ATTACHMENT 1

REVIEW OF FINAL REPORT #13 SUBMITTED BY THOMAS F. MANCUSO, M.D.

By

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In my opinion the results of nearly all tabulations and analyses given by the authors are largely subsumed by the analyses pertaining to Tables 11 and 23. These two tables control for one important variable, age at death; they deal with mutually exclusive groups and the statistical analysis is rather straight forward.

Table 11 (for males) and similarly Table 23 (for females) break down the all certified deaths by groupings of radiation doses and ages at death. For each cell defined by a particular age group and radiation category the percent of cancer deaths is computed. The percent of cancer deaths is also computed for each radiation group totaled over ages. The total group of Table 11 shows a rather consistent and appreciable rise in the percent of cancer deaths as one moves from the zero radiation subgroup to the 500 + centigrade subgroup. The same holds true for 70 + age group and to lesser degrees or not at all for other groups. However, for no age group do the data suggest a consistent downward trend. The data is certainly consistent with an upward trend for the higher age groups if allowances for plausible statistical variation are made. Table 23 provides similar results.

3. Caveats on Section 2 and criticisms on the Final Report.

In this section I shall discuss some aspects of the data and the analysis which indicate a cautious approach to the data and the results of the authors. The primary issue is death rates and cancer death rates among workers at risk rather than cancer death rates among deaths. Therefore a prospective type of analysis is preferable to a retrospective analysis. Moreover I feel that the logic of a prospective analysis is more direct and problems such as confounding are more apparent and tractable with the prospective approach. Beyond the issue of prospective vs retrospective analysis, I find that the data is very tricky and that much of the analysis by Mancuso et. al. is not convincing. These will be discussed with a few detailed examples rather than with exhaustive criticism.

Confounding of age and radiation dose.

The authors point out repeatedly that time related variables such as calendar year, years before death, and age are related to the respective dosages received or the proportion of workers exposed. I wish to point clearly to the relationship between cumulative dosages at given ages and cancer death rates. Table 21 lists the mean cumulative dose by age for non-cancers and two selected groups of cancer. The mean cumulative dose for non-cancers rises from about 10 centirads at low ages to a maximum of about 30 centirads for ages of 50 years to the mid-sixties and declines in the seventies.

This rise and fall is repeated for the two tabled cancer groups combined. Unfortunately we do not know the pattern for other cancers which on the average (see Table 4) had low mean cumulative doses. However, the non-cancers by themselves form the overwhelming majority of cases and the trend for them is very clear. In Table 11 we can see that the cancer rate of the non-exposed workers rises sharply to the fifties, reaches maximum in the sixties, declines in the seventies to a level roughly reached in the forties. If one looks at the total column the same pattern is observed. An inspection of U.S. statistics for the year of 1970 yielded the same pattern but roughly at twice the rates for Hanford workers. For one reason or another the sample of deceased Hanford workers is such that their mean cumulative doses are highest at the ages at which "natural" cancer deaths predominate.

The data of table 11 are perhaps more relevant since they show the cumulative doses at death. To show the confounding relationship requires moderately involved analysis. I have chosen one based on the analysis of contingency tables. Each cell of Table 11 has an observed frequency of death designated by the authors as "Nos." The expected frequencies for the cells are computed in such a manner that corresponding cells of any two columns are proportional to the respective column total, and with identical proportionality properties for rows. The differences between observed and expected frequencies indicate the manner in which proportial assignment is violated. The ratios of these differences to the respective expected frequencies seem to give a good quantitative measure of the shifts

from proportionality. Table A shows that in age groups with high cancer rates (50-59, 60-69) the differences are negative for low radiation groups and positive for high radiation groups. In colloquial language these two age groups get more than their fair share of high radiation. The opposite trend or a neutral trend is apparent for the other age groups.

