A CRITICAL EVALUATION OF THE MANCUSO, STEWART, AND
KNEALE REPORT AND A RE-ANALYSIS OF THEIR DATA

Final Report
October 1, 1978 - February 15, 1979

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Department of Community Medicine

Prepared for
U.S. Nuclear Regulatory Commission

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ABSTRACT

This report presents both a general and detailed critical analysis of the paper entitled Radiation Exposures of Hanford Workers Dying from Cancer and Other Causes, by T.F. Mancuso, A. Stewart, and G. Kneale.

We have concluded that the investigation was not conducted in a sufficiently rigorous manner to allow for any firm or defensible conclusions regarding the relationship between exposure to low level ionizing radiation and mortality from cancer. In addition, our re-analysis of these data did not reveal any convincing associations, although we recommend that the question of possible associations be resolved by a well designed and executed epidemiologic study.

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ACKNOWLEDGMENT

The preparation of this manuscript would have been impossible without the expertise and intelligence of Mrs. Anne Dawes, whom we gratefully acknowledge.

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A CRITICAL EVALUATION OF THE MANCUSO, STEWART, AND KNEALE REPORT AND A RE-ANALYSIS OF THEIR DATA

GENERAL COMMENTS

We will begin with a general presentation of our reactions to the study under review[1] and will follow this by a detailed examination of the paper itself. The reader should be aware of the fact that the specific justifications for the comments in this first section will appear with the detailed comments in the second section, to which reference should be made for more complete understanding of the foundations for our conclusions.

The major limitations of the paper can be summarized as follows: absence of a clear statement of design and rationale for analysis; lack of sensitivity for the limitations of a numerator data analysis; almost complete absence of control for potential confounders; use of means as the major measure of effects when odds ratios would be far more appropriate; and very selective and incomplete use of statistical tests of significance, especially when small observed differences may have been due to chance or confounding.

The most striking feature of the report is the general absence of a clear statement of the intent and design of the investigation, the neglect to state the specific hypotheses, if any, under scrutiny and the reasons for studying these hypotheses, and the failure to present the findings in a

[1]Mancuso, TF, Stewart, A., Kneale, G.: Radiation exposures of Hanford workers dying from cancer and other causes. Health Physics 33:369-385, 1977.

clear and orderly fashion which would enable the reader to
assimilate the information offered. Simply reading the
paper was a terribly difficult chore, while understanding
it was often impossible. The direction (or general scheme)
of the investigation and analysis were not evident, and the
reader could rarely anticipate the next step nor integrate
the bits of data presented into some meaningful whole.
This general absence of organization made the task of reviewing
the paper most unpleasant and may have occasionnally resulted
in the adoption of an overly critical attitude by the reviewers.

Regarding the absence of a statement of the specific
hypotheses under investigation, we must say that it is never
clearly stated whether this study is of the hypothesis
testing or generating type. If it is the former, we are not
advised of the questions under investigation; if it is the
latter, it appears as if any and all associations encountered
in the analysis are offered as hypotheses, or even firm con-
clusions, with little or no biomedical interpretation or
explanation of these relationships. For instance, numerous
cancers are cited as being associated with higher mean cumu-
lative radiation doses, but no evidence from other research
is presented concerning the similarity between doses and
latency periods observed in these data and those found by
other investigators for the suspect sites.

In addition, we were very troubled by the avoidance of
a discussion of possible alternate explanations of the
findings, such as the strong probability that smoking habits

may explain the observed excess proportion of lung cancer.
One must also be concerned with the absence of any dis-
cussion of the possible impact of earlier (non-Hanford)
occupational exposures, especially in view of the fact that
the mean age at hire for this group of employees was approxi-
mately 40. This leaves unexplained the 20 years of earlier
employment at younger ages (20-40), when sensitivity to
cancer induction is thought to be greatest. It is the
failure to engage in discussions of this nature which we
find very disturbing.

Of special concern to us was the inadequate expression
of appreciation, or perhaps even awareness, of the severe
limitations of a 'numerator' type study which is based
entirely on an analysis of deaths only, from a cohort of
workers (both living and dead) about whom very little is
known. This limitation brings into serious question the
validity of extending the findings (or making inferences)
to the general population and will be further discussed
below.

If one wishes to make statements, say, about the effects
of smoking on the incidence of lung cancer in the general
population, one would ideally conduct a cohort study,
drawing from the entire Population at Risk (PAR) an appropri-
ate (random or representative) sample of non-smokers and
smokers. These groups would then be followed for an
extended period of time (whence is derived the term
'prospective study'), and the occurrence of lung cancer would

be carefully noted.

After completion of this type of investigation, it would be appropriate to make inferences back to the PAR (all smokers and non-smokers) concerning the impact of smoking on the risk of developing lung cancer. Case-control (or retrospective) studies present greater problems for inference making. In the first place, the disease has already occurred, and the exposure must be determined retrospectively (usually by history). Secondly, we are not at all assured of having in our study a 'representative' sample of cases or controls.

Many of these problems are overcome in retrospective occupational studies by the identification of a cohort of workers - for instance, all men ever employed at Hanford, whether presently living or dead - from which all cases of the disease under study are drawn, and whose exposures are compared with an appropriately selected control group. The criteria for selection of this group is of paramount importance, since it is this group which will serve as the 'standard' from which 'expected' exposure levels will be derived. Everyone in the cohort should therefore be eligible for selection as a control, and control selection should not be limited only to those members of the cohort who are deceased, since this latter group may not be representative of the entire cohort.

If controls are selected properly, it would be reasonable to extend the findings back to the entire cohort from which cases and controls were drawn, and if this cohort is similar

to other cohorts or to the general population it would be reasonable to make inferences, with due caution, back to these other groups as well.

The present investigation is termed a 'numerator type' analysis since, from the original cohort, only the experiences of the deceased are utilized. Rates of specific diseases (which would require in the denominator the inclusion of all cohort members whether living or dead) are never presented, unfortunately, and the comparison group used throughout the study (the non-cancers) are drawn entirely from the deceased members of the cohort.

In view of the above discussion concerning the drawing of inferences from case-control studies, and in view of the method utilized in this investigation for 'control' selection, one must question the validity of even extending the findings back to the original cohort, and we must certainly object to the extension of the findings to the general population, as is strongly implied in the entire discussion of the 'doubling doses.' These objections seem reasonable even in the absence of effects of possible confounders; when we realize that the effects of confounders may have seriously distorted the observed associations, extension of the findings becomes completely unjustified.

A confounder can be simply described as a predictor (or alternate cause) of the disease under study, independent of exposure. In a study of the association between smoking and lung cancer, for instance, residence in a dirty urban

environment can be anticipated to be a confounder since
residents in these areas will experience higher rates of
lung cancer than those who live in clean environments,
irrespective (independent) of their smoking habits.
If residence is distributed differently in the case and
control groups (e.g., a higher proportion of controls
reside in urban areas with much pollution), confounding in
the estimate of effect can be expected. If the effects of
residence (the confounder) are not controlled for either in
the design of the investigation or during the analytic
phase, the estimate of the effect of smoking on lung cancer
will be distorted by (or confounded with) residence.
Therefore the presence of confounding within ones data,
which is considered to be the central methodologic issue in
the conduct of epidemiologic investigations, may entirely
invalidate all estimates of effect. It is this possibility
for distortion which leads experienced practitioners of
epidemiology to treat these potential confounders with
proper respect, and even reverence.

Throughout the entire paper, very little, or insuffi-
cient, attention has been directed at the possible effects of
confounding factors, such as age at and year of hire, dura-
tion of employment, intensity of exposure, and the sex and
race of the workers, among others. In every comparison of
'cases' and 'controls', for instance, a presentation of the
distribution of these factors, which would be helpful in
dispelling our fears, is omitted.

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Our next major area of concern relates to the general failure to use appropriate measures of effect and to determine the statistical significance of the observed differences between the compared groups.

The comparison of mean cumulative doses forms the foundation for the entire analysis, and we must question the reliance on this parameter for testing the associations between exposure and cause of death. A mean value is simply not an ideal measure of effect, especially because the mean may not be a good descriptor of the underlying distribution and also because it is really not a measure of effect. An examination of the medians for cumulative radiation dose, for instance, indicates that the means are being very heavily weighted by a few outlying doses, which leads to the conclusion that the mean is not an accurate summary statistic for the characterization of the exposures. Even if it were, however, one would still prefer true measures of effect, such as odds ratios or relative risks, which more directly express the relationship between exposure and the risk of developing the disease. Unfortunately, not a single odds ratio is presented in the paper.

Notwithstanding the possibility for distortion which is introduced by reliance on averages, we must further object to the arbitrariness in the use of statistical tests of significance as well. We are often presented with very small differences in means which are deemed to be of <u>causal</u>

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importance without the performance of appropriate statistical tests which would clearly establish the significance of the difference, while we also frequently encounter the use of tests of significance which are inadequately or not at all described. Even when measures other than means are used, significance testing is also arbitrary. For instance, the authors conclude that there is an excess of brain cancers, based on a ratio of observed: expected cases of 1.04, or a 4 percent excess; unfortunately, this conclusion is not based on a test of the significance of this difference. The instances of this type of neglect are simply too numerous for citation in this discussion.

There is, in addition to these problems, a pervasive use of terminology which either remains undefined or is used in a manner different from conventional use. Terms such as cohort, cohort resemblances, case-control contrast, high risk years, pre-death years, employment years, controlled analyses, and standard, among many others, cause continual problems for the reader in following the reasoning of the investigators and their presentation of findings. The latter is especially confusing in many ways, among which one can include the following: table titles are often misleading, the use of percentages is often inappropriate, denominators are generally not specified, and the totals presented are frequently entirely meaningless and only obfuscate the issue at hand.

Despite the enumerated limitations, and others which
have not been here discussed, the investigators do not hesi-
tate to make very strong conclusions and broad extrapolations
of their findings to the population-at-large. In the absence
of a clear description of the characteristics of the true
cohort of all Hanford workers, and the failure to establish
the existence, in acceptably rigorous fashion, of a real
excess in disease occurrence, there is nevertheless no
reluctance in making inferences back to this undefined
cohort, and in then boldly extending the data to all those
in the universe who receive low-level ionizing radiation,
even so far as to derive from these data estimates of the
dose needed to double the incidence of cancer at many sites.
Even if the biostatistical procedures are appropriate, one
must seriously question the legitimacy of this type of
extension of findings because of the inadequacy of the
epidemiologic design - namely, the numerator nature of the
analysis already discussed.

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SUMMARY

The paper by Mancuso, et al. demonstrates inappropriate use of limited data to support what seem to be a priori conclusions rather than hypotheses. Review of the report presented enormous difficulties caused by the failure of the authors to provide the following:

1. A clear statement of the intent and design of the study; the hypotheses under investigation and their rationale.

2. A logical sequence and clear presentation of findings.

3. Adequate expression of appreciation for the limitations of numerator data (i.e., without reference to a base population); the potential impact of unknown confounding factors such as age, sex, personal habits and co-morbidity; estimates of completeness of ascertainment of mortality; methodologic justification for shifting denominators; and biologic justification for aggregating cancer of multiple sites.

4. Clear partition of age/radiation dose categories and the application of age-adjustment to summary data.

Even if the deficiencies cited above were not present, the nature of the information cited by the authors would not support a statement of risk. Such a statement would require

estimates of incidence of cancer of specific sites, related
to radiation, among categories of exposed persons in whom
the prevalence of confounding factors such as cigarette
smoking would be known.

The reported levels of exposure cited in the paper are
several orders less than the estimate of carcinogenic effect
in other human experience. The need to document human
effects of chronic exposure to low level radiation, however
urgent, is incompletely served by the Mancuso report.

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SPECIFIC COMMENTS

This section will include specific comments on the paper, arranged by page and line number. While the preliminary discussion summarized our general impressions of the research and the possible limitations in interpretation, this section will elucidate, in detail, the reasons for our concern.

Page 370 - Preliminary Findings

. The expression 'certified deaths' is not self-explanatory. Does this refer to deaths for which a death certificate was found, or does it refer to nosologized death certificates? At any rate, 190 of 3710 deaths, which is more than ! percent, are not included in the present analysis for reasons not clearly stated. While on this topic, it should also be noted that throughout the entire analysis, only the underlying (presumably) cause of death is used, and its method of derivation is not specified.

C.L.-P.2*

The argument here is a bit circuitous but seems to be as follows: The greatest number of deaths occurred among those who were members of the earlier cohorts (mostly 1944), at which time there was both a high proportion of unexposed workers, while those who were exposed were likely to have low level exposures prior

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*This notation should be interpreted as follows:
 C.L. - the left column; C.R. - the right column;
 P.2 - the second paragraph which begins in the left column.

to 1954. Does it then follow from this argument that there were changes in the plant which explain the higher exposures beyond 1954? If so, there is no discussion of what these changes might have been and what possible impact they may have on deaths after 1973. The statement is also made that among both the cancer and non-cancer group, the proportions of those hired in 1944 and after 1948 are similar. What is the implication of this statement? Does this finding fit in with the above argument? How? Might not one argue that if radiation is predictive of cause of death, perhaps we would have expected a lower proportion of those who eventually died of cancer to have been hired during the low dose-low proportion of exposed worker period. One should not get too involved in these arguments, however, because they are based exclusively on year of hire, which is of major importance in an occupational study only if there were changes in some aspect of production, with concomitant differences in exposure following these changes.

While on this topic, it should be noted that Table 1, as are many of the other tables in this report, is presented in an awkward fashion which makes interpretation difficult. It would be of interest to examine each cohort (here defined as the group of workers hired during the specified year) separately and then to compare their characteristics with those of other cohorts. To accomplish this, the data should have been per-centaged across, not down. In other words, we would like to

know, say for the 1944 cohort, what proportion of the 5,256 members of this cohort survived, died of cancers and non-cancers, etc. We could then compare this with the 1949-1971 cohort, for instance, and compare the proportions in a manner

which would permit us to determine whether the cohorts truly resemble one another. As the data are presented, however, we are informed that, of the 21,206 survivors, for instance, 16.4 percent come from the 1944 cohort and 2.3 percent were in the 1946 cohort. What is the significance of this? By percentaging down instead of across, the characteristics of individual cohorts are obscured rather than clarified. It is only in the very last line that the across percentages are offered in summary, which again does not permit compari-son of individual cohorts.

C.L.-P.3

This paragraph opens with a statement about 'cohort resemblances' where the meaning of the term cohort is suddenly changed from members of the group of workers hired during a specified year, to members of the group of cancer and non-cancer deaths. This inconsistency in the definition of terms is misleading, and the conclusion that the cohorts' are 'similar' does not necessarily follow from the single piece of information offered in the paragraph above.

The reader is also referred to Table 2, from which it is deduced in the text that "men who eventually developed fatal cancers had been more often and more intensively exposed to external radiation than men with other causes of death." 1393 239

Table 2 does not provide evidence for either of these two
conclusions. There are no data whatsoever concerning how
'often' members of the two groups had been exposed, nor is
there any information presented concerning the 'intensity'
of exposure, which simply cannot be equated with mean cumu-
lative radiation dose without examining and including in the
calculations the duration of employment.

