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ABSTRACT

Two studies on Los Alamos workers exposed to plutonium have shown no increase in cancers of the lung, bone, and liver, three principal cancers of interest following plutonium deposition. A clinical study of 26 workers exposed 32 years ago shows no cases of cancer other than two skin cancers that were excised successfully. A mortality study of 224 workers, all persons with estimated depositions of 10 nCi or more in 1974, showed no excess of mortality due to any cause. No bone or liver cancers were present, while one death due to lung cancer was observed as compared to an expected three cases. These negative findings on such small groups are not able to prove or disprove the validity of commonly used risk estimates as recommended in the 1972 BEIR and 1977 UNSCEAR reports, but the data do indicate that much higher risk estimates are not warranted.

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STUDIES ON HEALTH RISKS TO PERSONS EXPOSED TO PLUTONIUM

by

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Man's first opportunity for exposure to potentially harmful amounts of plutonium was during World War II, when industrial scale production began in 1944. Ever since the United States has had an industry employing several thousands of persons who work with this long-lived alpha radiation emitter that has the important property of producing nuclear energy by fission.

The potential for plutonium to produce adverse health effects, if taken internally, was recognized already in 1944. Thirty years later this subject is vigorously debated with a wider range of subtopics than at any time in its history. One would think as information of health effects has accumulated from studies on animals exposed to plutonium and human follow-up studies, that the areas of controversy would narrow. That has not been the case, at least not in statements designed for public consumption. One of the purposes of this paper is to present data derived from the follow-up on Los Alamos plutonium workers and to evaluate some risk assessments used today to see how well they correlate with these preliminary results.

Studies on persons exposed to plutonium are now beginning to reach an important stage because of the length of time since first exposures. The long physical half-life of ^{239}Pu (24,400 years) and long biological half-time in the body (an estimated 100 years in bone and 40 years in liver)[1] make internal depositions a continuing lifetime exposure.

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Depositions in humans, now present more than 30 years in the early exposures, already extend well beyond any long-term experiments in animals. Both studies cited here are on persons with long term plutonium depositions, primarily through inhalation exposures.

I. Plutonium Workers on Manhattan Project at Los Alamos

In the early 1950s, 26 plutonium workers who had worked on the Manhattan Project at what is now the Los Alamos Scientific Laboratory, Los Alamos, New Mexico, were selected for clinical follow-up studies. These men were judged to have had the highest exposures to ^{239}Pu of any persons at Los Alamos in 1944 and 1945.

The study subjects, whose work histories indicated heavy exposure to plutonium, were selected on the basis of the amount of ^{239}Pu excreted in urine measured by methods available before 1950. The study has been reported in detail. [2,3]

The working conditions in 1944-45 and the circumstances of the plutonium exposures of these men support the notion that inhalation was the primary route of exposure. Eight workers in the group had potentially contaminated wounds and three had chemical burns by plutonium-containing solutions. Most wounds were excised promptly and did not contain plutonium of any significance. The highest quantity of plutonium measured in excised tissues was 2 nCi in one case. In another person, a known contaminated wound area on a finger is estimated to retain 5±2 nCi of ^{239}Pu.

The 1972 and 1977 examinations, done at Los Alamos, included *in vivo* counting of the chest, liver, and hands; analysis of urine and fecal samples; and comprehensive medical studies. No internally deposited radioactivity significantly above background was found by

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direct counting *in vivo* methods except for the one wound area described above. Plutonium excretion in urine was used to estimate internal depositions of plutonium by use of the PUQFUA code.[4] The estimated body burdens range from 7 to 230 nCi with an average of 58 nCi and a median value of 33 nCi. Eleven persons in the group exceed the 40 nCi maximum permissible body burden,[5,6] and 21 persons have depositions of 20 nCi or more.

Two individuals in the group have died: one due to a myocardial infarction and the other due to injuries sustained in an automobile-pedestrian accident. The expected numbers of deaths for the group adjusted for age and year of death, based on United States white male rates, were generated by means of a computer program developed and described by Monson[7] and compared to the observed deaths in Table 1. The low observed mortality is most likely due to positive selection for health status in this group: these men were military personnel in 1944-45 and have in general attained a high socioeconomic status.

