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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
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BETHESDA, MARYLAND 20014

NATIONAL CANCER INSTITUTE

March 3, 1978

Dr. Michael A. Parsont
Office of Standards Development
U.S. Nuclear Regulatory Commission
Mail Stop 5650-NL
Washington, D.C. 20555

Dear Dr. Parsont:

The enclosed review of the Mancuso-Stewart-Kneale publication on proportional mortality among Hanford workers does not necessarily reflect the views of anyone else, and any published report may be substantially different. Likewise the attached preliminary comments on the more recent analysis by the same authors reflects only my personal views.

Yours sincerely,

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Enclosure

CEL:sds

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1 Feb 1977

Draft - Charles Land

Review of Mancuso, Stewart, & Kneale:

Radiation Exposures of Hanford Workers Dying

From Cancer and Other Causes

I. Introduction

The studies of mortality in the Life-Span Study sample of Japanese A-bomb survivors[1-8] and non-exposed controls, and in the British patients whose spines were irradiated as part of their treatment for ankylosing spondylitis[9-10], have long been considered to be the best available basis for the assessment of long-term mortality risk to human populations from exposure to ionizing radiation. To a large extent this has been due to the large size of these studies, and to the rigor with which they were carried out, but another factor has been the relative simplicity of the exposures received, and consequent ease of interpretation of the study results. These studies have demonstrated that populations exposed to external doses of ionizing radiation have had increased mortality from cancer in general, and certain cancers in particular, notably leukemia, female breast cancer, and lung cancer. Moreover, cancer mortality has increased with increasing dose; that is, a dose response relationship of radiation to cancer mortality has been demonstrated in these studies. Studies of other irradiated populations have confirmed these findings[11-12]. However, the greater part of the evidence for the carcinogenic effects of ionizing radiation has come from the more heavily exposed parts of the irradiated populations, and estimates of risk for populations exposed to low doses of radiation have been obtained by assuming a smoothly increasing relationship between cancer risk and radiation dose, and fitting such a dose-response form to the data obtained over entire ranges of exposure. The radiation safety standards based on these estimates have been set so low that it has not seemed

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likely that we should ever have direct statistical evidence of radiation-induced cancers occurring in populations whose exposures were governed by these standards. This is not because no effect was assumed to exist at these dose levels, but rather because the effect was considered to be so low that practically unattainable sample sizes would be needed to demonstrate that any excess risk existed.

The paper by Mancuso, Stewart, and Kneale (hereafter denoted MSK)[13], describing a proportional mortality analysis of Hanford plutonium workers with respect to individual radiation exposures obtained from radiation badge readings, is the first published report relating cancer mortality to routine, monitored, low-level occupational exposure to radiation. Their findings have come as a great surprise because in an analysis of some 3500 deaths, 2200 of them among exposed workers with an average cumulative dose of less than 2 rem at time of death, they claim to have found statistical evidence of radiogenic cancer in general, and cancers of the lymphopoietic system, pancreas, and lung in particular. Their findings suggest doubling doses of around 12 rem for all cancers as a group, 7 rem for cancer of the pancreas, 6 rem for lung cancer, 2.5 rem for lymphatic cancers in general and 0.8 rem for bone marrow cancers. In addition, they claim that most of the excess cancers have been caused by exposures received before the age of 25 or after the age of 45, and that ages 25-45 are a period of minimal sensitivity to low-level radiation effects.

While the risk estimates obtained by MSK are an order of magnitude or more greater than those obtained in the vast majority of other studies, they cannot be dismissed out of hand, not least because they are based on direct observation of monitored and regulated industrial exposures. Estimates based

on other exposed populations, on the other hand, apply only by analogy to industrial exposures. Also, it is not enough to point out methodological weaknesses in the MSK study that could conceivably have biased their results; in order to fully assess the strength of their evidence it may be necessary to improve the analysis. In other words, the task before the present authors is to see whether the data used by MSK justify their conclusions.

The present report falls naturally into two parts: a review of the statistical methods used by MSK, without regard to the biological plausibility of their results, and a review of their conclusions, after any necessary revisions, from a biological point of view. Our review is incomplete in that we were unable to undertake a cohort analysis, including both living and dead workers, which we felt was the appropriate analysis for the Hanford workers. Instead, we limited ourselves to the proportional mortality approach used by MSK.

2. Review of Statistical Methods

A data tape was obtained from Oak Ridge National Laboratory giving cause of death, exposure status, and cumulative dose at death and at 3, 5, 10, 15, and 20 years prior of death for all deaths occurring between 1940 and December 31, 1973. Our data set contained 3610 deaths, including 2238 among exposed workers, as compared to 3520 deaths, including 2184 among exposed workers, in the MSK series. As can be seen from Table 1, the numbers of deaths and the cumulative doses at death agree well with those reported by MSK, by cause of death and exposure status. Exceptions are the numbers of deaths from external causes (ICD 800-999) and the average dose for ICD codes 500-796. We have been unable to explain the differences, but they do not appear to be important.