One possible way to define intensity would be mean
annual exposure, and while we have objected to the over
reliance on means earlier in our discussion and will not
here repeat our arguments, in the context of the manner in
which the data are presented, mean annual exposure would at
least incorporate duration of employment, a factor of utmost
importance which has received very little attention throughout
the entire publication. From the data presented in Table 2,
however, no conclusions can be drawn concerning how often or
intense the exposure has been, although it is reasonable to
conclude that a higher proportion of those who developed
cancer had been exposed at some time; in view of the rather
small observed difference in the proportion exposed (66 vs 61
percent), one wonders, however, why no test of the signifi-
cance of this difference was performed.

While we have already pointed out the central importance
of the possible impact of confounding in epidemiologic
investigations, it is well to remember, and it will not be
continually repeated, that in none of the analyses presented

was there appropriate control for the possible effects of the numerous suspect confounders, such as age at and year of hire, duration of employment, etc.

C.R.-P.1

The statement is here made, based on the data in Table 3, that for no specific non-cancer was the mean radiation dose higher than the average for all cancers combined. Clearly, the all cancer average is being fairly heavily weighted by a few sites with high mean doses (lymphatic leukemia, pancreatic and brain malignancies) and, in fact, the all cancer mean doses are not even presented, but instead the doses for RES neoplasms and solid tumors are presented separately.

A careful examination of the contents of the table reveals that the mean dose for many of the specific non-cancers exceeds the mean for many of the specific cancers, and while we once again mention the limitations of working with means, we must strongly object to the comparison of means (or overall means for a large group of all cancers) with the means for much smaller groups of specific non-cancers. One must also wonder, again, why tests of significance (such as T-Tests for the comparison of means) were not performed on these findings, although it would have been far more preferable to calculate the odds ratios, which is a commonly used

epidemiologic measure of effect, for the relationship between exposure and disease. Indeed, examination of the percent of exposed workers in each disease category intimates that most odds ratios would be close to unity.

In general, it should be stated here that even among those who developed cancer, approximately 40 percent were never exposed to any radiation at all, and one must wonder why they are left in the analysis, especially since their cancers cannot be attributed to the exposure under investigation. Indeed, the text often cites the Mean Cumulative Exposure for all workers, including those unexposed, as evidence of the effects of radiation, rather than consistently citing the mean dose for exposed workers only.

Page 371
C.L.-P.1

One generally, in the conduct of an epidemiologic investigation, would establish the existence of an excess in certain diseases within an employed cohort, and after the excess (along with its statistical significance) has been established, look for the possible effects of occupational exposures. More will be said shortly on the methods used to establish the existence of an excess, but it should first be pointed out that the data were apparently first examined for associations between cause of death and exposure, and this was followed, instead of being preceded, by identification of those deaths occurring in excess. In addition, the relationship between

excess deaths and higher than expected radiation doses is
inconsistent and not sufficiently, if at all, discussed.

For instance, from Table 4 we see that there was a
44 percent excess of neoplasms of the liver and gall-
bladder, while the mean radiation dose, from Table 3, was
exceptionally low, lower indeed than 8 of the 9 categories
of non-cancer. On the other hand, a case is made for a possi-
ble causal association between neoplasms of the brain and
large intestine, which appear at a 4 percent excess and a
3 percent deficit, respectively, or essentially which appear
at the expected frequency. The method used for establishing
the existence of an excess, aside from the conceptual prob-
lems summarized above, are not at all clear and may actually
invalidate any conclusions regarding the excess. The state-
ment is made that Table 4 presents the "expected number which
shows how the same diseases were distributed among the 1960
cancer deaths of U.S. white males." It seems, therefore, that
a proportional mortality analysis (PMR) of some sort was
performed, although it seems reasonable to conclude that the
PMR was not only not standardized for age or race, but
that indeed while the expected numbers are based on the
experience of U.S. white males, the observed numbers may
include blacks as well, a problem which did not
prevent the authors from generating observed:expected ratios.

We have here, therefore, a situation where the procedure
used to establish the occurrence of an excess (the propor-
tional mortality approach) is of dubious epidemiologic
validity even in the best of circumstances; that the procedure
did not even standardize for the common confounders only
furthers the difficulty in interpreting the findings.
One must seriously wonder why SMRs (Standardized Mortality.
Ratios) were not used, especially since from Table 1 one may
surmise that the appropriate denominators necessary for the
calculation of SMRs were indeed somewhere available.

Even despite these serious limitations, one must further
wonder why tests of significance were not performed on these
ratios, especially since not a single ratio reached a value
of 2 — that is, none of the diseases occurred at twice the
expected proportion. In view of these non-impressive excesses,
some statistical test is clearly indicated but none is offerred.
Instead, the Table draws the readers' attention to the mean
cumulative dose and how it compares with the mean for all
non-cancers — a comparison which has already been discussed
and which is replete with serious limitations.

C.L.-P.2

Despite the problems thus far enumerated, the authors
conclude that the "preliminary findings are compatible with
a causal association." The stated conclusion is clearly
unwarranted, although one might suggest at this point that

further analyses are appropriate in view of possible
associations. This section then continues with a descrip-
tion of what are called 'controlled analyses,' a term which
is entirely misleading. Presumably, this section addresses
the question of the effects of confounders, although this
is done either incompletely or inappropriately, if at all.
In fact, controlled analyses - properly defined as an analytic
procedure which describes the relationship between exposure
and disease after the effects of the confounder(s) have
been removed - were never at all performed. Instead, each
of the 5 listed "possible sources of false impressions" -
i.e., confounders - is described separately, and while differ-
ences between cases and controls are observed and noted,
analytic techniques capable of controlling for these differ-
ences are not used, or at least not presented.

C.R.-P.1

We will not repeat our objection, in examining the state-
ments made about the five possible confounders, that
"controlled analyses" were never actually performed, but
will instead examine whether the statements made about the
data presented are appropriate. The statement is made
concerning "calendar years," which is never clearly defined,
that "only during the high dose period [second half of study
period] were differences between cancers and non-cancers at
all pronounced." What does "differences" mean? Examination
of Figure 1 reveals that "differences" between the two groups

were never pronounced. Examination of Table 5, about which more will be said shortly, reveals that "differences" (either radiation dose or high risk year) were rarely pronounced. While much is made of the "high risk year" concept, the actual differences in radiation dose between the cancer and non-cancer groups are miniscule. For instance, the period 1958-1959 credits the cancer group with two high risk years, while the difference in mean dose (53.6 vs. 51.7) was 1.9 centirads. How significant, both biologically and statistically, is this difference, and does it warrant calling the entire period a high risk period for the cancer group? In fact, the entire Table 5 is presented in an awkward manner. The column "Exposed Workers" is misleading, for instance, because the 333 exposed cancer workers in 1946-47, for instance, may and probably does include the 237 from 1944-45. The totals of 3005 and 10,385 presented at the bottom of the columns therefore have no interpretation by themselves. Also, why are the 'calendar years' presented two at a time, while the 'high risk years' column separates the two years. Clearly, the authors had and used more data than they presented.

One must also question the pooling of these two-year periods - from Figure 1 we see that in 1944 approximately 18 percent of cancers were exposed, while in 1945 it rises to over 30 percent. Should these two years be pooled? Are the data being obscured by this procedure? Further comparison of Figure 1 with Table 5 causes even more problems. For instance,

from the Table we see that during 1946-47, 333 of the 670
cancers, or about half were exposed. The figure, on the
other hand, indicates an exposure rate for cancers which is
less than 40 percent!

While this may be explained by the use of a denominator
other than the 670 total cases of cancer, the reader is not
informed of the nature of the denominator; the most appropriate
one would be the number of workers employed at that time
(i.e., the total number eligible for inclusion in the numera-
tor). The central questions pertaining to this "controlled
analysis" and the others which follow are: do the"analyses"
really "control" for the confounders or do they merely describe
them; are the proper "differences" being examined - i.e., what
is the rationale for choosing these and not others, and
indeed, are the data presented internally consistent.

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C.L.-P.1

The section on "employment years" suffers from the same
general problems as those encountered in the calendar year
analysis already described, although one major additional comment
must here be made concerning this and the following ("pre-death
years") analysis: the two terms are simply not clearly defined,
making interpretation of the presented data extremely difficult.
In the introduction to the controlled analyses, the first factor
is referred to as "employment year of exposure" while in Table 6
it is referred to as "employed years," and in the text there is

a statement about the "progressive lengthening of the interval between hire and exposure." So the meaning of this term is ambiguous. Figure 2 reveals that the abcissa, which is employment year, takes on values from 0 to 29, which implies that Year 0 = 1943, or the first year of operation of the Hanford Works, while Year 29 is the last year included in this study, namely 1972. If this is true, then Figures 1 and 2, as well as Tables 4 and 5, should be exactly the same, and they are not, which still leaves open the definition and intended use of the term.

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C.L.-P.1

The same general objections can be made regarding the term "pre-death year," although a definition is offered in the footnote to Table 7: pre-death year = interval between exposure [presumably first exposure] and death. Apparently this is therefore synonymous with latency period, where this period is calculated from the first year of any exposure.

In this discussion, and in the discussion of the other four possible confounders, any and all observed differences are presented without any attempt to amplify on their meaning. For instance, what is the validity of pooling all cancers (both those occurring in excess and those not) and then presenting data on their latency period in the aggregate? In this section, for instance, we read that "when the interval...was less

than 8 or more than 20 years...there were over twice as many high risk years for non-cancers." What is the import and significance of this finding? How does it fit with the other conclusions? Is there duplication of these findings by other investigators?

In addition, there again appears to be an inconsistency between the data presented in Figure 3 and Table 7, unless we are interpreting the data improperly, which is possible. From the Table, for pre-death years 24-25, we see that 111 (of the 670) cancers, or approximately 15 percent, were exposed. Examination of the Figure for the same period suggests that the exposure rate for cancers was over 40 percent. Where does the error lie? Is it again due to undefined denominators?

C.R.-P.2

The data for exposure age, which is presumably age at hire, may have been improperly interpreted - the statement is made, for instance, based on Figure 4, that "the proportion of exposed workers was virtually independent of age." Examination of the Figure in question reveals quite a different picture. Among the cancer group, a considerably higher proportion of those who enter before the age of 35 are exposed. One can hardly conclude from these data that the proportion exposed is independent of age at hire, unless one pools the data for the cancer and non-cancer groups and obscures the true differences.

But aside from these problems in interpretation, what does this analysis tell us? It says, in essence, that the greatest danger for cancer induction, if there is indeed any danger at all, is found among those who were first exposed at the older ages, while biologic theory generally postulates that exposures among the young usually carry the heaviest ultimate penalties. Perhaps some valid underlying relation- snip with age at first exposure is being obscured here because of the pooling of all cancers - which includes many sites which were not in excess among Hanford workers and others with radically different estimated latency periods.

Page 375
C.L.-P.2

The first statistical test of significance is reserved for the analysis which presumably controls for age at death. Now age at death is clearly related to cause, even in the absence of any occupational exposures. For instance, we would expect that men dying of accidents will die at younger ages than those whose cause of death is lung cancer, indepen- dent of occupational exposures. What is the purpose, then, of this analysis? Why control for age at death itself, unless one demonstrates that this variable is related to another, say duration of employment, which can affect cumulative radiation dose. Questions are therefore immediately being raised con- cerning the very propriety of this analysis.

In addition to our fundamental concern for the rationale
of this analysis, we were also puzzled by the statistical
techniques chosen by the authors. All three variables
involved in this analysis - cumulative radiation dose,
proportion dying from cancer, and age at death - are continu-
ous variables, for which there exist numerous statistical
techniques which utilize fully the available interval data.
Why these continuous variates should be rank-ordered, with
the accompanying significant loss of information, before
statistical tests are applied is difficult to understand.

Aside from these fundamental biologic and statistical
objections, however, we find it difficult to understand the
meaning of the conclusions presented in the context of the
present investigation. For instance, we read the following:

> "although accidents were often causes of early
> death, men who eventually developed malignant
> diseases did not have appreciably longer life
> spans [i.e., lived slightly longer] than men
> with other causes of death."

How does this fit in with the hypotheses and relationships
under investigation? Is this expected or unexpected, impor-
tant or unimportant, etc.? In fact, we are being told that
those who die of cancer live longer than those who die of
other causes. Perhaps, then, radiation exposure is beneficial
and ought to be encouraged; on the other hand, perhaps it is
a function of the first objection concerning age at death
analysis discussed above. We are further informed that

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"between two thirds and three quarters of all the deaths occurred between 50 and 80 years of age." This sounds entirely reasonable, and in the absence of any comparison with other groups, contributes nothing to our understanding of the relationship between radiation exposure and cancer deaths.

Examination of Tables 9-12 reveals some very interesting things which are not all discussed. From Table 9 (which should have been percentaged across also) we see that 53.2 percent (26.9 + 20.1 + 6.2) of all the non-cancer group live to be 60 or older, while the corresponding figure for the cancer group is 55.5 percent (35.7 + 17.3 + 2.5). That is, a higher proportion of those who died of cancer, which is presumably associated with radiation exposures, are living until the age of 60, than are those who died of non-radiation-related conditions. Table 10 reveals that those with the highest cancer: non-cancer radiation dose ratio lived much longer (until the age range 70-79) than those with the lower ratios. What is the meaning of these and similar conclusions which can be extracted from the presented data?

Page 376
C.L.-P.I

The interpretation of the findings in Table 11 is difficult indeed. It should be recalled that our major objection concerned the transformation of continuous data into an ordinal scale, which is then subjected, after considerable loss of information, to a

statistical test of significance whose results (p-values) are
not consistently presented. That is, a rho was calculated
for the rankings in each of the five age groups, while the
p-value for these rhos are not presented. Apparently, only
the correlation coefficient (rho) for age at death among
those 70 and older is significant, and indeed that only
among those who die at the oldest ages is cancer a signifi-
cant cause of death among the highest exposure group - but
one should not lose sight of the fact that those in this
group, who had the highest exposure and highest cancer propor-
tion, are living the longest.

The mean for each exposure category is then calculated,
and a rho is calculated for the ranking of these means,
which is a statistical manipulation of dubious validity; it is
only for this procedure that a statement is made concerning the
significance of the derived correlation coefficient. Based
entirely on the result of these questionable analytic pro-
cedures (the actual p-value is not even presented), the authors
conclude that there was a "firm rejection of the null hypothesis
by the statistical test," a statement which hardly seems
warranted, or which at least requires further justification.

Page 376 - Special Tests of Radiation Associations

Reference is again made to 'controlled analyses' which, as
mentioned earlier, have for the most part not really been conduc-
ted. At this stage of the analysis, nevertheless, the authors

feel confident in attempting to describe the nature of a relationship whose very existence has not yet been firmly established. This section, along with the appendix in which many of the ideas are expanded, is quite biostatistical in nature, and since we are not biostatisticians, we will not offer a detailed reaction to the procedures used, although a few general comments are in order.

