November 2, 1976

TO: Mike Parsont
Chairman, Ad Hoc Group to Review the Mancuso Paper

FROM: Allen Brodsky

REVIEW OF PAPER BY MANCUSO, STEWART, AND KNEALE ON RADIATION EXPOSURE OF HANFORD WORKERS DYING FROM VARIOUS CAUSES, OCTOBER 1976

The following conclusions, recommendations, and statements are a revision of those provided to you prior to our ad hoc group meeting yesterday.

I. Conclusions

For the reasons enumerated below, I arrived at the following conclusions regarding the assertions and claimed findings of the subject paper (referred to as the Mancuso paper(1)).

1) From hearing the presentation as well as from my own reading of the Mancuso paper, I conclude that the data presented in the paper do not support the strong assertions in the introductory and concluding paragraphs of the paper that " ... these data provide an opportunity to discover whether there is a cancer hazard associated with low-level radiation."; nor do they support the claimed findings regarding the relationships between radiation exposures and cancers observed.

2) The type of approach used in the paper, together with the population, numbers of deaths involved, the levels of occupational exposure involved, and length of followup, cannot by themselves result in incontrovertible conclusions regarding cause-effect relationships between radiation exposure and diseases. This type of approach must be followed up by the more careful investigation of many factors and the continued follow up of the total employee populations

in prospective analysis - compared against several control populations, as originally planned and developed by Mancuso et. al. in all of their previous reports.

3) The sources of error in the Mancuso paper pointed out by the Marks and Gilbert (4) rebuttal paper also raise valid objections to the entire approach of the paper and to all of its conclusions.

II. Recommendations

1) The NRC should conclude, from its own independent staff review, that the paper by Mancuso, Stewart, and Kneale does not constitute a valid analysis of the data presented and that its conclusions regarding the findings of radiogenic cancers in the Hanford employee population can not therefore be considered valid.

2) The NRC should state that the data of the Mancuso project, collected for many years for several atomic energy plants, deserve careful and proper analysis to discern whether there may have been any health effects in employees of nuclear energy plants, and whether such human data can be used to establish any estimates of, or limits to, risks of radiation exposure resulting from licensed operations under present radiation protection standards.

3) The NRC should state that, in addition to the improper and inadequate methods of analysis used in the Mancuso, Stewart, and Kneale paper, the claimed findings are in disagreement with cancer risk estimates of the National Academy of Sciences, and estimates of other studies, based on more carefully analyzed studies of human populations. Thus, the Mancuso study data should

be made available for study by a group of independent scientists, in addition to the study currently underway at Battelle-Northwest for the past year and a half, although the Battelle-Northwest studies have already been used by Marks and Gilbert in a preliminary way to provide valid rebuttals of the validity of the Mancuso paper findings at the Health Physic Society midyear symposium.

4) That the NRC consider supporting an independent analysis of the Mancuso project data, including replications for the several plants at Oak Ridge and other facilities, and replications using several independent controls, by an independent team of scientists supported with the review and advice of an NRC Advisory Committee on Human Radioepidemiologic studies.

(If it is deemed helpful in obtaining an additional and early NRC analysis of the Mancuso data, I would be glad to make available a method of analysis already programmed and tested at Oak Ridge, presented for review at a previous meeting of Dr. Mancuso's "blue ribbon" advisory committee, and presented in one of Dr. Mancuso's own progress reports. This analytical method was used to independently check the findings presented by Dr. Barker Sanders for Dr. Mancuso at the Midyear Symposium of the Health Physics Society in Richland, Washington, in 1971. I also presented this analysis at the Richland symposium, and wrote an appendix stating the conclusions as part of my contribution to the publication in the proceedings.

