REPORT #1

CRITIQUE OF MANCUSO, STEWART AND KNEALE PAPER

ENTITLED "RADIATION EXPOSURES OF HANFORD WORKERS DYING FROM VARIOUS CAUSES"

SUBMITTED TO:

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These comments are meant as a critique and analysis of the paper "Radiation Exposures of Hanford Workers Dying from Various Causes" by Mancuso, Stewart and Kneale presented at the Saratoga meeting. They are given in response to a request by Dr. Kastner for an independent opinion of the paper, and were prepared without reference to other critiques of this document.

A considerable body of data has been amassed concerning deaths of former Hanford workers. There are two basic questions about this data:

(1) What evidence does it provide about the cancer producing effect of small doses of radiation?

(2) What implication does the data provide about a linear-risk model in which rate of mortaility is proportional to dose? Especially, what coefficients of proportionality are consistent with the data?

Drawing any conclusion here is impeded by three important factors. These are:

A. *Background:* People receive radiation from natural sources, (background radiation) such as cosmic rays. This radiation amounts to something like .1 rem per year, though it fluctuates with area of the country, altitude, air travel and other factors. In addition, the persons studied here doubtless received x-rays and were perhaps exposed to other man-made radiations. Background further makes it questionable to classify workers into "exposed" and "unexposed" classes. Very small exposure rates may

fail to be distinguishable from background. Exposure rates are in general *not* simply and unambigiously measured -- rather they involve subtraction of an expected background. Also it suggests that very small work related doses (cumulatively under say .25 rem) may disappear in effect amid fluctuations in a 20-year background of something like 2 rem.

b. *Latency:* It is generally believed that radiation effects do not always manifest themselves immediately. Radiation can, for example, induce mutations which produce a weakness that may lead to fatality some years later. Thus the radiation relevant to fatality may well be that ten or twenty years before death. This complicates analysis here, since one does not know which radiation exposure (total or up to five years before death or up to ten years before death, etc.) is the appropriate variable on which to focus attention. Much of the dosage considered in this study occurred within seven or eight years of death.

c. *Inhomogeneity:* The study here in part involves comparison of causes of death between those that received some work related radiation and those that received none. In fact, these groups differ in characteristics other than radiation. Thus, for example, the proportion of chemical workers is higher among irradiated employees (See the Gilbert paper), and chemical workers appear to die of cancer more than others for reasons unrelated to radiation. The study here suffers by not taking occupational factors into consideration.

The study may be divided for purposes of analysis into the following parts:

1. Irradiated and "nonirradiated" male employee deaths are classified by cause of death.

2. For each cause of death the *average* radiation received among thos irradiated is considered.

3. Average radiation readings are presented as a function of calendar year of death, length of employment at reading, age, and year before death for cancer deaths and non-cancer deaths.

4. Average cumulative dosage is present as a function of year before death for various causes of death including several types of cancer.

5. For cancer types showing higher levels of radiation estimates of "doubling dose" and of number of radiation induced deaths are made. [Some data for females is also presented.]

COMMENTS ON ITEM 1 OF STUDY:

The First Table of Data is as Follows:

Males	Total # of Cases	# of Exposed Cases	Average Exp. Dose rem	% Exposed
Cancer	670	441	2.05	65.8%
Non-Cancer	2851	1739	1.67	61%

It seems to give indication that "exposure" to radiation correlates with death by cancer to a considerable extent. 65.8% of the cancer cases showed exposure to irradiation while only 61% of non-cancer did so.

Even if the more conservative data of table 6 is used, there are similar results:

Males	# of Cases	% Exposed	Average Exp. Dose	# of Exposed Cases
Neoplasmas	680	65.5	2.04	445
Cardiovascular disease	1839	62.4	1.66	1148

According to the latter figures, if the proportionality of neoplasmas to cardiovascular deaths were the same independent of radiation status, one would expect to find 390 irradiated neoplasmas instead of 445, so that the data appears to indicate an excess of radiation deaths of 55. With the earlier quoted figures, this excess appears to be 83.