Table 21 which gives mean cumulative doses vs age bears further examination as to the peculiar nature of the confounding of mean cumulative radiation doses and age and the erratic nature of this confounding. Let us first look again at the non-cancers. That the cumulative doses rise with age is natural enough; the older a worker is the more chance he had to accumulate radiation. But why is there such a sudden drop (37%) between the ages of 65 and 70? Note that these means are based respectively on 1072 and 716 workers and presumably nearly all of the 716 workers in the 70 year group are also in the 65 year group. Among possible explanations are the following:

(a) New workers with no radiation were hired at ages above 65 thus diluting the mean.

(b) The mean cumulative doses are strongly influenced by a few workers with extremely large doses.

(c) The death rates between ages of 65 and 70 years are strikingly higher for workers with moderate radiation doses than for workers with less radiation (Note that these are non-cancer deaths).

(d) There is some peculiar age related assignment of radiation doses to workers.

While some of these explanations may be very implausible in this context and (d) appears perhaps to be the most plausible, with limited retrospective summaries it is difficult to decide with conviction. The comparison of the mean radiation dose at death (99 centirads, see Table 2).with the maximum mean radiation dose of all ages (83 centirads) presents a similar problem.

The mean cumulative doses for the two cancer groups listed in Table 21 also show very sharp changes in small age intervals suggesting caution in interpreting results. For example for Ras Neoplasm deaths the mean cumulative dose changes from 701 centirads to 34 centirads in one year. I do not wish to cast doubt on the accuracy of these numbers; however I do suggest that such numbers taken at face value can mislead. The authors apply blithely Students t- test to such numbers (in Table 21 as elsewhere) and seem to imply validity to these statistical tests.

An examination of analyses relating to Table 4.

Table 4 presents an analysis somewhat different from those discussed above. The authors argue from the fact that for cancers for which the cancer rate of Hanford workers was high relative to the cancer rate of the U. S. population the mean cumulative doses were also high. For example for myelomas the ratio of the rate of Hanford workers to the rate of the

U.S. population was highest among all cancers the authors list in Table 4, and at the same time the mean cumulative dose of Hanford workers dying with myelomas was also the highest. Among the 18 cancer groups considered by the authors the relationship between mean dose for the cancers and the respective ratio is not perfect but quite respectable as an examination of Table 4 will reveal. The correlation (Spearman's rho) between the dose and the ratio is .62 with a one-sided P value of about .003.

The authors summarize the relationship by contrasting the observed deaths with the expected deaths (based on U.S. experience standardized to achieve 670 deaths) for two groups of cancers, i.e. those with high mean cumulative doses and those with low cumulative dose. For the high dose group the observed number 391 is significantly larger than the expected number of 318.2. This difference as well as the above correlation suggest at first impression that high cancer rates are associated with radiation. The suggested relationship is not as simple as it might seem.

Let us examine the implication of the mean dose of 773 centirads for myelomas the cancer group with the highest ratio. First let us gather some facts. Table 4 indicates there were 11 cases of myelomas. From Table 3 not reproduced here it can be inferred that 3 of these 11 cases received no radiation whatsover. Finally we need the percentages of all cases in various radiation categories of Table 11 as well as the percentages of cancers in these groups.

Dose	Cases No.	Cases %	Cancers No.	Cancers %
0	1336	38.0	226*	33.7
1-19	625	17.8	98	14.6
10-99	894	25.4	194	29.0
100-499	511	14.5	113	16.9
500	154	4.4	39	5.8
Total	3520	100.(1)	670	100.0

*226 = 16.9 x 1336

The majority of all cancers come from workers with doses less than 99 centirads and the overwhelming majority from workers with doses less than 500 centirads. If myelomas follow the same pattern then the large average dose was caused by a few exceptional doses, in which case the observed phenomenon is aberant rather than typical. If extreme observations are ruled out then the doses of the 8 cases with radiation must center on about 900 centirads suggesting something like a threshold phenomenon and that lower radiations are protective. Remember that more than 90% of irradiated cases have doses less 500 centirads.

