

2nd PRELIM.
REVIEW OF CHR
PLAN

BCP

HARVARD UNIVERSITY
SCHOOL OF PUBLIC HEALTH
DEPARTMENT OF EPIDEMIOLOGY

702532



677 Huntington Avenue
Boston, Massachusetts, 02115

January 3, 1975

Dr. Warren K. Sinclair
Associate Laboratory Director
Biomedical and Environmental Research
Argonne National Laboratory
9700 South Cass Avenue
Argonne, Illinois 60439

Dear Dr. Sinclair,

Enclosed is a statement on the review of the Ad Hoc Committee for the Center for Human Radiobiology. I hope this will reach you in time for your needs.

This is marked "preliminary" in that it has not been reviewed by the other two committee members. It is now being circulated to them and will undoubtedly be revised in response to their comments. I hope, however, that it reflects the main thinking of this committee as it developed at the October meeting.

We did plan at that meeting to circulate the report to Dr. Rowland for comment before preparing its final version. In view of my slowness in preparing the report, I will not delay it further for Dr. Rowland's review. I hope, however, some exchange of thoughts with him will be possible before the final draft is submitted.

Sincerely,

George B. Hutchison

George B. Hutchison, M.D.

Encl. Second Preliminary Review
Comments on: Calculation of tumor incidence
from an incompletely-measured sample

REPOSITORY ARGONNE / CHR
COLLECTION RECORDS RELATING TO
INDUSTRIAL MEDICAL
EXPOSURES TO RADIUM
BOX No. BOX 121 ASH
BINDER
FOLDER #33 - CHR FACT SHEETS
REVIEW COMMITTEES
HISTORY OF CHR FROM ANL
REPORTS 0019871

January 3, 1975

Second Preliminary Review of the Plan of the Radium Project

Three members of the Ad Hoc Committee on the Experimental Plan for the Center for Human Radiobiology met on October 9, 1974. Members present were Dr. Seymour Jablon, Dr. Edythelena Tompkins, and Dr. George Hutchison, chairman.

The following information was considered.

- a. The Plan of the Radium Project of the Center for Human Radiobiology (The Yellow Book)
- b. Written comments on The Plan by committee members, Drs. Jablon, Tompkins
- c. Preliminary Review of the Plan of the Radium Project, August 29.
- d. Calculation of tumor incidence from an incompletely-measured sample using death certificates from the unmeasured cases (Paper received during the meeting).

The importance of the study of the exposed populations with radium burdens is well understood by the committee, and no consideration was given to the possibility of discontinuing this series of investigations. The following sections concern areas of concern to the committee relative to carrying these studies through to a conclusion reflecting the maximum understanding that can be obtained from information available or to be obtained from these populations.

I. Incompleteness of data.

A. Description

The single most important issue concerning interpretation of the radium burden data is that of incompleteness, with the associated problem of potential bias. The problem of incompleteness is considered with respect to each element of the data collection.

a. Initial identification of the exposed population.

The radium project serves both as a registration center and as an analytic center. The registration activity employs a broad range of techniques for identification of radium burden cases, as tabulated in Table I, page 16, of The Plan. The analysis activity will use different groups of registered patients for different types of study. The principal analyses of concern to the present committee will be prospective studies of persons identified through the fact of radium exposure. Sources in Group I and Group II in Table I identify persons of this type. Sources in Group III are potentially biased in that persons identified through these means may be selected on the basis of health effects of exposure. There will be an interest in the tumor incidences in total listings of patients in Group I and Group II listings. It is felt that bias in estimates of these total group incidences resulting from initial selection is essentially negligible. Bias may enter these estimates, however, as

0019872

a result of follow-up procedures, as described below. Bias may enter estimates of comparisons of incidences of different listed groups (for example incidence ratios or incidence differences) as a result of confounding factors, such as age.

b. Measurement of exposure

A principal interest in the study of the radium cases is in incidences in sub-groups of listed cases characterized by different radium burdens. Measurement of burden has necessarily been carried out in an opportunistic fashion. All exposed patients who could be located and who agreed to cooperate have been measured or will be measured. Deceased patients were measured when autopsy permission or exhumation permission could be obtained. Measurements have been obtained principally by whole body counter, but useful information has also been obtained in limited numbers of cases from specimens of expired air or from tissues.

