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Limitations and Problems in Deriving Risk Estimates for Low-level Radiation Exposure

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Some of the problems in determining the cancer risk of low-level radiation from studies of exposed groups are reviewed and applied to the study of Hanford workers by Mancuso, Stewart, and Kneale. Problems considered are statistical limitations, variation of cancer rates with geography and race, the "healthy worker effect," calendar year and age variation of cancer mortality, choosing from long lists, use of proportional mortality rates, cigarette smoking-cancer correlations, use of averages to represent data distributions, ignoring other data, and correlations between radiation exposure and other factors that may cause cancer. The current status of studies of the Hanford workers is reviewed.

There have been several papers in recent years purporting to give evidence that low level radiation ($\sim$ 10 rad) is more dangerous than indicated by conventional estimates like those of the National Academy of Sciences Committee on Biological Effects of Ionizing Radiation (BEIR) [1], the United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR) [2], and the International Commission on Radiological Protection (ICRP) [3]. The best known of these is the study by Mancuso, Stewart, and Kneale [4] (hereafter referred to as MSK) on workers at the Hanford Laboratory in the state of Washington, and it will be used as an example in many cases although all the problems to be discussed do not necessarily apply to that study. It was a proportional mortality study, determining what fraction of all Hanford workers who have died succumbed to various diseases, and correlating this with their accumulated occupational radiation exposure by a complex mathematical analysis. Their most important results, as well as those of a later paper by that group [5] designated KSM, are listed in Table 1 (from [6]). According to [1-3], the doubling dose for all cancer is about 2,000 rad, and the lowest doubling dose for any type of cancer is about 400 rad for leukemia, so MSK represents a claim that these estimates are low by about two orders of magnitude.

It is the purpose of this paper to show some of the problems in the MSK and similar analyses [6-29], and thereby to explain why they have not been accepted by the prestigious groups responsible for [1-3] or by any significant segment of the scientific community. There will be no attempt to cover the vast body of evidence supporting the more standard estimates; this has been reviewed in a previous paper [30].

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TABLE 1
Results of MSK and KSM Papers on Hanford Workers

Cancer Type	MSK (1977) Total Cases	MSK (1977) Due to Radiation	MSK (1977) Doubling Dose (rad)	KSM (1978) Doubling Dose (rad)
Bone marrow	14	9.7	0.8	3.6
Pancreas	31	6.0	7.4	15.6
Lung	130	12.6	6.1	13.7
All RES	47	11.1	2.5	–
All cancer	442	25.8	12.2	33.7

STATISTICAL LIMITATIONS

According to usual estimates, a 10 rad exposure increases one's risk of cancer by about .001. Since the normal cancer risk is about .20, this represents an increase of one part in 200. To measure such an effect with a statistical confidence of 95 percent, which corresponds to a deviation from the expected number of cases by two standard deviations, requires a study with a number of cancers, $N = (200)^2 \times 4 = 160{,}000$, or a total population of 800,000, all of whom were exposed to an excess of 10 rad!

Another approach would be to select a favorable type of cancer. The best choice would probably be leukemia because its normal incidence is rather low, .0084, and it has a high sensitivity to radiation—10 rad gives a risk of .0002, or an increased risk of one part in 42. To measure its effect with 95 percent statistical confidence requires $N = (42)^2 \times 4 = 7{,}000$ or again a total population of 800,000 all of whom were exposed to 10 rad. Of course if the radiation risk were larger than given by usual estimates, smaller sample sizes would be adequate.

GEOGRAPHICAL VARIATIONS

Populations of this size are available if one uses natural radiation, taking advantage of its geographical variations. For example, a citizen of CO, WY, NM, or UT receives about 3 rad/lifetime more than the U.S. average whereas citizens of FL receive about 1 rad less. Table 2 shows the cancer and leukemia rates in these states compared with the U.S. average [31]. The third column shows the expected rates for CO if the U.S. population were a suitable control group, with the only difference being radiation exposure.

In Table 2 we see that areas with higher radiation exposure have lower cancer and leukemia rates, and vice versa. From this we may conclude either that radiation *prevents* cancer, or that there is something wrong with the methodology. Nearly everyone would adopt the latter conclusion, but it is interesting to speculate on whether this attitude would have prevailed if the states with higher radiation levels happened to have *higher* cancer rates.