To the extent that irradiated cases have been dying more recently on the average than other cases, some of this effect may be spurious. (For two reasons: one, national statistics show an increased proportion of cancer deaths in recent years which would, therefore, correlate positively with radiation for this reason. Also since cancer deaths are usually diagnosed and treated, lacking a death certificate may tend to be overweighted with more recent (and hence irradiated) non cancer deaths. As deaths lacking death certificates are omitted from the study this may bias these figures in the same direction (Gilbert reported on July, 1976 that 34% of 1972 deaths lack death certificates, 17% in 1970 and 1971, 57% for earlier years.)

The distribution of radiation among those receiving it is such that the distinction between "radiated" and "irradiated" used here seems very arbitrary, so much as that the implications of radiation excess deaths stated above must be called into question. This distribtuion is not described in this paper.

However, from the work of Gilbert and Buschbom, it is apparent that a large proportion of those listed as irradiated received very small cumulative doses -- far less than background radiation, much of which was relatively recent. If such small radiation doses over background produced cancer in a measurable amount, the larger doses experienced by relatively fewer employees should presumably show much more dramatic effects. Thus the first place to look in these figures should be groups of workers receiving relatively higher doses. If these fail to show effects, the effects already noted almost have to be spurious. The authors are aware of this and try to draw conclusions from highly irradiated cases rather than the excess deaths noted above.

The distribution of radiation among workers here has the following form, as noted by Gilbert (it must be modified by the additional cases in this study)

Percentile	Dose in Rems	Percentile	Dose in Rems	Percentile	Dose in Rems
5	.00	40	.65	75	2.24
10	.05	45	.80	80	2.8
15	.12	50	1.00	85	4.3
20	.24	55	1.2	90	6.60
25	.32	60	1.4	95	20.0
30	.46	65	1.6	100	52.0
35	.56	70	1.9		

This form of distribution makes use of average radiation figures as data for the different causes of death misleading. The average is by no means characteristic of the group -- rather it represents an imperfect count of the relatively small number of group members receiving relatively high radiation doses (of say 10 rem).

Thus the use of neither "radiated vs. irradiated" nor "average radiation" figures as done in this study are not appropriate to the present context, given the existence of background, latency and the nature of the radiation distribution. It would have been much more appropriate if the authors would have divided the cases into groups depending upon the total level of radiation.

Furthermore, background should at least be considered in the classification.

COMMENTS ON ITEM 2 OF STUDY:

For the reasons just presented by average radiation dose can be misleading parameter, it certainly misleads when applied in detail to types of cancer. In fact, in the present case, it can lead to reassuring conclusions, as will be discussed below.

It is important to realize that if one takes an arbitrary large data set and breaks it arbitrarily into n pieces, we must expect the fluctuations in behavior of the data

among these pieces. We must expect that if there are twenty pieces and if the data involves some parameter λ, that in at least one of these pieces λ takes on a value that is significantly high at a 5% level. One must be careful *not* to take the most extreme piece as seriously as it might be taken if the others did not exist. Failure to consider this fact can lead to conclusions that are artifacts of procedure.

In the present instance the cancer data is categorized into on the order of twenty cancer varieties. It is tempting to focus attention on the cancer type having most radiation or highest percentage irradiated and to conclude that radiation causes this cancer. As noted in the last paragraph, this could easily be an artifact.

The actual data obtained by the authors breaks down by cancer-type as follows:

Solid Tumors	# Cases	# Exposed	Av. Radiation of Exposed (rem)	% rad
large intestine	61	49	1.68	80.3
lung	192	129	2.05	67.2
kidney	21	14	2.81	66.7
pancreas	49	31	4.16	63.3
(cardiovascular)				
brain	18	11	3.60	61.
(residue)	265	159	.94	60.
RES neoplasmas				
myeloma	11	9	9.48	81.8
lymphatic neoplasm	33	27	1.48	81.8
(residue)	9	6	.34	66.7
myeloid leukemia	11	5	2.23	54.5

This data shows that the cancer types with excess deaths (above 62.4%) are large intestine, lung and kidney, myeloma and lymphatic neoplasm.