The proportion of exposed patients who have been measured remains disappointingly small, as shown in Table 4, page 19, of The Plan, for the most satisfactory group of patients with respect to initial total group selection. When estimates are made of incidences within sub-groups of persons characterized by a given range of radium burden, the relevant selection procedures are selection for being measured rather than selection for being listed on a roster of Group I or II. Techniques are necessary to estimate the magnitude of the potential bias in selection of patients for measurement, recognizing that health effects may influence opportunities for measurement in complex ways. Illness may, for example, cause a person to come to attention or may cause a person to refuse to cooperate in a body burden measurement. Death may, similarly, influence patient availability for study. A principal follow-up technique is death search, so that patients otherwise lost to study may be located by this method. The fact of death, however, will be biased toward persons with malignant disease. On the other hand follow-up through later employment records or through personal contact will be favored by good health.

c. Measurement of outcome

Information on outcome, principally development of malignant tumors, has similarly been obtained opportunistically. This information is sought for both patients whose exposure has been measured and for patients whose exposure has not been measured. Availability of this information varies with factors similar to those affecting selection for exposure measurement and must be assumed to be potentially biased in complex ways.

In addition to the question of availability of outcome information, there exists a problem of validity of outcome data. Diagnosis of malignant tumor depends on adequacy of medical facilities. Positive identifications of tumors in this series are generally based on careful review of biopsy or autopsy material by competent pathologists and may be considered of essentially unquestioned validity. Questionable identifications may be made by statements on death certificates for which tissue confirmation was not given and cannot now be obtained. False negative reports may result

from inadequate medical investigation, and the present investigators may have no indication that tumor was suspected or should have been suspected. Errors in validity of diagnosis may or may not be correlated with level of radium burden. If correlated, estimates of risk may be increased or decreased and estimates of relative risks (risk ratios or risk differences) may be biased in complex ways. If errors occur in the same proportion in groups with different radium burdens, estimates of relative risks will systematically understate the true dose-effect association.

B. Discussion of incompleteness of data

Analysis of data with special attention to the question of bias is discussed in The Plan, particularly on page 27, and was identified to the investigators as an issue of special concern in the Preliminary Review submitted to Dr. Sinclair August 29, 1974. In partial response to this preliminary review the investigators prepared a document, Calculation of tumor incidence from an incompletely-measured sample (Dr. John Marshall). Detailed comments on the latter document are enclosed. In brief, the discussion of bias in The Plan and in the document on Calculation of incidence involves a comparison of two estimates of tumor incidence, one derived from the population with measured burden and complete follow-up, the other derived from the population without measured burden but dead and traced through death certificate. It is proposed (1) that the ratio of these two estimates of incidence is a measure of bias and (2) that the estimate of incidence obtained from the death certificate search of unmeasured cases is a satisfactory estimate of incidence in the total group without measured burden or without follow-up (including unmeasured survivors, deaths not traced, and deaths traced but not measured or not followed-up).

This procedure for estimating bias and correcting for bias is not felt to be an adequate treatment of the problem. Difficulties in this procedure may be considered in terms of the following table of incidences of the total population listed in one or more lists of Groups I and II (primary and secondary documents).

| | High burden | | Low burden | |
|----------|-----------------|---------------------|-----------------|---------------------|
| | <u>Measured</u> | <u>Not Measured</u> | <u>Measured</u> | <u>Not Measured</u> |
| Followed | J ₁ | L ₁ | J ₂ | L ₂ |
| Traced | L ₃ | K ₁ | L ₄ | K ₂ |
| Lost | L ₅ | L ₆ | L ₇ | L ₈ |
| Total | T ₁ | T ₂ | T ₃ | T ₄ |

The incidences J₁ and J₂ may be considered adequately determined in populations identified both as to exposure and outcome. The incidences K₁ and K₂ cannot be separately determined, since the high and low burden groups cannot be identified in the absence of measurement, but the combined incidence K, some weighted mean of K₁ and K₂, can be determined. This incidence K, determined from death certification, will potentially include some invalid information, and the investigators have presented a method for correction for invalid certification, false positive or false negative.

The incidences L_1 and L_2 are similarly not separately available, but their weighted mean value will be available and will be assumed to be free of misclassification error. The incidences L_3 and L_4 will be separately available and will require correction for possible invalid certification. The populations represented by the incidences L_5 and L_7 , measured but subsequently lost to follow-up, will be known, but incidences in these groups will be unknown. The populations with incidences L_6 and L_8 will not be separately known, but the size of the total of these populations will be known. The incidences L_6 and L_8 will be unknown.

The procedure proposed in The Plan and in the document on Calculation of incidence could be applied to the total population of all 12 cells in the above table. The incidence J (weighted mean of J_1 and J_2) would be compared with K . If these two values were equal, it would be assumed bias was absent, and their common value would be the incidence for the total. If J and K were not equal, K would be taken as an estimate of the incidences K_1 and K_2 , and L_1 to L_8 . The overall incidence would then be estimated as a weighted mean of J and K , using a weight for J proportional to the populations represented by J and a weight for K proportional to the total populations represented by K and the L 's. Clearly this is a questionable estimate for this total incidence, but one can make this computation and describe the assumptions involved.