TABLE 2
Cancer and Leukemia Rates ($\times 10^{-5}$/yr) in 1980

	FL	U.S.	CO exp	CO	WY-NM-UT
All cancer	239	183	183.3	120	120
Leukemia	7.8	7.2	7.25	6.2	4.4

The problem with our methodology is that the U.S. population is not a suitable control group for the state of Colorado. This points up the most serious problem in any study of this type—it is extremely difficult to find a suitable control group.

The reason for this is that cancer incidence varies markedly depending on many factors. For example, skin cancer is 200 times more prevalent in Queensland, Australia, than in Bombay, India; cancer of the esophagus is 300 times more prevalent in Northeastern Iran than in Nigeria; liver cancer is 70 times more prevalent in Mozambique than in Norway; and cervical cancer is 15 times more prevalent in Colombia than in Israel.

Even within the U.S. where life styles are rather uniform, there are large variations between states, as we have seen in Table 2. Some other state rates ($\times 10^{-5}$/yr) are [31] RI—239, PA—218, NY—207, NJ—206, as compared with AK—73, UT—106, CO—120, TX—155, VA—157, and NC—159. There are also rural-urban differences: for example, colon cancer rates in the U.S. northeast are 20×10^{-5} for urban and 18×10^{-5} for rural areas. For the U.S. southeast, these numbers are 13.5 and 11, respectively, again emphasizing geographical variations.

RACIAL DIFFERENCES

There are also racial differences. For example [31], in the U.S. blacks have only 81 percent as much risk of bladder cancer as whites; this ratio is 81 percent for kidney cancer and 94 percent for breast cancer. But blacks have 3.8 times as much cancer of the esophagus, 2.2 times as much prostate cancer, and 1.9 times as much stomach cancer as whites. With so much sensitivity to geography, race, and population density (urban-rural), it is reasonable to expect sensitivity to a large number of other factors, so extreme caution must be exercised in choosing a control group.

HEALTHY WORKER EFFECT

It is well known that steady employment by a large firm correlates strongly with good health, in what is called the "healthy worker effect." For example, the ratio of age-adjusted mortality rates to the U.S. average for some industry groups that have been studied are [32]:

Hanford workers	.75
Steel workers	.82
Rubber workers	.82
du Pont employees	.68
Teamster Union members	.74

It is not difficult to deduce contributing reasons for this, such as pre-employment screening, annual medical exams, better health care because of medical insurance and company medical facilities, organized recreation, paid vacations, regular hours, and so on. There are socioeconomic advantages to steady employment, and health is well known to correlate strongly with socioeconomic status; for example, the ratio of mortality rates for professionals/unskilled laborers [33] between ages 20–64 is .82/1.21 for all causes, .36/1.58 for tuberculosis, .50/1.73 for accidents, .57/1.53 for influenza and pneumonia, .89/1.16 for cancer, etc. In addition, drug users and alcoholics are unlikely to hold a long-term steady job.

The "healthy worker effect" does not apply equally to all diseases, and cancer is much less affected than most others. Thus, in a proportional mortality study, long-term steady employees would have a higher probability of dying of cancer. This important point was ignored in the MSK study.

TABLE 3
Age Adjusted Mortality Rates ($\times 10^{-5}$/yr), for U.S. Males from Lung and Bladder Cancer vs. Time [31]

Year	Lung Cancer	Bladder Cancer
1950	19	19
1960	32	13
1970	47	9
1976	54	7

TIME VARIATIONS OF CANCER MORTALITY

Table 3 shows the mortality rates in the U.S. vs. time for two types of cancer, and we see that the variations are very large, sometimes increasing and sometimes decreasing. In comparing observed with expected mortality rates, it is therefore very important to correct for calendar year. For example, MSK used the 1960 rate for lung cancer although the average calendar year of the deaths in their study was about 1970. It is clear from Table 3 that this represents an important error. In fact when it was corrected, their excess lung cancers due to radiation disappeared. There was also no correction for calendar year of death in the Gofman study of the Hanford workers [16].

AGE VARIATIONS OF CAUSE OF DEATH

It is well known that each cause of death has a distinct and separate variation with age. For example, Table 4 shows the ratio of heart disease to cancer mortality rates vs. age. It is clear that the fraction of people dying of cancer depends on their age at death. One can hope that the average age at death was the same for the exposed group and the controls, but this should be explicitly investigated and corrected for. This was not done by MSK or by Gofman in his analysis of the Hanford workers.