Once again we must state our objection to the over-reliance on arithmetic means as the central measure of effect. In addition, we must point out that N, which is defined as the size of the whole population, in the text, refers only to the population of certified deaths and not to the true cohort of all workers at Hanford. This is an extremely important point, because it is very possible, and indeed probable, that the cumulative radiation doses experienced by many of the survivors far exceeds those of the deceased members of the cohort, as the authors themselves state on the second page of the publication. How this can be ignored when making inferences about the potential effects on the general population (e.g., doubling dose) is most difficult to comprehend. As pointed out in the introduction, from a numerator type analysis one should be reluctant to extend the findings back to even the original cohort from which the deaths were drawn; extending the results to the general population should be tempered by even greater discretion. While we are not competent to evaluate the validity of the biostatistical modeling, and are willing to assume that it is appropriate, we nevertheless

feel that the use of an inappropriate N (all deaths and not all members of the cohort) raises serious doubts about the epidemiologic validity of the conclusions, especially when from these data inferences aie drawn concerning the antici- pated effects of exposure among the general population.

Page 377
C.L.-P.5

The statement is made that "there are strong grounds for believing that tissue specific cancers have characteristic, albeit long, intervals between initiation and death." How does this statement agree with the earlier finding that the "high risk years" for cancers occurred later (or closer to the year of death) than those for non-cancers, and the findings reported here where we see that for all sites examined, the only statisti- cally significant differences in exposure occurred rather shortly, and not a long time, before death? In not a single site was there significant excess exposure earlier than 18 years before death, which is certainly not a "long" interval, and the intervals for all sites, in general, fell between 18 and 0 years prior to death, which hardly demonstrates that each site has a "characteristic" interval. We should also mention at this point that there is no description of the specific statistical tests used for determining which exposures were significantly different from the experience of the non-cancer group, although p-values are presented.

The statement is also made that "sensitivity to the
cancer induction effects of any mutagen is strongly age-
dependent," although this idea is not further clarified.
Are we speaking of age at first exposure or age at which the
greatest exposure occurred, among other possibilities? Which,
in fact, are the most sensitive ages? How does this age-
dependence statement fit with the earlier observation (p. 375)
that the "proportion of exposed workers was virtually indepen-
dent of age." If workers are sensitive at a young age, for
instance, then we would expect that a higher proportion of
those destined to get cancer would have been exposed at younger
ages - yet this proportion is declared to be independent of
age on the basis of the data utilized in this study.

A further problem with the "age analysis" is that,
although referred to, it was never really done. The reader is
referred to Table 16, which again presents data relating to
"pre-death periods," meaning latency period or years prior to
death. This absolutely cannot be equated with age - for a man
who died at 80, an exposure which occurred 20 years prior to
death occurred when he was 60, while for the worker who died
at 60 the exposure occurred when he was aged 40. Analysis based
on "pre-death years" therefore say nothing about the actual age
at which the exposure occurred unless age at death is statisti-
cally controlled in the analysis, which was not done for
Tables 12-16, from which one therefore cannot make any deduc-
tions concerning sensitive ages for cancer induction.

It should also be noted, when discussing the data in these tables, that the cumulative radiation doses for other sites reported to be in excess in Table 4 (mouth and pharynx, liver and gallbladder) are not presented. In view of the fact that cancers at all sites did not occur in excess, and that not all sites showed significant excess cumulative exposure when compared with on-cancers, one must wonder why the investigators continued to pool all cancers and make inferences about this large aggregate.

C.B.-P.1

The discussion here attempts to enumerate additional characteristics of those cancers with "definite radiation associations," but as we have been indicating, we cannot agree that definite associations have indeed been established, which throws the appropriateness of all succeeding analyses into considerable doubt.

Page 378
C.R.-P.2

The investigators state here that the "critical interval between exposure and death" for all cancers was 12 years, while they further report "critical intervals" of 14, 11, and 9 years for lung cancers, RES neoplasms, and bone marrow cancers. Once again we must note that this is not in agreement with the earlier statement (p. 377) concerning the long and characteristic intervals between initiation and death for tissue-specific

from this major difficulty, one must further wonder how the category "all cancers" can be causally associated with radiation exposures in view of the preceding discussion concerning the biomedical validity of pooling so many different sites.

In anticipation of possible objections to such low estimates of doubling doses (0.8-12.2 rads) the authors cite Table 16 and state that from the observed and expected proportions of different cancers, Standardized Mortality Ratios (SMRs) were obtained. SMRs are based on a comparison of rates derived from the true cohort of all workers, whether living or dead, while the proportions presented in Tables 16 and 4 refer to proportions based only on the distribution of deaths. How one derives SMRs from a proportional mortality analysis, and obtains these estimates "in the usual way" is baffling. In addition, we are not told for which factors (age, race, sex) the SMRs were standardized. Indeed, if SMRs were available, they should have been presented as the very first piece of evidence concerning the existence of an excess and should have formed the foundation for all further analyses. While Table 17 presents "SMRs," the reader is referred back to Table 16 for an explanation of the manner in which they were derived and this Table, as already indicated, deals with proportions and not rates. Without further clarification, the interpretation of these calculations is impossible.

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C.R.-P.2

Since our data set did not include any information on internal radiation, we will not comment on this section and will instead resume our discussion with the section on age and sensitivity.

We must frankly admit that we do not understand the discussion and the data (Tables 21 and 22) on which it is based. Nevertheless, the statement is made that these data are "strongly suggestive of an exponential increase in cancer sensitivity with advancing age." Once again we must remind the reader that the entire analysis is based on numerators (deaths) only, from which it simply cannot be concluded that sensitivity (presumably among all workers) increases with age. Even if the data presented are accurate, from the fact that cases of cancer at age 45 had 15 percent higher than expected doses, while at age 50 there was a 50 percent higher cumulative exposure, one simply cannot conclude that the "risk of" (sensitivity to) cancer is increasing - after all, everyone in this group has already developed and died of the disease.

While this may be conceptually similar to the use of an Odds Ratio as an estimate of Relative Risk, this transformation is based on rigorous epidemiologic and biostatistical foundations which have been continuously re-examined, modified, and strengthened by countless investigators over a period of 20 years, and we cannot assume that the procedure used here is as defensible. We must therefore state our substantial concern with this entire section and the inferences drawn from the available data.

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C.R.-P.2

The approach used for the analysis of the female
experience is similar to that used for the male analyses and
we will not further discuss the issues already raised,
although a few comments are in order.

Presumably, females were not included in the earlier
analysis, although this is the first indication of this
analytic decision. We must wonder what the rationale is for
this separation. It is also not clear whether there were
126 or 127 deaths from cancer among females (perhaps this
is a typo), or how the 285 deaths from causes other than
cancer among the 412 women gives a percentage of 30. Despite
the statement that the "proportion of these workers with
records of external radiation was small" Table 23 ranks all
females for radiation exposure, which would be impossible if
data were not available for all of them. If the '0' in this
table refers to those for whom records were not available,
and not the truly unexposed, the statistical test becomes
inappropriate and the results misleading.

Page 382
C.L.-P.2

The procedure used to arrive at these estimates of
attributable risk are not at all clear to us. We must say,
however, that attributable risks are best derived from pros-
pective (or cohort) studies. While they are occasionally
derived from case-control studies, there are numerous methodologic

problems associated with this derivation, and the assumption is generally made that <u>all</u> members of the <u>cohort</u> were eligible for selection as controls. Since this present investigation was based on numerator data only, this assumption cannot have been met.

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Discussion

Based on the critique presented thus far, the four enumerated conclusions in the first paragraph are simply unwarranted. While the authors, in the following paragraph, finally acknowledge the possible impact of confounders, and indicate that the <u>next</u> stage of the analysis will include standardization for these factors, they do not hesitate to conclude, prior to the execution of these analyses, that there is a "now remote possibility that the positive findings were merely the result of the radiation exposures having associations with other cancer-related factors." One need only be reminded of the overwhelming impact of smoking on the incidence of lung cancer, for instance, as evidence for the inappropriateness, at least for now, of the stated conclusions.

ANALYSIS

General Comments

This analysis is being undertaken in an attempt to
replicate, in a manner of speaking, the efforts of
Mancuso, et al. We state again very emphatically however,
as we indicated in our examination of the paper, that the
design was inappropriate for a determination of the rela-
tionship between radiation exposure and disease.

It should also be recalled that we were not in
possession of denominators, which made it impossible to
rigorously establish the existence of an excess number of
deaths from any of the causes. We therefore relied entirely
on the data set as received from NCR, which contained the
following variables: age at death, years of hire and
departure, duration of employment, cause of death, race, sex,
exposure code, cumulative lifetime external radiation dose,
cumulative dose at 3, 5, 10, 15, 20 and 25 years prior to
death, and year of death. From these given variables we
determined year of birth, from which we further calculated
age at hire and age at departure; one must wonder why these
three variables were not originally provided.

While we mentioned above that we will attempt to
'replicate' the work of the investigators as presented in the
paper under examination, it should be pointed out here that
the data we received are not parallel to those used in the
paper, and we must wonder why. For instance, much is made of

the calendar year analysis, although we did not get doses for
specified calendar years; instead, we received cumulative doses
for specified (3-25) years prior to death, and 3 years prior
to death, for instance, rep esents different calendar years
for people who died in different years.

In addition, there are fully four tables in the paper
which utilize this 'years prior to death' analysis, and 15
categories of this variable are used in each of the tables.
We received values of this variable for 6 categories. It is
surprising that, of the 15 they used and the 6 we received,
only one coincides, which makes a replication of their
analysis impossible without extrapolating from the data at
hand, which is never as precise as the real thing. One must
wonder why the data have been presented to us in a non-
replicable manner.

Our reluctance to perform the analysis is thus far based
on both the inadequacy of the epidemiologic design and the
differences between the data received and those actually used
in the paper. In addition to these two factors, we performed
a rather cursory editing (internal consistency) check and
found, to our dismay, numerous definite and possible errors
which cast reasonable doubt on the accuracy of the information
and therefore on the question of whether the data merit
analysis.

Listed below are the inconsistencies and curiosities encountered, although it should be reiterated that we did not perform an extensive search for errors since we were laboring under the assumption that the data received were accurate, especially since we have no means for checking their accuracy. The list is therefore only partial and is limited to inconsistencies and illogicalities:

1. There were five individuals whose age at hire, according to our calculations as described above, was less than 17. The actual values were: -15, -11, -1, 2, and 3 years of age.

2. According to our calculations, there were 49 individuals whose age at hire was between 65 and 79 years, which seems highly unlikely, unless the retirement age was waived for those individuals because of the wartime manpower problems. Even allowing for a one year error in our calculations, there would still be a total of 32 people hired after the age of 65.

3. Along the same lines, we calculate that for 533 individuals, the age at departure was between 65 and 83; allowing for a one year error, the total would still be 370. While wartime expediency may explain some of these occurrences, it should be noted that, for instance, not all those whose age at hire was over 65 were hired during wartime years, and

also that working into one's mid-80's must be highly unusual under any circumstances.

4. Five individuals had 1900 listed as their year of hire; perhaps these are the same individuals whose age at hire was incorrect. In addition, there were 5 individuals with durations of employment exceeding 45 years, no doubt a function of the incorrect year of hire.

5. The most perplexing problem is the difference in the total number of workers on the file we received; our total was 3992 while Mancuso, et al. had 3520. While these investigators had 412 certified deaths among females, we had only 382. Adding both sexes would give a total of 3902, which means that an additional 90 deaths have appeared on our files. This cannot be explained even if blacks, who numbered 28, were handled separately by the original investigators.

From this superficial examination of the data, therefore, enough has been seen to at least provide grounds for questioning the accuracy of the data. Coupled with the concerns voiced earlier regarding the design and absence of denominators, the following analysis is being presented with serious reservations. In essence, we simply asked what a more appropriate analysis, given the data at hand, would reveal, although not much significance should be attached to the findings.

DATA ANALYSIS

Demographic Factors

Tables I-VI present the distributions for numerous varia-
bles of interest, from which the following points should be
noted:

1. Almost 70 percent of the workers included in this
   study were hired between ages 30 and 60. One must
   therefore be very concerned about the occupational
   histories of these individuals prior to employment
   at the Hanford Works, during which time other signifi-
   cant work exposures, in other industries, are likely
   to have occurred. The nature of these exposures is
   entirely unknown, at least to us, and the possible
   impact of these exposures on the health outcomes under
   investigation are not at all discussed in the paper
   under examination. In addition, over 61 percent of
   workers included in this study were hired between
   1943-1945, which of course were the war years, and
   given the added fact that approximately 15 percent
   of the workers were hired between the ages of 17 and 29,
   one must wonder whether these men were not drafted
   into the combat forces because of some health factor.
   If this occurred, we would have a sizeable proportion
   of workers who were 'unhealthy' in some rather serious
   way, a fact which may well have affected their causes

of death. We have therefore, if this reasoning is correct, a workforce which is less healthy, rather than being healthier, than the general population; this, of course, would be contrary to the general situation encountered in an occupational study, where workers, as a group, are healthier than the general population of comparable age.

2. Over 50 percent of the workers had a duration of employment which was less than two years. One must wonder whether this length of time, given the generally low doses to which they were exposed, is sufficient to justify their inclusion in the analysis. This is naturally related to cumulative dose, and over 80 percent of workers had lifetime doses under 100 centirads; the same question regarding inclusion of these workers in the study can be raised, especially since a one rad exposure is not uncommonly encountered in the use of diagnostic X-rays.

3. The table summarizing causes of death is an exact duplicate of the one presented in the paper, and the very same terminology was used for comparative purposes. It should be recalled that our total number of deaths did not match that of Mancuso, et al. and also that we did not separate the experiences of

males and females since there was no ready biological
justification for doing so. It will be especially
difficult for the reader to compare this table with
the one presented in the paper where the numbers of
deaths for the different causes were not presented
for females. In addition, one must wonder why the
authors did not report on mortality for breast cancer,
which the literature suggests may well be associated
with radiation exposure.

Radiation Associations

Table VII presents, in summary fashion, the characteris-
tics of workers dying from those causes for which Mancuso,
et al. claimed significant radiation associations: cancers of
the lymphatic and hematopoietic tissues, and cancers of the
large intestine, pancreas, lung, kidney, and brain.
Examination of the first and last rows of this table, which
compare all non-neoplasms with all malignant neoplasms,
immediately reveals that the characteristics of individuals
in the two groups are remarkably similar. Those dying of
malignant neoplasms, however, had a slightly longer duration
of employment which no doubt was at least partly, and
probably entirely, responsible for the difference in lifetime
dose.