The medical histories, clinical examination and diagnostic procedures, including blood chemistry profiles, hematology, urinalysis, roentgenograms of chest, teeth, and bones, electrocardiograms, pulmonary exfoliative cytology, and lymphocyte chromosome analysis, revealed findings in these individuals that appear to be within usual expectations of health problems for their ages, average of 56 years in 1976 with a range of 52 to 69 years. The most significant diagnoses were one case each of coronary heart disease, total blindness due to glaucoma, hypertension with possible left ventricular hypertrophy, and bronchitis and early emphysema in a heavy smoker. There are no cases

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of cancer within the group except for a history of two skin cancers that have been successfully excised.

II. Mortality Study of Highest Plutonium-Exposed Los Alamos Workers

A mortality study of every Los Alamos worker since the beginning of Los Alamos project who was estimated to have an internal plutonium deposition of 10 nCi or more was begun in 1974.[8] The group is made up of each individual estimated to have that level of exposure based on Los Alamos health physics records as of 1 January 1974. The body burden estimates were calculated with the version of the PUQFUA code[4] then in use. Subsequently a revised PUQFUA code[9] was developed that results in a more accurate estimate of internal depositions. These improved estimates are used in this paper for risk assessment analysis, but the original composition of the group has not been changed.

The group consists of 224 white male and 17 white female subjects. Mortality status was obtained on each individual in the study as of 30 June 1976. The follow-up is 100 percent complete despite the 30-year period of follow-up present for most subjects. Thus, there are no missing persons in this mortality study. The data on females is limited by the small numbers and is not discussed further, but is consistent with the mortality data presented here on the males.

The mortality data and some characteristics of the cohort of 224 white male plutonium workers are presented in Table 2. The average year of entry into the study, 1947, was determined by the time of the subjects's first recorded urine test for plutonium exposure or of the recorded accident resulting in the first presumed exposure. Most subjects would not have received their current or final body burden until some few years after entry into the cohort.

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The revised body burden estimates in the group range from <1 to 215 nCi with an average of 20 nCi and a median value of 9.5 nCi. Twenty-three persons in the group exceed the 40 nCi maximum permissible body burden and 54 persons have depositions of 20 nCi or more.

Expected mortality rates, age and calendar-year adjusted, are based on United States white male rates and generated by Monson's computer program.[7] The results for broad categories of deaths are shown in Table 2. The expected mortality calculated for this group does not incorporate healthy worker effects.

The standardized mortality ratio (SMR) for total mortality was 54 ($p<0.001$), malignant neoplasms 64 (not significant), and for diseases of the circulatory system 38 ($p<0.001$). An SMR of 100 is average. Mortality from malignant neoplasms were one each of the buccal cavity, stomach, large intestine, rectum, lung, bladder, and lymphopoietic system. For the cancer sites of greatest interest following plutonium exposures, liver or bone malignancies did not occur, and only one lung cancer appeared versus an expected 3.2. Tests of statistical significance are not useful for the small numbers of cancer cases present in this study.

The low mortality ratios found in this study are most likely explained by selection biases relative to the general United States population. These include the healthy worker effect for employed populations plus additional selection for security clearances required for all subjects and military selection for some of the earlier workers. The total influence of such factors is unknown, but healthy worker effects create SMR's between 70 and 90 depending on the precise cause of death and on age. In context our data do not suggest any excess of

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mortality due to any cause in these workers with the highest plutonium exposures at Los Alamos.

III. Discussion of Risk Assessments for Plutonium Exposure

The organs of concern for cancer development following plutonium exposure are primarily the lung, bone, and liver. In these studies, one lung cancer death occurred in the 224 workers, but as noted this is not an unusual finding in light of the three lung cancers expected by adjusted U.S. male statistics. No bone or liver cancers were found in the mortality study. No cancers of internal organs have been diagnosed in the 26 Manhattan District exposed persons who have had their plutonium depositions for over 32 years. Although these studies are limited by the small numbers of subjects studied, they are of interest to determine if the data tends to corroborate or dispute current risk assessment values.

