SM-224/510 1978;387-412.

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

6. Gofman JW. The question of radiation causation of cancer in Hanford workers. Health Phys 1979;37:617-639.

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

8. Gilbert ES, Marks S. An updated analysis of mortality of workers in a nuclear facility. Rad Res 1980;83:740-741.

9. Tolley DH, Marks S, Buchanan JA, et al. A further update of the analysis of mortality of workers in a nuclear facility. Rad Res 1983;95:211-213.

10. 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. Br J Ind Med 1981;38:156-166.

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

12. Gilbert ES, Fry SA, Wiggs LD, 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 1989;120:19-35.

13. Gilbert ES, Petersen GR, Buchanan JA. Mortality of workers at the Hanford site: 1945-1981. Health Phys 1989;56:11-25.

14. Petersen GR, Gilbert ES, Buchanan JA, et al. A case-cohort study of lung cancer, ionizing radiation and tobacco smoking among males at the Hanford site. Health Phys 1990;58:3-11.

15. Stewart AM, Kneale GW. An overview of the Hanford controversy. Occup Med 1991;6:641-63.

16. Taylor LS. Will radiation control be by reason or regulation? Health Phys 1988;55:133-138.

17. Wilson RH, Fix JJ, Baumgartner WV, et al. Description and evaluation of the Hanford personnel dosimeter program from 1944 through 1989. Richland, WA:Pacific Northwest Laboratory, 1990. (PNL publication no. 7447).

18. Checkoway H, Pearce N, Crawford-Brown DJ. Research methods in occupation epidemiology. 1st ed. New York, NY:Oxford University Press, Inc., 1989.

19. Gilbert ES, Buchanan JA. An alternative approach to analyzing occupational mortality data. J Occup Med 1984;26:822-828.

20. Gilbert ES. An evaluation of several methods for assessing the effects of occupational exposure to radiation. Biometrics 1983;39:161-171.

21. Gofman JW. Radiation & human health. 1st ed. San Francisco, CA:Sierra Club Books, 1981.

22. Experts Debate Level of Danger In Atom Doses; New York Times, July 2, 1979.

23. Upton AC, Hartl DL, Boecker BB, et al. Health effects of exposure to low levels of ionizing radiation BEIR V. Washington, DC:National Academy Press, 1990.

24. Kathren RL, Petersen GR. Units and terminology of radiation measurement: a primer for the epidemiologist. Am J Epidemiol 1989;130:1076-1087.

25. Kocher DC. Perspective on the historical development of radiation standards. Health Phys 1991;61:519-527.

26. International Commission on Radiological Units. Recommendations on the International Commission on Radiological Protection: 1977. Oxford: Pergamon Press, 1977. (ICRP publication no. 26).