The large intestine data shows a large excess of deaths: since only 12 non-irradiated employees died of it, one would expect perhaps 20 irradiated to have died; instead there were 49. This is a significant excess, which is mitigated by the previous discussion and the fact that the average radiation received by the individuals dying of this cancer is not excessive being very similar to what was seen for cardiovascular deaths. This translates into the fact that of those receiving relatively large doses of radiation there is not so much excess of large intestinal cancer death.

There is also a significant excess of lung cancer irradiated death here (21) mitigated again by the same factors as before. Here the average radiation is somewhat higher, indicating that there is some similar effect among those with relatively high doses.

Two things are remarkable about the remaining solid tumor data. One is, that there is a *negative* excess of 16 deaths for "residual" cancers (when compared to cardiovascular disease) coupled with a significantly low average radiation dose among these victims. This is quite as remarkable as the positive excess seen for lung cancer, especially since "residual cancer" apparently means those several cancer types that did

not show positive effects.

Secondly, there is a remarkable *negative* correlation between radiation dose as experienced by those dying of the diseases on the list and % of deaths among those radiated. The two parameters perversely seem to be at odds with one another. This is incomprehensible in terms of a model in which radiation is bringing about excess death. It is more reasonable as a random phenomenon, but is still somewhat unexpected.

Among neoplasms, the nine irradiated cases of myeloma showed relatively high average radiation of 9.48 rems. Since the number of cases is only nine the results are not significant, though suggestive. "Residue"again shows remarkably low dosage. In the other two varieties, we again see an inverse correlation between the last two columns of the chart. There appear to be perhaps 17 more cases of lymphatic neoplasm than expected; though there was not much excess death among those heavily radiated.

It is difficult to know what to make of this data. If the distinction between radiated and irradiated were sharp and decisive, one would be tempted to be impressed by the "excess deaths" attributable to radiation here. The distinction is neither sharp nor sensible -- in light of background, latency, etc.; and the authors, to their credit do not do this.

What they do instead is to focus attention on the diseases with high average radiation doses and more than 20 irradiated cases namely: pancreas, lung and "RES neoplasm" or "myeloid neoplasm" (the latter being myeloma and myeloid leukemia).

They then construct a model of radiation inducing cancer and use it to estimate how many deaths were radiation induced (using a linear regression with the significant data).

High average radiation doses here indicate that there were more than average deaths among the few relatively highly radiated. Fortunately for them and unfortunately for analytic purposes these were relatively few of these highly radiated individuals which means that limiting attention to them above severely limits the amount of data available. But the authors' approach here in terms of average dose and number of excess deaths is rather ad hoc and has peculiar consequences here.

We have observed that the data seems to show excess deaths in large intestinal cancer, lung cancer and lymphatic neoplasm. The approach used here concentrates attention on pancreatic lung and myeloma with the latter grouped with some other disease since there are so few cases of it.

The model conclusion is that six pancreatic cases were radiogenic, along with twelve lung cases and 9.5 myeloid neoplasm cases. The trouble with this is that there were really no excess pancreas cases observed -- and the myeloma data

is too small to justify this analysis. Since negative excess death occurred for radiated myeloid leukemia, it is surely rash to conclude that radiation induced deaths by that disease -- but silly to believe that 9.5 of the 9 irradiated deaths from myeloma were radiation induced.

It is not really fair to lump myeloma data with anything else, since the radiation levels experienced by its victims are enough produce a misleading effect. (In fact, these 9 cases above account for approximately half of the difference between the average radiation dose experienced by cancer victims and by victims of cardiovascular disease. (Pancreatic cancer accounts for the rest.))

The lung cancer results are not on their face objectionable but since they were produced by a scheme that produced questionable results, it is hard to have confidence in them.

The analogous result for breast cancers is hard to understand. By an apparent conceptual error, breast cancer cumulative doses don't accumulate in time; as a result certain "many years before death" data appears significant. From this wrong beginning a model is created which predicts that most of the observed breast cancer deaths (5.9 out of 7 or 8) were radiation induced. The peculiar part of this is that one would have expected 10 or 12 irradiated breast cancer deaths and it is, therefore, perfectly silly to claim that only two of the

deaths are natural here. I believe that the result here comes from one or two relatively highly irradiated breast cancer cases. If so, the results should be ignored.