The data on estimated plutonium deposition in the 224 workers are summarized in Table 3. The distribution of individual values of plutonium deposition is given in Figure 1 and nanocurie-years of exposure are distributed as shown in Figure 2. These exposures are predominantly due to ^{239}Pu, but include some cases of ^{238}Pu exposure. The ^{238}Pu depositions in the group represent about 10 percent of the total activity, but the relative accumulated exposures to ^{238}Pu are less because these exposures are more recent than those to ^{239}Pu. For the purposes of this discussion, ^{239}Pu and ^{238}Pu are combined.

Calculations of the radiation doses to the lung, bone and liver were done using two different assumptions on the plutonium distribution within the body. The first approach is based on the results of plutonium analyses of tissues from several of the deceased in the group

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and the plutonium was assumed to distribute as follows for the entire period of exposure: 40 percent in lung, 30 percent bone, 20 percent liver, and 10 percent in other soft tissues, including lymph nodes.

In the second approach, a simplified scheme of the ICRP lung model[1] for the inhalation of an insoluble (class Y) aerosol was used. The measured body burden was assumed to have resulted from an inhalation exposure. The initial lung burden that could have led to this body burden was evaluated from the lung model given in ICRP 19.[1] This lung burden was used to estimate the total lung dose assuming that 40 percent was eliminated in the first day and the remaining 60 percent was eliminated with a 500 day half-life. The bone and liver doses were estimated by assuming that 45 percent of the body burden was in each organ and that the time delays in transferring to these organs from the lung was negligible. This procedure gives high values for the total bone and liver doses because it does not include the 500 day half-life for transfer to the blood or lymph nodes or the 1000 day half-life for transfer from the lymph nodes to the blood.

Dose calculations by these two methods through 1976 are summarized in Table 4. A quality factor of 10 was used throughout and a dose distribution factor of 5 was used for the bone (5000g).

Evaluations of the risk of excess cancers developing in this group were made using several contemporary methods. These were made for both the lifetime risk from the exposure received as of 1976 and the excess risk already present by 1976.

a) Lifetime Excess Cancer Risk

Using the risk coefficients given in the UNSCEAR report[10] one can calculate a estimate of potential lifetime excess cancers that may

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occur as a result of the radiation doses delivered to the organs by 1976. These risk coefficients and the potential excess cancers calculated are listed in Table 5. The UNSCEAR risk coefficients are expressed per rad of low LET radiation. For the purpose of this calculation, a rad of low LET radiation was considered equivalent to a rem of plutonium alpha radiation.

Lung cancer is the principal risk identified by this calculation and shows a possible lifetime expectancy of one or two excess cases.

A risk hypothesis of Gofman[11] is cited frequently in the press and in expert testimony to assess possible excess lung cancer in persons exposed to plutonium. For weapons grade plutonium, the material present in the Los Alamos workers, Gofman equates 0.059 μg (3.6 nCi) of plutonium in the lungs of a cigarette smoker to one lung cancer, while 7.56 μg (465 nCi) in lungs of nonsmokers is said to produce one lung cancer. The smoking histories of the 224 plutonium workers is known for over 70 percent of these subjects. To simplify the problem of complex smoking histories over periods of more than 30 years, subjects were called smokers only if they were current smokers as of 1974 or later, or at the time of death. Past smokers were classified as nonsmokers if they stated they had quit smoking at the time of the last history. Several of these nonsmokers were one to two pack per day smokers for over 30 years, or essentially all the time of their plutonium depositions in the lung. The estimate required an extrapolation from the known percentage of current smokers or a random assignment to the remaining subjects on whom smoking data is not available yet. The error of this procedure is not believed to be significant for this type of estimate.