CHOOSING FROM LONG LISTS OF STATISTICAL DATA

An example of use of long lists is the Milham study of occupation-cause of death correlations for Washington state [34], a proportional mortality study involving hundreds of occupations and over a hundred causes of death. Some of the findings are listed in Table 5. It is very difficult to believe that many, if any, of these correlations is real, and it is not surprising that in such a long list of cases false positives will be found which apparently have more than 99 percent statistical confidence. Studies of this sort are interesting as suggestive evidence, but are certainly not conclusive. For example, only if similar correlations between poultry farmers and leukemia appeared in other independent studies would they be taken seriously.

To some extent MSK used the long list technique in considering 18 different cancer types. A portion of their list is shown in Table 6. They paid a great deal of further attention to the first three entries, but ignored the last three.

TABLE 4
Ratio of Heart Disease/Cancer Mortality Rates vs. Age for U.S. Males

Age	65–69	70–74	75–79	80–84	>85
Heart dis./cancer	1.72	1.84	2.15	2.65	4.1

TABLE 5
Occupation-Cause of Death Correlations Reported in [34] (The "min. obs/exp" Ratio Corresponds to 99 Percent Statistical Confidence That the Ratio Is Larger Than the Number Listed.)

Occupation	Cause of Death	Deaths		obs/exp	
		obs	exp	best	min
Accountants	CA-esophagus	21	9.3	2.27	1.32
Poultry farmers	leukemia	7	1.2	5.85	2.34
Insurance agents	multiple sclerosis	9	2.2	4.09	1.82
Taxi drivers	emphysema	15	6.0	2.50	1.32
Nurserymen	CA-pancreas	9	3.5	2.58	1.14

USE OF PMR (PROPORTIONAL MORTALITY RATIOS)

The PMR is defined (for cancer) as

$$\text{PMR} = \frac{\text{(cancer deaths/total deaths) for exposed}}{\text{(cancer deaths/total deaths) for non-exposed}}$$

This is an easy type of study to make as all one needs is a stack of death certificates which are then sorted by occupation. It is much easier than determining the SMR (standardized mortality ratio) defined as

$$\text{SMR} = \frac{\text{cancer mortality rate for exposed}}{\text{cancer mortality rate for non-exposed}}$$

since the latter requires following up the entire exposed cohort to find out whether or not they have died. However, the SMR has two important advantages over the PMR:

(1) It includes those still living which are usually the large majority of the exposed. The PMR ignores these.
(2) A high PMR can mean a high cancer rate, *or* a low total death rate, and there is no way to distinguish between these alternatives.

For these reasons, SMR are nearly always used wherever possible. It was ab initio highly unusual for MSK to use PMR when the SMR were readily available.

The SMR for the Hanford workers has been given by Gilbert [13] as follows:

Exposure (rad)	0–2	2–5	>5
SMR	.81 ± .19	1.00 ± .38	.67 ± .29

It is clear from this that there is no indication of a cancer rate increase with dose. Yet most of the MSK paper is based on an increase of PMR with dose. It is clear that this PMR increase is due to a decrease in total deaths rather than to an increase in cancer deaths. It is difficult to avoid the suspicion that MSK purposely avoided use of SMR to obscure this point.

The treatment of the Hanford data by Gofman [16] suffers from the same problem. He defines a quantity which we call G

$$G = \text{cancer deaths/non-cancer deaths}$$

and points out that for the Hanford workers with >10 rad exposure, $G = .42$, while for those with <10 rad, $G = .25$. The ratio of these numbers is very similar to the PMR. However, as for the PMR, one cannot tell whether the high ratio (.42/.25) is

TABLE 6
MSK Data on Deaths by Cancer Type among Hanford Workers

Cancer Type	obs	exp	o/e
Bone marrow	22	13.4	1.64
Pancreas	49	37.3	1.31
Lung	192	144*	1.33*
Genito-urinary	15	30.9	.49
Lymphatic leukemia	3	9.4	.32
Other RES	5	20.3	.24

*Based on 1960 statistics, although death year average ~1970. Correcting for this eliminates the effect.

due to a high cancer rate or to a low non-cancer death rate among the exposed. The answer to this question is given by Gilbert and Marks [15] with the following rates/1,000 at risk:

	>10 rad	<10 rad
Cancer	2.8 ± 1.1	2.9 ± 0.3
Non-cancer	6.8 ± 1.8	9.4 ± 0.5
Ratio (G)	.41	.31

The ratios differ slightly from Gofman's because he did not adjust for age and calendar year of death. But the important point is that the difference between the >10 rad and <10 rad groups is *not* in their cancer rates, but in their non-cancer rates. This point effectively destroys the thesis of the Gofman study.