The authors seem to reject the threshold phenomenon and strongly endorse the hypothesis of a linear relationship (page 12, "the only logical alternative"). In fact they base their computations of the doubling dose and excess mortality (EMR, page 13) on that assumption. If the linear hypothesis is true and the ratio of the intercept to the

0. <u>Preliminaries</u>.

The document under review is the Final Report #13 by Thomas F. Mancuso, M.D. submitted under contract to ERDA [1]. The substantive part relating cancers to radiation was written by Thomas Mancuso, Alice Stewart, and George Kneale. This part has also been published in the Health Physics Journal [2]. In this review the substantive part may be referred to as the Final Report or the Mancuso Study.

Several tables are reproduced from the Final Report and the table numbers of the Final Report are used. Footnotes by this reviewer have been added to some of these tables. Tables developed by this reviewer will be labeled with capital letters. Pages cited in this review refer to the page numbers of the Final Report.

1. <u>Introduction and approach to review</u>.

In his summary of the Final Report Mancuso states: "The study shows that there is a definite relationship between low level ionizing radiation and the development of cancer." While he also states more detailed conclusions, I shall deal primarily with the quote as the central issue because:

a. The broad issue is of greatest concern to NRC.

b. To the extent that the analyses of the Final Report support its conclusions, this-in my view-comes through at least as forcefully for the general conclusion as for more specific conclusions.

In Section 2, I shall discuss the support for the relationship. Section 3 will deal selectively with some shortcomings of the data and analyses performed by the authors. Section 4 will offer a summary view.

2. Support for the relationship between cancer an low lwevel ionizing radiation.

Table 2 of the Final Report breaks down the certified deaths (before 1973) of Hanford workers by cancer deaths and non-cancer deaths. It shows respectively for these two groups mean cumulative radiation doses of 138 and 99 centirads, and proportions of radiation exposed workers of 66.0 and 61.1%. This apparent association between cancer deaths and radiation suggests at face value a causal relationship. Many of the succeeding tables and graphs present the same data broken down by finer classifications such as exposures received in specific calendar years or at specific ages or broken down by specific types of cancers. As one would expect these refined breakdowns tend to show the same association between cancer deaths and exposure, and neither is it surprising that the association seems to be stronger for some subsets of the data than for others.

slope of the straight lines are proportional over cancer classifications then the mean doses for all cancers should be the same. Even without this restriction differences between mean doses on various types of cancer does not seem to be a good measure of the relative "risks" of cancer types to radiation.

Even though we may not be able to find a plausible explanation for the statistically significant correlation between mean doses and the ratio observed to expected it merits some attention. One can duplicate the authors' analyses substituting the percentage of exposed workers for the mean cumulative doses; the results are presented in Table 3. The difference between observed and expected for the "high-risk" cancers becomes very small and the correlation between percent exposed and the ratio has become slightly negative (rho = -.05). The fact that two correlated measures-percent exposed and mean doses-yield such strikingly different results again points to the fact that the data is tricky.

4. Summary View

In my opinion much of the Final Report is not relevant or of questionable validity. The remainder of the report is largely subsumed by the analyses of Tables 11 and 23; especially on those matters of greatest concern to NRC. This leaves us with the issue how valid are these analyses. These analyses are stratified (controlled) by age at death and therefore relatively invulnerable to confounding dose with this variable. However, age at death is not the only relevant time related variable.

I believe date of birth and some allowance for latency are important. A worker's date of birth determines whether he will reach before 1973 (cutoff date of study), the ages in which cancers deaths reach their highest proportions among deaths. The rather odd behavior of the mean cumulative dose as a function of age suggests that if latency is accounted for the apparent picture may change. Finally, since the radiation has been so strongly confounded with time related variables it seems plausible that it may also be confounded with other variables. In fact, differences in radiation exposure suggest differences in occupation and correlated characteristics.

There are no good scientific guidelines to evaluate these possibilities. The numerical relationship of cancer incidence and low level radiation, if it ever can be convincingly demonstrated, will most likely be demonstrated by a painstaking prospective study. Despite various reservations I feel that the results of Tables 11 and 13 should not be ignored in the formulation of regulatory policy until more definite studies have been carried out.