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In calculating the possible excess cancers by this method, an arbitrary 40 percent of the current total body deposition was considered to be the lung burden. This is the same assumption of lung distribution used in other estimates above. Although Gofman has indicated that his risk estimate can be based on the plutonium present in the lung initially after exposure, our calculation uses the estimated deposition of plutonium in 1976, nearly 25 years after exposure on the average for the group. The lifetime lung cancer risk by the Gofman method was limited by the authors to no more than one cancer per person although Gofman does not apply such an arbitrary limitation.

This method, using the above criteria, results in an estimate of 52 excess lung cancers in the 224 workers as shown in Table 6. (The estimate would have been 138 excess lung cancers if the lifetime risk per person had not been limited to one cancer per person). Gofman states that the "expected cancer fatalities will occur over about 30 years."[11]

b) 1976 Excess Cancer Risk

Another approach to estimating possible excess cancers due to radiation is described in the BEIR report.[12] Following a latent period, a risk of excess cancers per rem for each year is hypothesized according to the linear non-threshold model. Using the average exposure for the group (Table 3) and the average length of exposure, assuming a constant average body burden for this entire period, it is possible to calculate possible excess cancers. A latent period of 10 and 15 years was used in separate calculations to estimate a range. The risk coefficients and the results of the calculations for the exposures up to 1976 are shown in Table 7. These estimates suggest that

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excess cancer in the lung, bone, and liver by 1976 would total less than one-half a cancer for the group.

It is also of interest to consider the number of excess lung cancers that should have appeared by 1976 as predicted by the Gofman risk hypothesis.[11] For this purpose it was assumed that lung cancer at various ages might appear proportionately the same in this worker population as in the general U.S. population. The respiratory cancer mortality was taken from the National Center for Health Statistics, "Vital Statistics of the United States, 1970"[13] and 1970 population figures from the 1970 United States census[14] were used to estimate the percentage of cancers that occur by age 60, the average age of these workers in 1976. These data indicate that about 30 percent of lung cancer mortality occurs by age 60. If one takes 30 percent of the 52 excess cancers predicted by the Gofman hypothesis, it suggests that about 15 excess lung cancer deaths should have been registered in the group of 224 plutonium workers as of 1976. The possibility that exposure to plutonium accelerates the proportion of lung cancer present at earlier ages or that the higher risk estimate using multiple cancers for some persons is valid would cause the calculated expectation to be even greater than 15 lung cancers by 1976.

Conclusion

The estimation of the risk of cancer development following plutonium exposure is a matter of considerable importance for setting exposure standards and proper protection of workers and the public. A mortality study of 224 Los Alamos white, male workers with the highest exposures to plutonium has shown no excess deaths due to any cause compared to adjusted rates of white males in the United States population.

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Estimates, using risk values developed by scientific committees, such as the UNSCEAR[10] and BEIR,[12] suggest less than one-half a cancer total would be expected in the group by 1976, although lifetime experience may carry a potential of one or two excess cancers in the group. The mortality data in such a small group is not adequate to prove or disprove these estimates, although there is no suggestion of any excess deaths to date.

Other hypotheses suggest the risk due to plutonium is much higher. The Gofman risk hypothesis[11] suggests that 52 out of the 244 persons, or more than one out of five, will develop lung cancer. It is noted that the exposures occurred nearly 25 years ago on the average, so a relatively long latent period has already passed without the development of excess lung cancers in the group. The calculation that 15 excess lung cancer deaths should have been noted by 1976 is believed to be a reasonable, conservative interpretation of the Gofman risk hypothesis. The data in this study suggest that this hypothesis seriously overestimates the risk of lung cancer due to plutonium exposure.

In applying risk estimates, it seems reasonable to expect that predicted and observed excess cancers should correlate. Undoubtedly, risk estimates will be adjusted and refined as more information is compiled. Risk estimates significantly higher than those predicted by the UNSCEAR[11] and BEIR[13] reports are not supported by the human data presented here.

Additional data on workers at major plutonium facilities is now being collected at Los Alamos. It is estimated that nearly 5000 workers in the United States have had positive measurements of internal depositions of plutonium. A larger number of persons with potential

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exposure, but no evidence of internal deposition, will also be studied. Persons working for the same employer, but with no known potential for plutonium exposure, will be used as control populations. As studies on larger numbers of workers are completed, the human data will improve and we hope the risk estimates will be modified correspondingly.