CIGARETTE-SMOKING-CANCER CORRELATIONS

There are strong correlations between cancer rates and cigarette smoking [33], as shown in Table 7. It is also well known that some occupational, industrial, or social groupings smoke more than others. It is therefore important to consider correlations between radiation and smoking habits, especially when dealing with lung cancer. There was no such consideration in MSK.

INDISCRIMINATE USE OF AVERAGES IN CALCULATIONS

Some of the statistical treatments used in analyses are rather elaborate, and if one traces through the derivations on which they are based, it is often found that one cannot indiscriminately replace a data distribution by its average.

TABLE 7
Ratio of Cancer Mortality Rates, Age 35-84, for Men Smoking 2 or More Packs of Cigarettes per Day, to Non-Smoking Men [33]

Cancer Type	Ratio	Cancer Type	Ratio
All cancer	3.2	Pancreas	2.7
Lung	24	Kidney	2.6
Pharynx	22	Prostate	2.4
Buccal cavity	9.3	Stomach	1.7
Esophagus	8.4	Leukemia	1.4

A flagrant example of the perils in doing this is the treatment of multiple myeloma in MSK. In the eight cases, radiation exposures were 34, 29, 20, 0.85, 0.23, 0.18, 0.15, and 0.09 rad, a total of 85 rad, which gives an average exposure of 10.7 rad. MSK treated this as eight cases with 10.7 rad each, and at the end of their complex analysis concluded that six of the eight cases were due to radiation. This implies that exposures of 0.18 rad or lower caused multiple myeloma. In fact, if all but the highest three exposures were zero, the analysis would be essentially unchanged and the results would indicate that three cases were due to zero radiation!

Actually, all of the effects reported in MSK were essentially determined by exposures larger than 10 rad. This >10 rad group included 34 cancer deaths and 80 non-cancer deaths [16], so it is remarkable that MSK tried to draw such far-reaching conclusions from so little data.

IGNORING OTHER DATA

When one purports to draw scientific conclusions, one is ordinarily obligated to consider *all* data bearing on the question rather than just the data being presented. None of the papers purporting to find that low-level radiation is more dangerous than indicated by usual estimates does this. For example, MSK pays no attention to the data on the Japanese A-bomb survivors which provides an abundance of information in the same dose range. A comparison for all cancers is shown in Fig. 1 where the dashed line represents the MSK result. It is clearly in sharp disagreement with the A-bomb survivor data.

CORRELATION BETWEEN RADIATION EXPOSURE AND OTHER FACTORS THAT MAY CAUSE CANCER

Radiation exposure to the Hanford workers correlates with other factors, and it is important to consider the possibility that the excess cancers (if any) were due to these factors rather than to the radiation. This very important point was not considered by MSK.

A simple example is length of employment at Hanford. Clearly, short-term workers received less total radiation exposure than those who worked for 20 years or more. But short-term workers are subject to less influence from the "healthy worker effect," so they can be expected to die more frequently of diseases other than cancer.

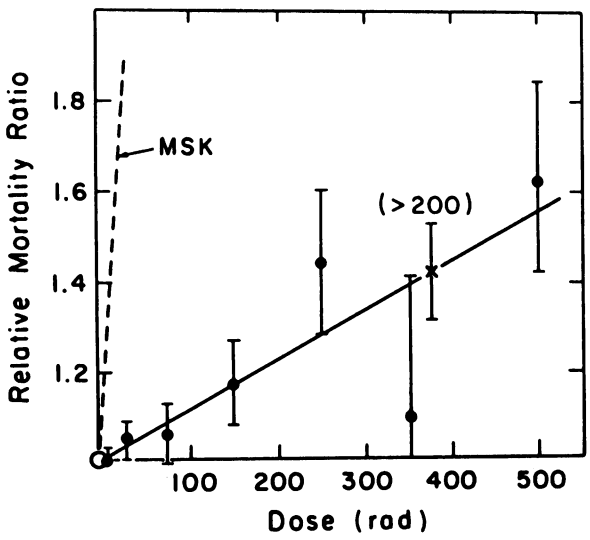

FIG. 1. Mortality due to all cancers vs. radiation exposure according to MSK (*dashed line*) and for the Japanese A-bomb survivors (*dots, solid lines*). The × designates the average of all data above 200 rad.