A potential source of bias in the MSK analysis that particularly concerned us was confounding between cause of death, cumulative dose, and age and year of death. For example, cumulative dose increases with time and therefore also with age, and cancer rates vary with age and also, sometimes over time. Our solution was to test for dose relationships by a summary contingency table approach[14-17], adjusting for age at death in three levels (20-49, 50-64, 65+) and year of death in three levels (1943-60, 61-67, 68-73). Columns of the tables corresponded to radiation dose intervals 0-24, 25-44, 45-64, 65-84, 85-104, 105-204, 205-404, 405-604, 605-1004, and 1005+ centirems, respectively. A single trend statistic, based on the average dose values for each of these intervals and the numbers of deaths in each, was used to test for increasing trends in proportional mortality with increasing dose. Test results without adjustment for age and year of death agreed well with those obtained by MSK.

In keeping with the MSK practice of using average cumulative doses as descriptive statistics, we have used averages adjusted to the age- and year-of-death distribution of all 2238 deaths among exposed workers.

Both the MSK test statistic and the trend statistic described above are approximately normally distributed under the null hypothesis of no dose relationship, assuming the dose distribution to be approximately symmetric. Pronounced skewness of the dose distribution tends to skew the distribution of both test statistics, so that extreme values corresponding to increasing proportional mortality for a given cause with increasing dose, judged by the normality criterion, appear to be more extreme than they really are. Accordingly, the present analysis adjusts for skewness by a formula based on the third and

fourth null moments of the trend statistic[18].

The present analysis also differs from that of MSK by including only deaths among exposed workers. The non-exposed workers obviously differ from the exposed workers with respect to job classification and length of employment, and demographic differences seem not unlikely. For example, the proportions of workers who had been employed at Hanford five years or more was .62 among deaths for exposed workers and only .11 among deaths for non-exposed workers. Proportionally more deaths among exposed workers than among non-exposed workers were due to cancer of the large intestine, rectum, and to digestive cancers in general, to lymphosarcoma, ischemic heart disease, and myocardial infarction; the opposite was true for cancers of the gallbladder and prostate, for unspecified neoplasms, chronic myocardial infarction, and acute respiratory diseases ($p<.05$ in each case for a one-sided test).

Table 2 shows summary contingency tables corresponding to each of the diseases in Table 1, plus all cancers. The analyses were computed using 10 dose intervals, but observed and expected values have been summed for adjacent dose intervals to give a more compact presentation in Table 2. Only for cancer of the pancreas and multiple myeloma is there any marked association of dose with proportional mortality. In the case of pancreatic cancer, the association hinges on 5 of the 32 cases having cumulative doses over 10 rem, while that for myeloma depends on 3 of the 8 cases having doses over 10 rems. If we ignore the non-cancers and consider that comparisons were made for 16 separate cancers, it is not unlikely that at least one of these should have corresponded to as extreme a p-value as those obtained for myeloma and pancreatic cancer (about .01) purely by chance, but it is unlikely that two such extreme p-values would occur by chance. Therefore, 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.

The MSK analysis looks not only at cumulative dose at the time of death, but also at various intervals before death. The approach is not unreasonable, in the sense that the latent period of a radiogenic cancer could make all exposures within a certain number of years before death irrelevant to the cause of deaths, but the approach nevertheless increases still further the chances of finding apparent associations between dose and certain cancers that are purely fortuitous. We have repeated the analyses of Table 2 only for cumulative doses 5, 10, and 15 years before death. Table 3 gives adjusted average cumulative doses corresponding to each interval before death and each cause, plus the p-values obtained from the appropriate contingency table analyses. For each interval before death, the average cumulative dose for all deaths is also given. The pattern of dose at 5 years before death is similar to that at death, except that the average dose value for cancer of the pancreas relatively was not as high (p barely less than .05). At 10 years before death, the dose distribution for all cancers, as a group, is barely suggestive of a dose relationship, and the same is true for cancer of the kidney. At 10 and 15 years before death, the dose distributions for deaths from myeloma are extreme, so much so that the pattern is reflected in the trend tests for all lymphopoietic cancers as a group, despite the very low average doses for lymphopoietic cancers other than myeloma. The association reported by MSK for lung cancer apparently was an artifact of an increasing trend over time of both lung cancer incidence and cumulative dose, because the adjusted analysis does not

suggest a dose relationship for lung cancer.

Overall, the analyses summarized in Table 3 strengthen the evidence for an association between radiation dose and myeloma , and perhaps slightly weakens the evidence corresponding to pancreatic cancer. There is no evidence of a dose relationship for cancers other than these two, considered as a group. Although cancer of the kidney appeared to be weakly associated with dose at 10 years before death, the evidence is weak indeed.