The method of analysis involved the derivation of a chi-square statistic from the data. This chi-square statistic was later verified by comparison with the chi-square function of one degree of freedom using data where the cumulative partition of chi-square showed non-significance in a particular

comparison of the employee population against controls. The method was designed particularly for large scale studies in which many tests of individual sub-groups are made, with the probability of observing numerous differences that could be attributable to chance sampling variations. The method allows supplementary analysis of individual sub-groups of the population (that might be more highly exposed), while at the same time providing an independent, objective test of an entire study by testing cumulative partitions of chi-square -- thus guarding against over-interpretation of the proportion of differences between sub-groups that are bound to occur from random (chance) sampling variations alone. The method also provides a very sensitive test, does objectively highlight differenc that do occur without prematurely concluding their significance, and is adaptable with minor programming modifications to an analysis of the data by causes of death. It is my firm belief that all epidemiologic studies should be subjected to this test, or a similar type of test, before any apparent findings of correlation between agents and diseases are presented as conclusive or significant.)

5) The NRC should form and implement the Advisory Committee as soon as possible in a manner similar to that presented in my informal memo of October 27, 1976, and the Advisory Committee should examine the above conclusions and recommendations, in addition to carrying out the charge as given in my memo.

III. Problems Found on Reading the Mancuso Paper

Without an opportunity for an independent analysis of all of the data on the Hanford and Oak Ridge data banks, an initial review must rely on the

small sample of data presented in the paper itself and the approach used, the presentation of the results, and the consistency and validity with which the assertions of the paper may be found to be supported by the data presented. Thus, the comments below are based on the paper itself as presented at the mid-year symposium of the Health Physics Society in October, 1976.(1)

1) The brief statement in the second paragraph of the Mancuso paper regarding incomparability of records of live and dead employees is not a sufficient reason for instituting such a retrospective analysis in place of the more detailed prospective analysis that the already collected data would allow, and as originally planned by Mancuso et. al. (2) Inconsistencies in listings of causes of death are well known, and would apply to either approach; however, a prospective analysis (outlined in all of Mancuso's progress reports and in his 1971 publication) (3) could allow many more checks and balances against spurious results.

2) In the third paragraph, first sentence, the word "systematically" may give the impression that the individual rows of data in the tables presented and indeed the presentations of the data in various ways among the several tables, are independent. This is not so.

3) It should first be observed that in Table 1 of the Mancuso paper, the 65.8% of the cancer cases having radiation exposure would have a binomial standard error of $\pm$ 1.8; the value of 61.0% for the noncancer cases (males) would have a standard error of 0.91 from purely statistical sampling variation alone, not to mention the many other possible sources of variation and selection in establishing the percentages of exposed

employees and average radiation doses in each of these two groups. This sampling variation alone would provide a value of t = about 2.3, which would not lie very far on the side of "statistical significance" at the 0.05 level for a two-tail test. Many factors other than sampling variation (or radiation exposure) could produce such a t value.

4) From Table 1 alone, one can compare the ratios of non-cancers to cancers for males and females, which become 4.25 and 2.28, respectively. Since one observes from the same Table that the males have received the higher average radiation exposures, then why do they have a much lower ratio of cancers? If the kind of proportional mortality reasoning presented in the Mancuso paper is indeed presumed to be valid in showing by other computative manipulations that this data has discovered the radiogenic induction of cancer then the above ratios should be in reversed order of magnitude.

5) In Table 2 of the Mancuso paper, where the data are broken down by calendar year of exposure, one can see that there is really not much difference between the average radiation doses of cancer cases and non-cancer cases.

6) The method of calculating standardized mortality ratios is not completely presented in the symposium version of the Mancuso paper, but these rates are apparently derived from assumptions involving the relative average exposures between the cancer and non-cancer groups, and not actually on mortality rates <u>per se</u>. Thus, no direct conclusions

regarding mortality rates from cancer can be derived from this data. Mancuso's paper can at most conclude that the probability, given death has occurred from cancer, that radiation exposure will be listed on the records of certain cancer categories might be somewhat higher (for various possible reasons other than cancer causation by radiation).

7) The presented methods of defining latent period and selecting the data for calculating doubling doses are completely invalid; this is so because their method is based on selecting random fluctuations between groups of data rather than a recognition that if the radiation exposures do indeed have a continuous probability of inducing cancers (and I believe they do, although at much lower probability levels than arrived at in the Mancuso paper) then the estimation of latent periods must be derived from analysis of the time variations of incidence of disease after each increment of exposure.

