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MEMORANDUM FOR: Jacob Kastner, Chief
Environmental Standards Branch, SD

FROM: Michael Parsont
Environmental Standards Branch, SD

SUBJECT: TRANSMITTAL OF STAFF COMMITTEE EVALUATION OF THE FINAL REPORT #13 SUBMITTED BY THOMAS F. MANCUSO, M.D.

The staff committee (M. Parsont, ESB, S. Yaniv, SAFER, and D. Rubinstein, EDO) has completed its evaluation of the above subject document. A copy of this evaluation is attached.

Final Report #13 contains the analyses of the Hanford Occupational Mortality experience as analyzed by Dr. T. Mancuso, A. Stewart, and Mr. G. Kneale. The analysis is the same as published in the November 1977 issue of Health Physics.

Michael Parsont

Michael Parsont
Environmental Standards Branch
Office of Standards Development

Attachment:
As Stated

THE STAFF COMMITTEE EVALUATION OF THE FINAL REPORT #13 SUBMITTED BY THOMAS F. MANCUSO, M.D.

Introduction

On October 13, 1976, Drs. Thomas Mancuso, Alice Stewart and Mr. George Kneale presented a paper (hereafter called the "Saratoga Springs paper") at a Health Physics Society Symposium in Saratoga Springs, New York.[1] The authors purported to demonstrate a causal and numerical relationship between low level radiation and the mortality from cancer in former employees of the Hanford Laboratories of Richland, Washington.

The authors reported an apparent association between the proportion of specific cancer mortalities and the amount of occupational radiation exposure received. The authors claimed the results indicated a much more pronounced radiation effect than had been concluded from previous studies in man and laboratory animals. If valid, the findings of these analyses would indicate significant implications for our assessment of radiation effect on the health and safety of the public. This applies not only to NRC-licensed activities, but also to other radiation exposure sources such as natural background radiation and medical X-rays. Therefore, a technical committee was established to study the "Saratoga Springs Paper" to provide technical judgments of its analyses and conclusions. "The Saratoga Springs Paper" was reviewed for competence of technical content, presentation and analytical techniques, and the staff committee reported its findings in November 1976.[2]

In November, 1977, Dr. Mancuso submitted Final Report #13 to ERDA[3] and published in the Health Physics Journal[4] that portion of the text which represented a reanalysis of the Hanford occupational mortality experience. Dr. A. Stewart and Mr. G. Kneale performed the analyses with Dr. Mancuso for the Final Report and coauthored the Health Physics Journal article.

The staff committee was recalled to evaluate the Final Report. That evaluation is the subject of this paper.

The original data used by Mancuso et al. were not available to us, and attempts to obtain these data were not successful. Therefore, the evaluation had to be based on the summary tables and graphs as given in the presentation by Mancuso et al.

Since the "Saratoga Springs Paper", there have been numerous versions and addenda on the same subject by Mancuso, Stewart and Kneale as well as papers by other authors. While we would have liked to study all relevant analyses, we were not able to perform comprehensive reviews of all pertinent papers.

Committee Findings

The Committee findings* are summarized below:

1. Subject to the caveats indicated in items 2-8 some of the author's tabulations were suggestive of the existence of excess cancer mortality among exposed Hanford employees larger than could have been predicted by other publications.[5,6,7,8]

2. The authors dealt with potentially confounding factors one or two at a time ignoring the complex interrelationships among factors. Confounding of cumulative radiation dose with age, calendar year and time of employment are particularly pronounced. In addition, medical radiation, demographic and other factors may have further confounded the analysis.

3. Small sample sizes, especially encountered in the analysis for specific cancer types, can be misleading. Particularly in the comparison of mean cumulative doses of small samples, the averages may be dominated by the exceptionally large doses to a few individuals.

4. The authors' presentation of doubling doses (ranging from 0.1 rads to infinity, and varying drastically with age) is bizarre. In order to accept doubling doses as low as 6 rads one would have to attribute all "spontaneous" cancers to natural background radiation.

5. In several instances the authors' conclusions cannot be supported by either their analysis or their presented data.

6. There are instances in which tabular material presented allows for multiple interpretation of the data.

7. The authors did not observe an increased leukemia mortality, which is the most readily observed radiation induced malignancy.

8. The use of a prospective approach to the epidemiological analysis would have been superior to the retrospective one taken by the authors.

A View of the Literature

In the committee review of the "Saratoga Springs Paper", reference was made to several refutations of the analysis by Mancuso et al. Since that time additional analyses have been made both on the publications of Mancuso et

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* One of us presents additional personal review in Attachment 1.

al., and of the Hanford mortality data themselves. All of these analyses agree to some extent with the conclusions of the staff committee. The statements below are short paraphrases of the authors' conclusions.