A comparison of observed proportional mortality with that expected according to national mortality rates for white males[13] resulted in the following observed/expected ratios for groups of cancers and pancreatic cancer, myeloma, and leukemia in particular (the packaged program did not allow multiple myeloma, ICD 203, to be treated separately):

	non-exposed	exposed	10+ rem
All cancer (140-209)	236/237	449/405*	20/16.5
Mount and pharynax (140-149)	9/8.1	14/13.9	1/0.6
Digestive organs (150-154)	67/76.6	146/124	6/46
Pancreas (157)	19/13.4	32/23.1	5/1.0**
Respiratory system (160-163)	66/68.6	138/126	5/6.0
Lymphatic system (200-209)	18/24.4	47/42.1	4/1.6
Myeloma, etc. (202,203,208)	4/4.1	10/7.7	3/0.35**
Leukemia (204-207)	9/10.4	11/17.2	1/0.62

* $p<.05$ ** $p<.01$

Besides the already noted high-dose excesses of myeloma and pancreatic cancer, which accounts for somewhat more than the observed high-dose excess of all cancers, notable results include a statistically significant excess of all cancers and a non-significant deficit of leukemia among all exposed workers.

The excess cancers, in the absence of a dose-response relation, invite an explanation in terms of population selection, and the deficit of leukemias emphasizes the lack of any dose relationship for these most radiosensitive cancers. Taken together, the similar but separately non-significant excesses of pancreatic cancer in exposed and non-exposed workers give a borderline significance value ($p<.05$). Pancreatic cancer is known to occur at higher than usual levels among chemical workers[20], and the above result suggests the possibility of involvement of an occupational carcinogen other than radiation.

The doubling dose estimates obtained from adjusted averages are not greatly different from those obtained by MSK, at least for the two cancers for which a dose relationship seems most plausible: 1.5, 0.9, 0.3, and 0.2 rem, respectively, for myeloma at death and 5, 10, and 15 years before death, while for pancreatic cancer the corresponding estimates are 5.1, 5.5, 4.8, and 7.8 rem. For all cancers as a group the doubling dose estimates are 107, 79, 25, and 12 rem, depending on the period before death. It is difficult to take such estimates seriously; even under the best of circumstances the doubling dose estimate has a relatively large error bound because it is distributed as the ratio of two random variables, and given the small numbers from the present data, the error bounds should be very large indeed.

The MSK abstract contains two sentences. The first states that the Hanford data show that sensitivity to the cancer induction effects of radiation is at a low ebb between 25 and 45 years of age. We can find no statistical justification for this conclusion. The statement appears to be based on comparisons of average cumulative doses at given ages, among workers employed by that age who had not yet died, but who died before 1974. Workers whose cause of

death was not cancer had smaller crude average doses than workers who died of lymphopoietic cancer, or workers who died of cancer of the pancreas, lung, brain, kidney, or large intestine, at ages 45+ or under 25 but not at ages 25-45. The comparisons, which are based on both exposed and non-exposed workers, are affected by the recruitment of new workers mostly at young ages, and by mortality mostly at older ages. In fact, at ages over 65, the changes in average dose with increasing age can only reflect mortality, because presumably, exposure stops with retirement. In this connection, the estimated doubling doses in Table 22 of MSK for cancers of the pancreas, lung, brain, kidney and large intestine, as a group, have an unreal quality; they include the values 0.1 rem for cumulative dose at age 22, 70 rem for cumulative dose at age 50, and 0.9 rem for cumulative dose at age 78.

3 Radiobiological Considerations

As a transition from statistical to biological considerations, it may be helpful to inquire what would be the reaction to the MSK study, and to the above reanalysis, if all the doses were multiplied by a factor of 10. We do not believe the MSK statements about radio-sensitive ages would be any more acceptable, but their claims of radiation dose relationship for various cancers would seem more reasonable. That is because other studies have also suggested the existence of radiogenic cancer, including myeloma and pancreatic cancer, at doses of 100 rem or more[8-10,21,23]. The results of the reanalysis would also seem plausible, because usually, higher doses than those of the Hanford workers, times 10, have been required to demonstrate radiation effects for most solid tumors. Only the absence of a leukemia effect, in the presence of effects for pancreatic cancer and myeloma, would seem remarkable.

At the low doses received by the Hanford workers, it is not surprising that

no leukemia effect has been demonstrated, because no other study has suggested an effect for adults exposed to such low doses. In this connection, it is distinctly unhelpful that MSK have lumped myeloma with myeloid leukemia as "bone marrow cancers", and the ICD codes 200-209 as "RES neoplasms". The effect is to suggest that a leukemia effect was found when, in fact, there is no suggestion of a dose relationship for any RES neoplasm except myeloma.