The point should be made here, and this point is as
important as any made in this paper, that a comparison of the
means and medians for duration of employment, cumulative

lifetime dose, and intensity of exposure immediately reveals, because of the substantial difference in the two, that the mean is not a good measure of central tendency on account of the skewness of the distribution. This then provides additional support for the contention that means should not have been used as the main measure of effect - in the best of circumstances, they are simply not a measure of effect, while in this instance they are quite misleading as well because of the presence of a few outliers which heavily weight the mean, and because of the high proportion of unexposed individuals in every group.

Further perusal of Table VII reveals that the characteristics of workers dying from select cancers are rather similar to those of workers dying from non-malignancies, with some differences in duration of employment and hence lifetime dose. It should be noted here that the numbers of people dying from select cancers ranged from 24 to 203, while the non-neoplasm and total malignant neoplasm groups numbered 3177 and 803, respectively, resulting in much more stable estimates for the latter groups. This is a constant problem in these comparisons, and while a statistical test for differences in means would incorporate sample size in its assignment of a p-value, we are clearly against the use of means as a measure of effect.

While we do not wish to spend too much time on this table, it would be profitable to examine closely the characteristics of the 24 individuals who died from multiple myeloma and

myeloid leukemia (ICD 203,205). While the means for duration of employment, lifetime dose, and intensity of exposure all appear to be high, the medians reveal quite a different story - the medians for each of these three variables were the lowest of all causes, including non-malignancies, presented in the table.

Table VII presented the data from the perspective of the outcome (cause of death), while Table VIII examines the data from the exposure perspective. The characteristics of four categories (unexposed, low, moderate, and high exposure) are presented. Once again, we are struck with the similarities in the values of the parameters, except of course for duration and cumulative dose, which are a direct function of the definition of the four categories. Perhaps the most interesting comparison is presented at the bottom of the table, where the proportions dying from all cancers and from lymphatic and hematopoietic cancers in each of the four groups are compared. Again, these proportions are strikingly similar. The chi-square test was performed on these proportions, and the results, as presented in Table IX, indicate that there is no significant association between dose and cause of death.

We will make a general comment here, which would be obvious from a careful examination of the tables, that we have consistently eliminated from the non-cancer group those individuals whos cause of death was listed as a benign neoplasm (ICD 210-239), and for this reason, the totals often fall 11 short of 3992, and these deaths have been effectively eliminated from most of the analyses.

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Finally, for each of the cancers which Mancuso, et al. claimed were associated with radiation exposure, we calculated odds ratios and confidence intervals for different definitions of exposure and non-exposure; that is, different definitions for non-exposure were tried, ranging from zero to anything less than 1000 centirads. The totals for each stratum within any table are therefore constant. By altering the definition of non-exposure (and hence exposure) we were, in essence, giving those with high exposures a chance to have an impact on the odds ratios, but examination of the findings in Tables X - XVII consistently reveals non-significantly elevated odds ratios for these different sites and definitions of exposure.

It should be noted here that we have used the 95 percent test-based confidence interval, defined as the $OR^{(1 \pm \mathcal{B}/x)}$, where $\mathcal{B} = 1.96$. While many of the point estimates of the odds ratios are slightly elevated, one concludes that the OR is not significantly high if the confidence interval includes unity (1), which it does in almost every instance.

Indeed, only for lung cancer were some of the odds ratios significantly elevated, but of all sites examined, we can put least faith in a possible association between radiation and lung cancer in the absence of availability of smoking histories, because smoking prevalence is generally higher among blue collar workers and approximately 80 percent of all lung cancers are attributable to prior smoking histories.

In summary then, analysis of the data as received does not indicate any association between cause of death and radiation exposure. To fully resolve this issue, however, a rigorously designed and executed epidemiologic investigation is necessary.

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Table I

Distribution for Age at Hire

Age at Hire	Number	Percent
<17*	5	0.1
17-19	43	1.1
20-29	526	13.2
30-39	973	24.4
40-49	1211	30.3
50-59	999	25.0
60-64	184	4.6
65+	51	1.3
TOTAL	3992	100.0

*According to our calculations (Age at Hire=(Year of Hire + 1900) - Year of Birth, where Year of Hire on the file is the last two digits only.

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Table II

Distribution of Age at Death

Age	Number	Percent
< 40	311	7.8
40-49	587	14.7
50-59	990	24.8
60-69	1130	28.3
70-79	766	19.2
80+	208	5.2
TOTAL	3992	100.0

Table III

Distribution of Duration of Employment

Duration (in years)	Number	Percent
< 1	1012	25.4
1-2	1060	26.5
3-7	723	18.1
8-11	419	10.5
12+	778	19.5
TOTAL	3992	100.0

Table IV

Race and Sex Characteristics

Race	Number	Percent
White	3964	99.3
Black	28	0.7
TOTAL	3992	100.0

Sex	Number	Percent
Male	3610	90.4
Female	382	9.6
TOTAL	3992	100.0

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Table V

Causes of Death

Cause (with ICD 8th Rev.)	Number	Percent
1. NON-CANCERS		
Infective (000-136)	37	0.9
Benign Neoplasms (210-239)	12	0.3
Endocrine & Blood (240-289)	75	1.9
CNS (290-389)	45	1.1
CVS (390-458)	2022	50.6
Respiratory (460-519)	207	5.2
Digestive (520-577)	164	4.1
Accidents (800-999)	515	12.9
Residue	112	2.8
SUBTOTAL	3189	79.9
2. RES Neoplasms		
Lymphomas (200-202)	39	1.0
Lymphatic Leukemia (204)	5	0.1
Myelomas (203)	11	0.2
Myeloid Leukemia (205)	13	0.3
Residue (206-209)	8	0.2
SUBTOTAL	76	1.9
3. SOLID TUMORS		
Mouth & Pharyngeal (140-149)	23	0.6
Stomach (151)	39	1.0
Large Intestine (153)	79	2.0
Rectum (154)	23	0.6
Other Intestinal (150,152)	20	0.5
Liver & Gallbladder (155-156)	20	0.5
Pancreas (157)	53	1.3
Lung (162-163)	203	5.1
Prostate (185)	43	1.1
Kidney (189)	25	6.3
Other GU (186-188)	15	0.4
Brain (191)	23	0.6
Residue	161	4.0
SUBTOTAL	727	18.2
TOTAL	3992	100.0

Table VI

Percentages for Cumulative External
Lifetime Radiation Dose

Dose*	Percentage
0	41.0
1-22	19.0
23-84	20.0
85-174	10.0
175-385	5.0
386-807	2.5
808-1781	1.5
1782-4421	1.0

*in centirads

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Table VII

Summary Table of the Characteristics of Workers with Select Causes of Death

Cause of Death	N	Age at Death		Age at Hire		Duration of Employment		Percent Unexposed
		Mean	Median	Mean	Median	Mean	Median	
All Non-Neoplasms (ICD ≠ 140-239)	3177	60	61	43	44	5.5	1.9	41
Lym. + Hemat Neos (ICD 200-209)	76	55	56	38	37	5.5	1.9	37
Mult Myel + My. Leuk (ICD 203, 205)	24	53	51	38	37	6.7	1.5	42
Neos Lg Int (ICD 153)	79	58	59	41	42	7.3	5.6	32
Neos of Pancreas (ICD 157)	53	60	60	43	45	6.1	2.0	38
Neos of Lung (ICD 162, 163)	203	61	61	42	42	6.7	3.3	35
Neos of Kidney (ICD 189)	24	59	59	43	43	6.2	2.3	30
Neos of Brain (ICD 191)	23	54	55	35	33	8.7	5.1	35
ALL MALIG NEOS (ICD 140-209)	803	59	60	42	42	6.1	2.8	40

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Table VII (contd.)

Summary Table of the Characteristics of Workers with Select Causes of Death

Cause of Death	N	Year of Hire		Lifetime Dose		Intensity of Exposure*	
		Mean	Median	Mean	Median	Mean	Median
All Non-Neoplasms (ICD ≠ 140-239)	3177	1946	1945	95	7.2	20.8	2.5
Lym. + Hemat Neos (ICD 200-209)	76	1947	1945	186	15.5	22.5	2.5
Mult Myel + My. Leuk (ICD 203, 205)	24	1946	1945	411	3.5	26.1	1.6
Neos Lg Int (ICD 153)	79	1946	1945	115	25.0	13.4	3.5
Neos of Pancreas (ICD 157)	53	1946	1944	244	12.0	27.1	3.3
Neos of Lung (ICD 162, 163	203	1947	1945	135	24.0	20.2	3.6
Neos of Kidney (ICD 189)	24	1946	1945	168	11.5	17.9	3.9
Neos of Brain (ICD 191)	23	1946	1945	179	36.0	22.3	3.3
ALL MALIG NEOS (ICD 140-209)	803	1946	1945	115	11.9	17.0	2.9

*Intensity = Mean per annum exposure (Lifetime Dose ÷ Duration of Employment)

Table VIII

Characteristics of Four Groups with Different Cumulative External Radiation Doses

Cumulative Lifetime External Radiation Dose (in centirads)

	0 (N=1638)		1-24 (N=775)		25-84 (N=778)		85+ (N=801)	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Age at Hire	43	45	44	45	43	45	40	40
Year of Hire	1946	1944	1947	1945	1946	1944	1947	1945
Year of Departure	1948	1946	1951	1950	1954	1953	1960	1961
Duration of Employment	1.9	0.4	3.9	2.4	7.5	6.9	12.9	13.3
Cumulative Dose	0	0	9.8	8.7	49	46	435	177
Year of Death	1962	1963	1963	1964	1963	1964	1966	1968
Age at Death	59	60	60	61	61	62	59	60
Year of Birth	1902	1902	1903	1901	1902	1901	1907	1907

Cumulative Dose

Proportions Dying From All Cancers (ICD 140-209) and From Lymph. and Hemat. Cancers (ICD 200-209)

0		1-24		25-84		85+	
ICD 140-209	ICD 200-209	ICD 140-209	ICD 200-209	ICD 140-209	ICD 200-209	ICD 140-209	ICD 200-209
N Percent	N Percent	N Percent	N Percent	N Percent	N Percent	N Percent	N Percent
327 20.0	28 1.7	138 17.8	15 1.9	169 21.7	16 2.0	180 22.5	17 2.1

Table IX

Chi-Square Tests for Association between Select Causes of Death
and Cumulative Lifetime External Radiation Doses

1. Cause = all Cancers (ICD 140-209) vs. Non-Cancers (ICD≠ 140-239)

	0	1-24	25-84	85+	Total
			DOSE		
Cancer	320	135	169	179	803
Non-Cancer	1311	637	609	621	3178
TOTAL	1631	772	778	800	3981

$x^2 = 7.32$ - there is therefore no significant association between Dose and Cause of Death $(x^2_{3,.05} = 7.81)$

2. Cause = Neoplasms of Lymph and Hemato Sys (ICD 200-209) vs
Non-Cancers (ICD≠ 140-239)

	0	1-24	25-84	85+	Total
			DOSE		
Cancer	28	15	16	17	76
Non-Cancer	1311	637	609	621	3178
TOTAL	1339	652	625	638	3254

$x^2 = 0.795$ - there is therefore no significant association between Dose and Cause of Death $(x^2_{3,.05} = 7.81)$

Table X

Odds Ratios (OR) and Tests of Significance for the Relationship
between Varying Levels of Exposure and Disease:
Cases = All Cancers (ICD=140-209) and
Controls = All Causes other than
Benign or Malignant Neoplasms
(ICD≠140-239)

1. Exposure ≥ 1 centirad

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	483	320			
			1.06	0.53	C.91-1.23
CONTROLS	1866	1311			

2. Exposure ≥ 100 centirads; all others unexposed

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	158	645			
			1.19	2.95	0.97-1.27
CONTROLS	543	2634			

3. Exposure ≥ 500 centirads; all others unexposed

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	41	762			
			1.32	2.33	0.92-1.89
CONTROLS	124	3053			

4. Exposure ≥ 1000 centirads; all others unexposed

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	21	782			
			1.31	1.10	0.79-2.17
CONTROLS	64	3113			

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Table XI

Odds Ratios (OR) and Tests of Significance for the Relationship
between Varying Levels of Exposure and Disease:
Cases = Neoplasms of Lymphatic and Hematopoietic Tissue (ICD=200-209) and
Controls = All Causes other than Benign or Malignant Neoplasms (ICD≠140-239)

1. **Exposure > 1 centirad**

	EXP	$\overline{EXP}$	OR	x^2	CONF INT
CASES	48	28			
			1.20	0.60	0.76-1.90
CONTROLS	1866	1311			

2. **Exposure ≥ 100 centirads; all others unexposed**

	EXP	$\overline{EXP}$	OR	x^2	CONF INT
CASES	16	60			
			1.30	0.82	0.74-2.28
CONTROLS	543	2634			

3. **Exposure > 500 centirads; all others unexposed**

	EXP	$\overline{EXP}$	OR	x^2	CONF INT
CASES	6	70			
			2.11	3.08	0.92-4.86
CONTROLS	124	3053			

4. **Exposure ≥ 1000 centirads; all others unexposed**

	EXP	$\overline{EXP}$	OR	x^2	CONF INT
CASES	4	72			
			2.70	3.82	0.39-1..7
CONTROLS	64	3113			

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Table XII

Odds Ratios (OR) and Tests of Significance for the Relationship
between Varying Levels of Exposure and Disease:
Cases = Multiple Myeloma and Myeloid Leukemia (ICD=203,205) and
Controls = All Causes other than Benign or Malignant Neoplasms (ICD≠140-239)

1. Exposure ≥ 1 centirad

	EXP	$\overline{EXP}$	OR	x^2	CONF INT
CASES	14	10			
			0.98	<0.001	upper bound <1
CONTROLS	1866	1311			

2. Exposure ≥ 120 centirads; all others unexposed

	EXP	$\overline{EXP}$	OR	x^2	CONF INT
CASES	4	20			
			1.19	0.10	0.40-3.57
CONTROLS	457	2720			

3. No further calculations since numbers are too small

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Table XIII

Odds Ratios (OR) and Tests of Significance for the Relationship
between Varying Levels of Exposure and Disease:
Cases = Cancer of Large Intestine (ICD 153) and
Controls = All Causes other than Benign or
Malignant Neoplasms (ICD≠140-239)

1. Exposure > 1 centirad

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	54	25			
			1.51	2.94	0.94-2.41
CONTROLS	1866	1311			

2. Exposure > 100 centirads; all others unexposed

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	17	62			
			1.33	1.06	0.77-2.28
CONTROLS	543	2634			

3. No further calculations since numbers are too small

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Table XIV

Odds Ratios (OR) and Tests of Significance for the Relationship
between Varying Levels of Exposure and Disease:
Cases = Pancreatic Cancer (ICD 157) and
Controls = All Causes other than Benign or
Malignant Neoplasms (ICD≠140-239)

1. <u>Exposure ≥ 1 centirad</u>

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	33	20			
			1.15	0.27	0.68-1.94
CONTROLS	1866	1311			

2. <u>Exposure ≥ 100 centirads; all others unexposed</u>

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	13	40			
			1.58	2.02	0.84-2.97
CONTROLS	543	2634			