One more comment, the rapid decline of the mean cumulative dose between ages of 65 and 70 does suggest among other possibilities an increased death rate caused by radiation. Until or unless better analyses are available NRC should not be oblivious to that suggestion.

References:

[1] Thomas F. Mancuso, M.D. - Study of Lifetime Health and Mortality Experience of Employees of ERDA Contractors; Final Report #13. Prepared for the U.S. Energy Research and Development Administration; September 30, 1977.

[2] F. Mancuso, A. Stewart, G. Kneale - Radiation Exposures of Hanford Workers Dying from Cancer and Other Causes. Health Physics 33.5: 369-385, 1977.

TABLE 2

External Radiation Records for Three Groups of Non-Survivors: Cancers, Non-Cancers and Uncertified Deaths +

on-Survivors	Cases	Exposed Workers (1)	Cumulative Radiation Dose	Exposed Workers	Mean Radiation Dose in Centirads (	
	Nos.	Nos.	Centirads	%	A	B
ancers	670	442	92657	66.0	210	138
on-Cancers	2850	1742	282961	61.1	162	99
11 Certified Deaths	3520	2184	375618	62.0	172	107

1) Men with one or more positive badge readings.

2) A = Mean cumulative radiation dose for exposed workers.

B = Mean cumulative radiation dose for all workers.

+ Reviewers comment: Apparently uncertified deaths are not included in this table.

TABLE 4

Observed and Expected Numbers of Specific Neoplasms Listed According to Mean Cumulative Radiation

	Neoplasms[1]	Mean Cumulative Radiation Dose Centirads	No. of Deaths[2] Observed	Expected	Ratio Obs:Exp
1.	Myelomas	775*	11	7.6	1.45
2.	Pancreas	253*	49	37.3	1.31
3.	Brain	220*	18	17.3	1.04
4.	Kidney	187*	21	15.0	1.40
5.	Lung	169*	192	144.4	1.33
6.	Large Intestine	135*	61	63.1	0.97
7.	Myeloid Leukemia	122*	11	5.8	1.90
8.	Lymphomas	119*	34	27.7	1.23
9.	Rectum	99	19	29.6	0.64
10.	Mouth & Pharynx	89	24	21.9	1.10
11.	Other Genito-Urinary	82	15	30.9	0.49
12.	Stomach	60	38	58.7	0.65
13.	Prostate	42	43	67.5	0.64
14.	Other Intestinal	32	18	18.0	1.00
15.	Liver & Gall Bladder	31	18	12.5	1.44
16.	Lymphatic Leukemia	19	3	9.4	0.32
17.	Other RES Neoplasms	12	5	20.3	0.25
18.	Other Solid	81	90	83.0	0.59
	1-8	188*	397	318.2	1.25
	9-18	65	273	351.8	0.78
	All Cancers	138*	670	670.0	1.00

(1) See Table 3.

(2) Observed see Table 3; expected see 1960 cancer deaths of white U.S. males in NCI Monograph 33.

* = Above the mean value for all certified deaths (107), see Table 2.

Table 11

Test for Correlation between the Percentage of Cancer Deaths and the Cumulative Radiation Dose after Standardization for Age at Death

Age at Death in years	Zero Nos.	Zero %Cancers	1-19 Nos.	1-19 %Cancers	20-99 Nos.	20-99 %Cancers	100-499 Nos.	100-499 %Cancers	500+ Nos.	500+ %Cancers	Total Nos.	Total %Cancers
	Mean Cumulative Radiation Dose for all Workers (in Centireds) †											
Under 40	108	9.3	55	10.9	58	8.6	24	8.3	9	22.2	254	9.8
40-49	185	13.0	82	15.9	137	21.9	74	23.0	17	11.8	495	17.3
50-59	331	19.3	137	16.1	200	24.5	155	21.9	58	31.0	881	21.2
60-69	360	22.2	142	21.6	240	26.6	184	25.0	53	22.6	1007	23.7
70+	352	13.6	189	11.6	251	17.5	74	18.9	17	29.4	883	15.1
Total	1316	16.9	625	15.7	894	21.7	511	22.0	154	25.3	3520	19.0