It is interesting that a recent survey of mortality among U.S. radiologists[21] found that among cohorts entering practice in 1920-1929, 1930-1939, and 1940-1949, excess leukemia, as compared with physicians in other specialties, was observed only for the two older cohorts, while excess lymphoma, and especially muliple myeloma, was observed only in the two younger cohorts. That is, leukemia rates among radiologists have decreased, and lymphoma rates have increased, during a period of presumably declining occupational radiation exposure among members of this specialty. The authors of that study hypothesize that frequent low-dose radiation exposures may have different effects than fewer and higher-dose exposures, resulting in stress on the immune system that increases risk of lymphoma rather than leukemia. The hypothesis is tentative, reflecting, among other things, the very small numbers of lymphomas involved, but it is interesting that it is similar to an implied conclusion of MSK, viz, that extremely fractionated exposures may have effects qualitatively different from those of exposures delivered in larger fractions. Of course, the hypothesis with respect to radiologists assumes a similarity between multiple myeloma and lymphomas while MSK have assumed multiple myeloma to be a bone marrow cancer closely related to myeloid leukemia, but neither of these two associations are crucial to the hypothesis.

A study of cancer incidence among women exposed to multiple chest fluoroscopies

during pneumothorax treatment at Massachusetts tuberculosis sanitoria found 2 leukemias versus 1.2 expected according to population rates among exposed women and 1 leukemia versus 0.7 expected among patients not given pneumothorax therapy; there were no multiple myelomas in the exposed and 2 in the non-exposed and 3 other lymphomas in the exposed and 1 in the non-exposed[22]. The exposed women received, on the average, 100 exposures of about 1.5 rads each in terms of average breast tissue dose and probably somewhat less to the spine. While there are obvious differences between the radiation exposures of the pneumothorax patients and those of the radiologists and the Hanford workers, fractionization of exposures in this case did not result in atypical findings with respect to cancers of the lymphatic and haemopoetic organs.

If the estimated radiation risks for myeloma and pancreatic cancer are discounted because of their disagreement with the results from other studies it does not follow immediately that no radiation relationship is reflected in these data. The most serious possibility is that the monitoring of radiation exposure has been defective. Radiation badges are not equally sensitive to all types of radiation, and are not generally considered to be ideal dosimeters[24]. However, the absence of a leukemia effect argues against this possibility.

Another possibility, which was considered by MSK, is that monitored external dose may have been correlated with exposure to internal radiation emitters. The MSK treatment of this possibility is not conclusive, leaving it open as a possible explanation of their findings. However, an inquiry to the radiation monitoring group at Hanford disclosed that the MSK definition of exposure to internal emitters included any positive urinalysis, including those later determined to be due to contamination of the sample. Since most such readings were determined to be false positives on the basis of follow-up

examinations[24], the MSK data on exposure to internal emitters are essentially valueless.

The possibility of an occupational exposure to other carcinogens, such as chemicals, would require an analysis including occupational group.

4. Summary

An analysis of the MSK data adjusted for age and date of death reduces the number of cancers for which radiation dose relationship can be suggested to two, myeloma and pancreatic cancer. There is no suggestion of a radiation relationship for lymphatic cancers other than myeloma, or for solid tumors of sites other than the pancreas, with the possible, and very weak, exception of the kidney. The MSK conclusions about variations in sensitivity to radiation by age at exposure appear to be untenable. Radiobiological considerations, including the results of other studies, suggest that the excess proportional mortality at relatively high doses for myeloma and pancreatic cancer is likely to be explainable in terms of a correlate of dose rather than the radiation itself, although the existence of a true radiation induced excess cannot be ruled out without further analysis. A cohort analysis of the Hanford experience would be a great improvement over the current proportional mortality analyses.

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Table 1. Comparison of data used in the present analysis with those used by MSK (See MSK Table 3)

Cause of death		Total deaths		Exposed workers		Average cumulative dose among exposed workers	
		Present	MSK	Present	MSK	Present	MSK
Non-cancers:							
Infective & Parasitic	(000-136)	32	29	18	16	89	79
Benign neoplasma	(210-239)	10	10	4	4	39	39
Endocrine & blood	(244-289)	65	54	40	34	243	153
Nervous	(290-389)	37	36	21	20	162	169
Cardiovascular	(390-458)	1885	1837	1184	1149	168	167
Respiratory	(460-519)	194	194	107	108	134	133
Digestive	(520-577)	140	139	86	83	221	190
External causes	(800-999)	243	450	145	271	164	156
Residue	(580-796)	100	101	55	57	79	151
Lymphopoietic cancers:							
Lymphomas	(200-202)	35	34	28	28	146	145
Multiple Myeloma	(203)	11	11	8	8	1066	1066
Lymphatic Leuk	(204)	3	3	2	2	29	29
Myeloid Leuk	(205)	12	11	6	6	223	223
Residue	(206-209)	5	5	3	3	19	19
Solid tumors:							
Mouth & pharynx	(140-149)	23	24	14	14	130	152
Stomach	(151)	38	38	26	26	85	86
Large intestine	(153)	63	61	50	48	168	171
Rectum	(154)	19	19	16	16	118	118
Liver & Gall Bladder	(155-156)	19	18	10	10	56	58
Pancreas	(157)	51	49	32	31	404	399
Lung	(162-163)	195	192	129	130	214	249
Prostate	(185)	43	43	21	21	87	87
Kidney	(189)	23	21	15	14	263	281
Other GU	(186-188)	15	15	10	10	123	123
Brain	(191)	21	18	14	11	291	361