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FIGURE CAPTIONS

FIGURE 1: Distribution of Body Burdens

FIGURE 2: Distribution of Cumulative Exposures

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FIGURE 1

DISTRIBUTION OF BODY BURDENS

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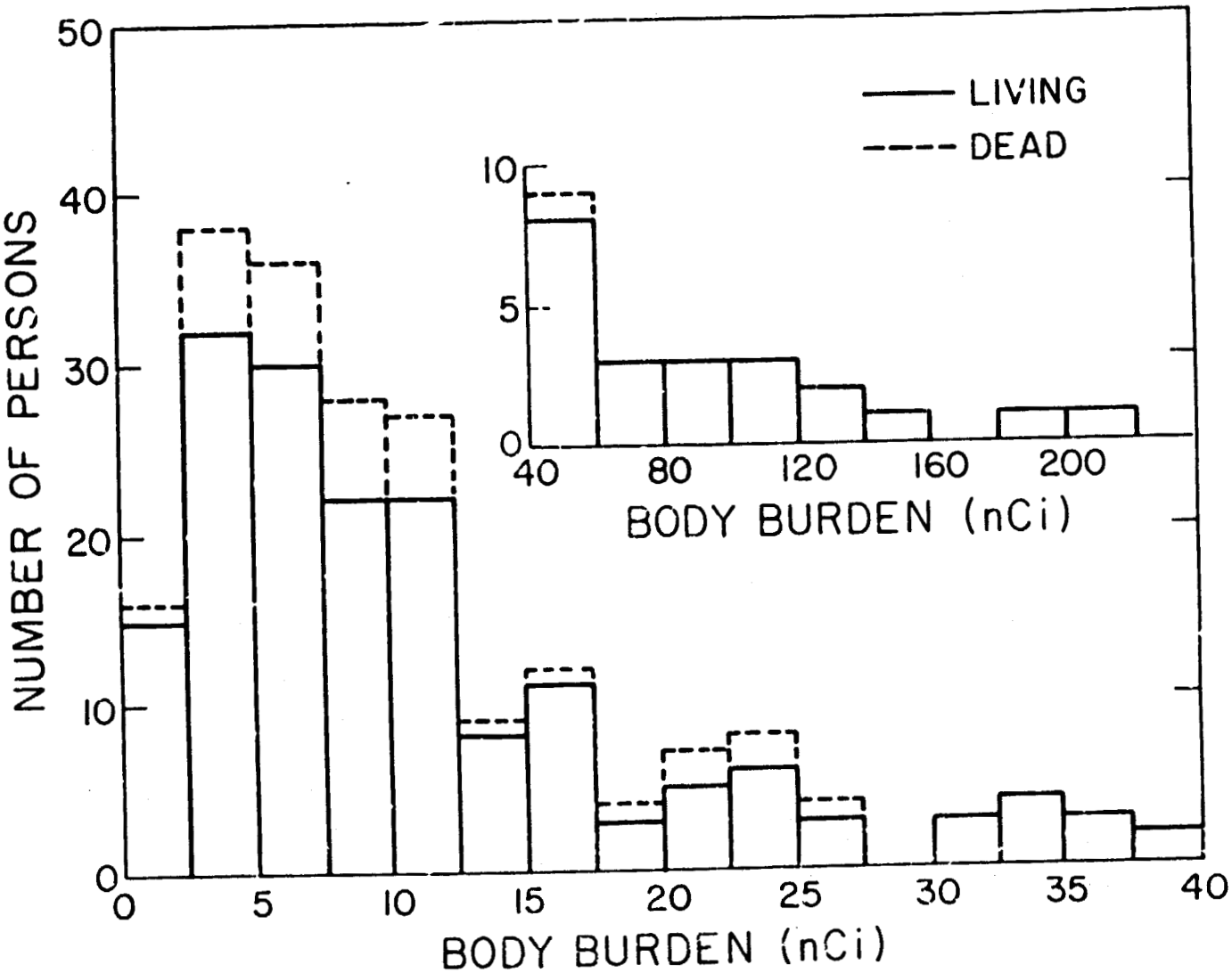