COMMENTS ON ITEMS 3 AND 4

The charts in this part of the paper convey very little, except that radiation appears to have been heaviest within ten years of death, a period which would be irrelevant if latency of effects were significant.

Some of the charts are peculiar because the averages are apparently taken only over those who were actually employed rather than over the entire class of individuals involved. In considering the average cumulative work related radiation dose k years before death one finds that in some cases this is not a decreasing function of k. In fact this is improper -- it must be a decreasing function of k and it is wrong to remove people from the denominator in computing these averages because they were not in the work force. It appears (in the case of breast cancer) that this leads to one of the sillier conclusions of the paper.

The charts suffer from the fact that they involve average radiation which are misleading as already noted because of the peculiar distribution of radiation among those exposed. Thus in the breast cancer case the figures for one or two

individuals seem to dominate the average, particularly many years before death.

Similarly the relative large (9 rem average) radiation, doses among those dying of multiple myeloma (9 irradiated cases) add to relatively low radiation doses for other cancer types to give what appears to be relatively high figures for a grouping of cancer types. This figure is certainly misleading. The breast cancer figures are improperly normalized.

If radiation ten or twenty years ago was responsible for death, the fact that most radiation was closer in time to death means that the relatively small doses received years before are the culprit or radiation is the culprit at all. Thus estimating doubling doses from *total* radiation in this case could underestimate the effect. It is difficult to know how to handle this.

COMMENTS ON THE 5TH ITEM

The radiation models attempted here appear to be reasonable efforts to answer the question posed at the beginning of these remarks, i.e., what quantitative effect or "doubling dose" is suggested by this data. The analysis suffers from the limited amount of data from individuals with relatively high radiation. The low doubling dose for myeloid neoplasms is based on an arbitrary grouping of the 11 myeloma cases (9 irradiated) which in itself is insufficient to draw conclusions

from. The breast cancer results are dominated by one or two cases. The pancreatic tumor radiation excess seems to be peaked in the eight years before death which is strange from the latency viewpoint. The lung cancer results may be more solid but it is hard to be convinced of this by the presentation here -- [certainly age, time, smoking habits, and occupational type should be considered before one is entitled to draw the sweeping conclusion of the abstract of the paper].

It is if anything damaging to belief in the linear models used here that the results they produce are apparently less successful in predicting excess irradiated death than chance. In this sense, the paper suggests the invalidity of these models. It certainly does not at all justify the conclusion that "For adults of working age, there is a hazard associated with low level radiation". In fact the obvious conclusion here is that even among the 680 Hanford cancer deaths, there is insufficient data to draw such a conclusion.

GENERAL COMMENTS

It is possible that small radiation doses produce cancer. In order to establish this, or measure the probable cancer producing effect of small amounts of radiation, it is important that correlations of the data with extraneous factors be examined to make certain that these factors do not produce the observed results in themselves.

This paper lacks analysis of the more important factors, such as occupation. Without such analysis, all conclusions are suspect. Even ignoring this problem; the results here do not inspire confidence. To summarize the following are defects of this study; as:

1. As justed noted, no attempt is made to assess effects of lack of death certificates or of occupational or time factors.

2. Irradiated vs. radiated data in presence of background much greater (given latency) than dose gotten by most of the irradiated group is quite an arbitrary distinction.

3. Use of average radiation dose figures when distribution is highly skewed is inappropriate.

4. The authors erroneously average only over employed individuals in computing cumulative doses.

5. Diseases are grouped for analysis in a misleading manner.

6. Minor inconsistencies in data appear.

7. The regression model is used with quite insufficient data in some cases.

8. The results obtained do not justify the conclusions stated.

Thus, in my opinion, the paper does not strengthen the positive findings of Gilbert and Buschbom or Gilbert and does not have the intellectual weight to overcome Gilbert's negative findings. From Gilbert's data occupational effects may be important and necessary correctives are needed before conclusions can be drawn here.

REFERENCES

1. Gilbert, Ethel S. and Buschbom, Ray L., "An Evaluation of Milham's Analysis of Hanford Deaths", July, 1975.

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