Table 2. Summary contingency table analyses of proportional mortality by cause of death, using cumulative dose at time of death.

Cause of death	ICD		Dose Interval (Rems) 0-.2	.2-.6	.6-1.	1.-4.	4.-10.	10+	Total	Trend test
Non-cancers:										
Infect. & parasitic	000-136	O	4	7	2	5	0	0	18	.75
		E	6.6	5.0	2.2	3.2	0.6	0.4		
Benign neopl.	210-239	O	2	1	1	0	0	0	4	.76
		E	1.3	1.0	0.5	0.8	.2	.2		
Endocrine	244-289	O	13	12	5	6	1	3	40	.30
& blood		E	12.5	9.5	5.1	9.0	2.3	1.6		
Nervous	290-389	O	8	4	1	7	0	1	21	.52
& Sense Organs		E	6.8	5.2	2.7	4.5	1.0	0.8		
Cardiovascular	390-458	O	402	293	152	241	55	41	1184	.62
		E	387.6	203.4	149.8	246.6	54.5	42.2		
Respiratory	460-519	O	31	27	16	24	7	2	107	.53
		E	35.7	28.7	14.3	20.6	4.3	3.3		
Digestive	520-577	O	31	19	5	22	5	4	86	.48
		E	26.9	20.2	10.1	19.9	5.0	3.9		
Residue	580-796	O	22	12	8	12	1	0	55	.96
		E	18.0	14.2	7.0	11.3	2.6	2.0		
External	460-510	O	54	34	16	30	4	7	145	.30
causes		E	48.0	37.8	18.7	29.4	6.2	4.9		
Cancers:										
Mouth &	140-149	O	6	4	1	2	0	1	14	.44
Pharynx		E	4.6	3.6	1.7	2.9	0.7	0.5		
Stomach	151	O	8	10	1	6	1	0	26	.80
		E	9.2	6.9	3.1	4.0	1.0	0.8		
Large intestine	153	O	13	14	8	12	2	1	50	.71
		E	16.0	12.4	6.3	10.8	2.5	1.9		
Rectum	154	O	4	6	2	3	1	0	16	.56
		E	6.0	4.5	1.9	2.7	0.5	0.4		

Continuation of Table 2.

Cause of death	ICD		Dose Interval (Rems, 0-.2	.2-.6	.6-1.	1.-4.	4.-10.	10+	Total	Trend test
Liver &	155-156	O	4	2	1	3	0	0	10	.81
Gall bladder		E	3.3	2.5	1.3	2.1	0.5	0.4		
Pancreas	157	O	7	8	4	6	2	5	32	.011
		E	10.4	8.0	3.7	6.9	1.7	1.4		
Lung	162-163	O	29	32	19	33	11	5	129	.18
		E	40.9	31.4	15.7	28.8	6.8	5.3		
Prostate	185	O	5	8	3	5	0	0	21	.82
		E	6.9	5.4	2.7	4.3	1.0	0.8		
Kidney	189	O	4	4	4	2	0	1	15	.14
		E	5.3	4.4	2.1	2.6	0.4	0.3		
Other GU	186-188	O	1	3	2	4	0	0	10	.52
		E	3.6	2.8	1.2	1.8	0.4	0.3		
Brain	191	O	2	3	3	3	1	2	14	.15
		E	3.7	2.5	1.6	4.2	1.1	0.9		
Lymphopoietic	200-209	O	15	13	3	10	2	4	47	.11
		E	14.7	11.2	5.8	10.9	2.5	2.0		
Lymphomas	200-202	O	6	9	2	9	2	0	28	.67
		E	8.9	6.8	3.4	6.4	1.4	1.1		
Multiple	203	O	4	0	1	0	0	3	8	.009
Myeloma		E	2.4	1.8	1.0	2.0	0.5	0.4		
Lymphatic	204	O	1	1	0	0	0	0	2	-
Leukemia		E	0.7	0.5	0.2	0.4	0.1	0.1		
Myeloid	205	O	2	2	0	1	0	1	6	.17
Leukemia		E	1.8	1.4	0.8	1.4	0.3	0.3		
Other	206-209	O	2	1	0	0	0	0	3	-
Lymphatic		E	1.0	0.8	0.4	0.6	0.2	0.1		

Continuation of Table 2.