Dr. Charles Land of the National Cancer Institute analyzed Hanford Mortality Data which was similar to the data analyzed by Mancuso et al.[9] There were differences in the data bases because Dr. Mancuso refused to supply to others additional data which he used. Land found excesses of multiple myeloma and pancreatic cancer. However, he stated "...the data suggest that one of the two cancers, but not necessarily both, may be associated with dose. The association is not necessarily causal, in the sense that both dose and the cancer could be causally associated with a third variable, but not with each other." In addition, Land stated that the conclusions by Mancuso et al., about variations in sensitivity to radiation by age at exposure appear to be untenable although the existance of a true radiation-induced excess cannot be ruled out without further analysis. He suggested that a cohort analysis of the Hanford experience would be a great improvement over the proportional mortality analysis.

Dr. Daniel Kleitman, an applied statistician at MIT and an NRC consultant, performed an independent analysis of the final report.[10] His principle findings were that 1) none of the conclusions by Mancuso et al., are justified by their data analysis, 2) no effort is made to consider the effects of other potentially carcinogenic agents, 3) a majority of the conclusions by Mancuso et al., are based on eight cases of multiple myeloma, and while these cases deserve investigation, in the context of what is known about the epidemiology of multiple myeloma, they are insufficient to support their conclusion, and 4) no effort is made to assess the validity of the linear models used or to obtain confidence intervals on the doubling doses.

Dr. Barkev Sanders, who worked with Dr. Mancuso on the Health and Mortality Study, performed an independent analysis of the Hanford Mortality data. His analysis will be published in the Health Physics Journal.[11] Sanders concluded that there was no indication that radiation caused the observed somewhat higher proportion of cancer deaths among male Hanford employees, as compared to males in the general population of the state of Washington. In addition, Sanders compared longevity of exposed Hanford employees with a control group of their siblings and found higher longevity in the employee population. He found also that exposed employees have higher longevity than nonexposed workers and matched controls, and that nonexposed employees have lower longevity than their siblings and matched controls. However, he did not look at specific cancer types. Sanders also concluded that radiation should not be eliminated as having played at least a contributory role in carcinogenesis, and that it is plausible that further observations may indicate a measurable adverse effect. He also

called attention to uncertainties in dosimetry and the possibility that other carcinogenic agents may have acted synergistically with radiation to cause cancer.

Dr. L. A. Sagan, Electric Power Research Institute, questioned the final report in the areas of Dose Estimates and Methodology.[12] The major thrusts of his analysis were based on 1) the skewness of the dose distribution in which the average doses were dominated by a small number of high doses, 2) the lack of consideration of actual radiation exposures received by Hanford employees either prior or subsequent to their Hanford employment, 3) the lack of consideration of other possible variables which may have influenced the risk of cancer and 4) the use of a proportional mortality approach.

Marks et al., performed a cohort, or population base study, of the Hanford Mortality Data.[13] This included examination of the health experience of some 29,000 Hanford employees. They observed an increase in multiple myeloma and pancreatic cancers as did both Land and Mancuso et al. However, because increases in diseases more commonly associated with radiation were not observed they did not consider the results to be definitive. In addition, they found no other significant increase in mortality over normal expectations for all causes, all cancer types and remaining specific cancer types. They concluded that their analysis showed a "healthy worker effect" -- that being a reduction in the standardized mortality ratio (SMR), which is observed frequently in the case of workers in industries free of serious life threatening hazards. Therefore, the SMRs are likely to be higher for cancer than for most other diseases because the factors responsible for this effect are less likely to be effective for most cancer types than for other causes of death. This differential effect would tend to bias proportional mortality analyses, such as performed by Mancuso et al., toward falsely indicating an excess of cancer.

Dr. Irwin D. J. Bross, Jr., has indicated an increased effect of low level ionizing radiation (in the range of doses from 100 mrads to 10 rads, which he calls the 1 rad range).[14] Bross concluded that his results are supported by those of Mancuso et al. Bross examined leukemia in exposed adults, in children exposed in utero and in the offspring of parents who were exposed either singly or both to preconception radiation.

Rotblat[15] also found an apparent increase in the incidence of leukemia among early entrants to Hiroshima following the atomic bomb explosion.

Summary of Conclusions

1. We believe that the Final Report cannot be considered as a definitive study because:

   (a) There is confounding among relevant factors.

   (b) The retrospective analysis, confined to workers dying before 1973, ignores the distribution of radiation doses among the surviving Hanford employees.

   (c) Much of the analysis is questionable, deficient and ambiguous.

2. Subject to the above caveats we find that some tabulations and analyses of the Final Report are suggestive of a radiation effect more pronounced than previously thought.

3. The committee repeats the recommendation of its previous report[2] that a painstaking analysis of the relationship of cancer to low level radiation is of utmost importance. Such an analysis should be a well controlled prospective type study on as large as feasible sample of occupationally exposed workers.

   This study will be of particular importance to NRC because it is most conducive to narrowing the uncertainty in risk estimates from exposure to low level ionizing radiation, and to providing a more solid basis for standard setting.

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