Ranking Nos. for Cancer Proportions

Age at Death	Zero	1-19	20-99	100-499	500+	Value of rho[(1)]
Under 40	3	4	2	1	5	0.1
40-49	2	3	4	5	1	0.0
50-59	2	1	4	3	5	0.8
60-69	2	1	5	4	3	0.5
70+	2	1	3	4	5	0.9
Means	2.2	2.0	3.6	3.4	3.8	0.46 ± 0.22*

(1) Value of Spearman's rank correlation coefficient between the percentage of cancer deaths and the radiation dose level.

*This value is statistically significant at the 5% level.

† The column headings were interpreted as class intervals for cumulative dose rather than mean cumulative radiation dc

TABLE 21

Mean Cumulative Doses of External Radiation by Stated Ages: Non-Cancers, RES Neoplasms and Other Selected Cancers[1]

Age in Years	Non-Cancers R[2]	RES Neoplasms R	RES Neoplasms t[3]	Other Cancers[1] R	Other Cancers[1] t	Nos. of Cases: Non-Cancers	Nos. of Cases: RES Neoplasms	Nos. of Cases: Other Cancer
21	8	-	-	39	2.3	43	1	6
22	7	2	-	39	3.1	87	2	7
23	9	7	-	47	3.2	118	3	7
24	13	11	-	40	2.1	145	3	9
25	19	11	-	34	-	177	3	12
30	38	37	-	40	-	353	13	43
35	51	39	-	42	-	623	22	85
40	56	35	-	48	-	870	30	126
45	59	68	-	66	-	1,093	34	175
50	73	116	-	105	2.0	1,302	33	205
55	83	230	2.5	154	3.2	1,397	30	213
60	80	211	2.0	130	2.1	1,326	25	169
65	76	458	5.3	132	2.0	1,072	15	112
70	48	701	9.2	80	-	716	8	59
71	43	701	9.9	89	-	645	8	52
72	43	34	-	98	2.7	587	5	40
73	38	34	-	100	3.5	521	5	29
74	37	35	-	98	3.1	454	4	25
75	36	45	-	98	2.8	386	3	22
76	35	45	-	115	3.3	338	3	16
77	35	45	-	112	3.0	278	3	15
78	37	68	-	119	2.5	231	2	10

(1) Cancers of the pancreas, lung, brain, kidney, and large intestine (see Table 3).

(2) R = Mean cumulative dose of external radiation.

(3) t values greater than the critical value of 2.0.

TABLE 23

Cancer and Non-Cancer Deaths of Females by Age and Radiation Dose

Age at Death	Radiation Doses Levels (Centirads)	No. of Deaths (N)	No. of Deaths (C)	Cancers %(1)	Cancers Rank	Cancers rho(2)	Radiation Doses in Centi[illegible] Totals (N)	Totals (C)	Means f[illegible] Exposed Wo[illegible] (N)	([illegible]
20-49	0	71	35	33.0	(2)					
	1-	24	11	31.4	(1)					
	50-	4	3	42.9	(4)					
	100+	2	1	33.3	(3)					
	Σ	101	50	33.1		0.6	1,071	564	33	
50-59	0	31	30	49.2	(3)					
	1-	10	5	33.3	(2)					
	50-	6	2	25.0	(1)					
	100+	3	4	57.1	(4)					
	Σ	50	41	45.1		0.2	1,190	2,172	63	[illegible]
60-69	0	46	13	22.0	(2)					
	1-	9	1	10.0	(1)					
	50-	5	2	28.6	(3)					
	100+	6	3	33.3	(4)					
	Σ	66	19	22.4		0.8	2,451	1,372	123	[illegible]
70+	0	52	11	17.5	(2)					
	1-	11	--	0.0	(1)					
	50-	4	4	50.0	(3)					
	100+	1	2	66.7	(4)					
	Σ	68	17	20.0		0.8	1,085	927	68	[illegible]
All Ages	0	200	89	30.8	(2.25)					
	1-	54	17	23.9	(1.25)					
	50-	19	11	36.7	(2.75)					
	100+	12	10	45.5	(3.75)					
	Σ	285	127	30.8		0.60* ±0.29	5,797	5,035	68	[illegible]

(1) % of all certified deaths.