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FIGURE 2

DISTRIBUTION OF CUMULATIVE EXPOSURES

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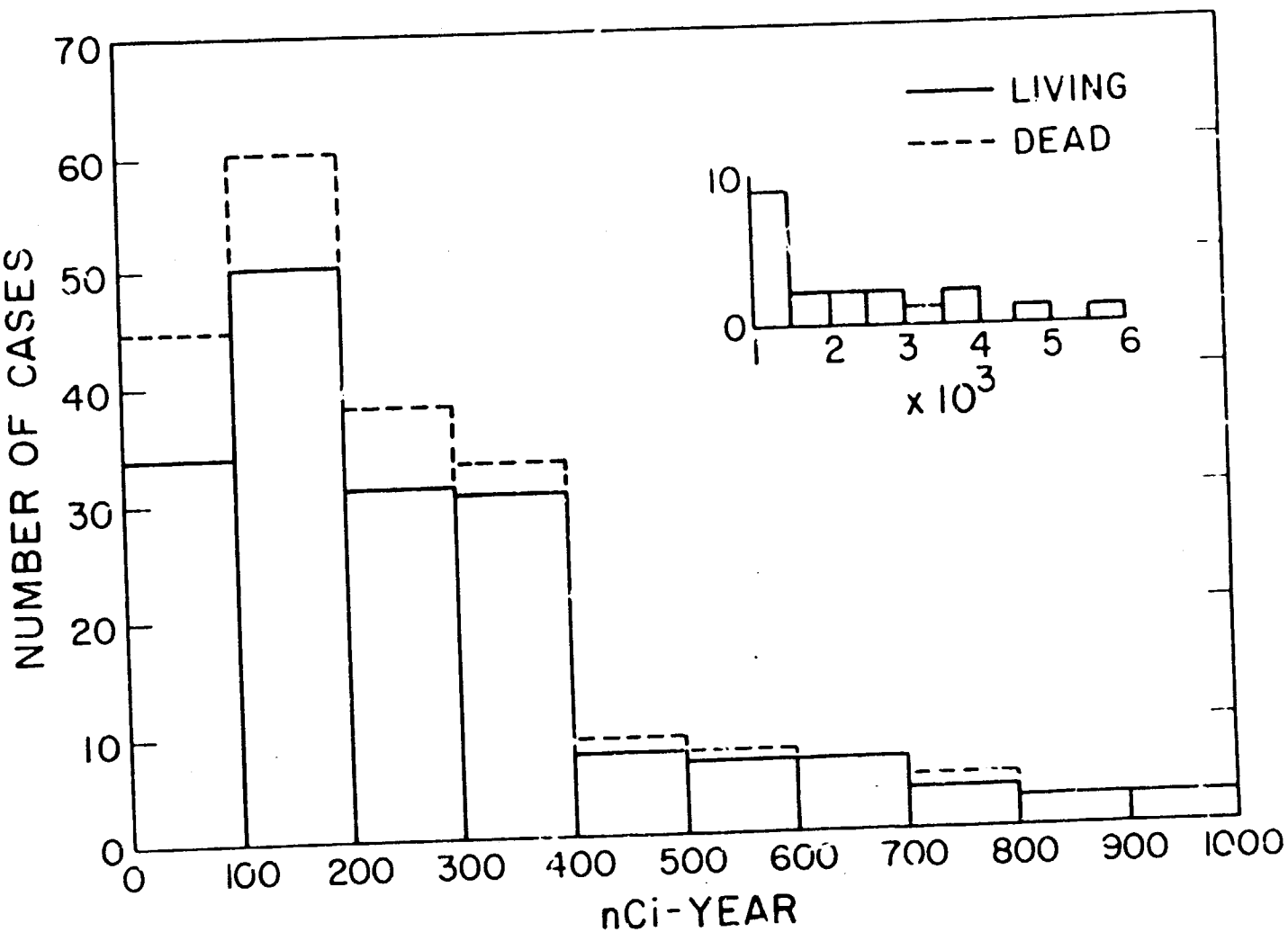