8) If one accepts the estimated doubling doses of the Mancuso paper and examines the doubling dose values of Table 5, then one must conclude that the natural background radiation exposure accumulated over a lifetime must be responsible for practically all cancers. This ridiculous conclusion would be at variance with Mancuso's own findings of cancer-causing chemicals in the environment of various industries including those at Hanford. They would also be at variance with the fact that average exposures to all monitored employees at Hanford over the first 20 years of operation were about 0.25 rem per year. Thus, according to the Mancuso paper, cancer rates in the Hanford population of workers should be considerably higher than those of suitable control groups. Mancuso's first publication showed no significant differences in gross mortality rates between Hanford employees with one or more brothers or sisters and siblings of the

same sex. (3) Also, as Marks and Gilbert(4) have shown, cancer mortality rates for workers who have been employed for longer periods and who thus include the more highly exposed groups are the same as those for employees with shorter work histories at Hanford.

9) The average doubling doses presented in the Mancuso paper are up to 2 orders of magnitude lower than those in the BEIR report. (5) Also, the Mancuso breast cancer doubling dose,, based really on the chance radiation exposure of one case, is more than an order of magnitude lower than estimates from recent breast-cancer studies. (6)

10) It is obvious that the higher average radiation exposures (really, low exposures compared to permissible levels) in certain cancer subgroups can be attributed to only one or a few higher-exposed individuals in these respective sub-groups. Marks and Gilbert have indeed shown that this is so.(4) If one considers that the estimated standard mortality ratio and doubling doses for breast cancer given in the Mancuso paper are valid, then one must ask the question, "Why were all of the other observed breast cancer cases for women, excluding the single person with an exposure of 14.39 rem, observed to have lower average exposures than the control group?" It should be obvious to anyone, not only an epidemiologist, that the single case of breast cancer on which all of the Mancuso papers' calculations depend for this group could have been induced by many other causes, including the industrial chemical exposures at Hanford on which the Mancuso project has carried out a pilot study. No examination has been presented in this paper of the possibility of other agents to which this one case of breast cancer

might have been exposed. Nor is the large probability of other causes for this case pointed out in the Mancuso paper. Marks and GIlbert present in their Figure 6 the drastic change in the data that occurs when this one case is removed from the data.

11) The answers to the Marks and Gilbert paper by G. W. Kneale [7] do not effectively refute the comments made above.

REFERENCES

(1) T. F. Mancuso, A. M. Stewart, and G. W. Kneale, "Radiation Exposures of Hanford Workers Dying from Various Causes," ERDA Report COO-3428.8, presented at the Tenth Midyear Symposium of the Health Physics Society, Saratoga Springs, New York, October 13, 1976 (to be published in the proceedings.)

(2) T. F. Mancuso, B. S. Sanders, and A. Brodsky, Progress Report No. 1, AEC Contract No. AT (30-1)-3394, "Feasibility Study of the Correlation of Lifetime Health and Mortality Experience of AEC and AEC Contractor Employees with Occupational Radiation Exposure," 1965.

(3) T. F. Mancuso, B. S. Sanders, and A. Brodsky, 1971, "Study of the Lifetime Health and Mortality Experience of Employees of AEC Contractors, Part I: Methodology and Some Preliminary Findings Limited to Mortality for Hanford Employees," presented at the November, 1971 topical symposium of the Health Physics Society in Richland, Washington, and published in Volume III of "Proceedings, Radiation Protection Standards: Quo Vadis," Columbia Chapter, Health Physics Society, 1972.

(4) S. Marks and E. Gilbert, comments on the paper by Mancuso, Stewart, and Kneale (Ref. 1) to be published in the same proceedings of the Tenth Midyear Symposium of the Health Physics Society.

(5) Report of the Advisory Committee on the Biological Effects of Ionizing Radiations, "The Effects on Populations of Exposure to Low Levels of Ionizing Radiations," National Academy of Sciences - National Research Council, Washington, D.C.,1972.

(6) Dr. John Boice, epidemiologist, Bureau of Radiological Health, personal communication, 1976.

(7) G. W. Kneale, Answers to Comments by S. Marks on the Paper by Mancuso, Stewart, and Kneale, to be published in the proceedings, Ref. 1, op. cit.