Cause of death	ICD		Dose Interval (Rems) 0-.2	.2-.6	.6-1.	1.-4.	4.-10.	10+	Total	Trend test
All cancer	140-209	O	121	126	59	99	24	20	449	.13
		E	145.9	112.0	55.8	96.7	22.1	17.5		

Table 3. Summary of analyses by cause and period before death: adjusted cumulative doses and trend test p-values.

Cause of death (ICD)		# deaths (exposed)	cumulative dose in centirems and p-value for trend test: at death	death-5	death-10	death-15
Non-cancers:						
Infective and parasitic	(000-136)	18	93 (.75)	68 (.73)	46 (.63)	41 (.33)
Benign and unspec. neoplasms	(210-239)	4	20 (.76)	16 (.72)	8 (.71)	6 (.73)
Endocrine & blood	(244-284)	40	234 (.30)	140 (.59)	71 (.58)	45 (.52)
Nervous and sense organs	(290-389)	21	146 (.52)	140 (.41)	96 (.39)	40 (.63)
Cardiovascular	(390-458)	1184	175 (.62)	133 (.58)	75 (.65)	39 (.84)
Respiratory	(460-519)	107	125 (.53)	112 (.33)	71 (.49)	44 (.28)
Digestive	(520-577)	86	182 (.48)	151 (.48)	88 (.38)	50 (.07)
Residue	(580-796)	55	78 (.96)	63 (.95)	34 (.95)	21 (.93)
External Causes	(800-899)	145	152 (.30)	114 (.22)	45 (.91)	22 (.96)
Cancers:						
Mouth & Pharynx	(140-149)	14	189 (.44)	118 (.31)	56 (.71)	29 (.79)
Stomach	(151)	26	113 (.80)	95 (.81)	78 (.75)	40 (.77)
Large intestine	(153)	50	161 (.71)	131 (.56)	85 (.23)	47 (.44)
Rectum	(154)	16	157 (.56)	75 (.71)	51 (.60)	41 (.44)
Liver & gall bladder	(155-156)	10	61 (.81)	34 (.84)	18 (.87)	17 (.82)
Pancreas	(157)	32	459 (.011)	316 (.043)	148 (.064)	51 (.13)
Lung	(162-163)	129	187 (.18)	148 (.25)	93 (.14)	47 (.23)
Prostate	(185)	21	117 (.82)	90 (.81)	57 (.78)	33 (.72)
Kidney	(189)	15	339 (.14)	233 (.10)	122 (.041)	29 (.44)
Other GU	(186-188)	10	133 (.52)	92 (.60)	69 (.45)	61 (.14)
Brain	(191)	14	213 (.15)	148 (.39)	62 (.37)	35 (.29)

Continuation of Table 3.

Cause of death (ICD)		# deaths (exposed)	cumulative dose in centirems and p-value for trend test at death	death-5	death-10	death-15
Lymphopoietic system	(200-209)	47	360 (.11)	314 (.12)	213 (.032)	104 (.003)
Lymphomas	(200-202)	28	109 (.67)	74 (.73)	59 (.54)	33 (.55)
Multiple myeloma	(203)	8	777 (.009)	707 (.001)	464 (.0001)	[illegible] (.0001)
Lymphatic leukemia	(204)	2	19 -	18 -	18 -	17 -
Myeloid leukemia	(205)	6	163 (.17)	121 (.54)	55 (.54)	32 (.43)
Other lymphatic	(206-209)	3	20 -	20 -	20 -	18 -
All cancer	(140-209)	449	190 (.13)	148 (.22)	92 (.041)	47 (.07)
All deaths:		2238	172 -	132 -	76 -	41 -

Appendix Table 1. Deaths from pancreatic cancer (ICD 157) among white males Hanford workers, 1964-1973.