3. No further calculations since numbers are too small

Table XV

Odds Ratios (OR) and Tests of Significance for the Relationship
between Varying Levels of Exposure and Disease:
Cases = All Lung Cancers (ICD=162,163) and
Controls = All Causes other than Benign or
Malignant Neoplasms (ICD≠140-239)

1. Exposure ≥ 1 centirad

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	132	71			
			1.31	3.28	0.91-1.23
CONTROLS	1866	1311			

2. Exposure ≥ 100 centirads; all others unexposed

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	51	152			
			1.63	8.49	1.17-2.26
CONTROLS	543	2634			

3. Exposure ≥ 500 centirads; all others unexposed

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	15	188			
			1.96	5.88	1.13-3.38
CONTROLS	124	3053			

4. Exposure ≥ 1000 centirads; all others unexposed

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	5	198			
			1.23	0.44	0.48-3.09
CONTROLS	64	3113			

Table XVI

Odds Ratios (OR) and Tests of Significance for the Relationship
between Varying Levels of Exposure and Disease:
Cases = Kidney Cancer (ICD 189) and
Controls = All Causes other than Benign or
Malignant Neoplasms (ICD$\neq$140-239)

1. **Exposure $\geq$ 1 centirad**

	EXP	$\overline{EXP}$	OR	x^2	CONF INT
CASES	17	7			
			1.71	1.44	0.71-4.10
CONTROLS	1866	1311			

2. **Exposure $\geq$ 100 centirads; all others unexposed**

	EXP	$\overline{EXP}$	OR	x^2	CONF INT
CASES	4	20			
			0.97	0.003	0.35-2.62
CONTROLS	543	2634			

3. No further calculations since numbers are too small

Table XVII

Odds Ratio (OR) and Tests of Significance for the Relationship
between Varying Levels of Exposure and Disease:
Cases = Brain Cancers (ICD 191) and
Controls = All Causes other than Benign or Malignant
Neoplasms (ICD≠140-239)

1. **Exposure ≥ 1 centirad**

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	15	8			
			1.32	0.40	0.56-3.13
CONTROLS	1866	1311			

2. **Exposure ≥ 100 centirads; all others unexposed**

	EXP	$\overline{EXP}$	OR	χ^2	CONF INT
CASES	7	16			
			2.12	2.86	0.89-5.07
CONTROLS	543	2634			

3. No further calculations since numbers are too small

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APPENDIX

Report being Evaluated

(copy follows)

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RADIATION EXPOSURES OF HANFORD WORKERS DYING FROM CANCER AND OTHER CAUSES*

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Abstract—Data from the Hanford study have shown that sensitivity to the cancer-induction effects of radiation is at a low ebb between 25 and 45 yr of age. Nevertheless, at younger and older ages there is probably a cancer hazard associated with low level radiation which affects bone marrow cancers more than other neoplasms and cancers of the pancreas and lung more than other solid tumors.

INTRODUCTION

HANFORD Works in Richland, Washington is one of the largest atomic plants in the United States, and most of the staff are in some way concerned with the manufacture of radioactive substances. For these workers, who are predominantly white males, there is systematic recording of data under the following headings as part of a study of the lifetime health and mortality experience of employees of ERDA contractors (Ma71):

(1) Sex, date of birth, date of hire and social security number.

(2) Dates of entering and leaving specified occupations.

(3) External and internal radiation.

(4) Date and cause of death.

The wearing of radiation badges in all workshops and laboratories is obligatory, and the badges are read at frequent intervals to ensure that no worker ever receives more than the maximal permissible dose of 5 rems/yr (BRPC71). In several high risk occupations the workers are also examined (at regular intervals and following accidents or radiation "leaks") for internal depositions of radioactive substances. Therefore, there are both records of the total amount of external penetrating radiation received by each worker by the end of each calendar year (annual

doses in centirads) and similar records relating to intakes of radioactive materials (positive urine analyses or internal radiation).

Deaths of Hanford employees are identified through death benefit claims by a nationwide system of social security numbers. These numbers probably provide better identification of males than females but the method of death identification has two major advantages: intervals between discharge and death may be of long duration and there is coverage of all deaths in any U.S. state or territory. Finally, certified causes of death are taken direct from death certificates, copies of which are obtained from official sources and filed with the other records.

Radiation monitoring has been in operation since 1943 and sufficient time has now elapsed for most of the non-survivors to be men who died 10 or more years after leaving the industry. Therefore, from the records of men with certified causes of death we should be able to discover whether NCRP recommendations for protection of radiation workers (BRPC71)—which are strictly enforced by all ERDA contractors—have succeeded in eliminating the cancer hazard or, failing that, are keeping the risk within reasonable bounds. As a first approach to this problem we have examined the records of workers who died within 29 yr of Hanford Works going into full production (1944).

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PRELIMINARY FINDINGS

Death benefit claims on behalf of men who died before 1973 totalled 3710 and included 3520 certified deaths for the period 1944–1972 (Table 1). Compared with the much larger number of survivors from the same work force, these deaths were strongly biased in favor of the first and largest work cohort. Among the men who were hired during 1944 were some workers who, strictly speaking, were not members of the monitored population (e.g. construction workers). Nevertheless, these men ha' always been so regarded (Ma74), since, in the early records, there is difficulty in distinguishing between workers in monitored occupations who never received any radiation (non-exposed workers) and workers who were not obliged to wear radiation badges (non-monitored occupations).

The high proportion of non-exposed workers in the 1944 cohort and the relatively low doses recorded before 1954 and by men with short periods of employment (Tables 5 and 6), are reasons why we would expect non-survivors to have lower radiation doses than survivors. This has been a constant feature of earlier analyses of Hanford data (Ma74) and will be mentioned again after we have completed the analysis of certified deaths (see discussion). Meanwhile, it should be noted that division of the certified deaths into cancers (670 cases) and non-cancers (2850 cases) left both groups with the same proportions of men hired in 1944 (48%) and men hired later than 1948 (16%).

In spite of their cohort resemblances the two groups of certified deaths had dissimilar radiation records, also ones which showed that men who eventually developed fatal cancers had been more often and more intensively exposed to external radiation than men with other causes of death (Table 2). Thus the proportion of exposed workers (or men who had one or more positive badge readings) was 66% for cancers and 61% for non-cancers, and for these workers the mean cumulative radiation dose was higher for the cancers (210 centirads) than for the non-cancers (162). Therefore, the "all-worker dose" was appreciably higher for cancers (138) than non-cancers (99).

A classification of the deaths by ICD Nos. showed that for none of the Main Orders of non-malignant diseases was the level of radiation dose higher than the level for all cancers (Table .). But within the group of malignant diseases there was wide variation in the dose level. Also higher doses for RES neoplasms (ICD Nos. 200–209) than solid tumors (ICD Nos. 149–199), and exceptionally high doses for a small group of bone marrow cancers (ICD Nos. 203 and 205). For example, the "all-worker" dose averaged 94 for accidents, 105 for cardiovascular diseases, 114 for digestive diseases, 130 for solid tumors, 219 for RES neoplasms and 449 for bone marrow cancers. Other malignant dis-

Table 2. External radiation records for two groups of non-survivors: cancers and non-cancers

Non-survivors	Cases (Nos.)	Exposed* workers (Nos.)	Cumulative radiation dose (centirads)	Exposed workers %	Mean radiation dose in centirads A	B
Cancers	670	442	92657	66.0	210	138
Non-cancers	2850	1742	282961	61.1	162	99
All certified deaths	3520	2184	375618	62.0	172	107

*Men with one or more positive badge readings.
†A = Mean cumulative radiation dose for exposed workers.
B = Mean cumulative radiation dose for all workers.

Table 1. Hanford workers: survivors and non-survivors from 1944 to 1971 work cohorts

Cohort*	% Survivors*	% Non-survivors* Uncertified deaths	Cancers	Non-cancers	Totals Nos.	Early discharges*
1944	16.4	41.3	48.7	47.8	1256	49.4
1945	4.7	14.7	12.5	14.5	1524	42.7
1946	2.3	2.0	2.1	3.1	597	19.9
1947	10.3	11.3	12.5	11.0	2615	14.5
1948	7.8	10.7	8.2	7.5	1927	48.6
1949–71	58.5	20.0	16.0	16.1	13,020	52.3
Total Nos.	21,206	213	670	2850	24,939	9410
Total %	85.0	0.9	2.7	11.4	100.0	37.7

*Cohort = year of hire.
Survivors = alive in 1973.
Non-survivors = pre-1973 deaths.
Early discharges = men discharged during the calendar year of hire or the following year.

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Table 3. External radiation records for stated causes of certified deaths

Certified causes of death (ICD Nos.)	Totals (Nos.)	Exposed workers* (Nos.)	Cumulative radiation dose (centirads)	Exposed workers* (%)	Mean R dose (centirads*)	
					(A)	(B)
Non-cancers:						
Infective (000–136)	29	16	1258	55.2	79	43
Benign neoplasms (210–39)	10	4	155	40.0	39	15
Endocr. & blood (244–89)	54	34	5199	63.0	153	96
C.N.S. (290–389)†	36	20	3389	55.6	169	94
C.V.S. (390–458)‡	1837	1149	191,987	62.5	167	105
Respiratory (460–519)	194	108	14,330	55.7	133	74
Digestive (520–577)	139	83	15,807	59.7	190	114
Accidents (800–999)	450	271	42,244	60.2	156	94
Residue (580–796)	101	57	8592	56.4	151	85
RES neoplasms:						
Lymphomas (200–2)	34	28	4049	82.4	145	119
Lymphatic Lk (204)	3	2	57	66.7	29	19
Myelomas (203)	11	8	8530	72.7	1066	775
Myeloid leukemia (205)	11	6	1337	54.5	223	122
Residue (206–9)	5	3	58	60.0	19	12
Solid tumors:						
Mouth & pharynx (140–9)	24	14	2134	58.3	152	89
Stomach (151)	38	26	2227	68.4	86	60
Large intestine (153)	61	48	8222	78.7	171	135
Rectum (154)	19	16	1887	84.2	118	99
Other intestinal (150; 152)	18	10	581	55.6	58	32
Liver & gail bl. (155–6)	18	10	557	55.6	56	31
Pancreas (157)	49	31	12,377	63.3	399	253
Lung (162–3)	192	130	32,384	67.7	249	169
Prostate (185)	43	21	1817	48.8	87	42
Kidney (189)	21	14	3935	66.7	281	187
Other G.U. (186–8)	15	10	1225	66.7	123	82
Brain (191)	18	11	3967	61.1	361	220
Residue	90	54	7313	60.0	135	81
Totals:						
Non-cancers	2850	1742	282,961	61.1	162	99
RES neoplasms	64	47	14,031	73.4	299	219
Solid tumors	606	395	78,826	65.2	199	130

*See footnotes to Table 2.
†C.N.S. = Neurological diseases.
‡C.V.S. = Cardiovascular diseases.

eases with high radiation doses were cancers of the pancreas (253), brain (220), kidney (187), lung (169) and large intestine (135).

In Table 4, the various neoplasms are listed in accordance with the all-worker dose and the number of cases in each diagnostic category is compared with an expected number which shows how the same diseases were distributed among the 1960 cancer deaths of U.S. white males (Bu71). For 8 neoplasms, the radiation dose was higher than the level for all certified deaths (107 centirads) and for 9 the dose was below this level. For the group with above average doses, the observed and expected numbers were 397 and 318 (ratio 1.25), and for the other group they were 273 and 352 (ratio 0.78).

Controlled analyses

The preliminary findings were compatible with a causal association between the radiation exposures and some of the cancer deaths. Therefore comparisons between the two main groups of certified deaths (cancers and non-cancers) were continued in analyses which controlled separately for five possible sources of false impressions, namely:

(1) Calendar year of the exposures.
(2) Employment year of the exposures.
(3) Pre-death year of the exposures.
(4) Exposure age or age at the end of each badge-reading year.
(5) Death age.

Calendar years (Table 5 and Fig. 1)

The calendar year classification showed that: (i) the proportion of exposed workers was higher during the first half of the study period than the second half, but the opposite was true of the annual radiation doses of exposed workers (AREW doses in centirads) and (ii) only during the high dose period were differences between cancers and non-cancers at all pronounced.

Each year the proportion of exposed workers remained a fraction higher for cancers than non-cancers (Fig. 1). However, from

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Table 4. *Observed and expected numbers of specific neoplasms listed according to mean cumulative dose of external radiation*

No. Neoplasms*	Mean cumulative radiation dose (centirads)	No. of deaths† Observed	No. of deaths† 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	80	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	63.0	0.59
Nos. 1-8	188‡	397	318.2	1.25
9-18	65	273	351.8	0.78
All cancers	138‡	670	670.0	1.00

*See Table 3

†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
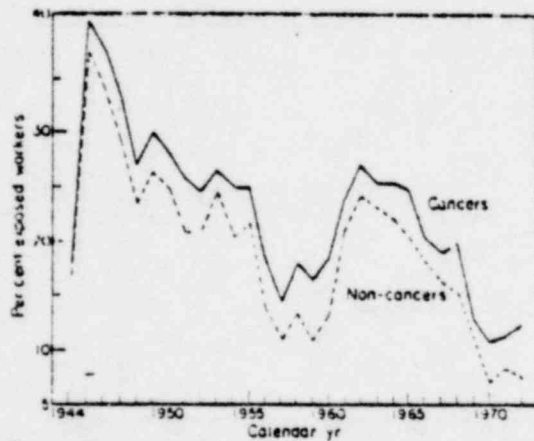
FIG. 1. Per cent of exposed workers by calendar years cancer and non-cancer deaths of males.
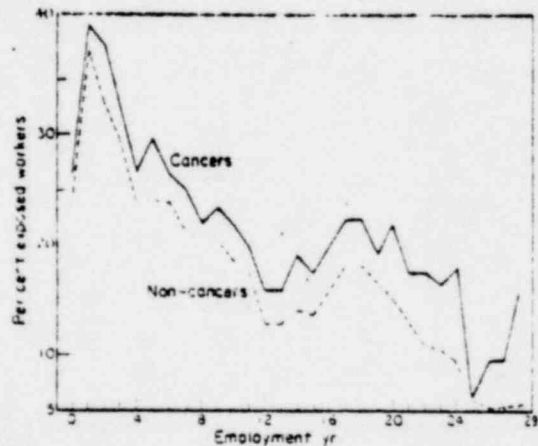
FIG. 2. Per cent of exposed workers by employment years cancer and non-cancer deaths of males.

1944 to 1957 (when AREW doses averaged 14.9 for cancers and 18.7 for non-cancers), there were equal numbers of years with above average doses for the two causes of death (high risk years); and from 1958 to 1972 (when AREW doses averaged 51.3 for cancers and 47.7 for non-cancers), there were more high risk years for cancers (11) than non-cancers (4) (Table 5).

Employment years (Table 6 and Fig. 2)

The employment year classification showed that: (i) the proportion of exposed workers decreased with progressive lengthening of the interval between hire and exposure but the trend for AREW doses was in the opposite direction, and (ii) only during the high dose period were differences between cancers and non-cancers at all pronounced.