Another important example is the correlation between radiation exposure and occupation. Radiation is received mainly by "blue collar" workers, like technicians and operators; there is normally very little radiation exposure to "white collar" workers like administrators, secretaries, clerical workers, and so on.

But "blue collar" workers are also exposed to more chemical carcinogens, dust, and abnormal physical conditions, and these might cause excess cancers. Moreover, occupation correlates with social class and with cigarette smoking habits, and these have been shown to have an important influence on cause of death. Some evidence that cancer and total mortality rates, and their ratio, depend on occupation is shown in Table 8. The occupational orders above the line are all those of a type that might be expected to receive radiation at Hanford, and those below the line are all those of a type that would be expected not to be exposed to much radiation. We see that the first group experiences a larger probability of dying from cancer, even though radiation is not a factor in Table 8.

STATUS OF THE MSK ANALYSIS

There have now been three completely independent analyses of the data on Hanford workers used by MSK [15,17,29], and all of them conclude that the only statistically meaningful data are excesses of multiple myeloma and cancer of the pancreas among those with large exposures. For exposures >15 rad, the data on these are:

multiple myeloma: 3 obs, 0.4 exp
CA of pancreas: 3 obs, 1.0 exp

The question is whether these excesses are due to radiation or perhaps due to other exposures such as chemicals experienced by those who work with radiation. The most obvious approach to settling this question is to check on whether these diseases occur in excess among other groups exposed to radiation, such as the Japanese A-bomb survivors.

The data on cancer of the pancreas are shown in Fig. 2 where the dashed line represents the KSM result [5]; the MSK result is 2.1 times steeper. The open square shows the 3 obs vs. 1 exp, at an average dose of 28 rad. We see that the A-bomb survivor data, shown by black dots, includes a point in the same dose range (10–50 rad) with far better statistical accuracy, and the effect is orders of magnitude smaller than that among the Hanford workers. This very strongly indicates that the excess cases of cancer of the pancreas among the Hanford workers are *not* due to radiation.

TABLE 8
SMR for All Causes of Death and for Cancer for British Workers (age 15–64) in Various Occupational Orders [35] (Data are for 1970–72.)

Occupational Order	SMR		Cancer
	Total	Cancer	Total
Gas, coke, chemical	107	118	1.10
Furnace, forge, foundry	122	135	1.11
Glass, ceramic	109	119	1.09
Electrical, electronic	104	107	1.03
Machinery operators	103	105	1.02
Clerical	99	87	.88
Administrators, managers	73	74	1.01
Professional, technical	75	72	.96

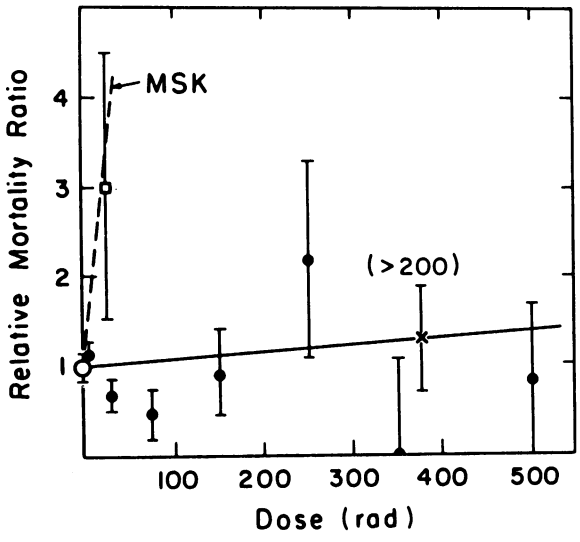

FIG. 2. Mortality due to cancer of the pancreas vs. radiation exposure according to MSK (*dashed line*), and for the Japanese A-bomb survivors (*dots, solid line*). The × designates the average of all data above 200 rad. The open square is the point given in the text, 3 obs vs. 1 exp.

On multiple myeloma, the data on the Japanese A-bomb survivors include only 4 cases vs. 1.9 expected, so one can hardly plot a figure. The totals give a doubling dose of about 100 rad (vs. 0.8 rad in MSK), and predict only .06 cases among the Hanford workers. Data on medical exposures (at higher doses) predict even smaller effects. It thus seems clear that the excess cases of multiple myeloma among the Hanford workers were not due to radiation. Little is known about causes of pancreatic cancer or multiple myeloma, but there are reports of increased incidence of the former among chemists [36] and aluminum workers [37].