(2) See Table 11.

N = Non-Cancers

C = Cancers

*This is a significant finding at the 5% level.

TABLE A

Contingency Table: Age at Death Vs Radiation Doses

Age		RADIATION DOSES 0	1-19	20-99	100-499	500+	Totals:
<40	obs	108	55	58	24	9	254
	exp	96.4	45.1	64.5	36.9	11.1	254
	diff	11.6	9.9	-6.5	-12.9	-2.1	
	diff/exp	.12	.22	-.10	-.35	-.19	
40-49	obs	185	82	137	74	17	495
	exp	187.9	87.9	125.7	71.9	21.7	495.1
	diff	-2.9	-5.9	11.3	2.10	-4.7	
	diff/exp	-.02	-.07	.09	.03	-.22	
50-59	obs	331	137	200	155	58	881
	exp	334.4	156.4	223.8	127.9	38.5	881
	diff	-3.4	-19.40	-23.80	27.1	19.5	
	diff/exp	-.01	-.12	-.11	.21	.51	
60-69	obs	360	162	248	184	53	1007
	exp	382.2	178.8	255.8	146.2	44.0	1007
	diff	-22.2	-16.8	-7.80	37.80	9.0	
	diff/exp	-.06	-.09	-.03	.26	.20	
70+	obs	352	189	251	74	17	883
	exp	335.1	156.8	224.3	128.2	38.6	883
	diff	16.9	32.2	26.7	-54.20	-21.60	
	diff/exp	.05	.21	.12	-.42	-.56	
Totals:	obs	1336	625	894	511	154	3520
	exp	1336	625	894.1	511.1	153.9	

TABLE 3

SELECTED SUMMARIES FROM TABLES 3 AND 4 WITH CANCER DIAGNOSES ORDERED BY DECREASING PERCENT EXPOSED

CANCERS	%EXPOSED	CASES OBSERVED	CASES EXPECTED	RATIO OBS/EXP VALUE	RATIO OBS/EXP RANK	MEAN CUM DOSE VALUE	MEAN CUM DOSE RANK
Rectum	84.2	19	29.6	.64	13.5	99	9
Lymphomas	82.4	34	27.7	1.23	7	119	8
Large Intestine	78.7	61	63.1	.97	11	135	6
Myelomas	72.7	11	7.6	1.45	2	775	1
Stomach	68.4	38	58.7	.65	12	60	3
Lung	67.7	192	144.4	1.33	5	169	5
Kidney	66.7	21	15.0	1.40	4	187	4
Lymphatic LK	66.7	3	9.4	.32	17	19	17
Other G.U.	66.7	15	30.9	.49	16	82	11
Pancreas	63.3	49	37.3	1.31	6	253	2
Brain	61.1	18	17.3	1.04	9	220	3
Residue (Solid Tumors)	60.0	90	83.0	.59	15	81	12
Residue (RES Neoplasms)	60.0	5	20.3	.25	18	12	18
Mouth & Pharynx	58.3	24	21.9	1.10	8	89	10
Liver & Gall Bladder	55.6	18	12.5	1.44	3	31	16
Other Intestinal	55.6	18	18.0	1.00	10	32	15
Myeloid Leukemia	54.5	11	5.8	1.90	1	122	7
Prostrate	48.8	43	67.5	.64	13.5	42	14
Totals: 1-9		394	386.4				
Totals: 10-18		276	283.6				
All Cancers		670	670				
rho with % Exposed				-.05		.40	