Each year the proportion of exposed workers remained a fraction higher for cancers than non-cancers (Fig. 2). However, when intervals from hire to exposure were shorter than 10 yr (and AREW doses averaged 21.5 for cancers and 21.1 for non-cancers), there

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Table 5. Mean annual radiation doses for exposed workers (cancer and non-cancers) (calendar years)

Calendar years	Exposed workers*		Radiation doses†		High risk years‡	
	Cancers	Non-cancers	Cancers	Non-cancers	Cancers	Non-cancers
1944–45	237	901	26.5	26.0	2	—
1946–47	333	1258	11.9	13.2	—	—
1948–49	325	1169	12.6	8.4	1	1
1950–51	311	1101	12.4	12.8	—	2
1952–53	302	1119	22.2	20.2	2	—
1954–55	288	1007	23.4	23.1	2	—
1956–57	185	568	40.8	41.6	—	2
1958–59	183	524	53.6	51.7	2	—
1960–61	203	661	53.0	47.8	2	—
1962–63	227	799	47.4	43.2	2	—
1964–65	184	599	63.1	59.6	1	1
1966–67	120	390	44.1	46.6	1	1
1968–69	75	213	39.0	43.1	1	1
1970–72	32	76	42.8	19.4	2	1
Total	3005	10,385	30.6	27.8	18	11
1944–57	1981	7133	19.9	18.7	7	7
1958–72	1024	3252	51.3	47.7	11	4

*Number of workers with positive badge readings in each year.
†Mean annual radiation doses of exposed workers in centirads (AREW doses).
‡Number of years with higher doses for cancers than non-cancers or vice versa.
Note there are small differences in the totals for Tables 5–8 which are due to the time units being measured to the nearest whole year.

Table 6. Mean annual radiation doses for exposed workers (cancers and non-cancers) (employment years)

Employed years	Exposed workers*		Radiation doses*		High risk years*	
	Cancers	Non-cancers	Cancers	Non-cancers	Cancers	Non-cancers
0–1	463	1786	21.8	23.1	—	2
2–3	475	1747	15.6	16.8	—	2
4–5	368	1294	18.3	17.2	2	—
6–7	171	1162	24.5	22.7	1	1
8–9	273	985	34.4	28.1	2	—
10–11	232	811	41.9	33.1	2	—
12–13	164	528	47.5	44.4	1	1
14–15	171	521	54.9	47.8	2	—
16–17	171	543	47.2	45.6	1	1
18–19	144	461	46.5	43.1	1	1
20–21	103	294	53.3	52.4	1	—
22–23	73	160	40.3	37.0	2	—
24–25	35	74	27.0	21.7	2	—
26–29	14	22	14.4	16.1	—	2
Total	3007	10,386	30.1	27.8	18	11
Under 10 yr	1900	6974	21.5	21.1	5	5
Over 10 yr	1107	3412	46.3	41.7	13	6

*See footnotes to Table 5

were equal numbers of high risk years for the two causes of death. When intervals from hire to exposure were longer than 10 yr (and AREW doses averaged 46.3 for cancers and 41.7 for non-cancers), there were twice as many high risk years for cancers (13) as non-cancers (6).

Pre-death years (Table 7 and Fig. 3)

The pre-death year classification showed that: (i) the proportion of exposed workers decreased with progressive shortening of the pre-death period, but the trend for AREW doses was in the opposite direction and (ii) in the middle of the time scale, the radiation doses were consistently higher for cancers than non-cancers but towards the beginning and end of the range, the radiation doses

were frequently lower for ca[...] than non-cancers.

Each year the proportion o[...] [...]sed workers remained a fraction highe. [...] or cancers than non-cancers (Fig. 3). However, when the interval between exposure and death was less than 8 or more than 20 yr (and AREW doses averaged 30.1 for cancers and 30.6 for non-cancers), there were over twice as many high risk years for non-cancers (12) as cancers (5). Between these extremes (when AREW doses averaged 31.0 for cancers and 25.1 for non-cancers), there was an unbroken series of high risk years for cancers (Table 7).

Exposure age (Table 8 and Fig. 4)

The exposure age analysis, which was restricted to men between 20 and 65 yr and to

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Table 7. Mean annual radiation doses for exposed workers (cancers and non-cancers)

Pre-death years†	Exposed workers* Cancers	Exposed workers* Non-cancers	Radiation doses* Cancers	Radiation doses* Non-cancers	High risk years* Cancers	High risk years* Non-cancers
0–1	156	675	29.6	25.8	1	1
2–3	241	854	41.8	15.4	2	—
4–5	273	974	39.8	42.4	1	1
6–7	305	1015	37.1	39.1	—	2
8–9	310	1022	34.8	32.7	2	—
10–11	283	933	33.4	28.2	2	—
12–13	242	848	35.1	25.4	2	—
14–15	257	661	29.0	22.2	2	—
16–17	239	661	27.3	21.3	2	—
18–19	210	724	21.4	18.2	2	—
20–21	186	592	12.9	14.2	—	2
22–23	143	481	14.9	15.4	—	2
24–25	111	353	18.2	16.9	1	1
26–28	96	172	15.7	23.5	—	3
Total	3012	10,388	30.6	27.8	17	12
8–19 yr	1541	5271	31.0	25.1	12	—
Other yr	1471	5117	30.1	30.6	5	12

*See footnotes to Table 5.
†Interval between exposure and death (in yr).

Table 8. Mean annual radiation doses for exposed workers (cancers and non-cancers)

Exposure age in years†	Exposed workers* Cancers	Exposed workers* Non-cancers	Radiation doses* Cancers	Radiation doses* Non-cancers	High risk years* Cancers	High risk years* Non-cancers
20–22	11	22	25.2	33.8	2	1
23–25	21	99	11.4	21.4	1	2
26–28	55	172	25.9	23.9	1	2
29–31	93	272	22.3	30.0	—	1
32–34	111	419	14.4	30.9	—	3
35–37	150	536	19.7	23.8	2	2
38–40	160	509	20.9	21.3	2	1
41–43	224	665	25.8	24.9	2	1
44–46	233	744	28.9	26.4	2	—
47–49	253	777	37.6	31.9	3	—
50–52	231	876	33.7	30.7	3	—
53–55	265	930	34.3	26.0	3	—
56–58	235	863	30.7	25.3	2	1
59–61	196	708	28.4	24.5	3	—
62–64	160	527	34.5	24.2	3	—
Total	2448	8219	28.9	26.5	28	17
Under 35 yr	291	984	18.4	28.4	4	11
35–55 yr	1566	5137	30.0	26.8	16	5
Over 55 yr	591	2098	31.0	24.3	8	1

*See footnotes to Table 5.
†Excluding exposures before 20 yr of age, or after 65 yr, or within 5 yr of death.
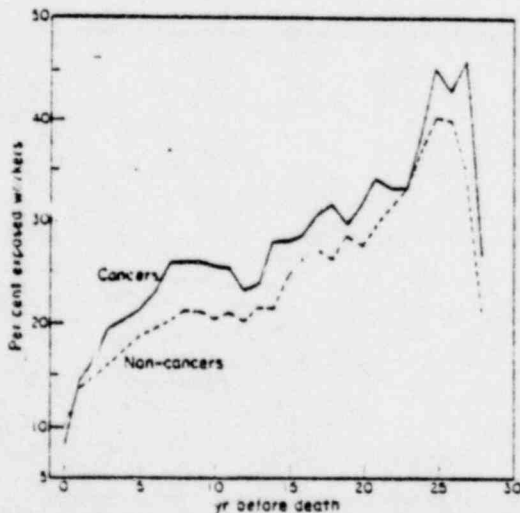

FIG. 3. Per cent of exposed workers by years before death cancer and non-cancers deaths of males.
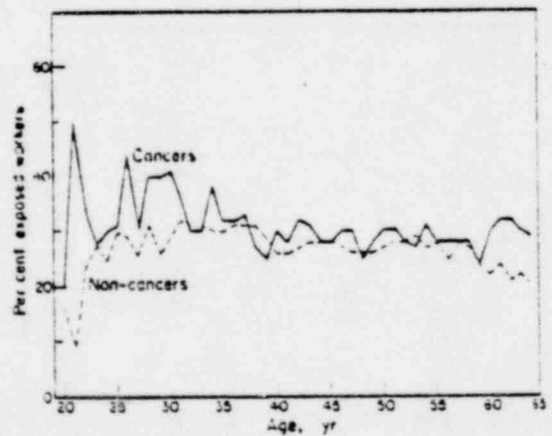

FIG. 4. Per cent of exposed workers by exposure age (excluding exposures within 5 yr of death).

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exposures more than 5 yr before death, showed that: (i) the proportion of exposed workers was virtually independent of age (Fig. 4) and (ii) only after 40 yr were the radiation doses noticeably higher for cancers than non-cancers.

From 20 to 35 yr of age, there were more than twice as many high risk years for non-cancers (11) as cancers (4) and AREW doses were also higher for non-cancers (28.4) than cancers (18.4). However, for the group with initially high radiation doses there was a decrease with age (non-cancers) and for the group with initially low doses there was an increase with age (cancers). Therefore, by 40 yr the men who eventually developed fatal cancers were recording higher doses than the men with other causes of death. Thus, from 35 to 55 yr there were 16 high risk years for cancers and 5 for non-cancers, and from 56 to 65 yr the corresponding numbers were 8 and 1. In the younger of these two age groups the AREW doses were 30.0 for cancers and 26.8 for non-cancers, and in the older age group they were 31.0 and 24.3.

Age at death

With recurrent events as controlling factors (e.g. exposure years and exposure ages), there was no way whereby men who re-mained in the monitored population for short periods of time could contribute as much to the final results as men who remained for long periods and no way whereby the findings for each subgroup could be totally independent. However, with age at death as the controlling factor, there was no difficulty in obtaining strictly independent findings for any number of subgroups. Therefore, the analysis proceeded along new lines and was directed towards obtaining a stringent test of the null hypothesis of no correlation between the radiation dose and the proportion of cancer deaths after controlling for age at death (see Spearman's rank correlation coefficients in Table 11).

The basic data for this test were: (i) age at death for subgroups defined by cause of death (Table 9); (ii) radiation doses for subgroups defined by age and cause of death (Table 10); and (iii) cancers as a proportion of all certified deaths in groups defined by age at death and radiation dose (Table 11). Thus Table 9 shows that: (i) although accidents were often causes of early death, men who eventually developed malignant diseases did not have appreciably longer life spans than men with other causes of death and (ii) between two thirds and three quarters of all the deaths occurred between 50 and 80 yr of age.

Table 9. Age distributions of cancer and non-cancer deaths: stated causes of death (and I.C.D. Nos.)

Age at death in years	Cardiovascular (390-458) %	Respiratory; digestive (460-577) %	Accidents (800-999) %	Other non-malignant %	All non-cancers %	Cancers (140-209) %	All causes %
Under 40	2.6	5.1	50.0	12.6	8.0	3.7	7.2
40-49	11.9	12.3	27.3	11.7	14.4	12.8	14.1
50-59	25.3	20.7	21.6	27.0	24.4	27.9	25.0
60-69	29.0	32.5	16.2	23.9	26.9	35.7	28.6
70-79	23.4	24.9	4.2	17.8	20.1	17.3	19.6
80+	7.8	4.5	0.7	7.0	5.2	2.5	5.5
Totals: Nos.	1837	133	450	230	2850	670	3520
%	52.2	9.5	12.8	6.5	81.0	19.0	100.0

Table 10. Mean cumulative radiation doses for stated causes of death and stated age at death

Age at death in years	Mean cumulative doses (R) in centirads								Radiation dose Ratios*	
	Cardiovascular (390-458)	Accidents (800-999)	Other non-cancers	Solid tumors (140-199)	RES neoplasms (200-209)	All cancers (140-209)	All non-cancers (001-136; 210-999)	All deaths (001-999)	Ca: Non-Ca	RES: Solid
Under 40	59	47	76	55	40	52	56	55	0.93	0.73
40-49	95	114	104	100	57	91	102	100	0.91	0.57
50-59	157	133	64	187	329	201	136	140	1.48	2.19
60-69	132	116	125	145	92	140	129	132	1.09	0.62
70-79	66	24	72	60	787	103	51	60	2.02	13.12
80+	39	6	13	17	97	22	34	33	0.65	2.94
All ages	105	94	68	130	219	138	99	107	1.39	2.05

*Ca = Cancers; Non-Ca = Non-cancers; RES = RES Neoplasms; Solid = Solid tumors.

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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	Mean cumulative radiation dose for all workers (in centirads)											
	Zero		1-19		20-99		100-499		500+		Total	
	Nos.	% Cancers	Nos.	% Cancers	Nos.	% Cancers	Nos.	% Cancers	Nos.	% Cancers	Nos.	% Cancers
Under 40	108	9.3	55	10.9	58	8.6	24	8.3	9	22.2	254	9.8
40-49	185	17.0	82	15.9	117	21.9	74	23.0	17	11.8	495	17.3
50-59	311	19.3	137	16.1	200	24.5	155	21.9	58	17.0	881	21.2
60-69	941	22.2	162	21.6	248	26.6	184	25.0	53	22.6	1047	21.7
70+	152	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	25.1	1920	19.0

	Ranking Nos. for cancer proportions					Value of rho
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	7.4	3.8	0.46 ± 0.22*

*This value is statistically significant at the 5% level.
†Value of Spearman's rank correlation coefficient between the percentage of cancer deaths and the radiation dose level.

Table 10 shows that division of men who lived for more than 50 and less than 80 yr into three age groups still left each subgroup of cancers with a higher radiation dose than the corresponding group of non-cancers and still left each subgroup of RES neoplasms with a higher dose than the corresponding group of solid tumors.

Finally, Table 11 includes the results of the correlation test and shows that division of the certified deaths into 5 age groups and 5 dose levels still left the highest radiation dose groups (over 500 centirads) with the highest proportion of cancer deaths. As a result of this consistent trend, there was a firm rejection of the null hypothesis by the statistical test. Thus in three age groups Spearman's rank correlation coefficient (between the proportion of cancer deaths and the radiation dose level) had a value equal to or greater than 0.5 and the mean coefficient over age had a value of 0.46 ± 0.22. This is a statistically significant result since the coefficient for (n) observations has a variance of $(1/n - 1)$. Therefore, for a mean coefficient from 5 age groups, each with 5 dose levels, the variance is $(1/20)$ implying a standard error of 0.22.

SPECIAL TESTS OF THE RADIATION ASSOCIATIONS

The impression of a causal association between the exposures to external radiation and the cancer deaths was strengthened rather than weakened by the controlled analyses. Therefore it only remained to test the safety

threshold hypothesis (i.e. the theory that below the maximal permissible dose radiation has no carcinogenic properties) against the only logical alternative, namely, that with any exposure to ionizing radiation there is a cancer hazard which is proportional to the dose.