exposed ?	Cumulative dose (rem) at death	Cumulative dose (rem) at death-10	Year of death	Age at death	Employment 1st year	Employment Last year	Employment Total yea
no	0	0	1949	38.4	1947	1948	1.7
no	0	0	1949	62.8	1944	1945	1.0
no	0	0	1950	52.3	1944	1945	0.1
no	0	0	1950	57.9	1944	1950	6.0
no	0	0	1952	59.9	1944	1945	0.8
no	0	0	1953	53.6	1947	1947	0.0
no	0	0	1953	55.8	1944	1945	0.2
no	0	0	1953	63.0	1945	1945	0.4
no	0	0	1954	70.3	1944	1945	0.3
no	0	0	1963	69.0	1944	1945	0.1
no	0	0	1964	48.1	1944	1944	0.0
no	0	0	1965	70.8	1944	1945	0.6
no	0	0	1966	74.6	1947	1952	4.3
no	0	0	1967	66.9	1944	1944	0.7
no	0	0	1968	71.8	1947	1948	1.1
no	0	0	1969	66.0	1944	1947	2.1
no	0	0	1970	56.0	1944	1945	0.3
no	0	0	1970	58.2	1947	1947	0.0
no	0	0	1972	62.7	1948	1948	0.1
yes	0.01	0	1953	62.1	1944	1945	0.1
yes	0.01	0.01	1971	67.9	1944	1945	0.3
yes	0.04	0.04	1964	66.5	1944	1953	9.0
yes	0.05	0.05	1967	36.9	1951	1953	2.0
yes	0.06	0.06	1971	69.2	1944	1945	0.3
yes	0.07	0.07	1961	38.1	1947	1949	2.0
yes	0.12	0	1972	48.6	1966	1967	1.0
yes	0.18	0.18	1959	76.8	1945	1947	2.9
yes	0.27	0	1958	65.7	1947	1958	10.3
yes	0.28	0.28	1972	54.0	1949	1953	3.9
yes	0.31	0.18	1957	59.5	1944	1957	12.5
yes	0.34	0.34	1972	30.0	1944	1946	0.9
yes	0.41	0.14	1955	56.2	1944	1955	11.4
yes	0.43	0.43	1963	70.4	1944	1959	13.6
yes	0.46	0.46	1964	40.9	1944	1945	1.3

Continuation of Appendix 1.

Exposed ?	Cumulative dose (rem) at death	at death-10	Year of death	Age at death	Employment 1st year	Last year	Total years
yes	0.64	0.23	1964	46.7	1944	1964	19.5
yes	0.71	0.42	1960	62.1	1947	1960	12.9
yes	0.73	0.47	1962	59.3	1944	1962	13.5
yes	0.74	0.37	1960	71.6	1944	1953	9.2
yes	0.88	0.88	1970	56.8	1944	1945	1.2
yes	1.09	0.83	1963	66.8	1944	1961	16.8
yes	1.24	1.24	1970	57.2	1945	1946	1.4
yes	1.49	0.59	1969	45.5	1945	1945	0.7
yes	1.68	0.52	1970	53.7	1944	1956	12.4
yes	1.72	1.22	1964	71.4	1944	1958	13.8
yes	1.77	0.76	1971	54.3	1946	1954	7.4
yes	4.58	2.05	1965	42.7	1948	1958	10.1
yes	5.05	2.28	1971	61.1	1944	1971	27.7
yes	10.11 millwright	0	1962	52.8	1955	1962	7.1
yes	10.75 chem. operator	0.51	1964	68.3	1944	1961	16.6
yes	21.98 reactor operator	2.82	1966	57.2	1947	1955	7.8
yes	26.91 steamfitter	14.91	1971	65.7	1947	1965	18.2
yes	34.15 reactor operator	13.25	1968	63.1	1944	1968	23.3

Appendix Table 2: Deaths from multiple myeloma (ICD 203) among white male Hanford workers, 1944-1973.

	cumulative dose				employment		
Exposed?	at death	at death-10	year of death	age at death	1st year	last year	total years
no	0	0	1951	63.6	1944	1950	5.6
no	0	0	1968	76.6	1945	1945	0.4
no	0	0	1970	60.3	1944	1944	0.1
yes	0.09	0.09	1972	61.1	1944	1945	1.1
yes	0.15	0.15	1951	63.6	1944	1950	5.6
yes	0.18	0.18	1967	49.5	1944	1951	7.0
yes	0.23	0.23	1965	67.7	1945	1945	0.3
yes	0.85	0.55	1963	63.9	1945	1963	18.2
yes	19.98	14.10	1971	70.2	1947	1964	16.7
yes	29.44	10.51	1967	57.4	1947	1967	19.1
yes	34.38	25.28	1971	71.8	1945	1965	20.0

Preliminary comments on the new, expanded Mancuso-Stewart-Kneale proportional mortality study of Hanford plutonium workers

Charles E. Land

Mancuso, Stewart, and Kneale (MSK) have prepared a new proportional mortality study of the Hanford plutonium workers, in preparation for the current congressional hearings on health effects of low-level ionizing radiation. The preliminary report (attached) of their new study differs from their published report in several important ways. While I would need access to their original data in order to evaluate the new study with the same thoroughness as for the published study, the following comments may be helpful.

1. The new analysis is confined to exposed workers, an improvement in my opinion. However, a less restrictive definition of "exposed" has been used than in the published analysis.

2. Among male "exposed" workers, the number of deaths has increased from 2184 to 3741 and the number of cancer deaths from 442 to 743. Many of the additional deaths occurred after the cutoff date for the publisned study (i.e., during 1974-1977), and others presumably were included because of the new definition of "exposed".