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TABLE 1

THIRTY-YEAR MORTALITY IN 26 WHITE MALE LOS ALAMOS MANHATTAN DISTRICT PLUTONIUM WORKERS

	Observed	Expected	Obs/Exp
All causes of death	2	4.22	0.47
All malignant neoplasms	0	0.77	0.00
All diseases of circulatory system	1	1.80	0.55
All respiratory diseases	0	0.18	0.00
All external causes	1	0.31	1.23
Other	0	0.69	0.00

Average year of entry : 1945.35

Average age of entry : 24.58

Total person-years of survival: 782.40

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TABLE 2

30-YEAR MORTALITY IN 224 WHITE MALE PLUTONIUM WORKERS

	Observed	Expected	Obs/Exp
All causes of death	33	61.3	0.54
All malignant neoplasms	7	10.9	0.64
All diseases of circulatory systems	12	31.8	0.38
All respiratory diseases	3	3.3	0.92
All external causes	8	6.9	1.16
Other	3	8.4	0.36

Average year of entry : 1947.4

Average age of entry : 30.9

Total person-years of survival: 6205

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TABLE 3

PLUTONIUM EXPOSURE ON 224

LOS ALAMOS PLUTONIUM WORKERS

	Living	Dead
Number of workers	191	33
Average Deposition	20 nCi	11 nCi
Average nCi-year Exposure	461	171
Total nCi-year Exposure[a]	88,139	5652

[a]Summed to 6/30/76 or date of death.

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TABLE 4

TOTAL ESTIMATED DOSES IN REMS TO 224

LOS ALAMOS PLUTONIUM WORKERS AS OF 1976

	Tissue Analysis Assumptions (rem)	Modified ICRP Model (rem)
Lung	35,800	16,800
Bone	26,800	36,400
Liver	10,500	24,000

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TABLE 5

POTENTIAL LIFETIME EXCESS CANCERS IN 224

LOS ALAMOS PLUTONIUM WORKERS

	UNSCEAR Risk (per rad)	Excess Cancers[a]
Lung	50×10^{-6}	0.8 - 1.8
Bone	$2 - 5 \times 10^{-6}$	0.05 - 0.18
Liver	$4 - 10 \times 10^{-5}$	0.04 - 0.24
Total		0.89 - 2.22

[a]Range due to different assumptions used for dose calculations.

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TABLE 6

POTENTIAL EXCESS LUNG CANCERS

PREDICTED BY GOFMAN HYPOTHESIS[a]

IN 224 LOS ALAMOS PLUTONIUM WORKERS

Persons At Risk	Lung Cancer Dose[b] (In Micrograms)	Total Lung Cancers Predicted[c]	Limited Lung Cancer Estimate[d]
Smokers	0.059	135.9	49.6
Nonsmokers	7.56	2.6	2.6
Total		138.5	52.2
Number of first lung cancers calculated to occur by 1976		25	15

[a]Reference 11.

[b]The quantity of weapons grade plutonium in the lung that equates to one lung cancer according to Gofman.

[c]Gofman risk estimate used without limitation on number of cancers predicted per person.

[d]Gofman risk estimate arbitrarily limited to a lifetime lung cancer risk not in excess of one lung cancer per person.

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TABLE 7

POTENTIAL EXCESS CANCERS BY 1976 IN 224

LOS ALAMOS PLUTONIUM WORKERS

	BEIR Risk (per year per rem)	Excess Cancers[b] by 1976
Lung	1.3×10^{-6}	0.02 - 0.3
Bone	0.2×10^{-6}	0.02 - 0.05
Liver[a]	4.0×10^{-7}	0.01 - 0.06
Total		0.05 - 0.41

[a]Risk coefficient derived by EPA from thorotrast exposures. No BEIR value available.

[b]Range due to different assumptions used for dose calculations, and include latent periods of both 10 and 15 years.

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