The choice of statistical test was influenced by the following assumptions: first, the most plausible alternative to the safety threshold hypothesis is a dose-response relationship that is either linear or at least monotonically increasing. Secondly, in Hanford data the stimulus or radiation dose, is continuously variable and the response or development of a fatal cancer, is a binary one (or an all-or-nothing response). Therefore, the most appropriate statistical model was the logistic or log-linear one which states that the logarithm of the odds-ratio of a response is linearly related to the stimulus over a suitable range of intensity (Co70).

Under the assumptions of this model the most powerful test of the null hypothesis was the permutation test of the difference between the mean cumulative radiation dose for men developing fatal cancers and the mean for all certified deaths. Therefore the test could be carried out in three stages:

(1) *Test for cancers with definite radiation associations*

Let N = size of whole population:
n = size of subpopulation of cancer deaths:

R = average value of radiation dose for the whole population;

r = average value of radiation dose for the subpopulation cancer deaths;

S = average value of the squared dose for the whole population.

Then, the estimate of variance in whole population $(V) = (N/(N-1))(S - R^2)$ and $t = [(r-R)/\sqrt{V[(1/n)-(1/N)]}]$ where this statistic is approximately distributed as a t statistic with $(N-1)$ degrees of freedom for testing the null hypothesis (see Appendix).

(2) Quantitative estimates of radiation sensitivity (doubling dose)

Should the null hypothesis of no associations between the radiation doses and the cancer deaths be rejected by the first test (as a result of t exceeding a critical value of approx +2.0), a quantitative estimate of radiation sensitivity would be required and could be obtained in the following way:

Let D = the radiation dose which is just sufficient to double the normal risk of a cancer death (doubling dose). Then r will have an expected value of $(R + S/D)/(1 + R/D)$ (see Appendix).

Therefore, by solving this equation with observed values of r, one could obtain for any cancer with definite radiation associations an estimate of the doubling dose (D).

(3) Quantitative estimates of radiosensitivity in relation to pre-death years and ages

There is no reason why the above formulas should not be used in relation to radiation doses for stated time periods or ages: and there are strong grounds for believing that: (i) tissue specific cancers have characteristic, albeit long, intervals between initiation and death, and (ii) sensitivity to the cancer-induction effects of any mutagen is strongly age dependent. Therefore, in Hanford data, the search for radiosensitive cancers can be directed towards discovering which of several pre-death years or ages (in relation to tissue specific cancers) are associated with statistically significant differences between observed and expected radiation doses (or t values equal to or greater than 2.0).

By taking this approach the identification of cancers with definite radiation associations (radiosensitive cancers) can be combined with estimates of: (i) the relative sensitivity of different tissues (as measured by doubling doses for the relevant cancers); (ii) characteristic intervals between initiation dates and death (or the pre-death years showing the maximum contrast between observed and expected radiation doses); and (iii) the ages of maximal and minimal sensitivity to the cancer-induction effects of ionizing radiation (or the ages showing maximum and minimum differences between observed and expected doses). Therefore, the search for radiosensiti . cancers (and other diseases with radiation . ssociations) was pursued, first in relation to pre-death periods (Tables 12–15), then in relation to age (Table 16).

Table 12. Cumulative radiation doses for stated pre-death periods

Pre-death years	Non-cancers Mean cumulative radiation doses in centirads			
	All non-cancer deaths	Cardiovascular diseases	Accidents	Other non-cancers
28	12	34	0.0	12
26	15.8	15.3	7.1	19.2
24	19.4	17.4	10.9	28.2
22	22.4	20.6	18.3	29.4
20	24.1	22.7	20.0	30.7
18	29.0	27.9	23.5	35.1
16	35.2	24.8	32.3	38.1
14	41.3	41.3	37.1	43.2
12	48.2	48.9	44.3	47.9
10	56.6	57.2	54.8	55.5
8	67.3	66.0	64.4	66.6
6	80.0	71.6	76.4	76.7
4	92.6	84.6	91.0	86.6
2	100.9	104.0	100.5	90.7
0	106.0	110.9	101.4	93.2
Number of deaths	2850	1817	290	961

*See footnote to Table 7.
†Standard values, see later tables.

Table 13. Cumulative radiation doses for stated pre-death periods

Pre-death years	Cancers		
	All cancers	RES neoplasms	Solid tumors
28	1.9	0.7	2.2
26	12.5	24.6	11.5
24	18.9	14.3	19.3
22	22.7	23.1	22.7
20	25.2	33.0	24.5
18	34.0	42.2*	32.3
16	44.3	83.0†	40.6
14	54.3*	105.2*	49.1
12	65.0*	126.0*	55.8
10	76.7*	154.0*	69.1
8	90.4*	175.4†	81.7
6	104.2	194.5*	95.0
4	116.6	200.9*	107.7
2	129.0	216.2*	119.6
0	134.4	223.1*	125.0
Number of deaths	670	64	606

Figures in italics significantly differ from the standard values in Table 12.
Levels of significance:
*P < 0.05.
†P < 0.01.
‡P < 0.001.
§See footnote to Table 7.

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Table 14. Cumulative radiation doses for stated pre-death periods

	Mean cumulative radiative radiation doses in centirads†	
Pre-death years*	Bone marrow (203; 205)	Other sites (200–2; 204; 206–9)
28	1.0	0.0
26	3.0	57.0
24	4.2	26.4
22	19.0	36.7
20	37.6	29.1
18	53.1	51.1
16	121.6‡	50.5
14	180.5‡	54.0
12	231.1‡	60.7
10	310.2†	63.4
8	401.4‡	62.3
6	446.9‡	65.0
4	418.5‡	72.9
2	446.1‡	90.3
0	449.2‡	100.1
Number of deaths	22	42

*See footnote to Table 7.
†See footnotes to Tables 12 and 13.
‡See significance levels in Table 13.

Table 15. Cumulative radiation doses for stated pre-death periods

	Solid tumors Mean cumulative radiation doses in centirads†					
Pre-death years*	Large intestine (153)	Pancreas (157)	Lung (162)	Kidney (189)	Brain (191)	Other solid tumors
28	0.0	12.0	4.0	1.0	0.0	0.0
26	8.7	12.0	15.0	2.0	40.0	6.3
24	19.1	25.6	18.4	1.3	39.2	17.8
22	27.9	33.6	23.3	2.6	36.5	18.9
20	25.7	35.9	25.0	3.0	44.9	21.2
18	45.2	35.9	35.3	13.7	59.3	25.8
16	54.7	48.2	45.7	24.9	70.7	30.9
14	63.1	65.5	61.6‡	35.9	70.8	32.2
12	74.3	90.1	72.1‡	74.8	93.7	35.3
10	92.3	119.9‡	86.9	88.9	98.1	37.7
8	106.5	142.7‡	103.4	98.1	124.8	43.9
6	125.1	173.9‡	117.1	123.6	158.4	49.4
4	129.6	214.5‡	132.6	159.9	193.9	54.1
2	137.0	247.0‡	147.5	172.7	226.8	59.1
0	141.8	269.0†	153.4	171.3	233.4	62.6
Number of deaths	61	49	192	21	18	265

*See footnote to Table 7.
†See footnotes to Tables 12 and 13.
‡See significance levels in Table 13.

Table 16. Estimated doubling doses for critical pre-death years*

Radio-sensitive cancers	Critical pre-death periods		Proportion of all deaths	
	Years before death	Estimated doubling dose in rads	Observed %	Expected† %
Bone marrow	9	0.8	0.62	0.30
Pancreas	0	7.4	1.39	0.85
Lung	14	6.1	5.45	3.26
All RES neoplasms	11	2.5	1.82	1.15
All cancers	13	12.2	19.02	15.15

*The years before death which showed the maximum contrast compared with the standard group of all non-cancer deaths (see Tables 13–15).
†See U.S. Vital Statistics for deaths of white males (1960).

radiation was 48.2 centirads for all non-cancer deaths' (standard or control group). For cardiovascular deaths, the corresponding dose was 48.9 (case: control ratio 1.01), for fatal accidents 44.3 (ratio 0.92) and other non-cancer deaths 47.9 (ratio 0.99). There were, however, positive findings for all cancers and for some of the neoplasms with exceptionally high radiation doses.

Thus for all cancers (ICD Nos. 140–209), there were positive findings (i.e. significant differences between observed and expected doses of external radiation) over a period of nearly 10 yr, namely, 7–15 yr before death; and for RES neoplasms there were positive findings over a period of nearly 20 yr, namely, from 0 to 18 yr before death (Table 13). For bone marrow cancers there were exceptionally strongly positive findings for the period 0–17 yr before death (Table 14), and for 2 of the 5 solid tumors with high radiation doses some of the differences between observed and expected doses were statistically significant. Thus, for pancreatic tumors, there were positive findings for the period 0–11 yr before death, and for lung cancers there were similar findings for the period 11–14 yr before death (Table 15).

For all cancers the critical interval between exposure and death—or the period of maximum case: control contrast as indicated by the *t* value—was 12 yr (case: control ratio 1.35 and *t* + 2.4). For RES neoplasms the

RADIOSENSITIVITY AND CRITICAL PRE-DEATH PERIODS

Division of the non-cancer deaths into several subgroups failed to produce any evidence of radiation associations in either the pre-death period or the age analysis (Table 12). For example, 12 yr before death the mean cumulative radiation dose for external

corresponding period was 11 yr (ratio 2.71 and *t* + 3.7), and for bone marrow cancers 9 yr (ratio 5.86 and *t* + 6.1). For lung cancers the critical interval was 14 yr (case: control ratio 1.50 and *t* + 2.0), and for pancreatic tumors under 1 yr (ratio 1.50 and *t* + 3.0).

For other cancers with high radiation doses, there was less certain evidence of a

causal association. However, for brain tumors there was a period of 3 yr when observed doses were twice as high as expected doses and t values were greater than $+1.5$ (i.e. 17–19 yr before death), and for cancers of the large intestine the observed dose 18 yr before death was 58% above the expected dose ($t + 1.3$). Finally, there were two findings which suggested that, given a longer period of records, there might have been a wider range of radiosensitive cancers. As a result of the study being restricted to men who died before 1973, there were very few records of radiation exposures 26 yr before the final (death) year. However, in this rare group 3 cases of brain tumors recorded a radiation dose which was almost 3 times as high as the expected dose ($t + 1.3$), and 2 cases of lymphosarcomas recorded a radiation dose nearly 4 times as high as the expected dose ($t + 1.8$).

DOUBLING DOSES FOR RADIOSENSITIVE CANCERS

From the records for critical pre-death periods, estimates were made of the amount of radiation which would be needed to double the normal risk of developing any of the cancers with definite radiation associations (see doubling doses in Table 16). According to these estimates, 12.2 rads would be needed to double the normal risk of dying from any form of cancer. For cancers of pancreas or lung the doses would be somewhat lower (7.4 or 6 rads) and for RES neoplasms or bone marrow cancers, they would be even lower (2.5 or 0.8 rads).

These suggested doses are so much lower than the estimates based on atom bomb survivors (Co70) that they are unlikely to go unchallenged. Therefore, we have included in Table 16 the proportions of certified deaths caused by the cancers with definite radiation associations, and the proportions of these cancers expected on the basis of all certified deaths of U.S. white males in 1960 (VSUS60). From these observed and expected proportions, standardized mortality ratios (SMRs) were obtained in the usual way and compared with the results of solving the following equation with observed values of D and R:

$$EMR = 100 \times \left(1 + \frac{R}{D}\right)$$

where $EMR =$ excess mortality from a radiosensitive cancer relative to a standard risk of 100 for all certified deaths.

According to the SMRs, the risks for Hanford workers were increased by 26% for all cancers, by 58% for RES neoplasms, and by 107% for bone marrow cancers (Table 17) and, according to the EMRs, the risks were increased by 4% for all cancers, by 21% for RES neoplasms, and by 79% for bone marrow cancers. Since the more conservative estimates were based on the doubling doses in Table 16, we are faced with two alternatives: either the actual doubling doses were even smaller than the estimates in this table; or, more likely, external radiation was not the only source of trouble for Hanford workers. In other words our analysis of the records relating to external radiation has shown the need for a similar analysis of the records relating to internal radiation.

Table 17. *Excess cancer mortality of Hanford workers: Comparisons between conventional SMRs and estimates based on radiation doubling doses (EMRs)*

Cancers with definite Radiation associations	SMRs*	EMRs†
Bone marrow	207	179
Pancreas	163	114
Lung	167	107
All RES neoplasms	158	121
All cancers	126	104

*See Table 16. (Standard = 100)
†See text

INTERNAL RADIATION

The data relating to depositions of radioactive substances are not yet in a form suitable for testing the null hypothesis of no trouble from this potential source of radiation-induced cancers. It is, however, possible to distinguish between Hanford workers with and without positive urine analyses and thus discover whether the positive findings in Tables 13–15 were due solely to workers in high risk or doubly monitored occupations or partly to men in low risk occupations or ones which were only monitored for external radiation.

Division of the certified deaths into two

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groups (with and without records of internal radiation) showed that: (i) the proportion of cancer deaths was higher in the positive group (22%) than in the negative group (18%) (Table 18) and (ii) the all-worker dose for external radiation was much higher in the positive group (357 centirads) than in the negative group (23). However, even in the low dose group the external radiation dose was higher for cancers (29) than non-cancers (21), and in both groups a pre-death period analysis produced positive findings in relation to RES neoplasms (Tables 18 and 19).

In the high dose group there were 17 RES neoplasms and 7 bone marrow cancers, and in the low dose group there were 47 RES neoplasms and 15 bone marrow cancers. In the first of these two groups there were positive findings in relation to these neoplasms for 8 of the 29 pre-death years (Table 18), and in the second group there were positive findings for 5 of these years (Table 19). Also,

Table 18. External radiation doses of workers with positive and negative records of internal radiation

Internal radiation*	Diagnostic categories	Cases Nos.	%	External radiation in centirads Total	Mean
Positive	Cancers	194	21.9	79.004	407
	Non-cancers	691	78.1	236.940	343
	Total	885	100.0	315.944	357
Negative	Cancers	476	18.1	13.653	29
	Non-cancers	2159	81.9	46.021	21
	Total	2635	100.0	59.674	23
Both	Cancers	670	19.0	92.657	138
	Non-cancers	2850	81.0	282.961	99
	Total	3520	100.0	375.618	107

*One or more depositions of radioactive substance.

Table 19. Cumulative doses of external radiation for stated pre-death years

Pre-death years	Men with positive urine analyses			
	Non-cancers	RES neoplasms	Lung and pancreas	Other solid tumors
28	13.7	—	27.6	4.9
26	21.5	17.0	15.5	11.8
24	28.4	26.2	29.2	26.2
22	36.7	33.2	49.1	11.5
20	47.2	89.2	54.9	37.0
18	59.4	159.1*	78.6	52.3
16	76.1	201.2*	114.4	75.7
14	99.9	243.3*	130.2	96.3
12	127.6	257.1*	172.3	135.0
10	158.4	300.1	224.8	174.4
8	198.2	312.5	269.3	212.1
6	245.2	376.6	323.8	250.7
4	292.1	396.2	379.1	302.5
2	324.6	407.6	409.5	335.9
0	380.3	418.7	460.4	381.1
Number of deaths	691	17	86	91

*See significance levels in Table 13.