The MSK group did an improved analysis of the Hanford worker data which was said to have been submitted to the *British Journal of Industrial Medicine* in 1979, but as of April 1981, it had not yet appeared in print. However, a copy was made available to the GAO Study Group which comments on it as follows [29]:

> . . . Kneale's revised analysis (1979) . . . shows a slight but not statistically significant effect of dose on "high sensitivity" cancers, and a counter-balancing negative effect for all other cancers. . . . [He] also finds a so far unexplained tendency for surviving workers to have a higher average dose-per-year than those who have died.

This seems to imply that the MSK group now concedes that there is no significant excess of cancer among the Hanford workers.

REFERENCES

1. National Academy of Sciences Committee on Biological Effects of Ionizing Radiation (BEIR): The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. Washington, DC, 1980
2. United Nations Scientific Committee on Effects of Atomic Radiation: Sources and Effects of Ionizing Radiation. New York, 1977
3. Annals of the International Commission on Radiological Protection: ICRP Publication 26. Vol 1, No 3, 1977
4. Mancuso TF, Stewart A, Kneale G: Health Physics 33:369, 1977 (MSK)
5. Kneale G, Stewart A, Mancuso TF: IAEA Symp. on the Late Biological Effects of Ionizing Radiation. Vienna, March 1978 (KSM)
6. Reissland JA: An Assessment of the Mancuso Study. UK National Radiological Protection Board Publ NRPB-79, 1978

7. Anderson TW: Health Physics 35:743, 1978
8. Brodsky A: Testimony for US House of Representatives Subcommittee on Health and the Environment, 8 February 1978
9. Cohen BL: Health Physics 35:582, 1978
10. Cohen BL: Health Physics 38:712, 1980
11. Gertz SM: Health Physics 35:723, 1978
12. Gilbert ES: Methods of Analyzing Mortality of Workers Exposed to Low-levels of Ionizing Radiation. Battelle Pacific Northwest Laboratory Rep BNWL-SA-634, May 1977
13. Gilbert ES: Testimony for US House of Representatives Subcommittee on Health and the Environment; also available as Document PNL-SA-6341 Rev, 1978
14. Gilbert E, Marks S: Health Physics 37:791, 1979
15. Gilbert ES, Marks S: Health Physics 40:125, 1981
16. Gofman JW: Health Physics 37:617, 1979
17. Hutchinson GB, MacMahon B, Jablon S, et al: Health Physics 37:207, 1979
18. Kleitman DJ: Critique of Mancusco-Stewart-Kneale Report. Submission to US Nucl Reg Comm, 2 March 1978
19. Marks S, Gilbert ES, Breitenstein BD: Cancer Mortality in Hanford Workers. IAEA Document IAEA-SM-224, 1978
20. Mole R: Lancet i:582, 1978
21. US Nucl Reg Comm: Staff Committee Report of November 1976, 1976
22. US Nucl Reg Comm: Staff Committee Report of May 1978, 1978
23. Parker (Hon Mr Justice): The Windscale Inquiry, 26 January. London, HMSO, 1978
24. Rubenstein D: Report to US Nuclear Regulatory Commission. 1978
25. Sagan LA: Low Level Radiation Effects: The Mancuso Study. EPRI Report; Atom 262: (August) 1978
26. Sanders BS: Health Physics 34:521, 1978
27. Spiers FW: Health Physics 37:784, 1979
28. Tait GWC: Health Physics 37:251, 1979
29. US General Accounting Office: Report EMD-81-1, 1981
30. Cohen BL: Health Physics 39:659, 1981
31. Garfinkel L, Poindexter CE, Silverberg E: Cancer Statistics, 1980. American Cancer Society, 1980
32. Cohen BL: Health Physics 40:703, 1981
33. Cohen BL, Lee IS: Health Physics 36:707, 1979
34. Milham S: Occupational Mortality in Washington State, 1950–71. Cincinnati, NIOSH, 1976
35. Registrar-General: Occupational Mortality. London, Her Majesty's Stationery Office, 1978
36. Li FP, Fraumeni JF, Mantel N, et al: J Natl Cancer Inst 43:1159, 1969
37. Milham S: Ann NY Acad Sci 271:243, 1976