3. Deaths among female workers (291 total, 89 cancers) have also been included.

4. A Mantel-Haenszel contingency table analysis of proportional mortality due to all cancer, by cumulative dose at death, has been performed. This

analysis adjusts for possible confounding of dose with the "controlling factors" sex, age at death, year of death, monitored internal radiation, and number of years exposed to radiation. A summary test statistic for increasing trend with dose gives a one-sided p less than .05. If done correctly this analysis is a considerable advance over the age-adjusted analysis in the first paper. However, my own extensive experience with this kind of analysis leaves me with a number of questions. For example, I am not sure about the effects of subdividing 832 cancer deaths and 4032 total deaths into 1680 cells (7 dose levels times 240 = 2x4x5x3x2 levels of the controlling factors). I am certain that many of these cells were empty, and I wonder how empty cells were treated. (I discussed this with Kneale on Feb. 7, and my impression was that his analysis was technical correct. I continue to be uneasy about it, however, because the effects of zero column marginals on the null distribution have never been studie

5. The new treatment of internal radiation, using another Mantel-Haenszel analysis, is very nice. However, as in the published paper, most of the "monitored positive" deaths were false positives, according to the radiation safety people at Hanford (Ken Heid, personal communication). (Heid found only 32 deaths up to 1975 among workers with confirmed internal deposition of plutonium. 3 were from cancer.)

6. As in the published paper, the analyses with respect to particular cancers and groups of cancers, other than the group, all cancers, were not adjusted for possible confounding of dose with any of the controlling factors. Thus lung cancer again is given as a radiation-related cancer in the Hanford workers, when our reanalysis of the data used for the published report indicated rather clearly that the reported relationship was an artifact of the increasing trend in lung cancer incidence over time.

7. As before, the estimated doubling doses are based on unadjusted mean doses and are therefore subject to bias. Except for lung cancer, however,

I doubt that this explains the smallness of the obtained estimates.

8. MSK have improved their testing procedure by testing for dose relationships for four broad groups of cancers, as defined accoring to an ICRP classification of organs according to sensitivity to radiation: organs of established high sensitivity (bone marrow and throid), apparent high sensitivity (lymph nodes, reticular tissue, pharynx, lung, pancreas, stomach, and large intestine), organs of low sensitivity, and "not classified" organs (including breast, bladder, and, according to MSK, the organs from which lymphatic leukemia (ICD 204) and other hemapoetic cancers (ICD 206-209) arise)(ICRP Publication 14, 1969). It is clear that the ICRP classification of bone marrow as an organ of established high radiation sensitivity is based on the generally observed association of myeloid leukemia risk to radiation exposure, but the suggestion to treat myeloid leukemia and multiple myeloma as a group comes originally from ICRP and not from MSK. On the other hand, ICRP 14 seems clearly to place ICD codes 204 and 206-209 in the second category, rather than the fourth.

9. Although the use of the four broad ICRP groups of cancer for initially testing for radiation dose relationships is a sound strategy, the strategy of computing doubling doses for subgroups of these cancers can be deceptive. It is not helpful to derive doubling dose estimates for multiple myeloma and myeloid leukemia as a group. The logic seems to work like this: We know bone marrow cancers are caused by radiation because myeloid leukemia is caused by radiation. In the current study, we have an excess of a bone

marrow cancer (multiple myeloma) and, as a group, of all bone marrow cancers, and so it somehow appears that an excess of myeloid leukemia has been demonstrated in the Hanford workers, when, in fact, one has not. Nowhere is there a discussion of the very intriguing question of why there should be this strange reversal of the usual finding, excess myeloid leukemia and not multiple myeloma. It is interesting that adding another 68% of cancer deaths has not changed this fact. The same remark holds for the grouping of cancers of the pancreas, stomach, and large intestine.

10. The problem faced by MSK is that they want to show that their results are in the main stream of radiation carcinogenesis results as to the cancers that are induced by radiation, but that because the dose range and the amount of of fractionization of exposures are drastically different from those in other studies, the quantitative aspects of their results are different. If this argument is accepted, then it follows that low-level occupational exposures are far more dangerous than had previously been supposed. If their argument is not accepted, then a new hypothesis is required, that low-level, highly fractionated exposures induce a different spectrum of cancers than higher level exposures delivered in fewer fractions. Some other results also suggest such an hypothesis (e.g., Matanoski et al, Am J Epid 101, 199-210), but obviously the impact of their results would be less using the second approach because more logical steps would be required to reach the desired conclusions.

11. In summary, I feel that the new analysis is better in some ways than the published one, not least because its scope is less broad. Most of the

defects of the published analysis are present in the new one, however. Analyses for effects other than all cancers are not adjusted for potentially confounding factors, and the fact that the radiation relationships are restricted to two rather unlikely cancers, multiple myeloma and pancreatic cancer, is obscured.