Table 20. Cumulative doses of external radiation for stated pre-death years

Pre-death years	Men with no record of internal radiation			
	Non-cancers	RES neoplasms	Lung and pancreas	Other solid tumors
28	7.8	0.5	20.5	24.5
26	12.5	1.7	14.5	19.8
24	14.1	14.4	19.0	19.5
22	16.0	12.3	16.4	18.2
20	16.0	15.1	15.4	18.6
18	17.5	24.7	18.0	20.6
16	18.6	27.2	17.3	22.1
14	19.1	29.8	19.7	22.5
12	19.9	36.0*	22.2	25.2
10	22.0	42.0*	24.5	25.5
8	24.5	44.6*	29.2	27.2
6	27.1	44.3	30.9	28.2
4	29.3	46.4	34.6	30.1
2	31.8	49.9	34.7	32.5
0	40.1	51.7	36.2	39.7
Number of deaths	2159	47	155	274

*See significance levels in Table 13.

for the period associated with positive findings in both high and low dose groups (i.e. 12 yr before death), the estimated doubling doses were not significantly different for the two occupational groups.

AGE AND SENSITIVITY TO THE CANCER-INDUCTION EFFECTS OF RADIATION

The search for sensitive age groups utilized a single set of controls (all non-cancer deaths) and two sets of cases, viz RES neoplasms and solid tumors with high radiation doses (see pancreas, lung, brain, kidney and large intestine in Table 3).

Towards the beginning and end of the age range of external radiation records (which covered the period between 21 and 78 yr), there was virtually no data for the smaller case group (RES neoplasms), but between 30 and 70 yr of age the records for this group were strongly suggestive of an exponential increase in cancer sensitivity with advancing age. Thus, between 30 and 40 yr of age the observed doses were consistently lower than the expected doses. However, by 45 yr the observed doses were 15% higher than the standard dose; and by 50 yr they were 50% higher. These differences were not statistically significant, but by 55 yr there was a threefold difference between the observed and expected doses ($t + 2.5$), and by 70 yr a 14-fold difference ($t + 9.2$).

For the larger case group, there were positive findings at both ends of the age scale and a lull period between 25 and 40 yr. Thus, in

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Table 21. Mean cumulative doses of external radiation by stated ages: Non-cancers, RES neoplasms and other selected cancers*

Age in years	Non-cancers R*	RES neoplasms R	t	Other cancers* R	t	Nos. of observations Non-cancers	RES Neoplasms	Other cancers
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	—	80	2.1	145	3	9
25	19	11	—	54	—	177	3	12
30	18	37	—	40	—	353	13	43
35	51	39	—	42	—	623	22	85
40	56	35	—	44	—	870	30	126
45	59	58	—	56	—	1093	34	175
50	73	116	—	105	2.0	1302	33	205
55	83	230	2.5	154	3.2	1397	30	213
60	80	211	2.0	130	2.1	1326	25	169
65	76	458	5.3	132	2.0	1072	15	112
70	48	701	9.2	40	—	716	8	49
71	41	701	9.9	89	—	645	8	42
72	41	14	—	98	2.7	587	5	40
73	18	14	—	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	—	113	3.3	338	3	16
77	35	45	—	112	3.0	273	3	15
78	37	68	—	119	2.5	231	2	10

*Cancers of the pancreas, lung, brain, kidney, and large intestine (see Table 3).
*R = Mean cumulative dose of external radiation.
t: values greater than the critical value of 2.0.

the youngest age group (21 yr with 6 cases and 43 controls), the observed and expected radiation doses were 39 and 8 (t = 2.3). In the next three age groups (22–24 yr), differences between observed and expected doses remained statistically significant, but from 25 to 45 yr there was nothing to choose between the observed and expected doses. Thereafter there was a steady increase in the cancer: non-cancer contrasts and by 60 yr the observed dose was 63% higher than the expected dose (t = 2.1). Finally, by 72 yr there was a twofold difference between the observed and expected doses (t = 2.7), and by 78 yr a threefold difference (t = 2.5).

These findings were suggestive of greater sensitivity to the cancer-induction effects of radiation in early and late adult life than during the intervening period and this impression was re-enforced by doubling dose estimates for various ages (Table 22). These estimates were also based on RES neoplasms and solid tumors with high radiation doses, and they showed that (i) for men between 25 and 40 yr of age the exposures to external radiation probably had no delayed effects; (ii) for older men the doubling doses decreased rapidly with age; and (iii) for younger men the trend was probably in the opposite direction.

Table 22: Estimated doubling dose for stated ages: RES neoplasms and other selected cancers*

Age in years	Estimated doubling doses in rads RES neoplasms	Other selected cancers†
21	—	0.2
22	—	0.1
23	—	0.2
24	—	0.4
25	—	1.5
30	∞	49.2
35	∞	∞
40	∞	∞
45	30.0	70.4
50	13.0	17.9
55	8.2	14.6
60	6.8	18.1
65	1.2	14.8
70	9.1	16.0
71	9.1	8.7
72	—	2.5
73	—	1.1
74	—	1.1
75	—	1.2
76	—	0.8
77	—	0.9
78	—	0.9

*See Table 21 for the number of cases for each estimate
†Cancers of the pancreas, lung, brain, kidney, and large intestine.

Females

Certified deaths of female workers totalled 412 and included 126 or 31% of cancers. The proportion of these workers with records of external radiation was small compared with the men and equally small for 127 women whose deaths were ascribed to cancers and 285 women with other causes of death (30%). Nevertheless, within the group of exposed workers the mean cumulative radiation dose was twice as high for cancers (133) as non-cancers (68).

Division of the cancer and non-cancer deaths of females into 4 age groups (Table 23)

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Table 23. Cancer and non-cancer deaths of females by age and radiation dose

Age at death	Radiation dose levels (centirads)	No. of deaths (N)	(C)	%*	Cancers Rank	rho†	Radiation doses in centirads Totals (N)	(C)	Means for exposed workers (N)	(C)
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	1072	564	33	38
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	1190	2172	63	197
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	2451	1372	123	229
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	1085	927	68	155
All ages	0	208	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	5797	5035	68	133

*% of all certified deaths.
†See Table 11.
N = Non-cancers
C = Cancers
‡This is a significant finding at the 5% level.

showed that: (i) radiation dose levels were always higher for cancers than non-cancers; (ii) cancer: non-cancer contrasts were greater for deaths after 50 yr of age than for earlier deaths; and (iii) in three age groups the proportion of cancer deaths was highest for the top level of radiation dose (over 100 centirads .

Finally, despite the small numbers of female workers with records of external radiation, the null hypothesis of no correlation between the radiation dose and the proportion of cancer deaths after controlling for age was rejected by a correlation test. According to this test, 3 of 4 Spearman's rank correlation coefficients (between proportions of cancer deaths and radiation dose levels) were equal to or greater than 0.6 and the mean coefficient over age had a value of 0.60 ± 0.29 (which is significant at the 5% level).

Estimates of the number of cancer deaths attributable to external radiation

In the final stages of the analysis, the best estimates of risk were used to discover how many of the cancers with records of external

Table 24. Estimated frequency of radiation-induced cancers among certified deaths of Hanford workers*

Certified causes of death	Exposed workers Nos.	Radiation-induced cancers Nos.	%
Bone marrow	14	9.3	69.3
Pancreas	31	6.0	19.4
Lung	130	12.6	9.7
RES neoplasms	47	11.1	23.6
All cancers	442	25.8	5.8
All certified deaths	2184	25.8	1.2

*Provisional estimates for deaths during the period 1944–72.

radiation (442 cases) were attributable to these exposures (Table 24). For 14 bone marrow cancers, the estimated number of radiation-induced cases was 9.3, and for 161 cancers of the pancreas or lungs, the estimate was 18.6. The estimate for all cancers (25.8) was a fraction smaller than the sum of the estimates for the three cancers with definite radiation associations (27.9), and the estimate for all RES neoplasms (11.1) was a fraction larger than the estimate for bone marrow cancers (9.3). Therefore, the proportion of radiation-induced cancers among the exposed cases probably lay between 6 and 7%, and the corresponding proportion for all certified deaths probably lay between 1% and 2%.

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DISCUSSION

A preliminary analysis of the records relating to external radiation has shown that there is sufficient data in the Hanford study to: (i) identify some of the more radiosensitive cancers; (ii) quantify the radiosensitivity of these neoplasms; (iii) obtain estimates of characteristic intervals between initiation and death; and (iv) recognize the ages of maximum and minimum sensitivity to the cancer induction effects of radiation.

Further analyses will be needed to rule out the now remote possibility that the positive findings were merely the result of the radiation exposures having associations with other cancer-related factors. These analyses will proceed in two directions. First, there will be joint standardization for all the factors with known or suspected radiation or cancer associations (e.g. exposure age, interval between hire and exposure, intervals between exposure and death, and depositions of radioactive substances). Secondly, there will be an extension of these analyses from non-survivors with certified causes of death to other members of the monitored population, or workers who are still alive at the time of follow-up.

Meanwhile cursory inspection of the records relating to men who were still alive in 1973 (Table 1) has shown that one of the reasons why the doses of external radiation have always been higher for survivors than non-survivors (Ma74) is because the survivors include a disproportionately large number of men with positive urine analysis (Table 25). This bias is due to an association between high risk occupations and young recruits, which has caused the proportion of young recruits to be different for: (i) singly and doubly monitored occupations; (ii) men with positive and negative urine analyses and (iii) survivors and non-survivors.

Since workers with positive urine analyses were more often and more intensively exposed to external radiation than other workers (Table 18), it is essential, when comparing survivors with non-survivors, to include internal radiation among the con-

Table 25. Age distributions of men monitored for internal and external radiation

Age at hire in years	Doubly monitored* (A) %	(B) %	Singly monitored* %	Survivors† %	Certified deaths %
Under 30	54.8	49.1	41.1	55.8	13.1
30-39	38.1	26.4	28.4	28.6	24.5
40-49	3.2	12.4	17.7	11.7	31.0
50-59	3.7	10.8	10.2	3.6	25.4
60+	0.2	1.3	2.6	0.3	6.0
Σ Nos.	12,095	3716	9128	21,206	3520
%	48.5	14.9	36.6	85.0	14.1

*Doubly Monitored = Monitored for internal and external radiation.
  A = Positive urine analyses.
  B = Negative urine analyses.
 Singly monitored = Only monitored for external radiation.
†See Table 1.

Table 26. Standardized radiation doses of survivors and non-survivors in relation to various controlling factors

Controlling factors	Standardized radiation doses* (1)	(2)	(3)
Nil	156	63	51
Exposure year (E)	142	71	57
Cohort or year of hire (C)	138	72	90
E + C	127	79	94
E + C + internal radiation	101	84	112

*Standard (100) = External radiation doses recorded by the 1973 Survivors and certified deaths in Table 1.
 (1) = 1973 Survivors.
 (2) = Non-cancer deaths.
 (3) = Cancer deaths.

trolling factors. This necessity is clearly seen in Table 26 where 5 sets of standardized radiation doses are shown for 3 groups in Table 1 (survivors, non-cancers and cancers). For instance even controlling for two factors simultaneously (i.e. exposure year and cohort), still left the survivors with a higher dose (127) than the non-cancers (79) or the cancers (94), but when internal radiation was added to the other controlling factors, the standardized dose was not only lower for non-cancers (84) than cancers (112) but also lower for the survivors (101) than cancers.

Nevertheless, the absolute doses were higher for the men who were still alive in 1973 than for the non-survivors included in the present investigation, and for Hanford workers as a whole, the trend of radiation doses (and proportions of exposed workers) is in an upward direction. Therefore we should be prepared for future analyses of Hanford data to show both a wider range of cancers with definite radiation associations (due to better representation of cancers with long latent periods) and a higher proportion of radiation-induced cancers among the exposed workers.

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APPENDIX
PROOFS OF STATISTICAL FORMULAE

(I) *Optimality of tests of mean doses in a linear logistic model* [after Cox (Co70)]

The assumed model is given by:

$$\ln\left(\frac{p_i}{1 - p_i}\right) = \alpha + \beta x_i$$

where:

p_i = probability of individual i developing cancer;
x_i = dose of individual i; and
α and β are parameters (β for the effect of dose).
Then the log-likelihood is given by:

$$L = \sum_i z_i(\alpha + \beta x_i) - \sum_i \ln(1 + e^{\alpha + \beta x_i})$$

where:

$z_i = 1$ if individual i develops cancer, 0 otherwise.
so $L = n\bar{z} + nr\beta - \sum \ln(1 + e^{\alpha + \beta x_i})$ in terms of n and

r (defined in text). Since the only random variables occurring in this equation are n and (nr), they are jointly (and in fact individually) sufficient for α and β. Therefore by the principle of conditional test construction known to be optimal in such exponential type distributions, the best test of $\beta = 0$ is based on the distribution of (nr) given n and the set of values x_i. Evidently this is the permutation distribution of the mean of a sample of n from a population of size N, and this reduces by standard arguments to the t-test described in the text if N is sufficiently large and the distribution of the set x_i is suitably regular.

(II) *Estimation of the doubling dose in a linear model*

The assumed model is given by:

$$P\{cancer | dose\ x\} = A(1 + x/D)$$

where A = spontaneous cancer rate and D is defined as in the text. Let $P\{dose\ x$ in whole population$\} = f(x)$.
So that R (defined in text) $= \int_0^\infty x f(x)\,dx$.
Then, by Bayes theorem:

$$P\{dose\ x | cancer\} = \frac{A(1 + x/D)f(x)}{\int_0^\infty A(1 + x/D)f(x)\,dx}$$

Evaluating r (the mean dose given cancer) from this formula, and simplifying, one arrives at the formula quoted in the text, since:

$$r = E\{x | cancer\} = \int_0^\infty x P\{dose\ x | cancer\}\,dx.$$

(III) *Validity of normal theory approximation for the t-value distributions*

The question whether the radiation dose distributions were sufficiently regular for the standard

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test to apply) was answered by estimating the empirical distributions of the t-values by Monte Carlo simulations. In 1000 simulated random samples of size $n = 22$ (corresponding to bone marrow neoplasms) from the distribution of doses of $N = 1520$ certified deaths, only 6 random samples had t-values equal to or greater than 4.48 (or the actual value for the sample of bone marrow neoplasms). Thus the empirical probability is $P < 0.060$ compared with a theoretical value (based on a normal theory approximation) of $P < 10^{-4}$. A similar experiment with $n = 48$ (corresponding to pancreatic tumours) gave an empirical probability (to the t-value of 2.99 for pancreatic tumours) of $P < 0.010$ compared with a theoretical value of $P < 10^{-3}$. Thus in neither case is the probability increased so much as to give a false conclusion at the 1% level of confidence.

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