A more difficult problem arises when it is desired to obtain differential estimates of incidences associated with high and low burdens. For this purpose only the incidences J_1 , J_2 , L_3 , and L_4 are available. Neither the separate incidences K_1 and K_2 nor the sizes of the populations T_2 and T_4 are known. Therefore the bias within a group of known burden cannot be estimated by comparison of J and K , nor can a weighted mean incidence with known burden be computed.

2. Registration versus analysis

It has been mentioned above that the radium project has functions of both registration and analysis. The registration function is concerned with all populations that have been exposed to radium burdens with measurement and follow-up of all such groups. The analysis function must be concerned with feasible problems to be studied in appropriate population sub-groups. A protocol of the analysis function must necessarily be a composite of sub-protocols. It is felt that the present document, The Plan of the Radium Project, represents an attempt at comprehensiveness, designed to describe analysis of all possible epidemiologic studies to be derived from the registration. Such comprehensiveness is probably not feasible at this time, and individual protocols of limited studies are needed. In the development of such protocols it may become apparent that no study is desired for some registered populations.

It is noted in The Plan, Foreward, page i, that the study of radium "is not a conventional epidemiologic study." A major present effort, nevertheless, is being devoted to the follow-up of exposed human populations and association of measure of exposure with measure of late health status. This effort is a conventional epidemiologic study and because of its magnitude should receive expert epidemiologic attention. This analytic

effort will make use of the registration activity and of various laboratory investigations of radium effects. One or more senior investigators should be committed to this epidemiologic study as an activity to be defended in its own right.

3. Preliminary report.

A substantial body of data has now been accumulated on the exposure and outcome of populations with radium burden. Further such data will continue to be acquired for an indefinite time in the future. One or more detailed reports of the observations to date, including a detailed consideration of the nature of the basic data, should be submitted to an appropriate scientific journal in the near future. The preparation of such a report would focus attention on the analytic problems of the study. The dissemination of the report would inform the scientific community and, through its feedback to the investigators, would alert them to problems to be considered in the future conduct of the data collection and analysis.

4. Nature of the analysis

A Major emphasis in The Plan of the Radium Project is given to the question of distinguishing between two specific theories as to the mathematical form giving the best fit to the observations. On page 21 and 26 it is indicated that an analysis that fails to distinguish between these two hypotheses is unacceptable, and pages 31 to 40 and Appendix B are devoted to sample size considerations relative to this problem. A retrospective study is described, pages 29, 30, which is designed specifically to obtain data required to examine these two hypotheses.

While the distinction between these two hypotheses is of some interest, it is probable that the most important results of these studies will come from the observations in the higher burden ranges, where high tumor incidences are known to occur. The major interest in analysis should be to obtain the best description possible of risk and of the degree of certainty that can be associated with this risk at whatever ranges of burden useful estimates can be made. It may have to be accepted that these findings may never permit a distinction between the principal competing hypotheses as to the mathematical nature of the dose-effect relationship. This failure, if it should occur, would not constitute a major deficiency of these studies.

5. The retrospective study.

A new study, the retrospective study, is described on pages 29 and 30. The plan of study is obscure as given and incorporates features of cohort design, case-control design, and general population study design.

In a general population study, exposure frequencies and outcome frequencies (for example, tumor incidences) are determined for a population defined without regard to exposure or outcome, as for example, a population defined by geographic or political boundaries. The analysis of such a study may take the form of either (1) comparing outcome risks in various exposure groups or (2) comparing exposure frequencies of various outcome groups. The

present study is described as a study of all cases in two areas, the Ottawa, Illinois, area and the Waterbury, Connecticut, area. The exact definition of the areas is not given, but presumably the cities themselves or the cities plus one or more contiguous counties are to be included. Tumor mortality for these total areas during specified years will be determined. Radium burden information, however, will not be determined for the areas but only for the persons with tumors. Nevertheless certain occupational groups in these areas have been studied extensively, and it may be assumed that the exposure frequency of the areas is entirely the result of exposures of the studied occupational groups. Under that assumption, the study design may be considered that of a general population type study.

In a case-control study design some groups of persons with outcomes of interest (for example, certain tumors) are compared with appropriate persons without these outcomes. Analysis involves comparison of prior exposure frequencies of the two groups. The principal feature of the proposed study is determination of exposure frequencies in patients with tumors, suggesting a case-control design. No comparison population is mentioned, however, so it is not clear what these exposure frequencies will be compared with. Again, as with the general population study, it may be assumed that the prior occupational studies are adequate to give information on exposure of an appropriate comparison group, assuming there is no significant frequency of radium exposure in the population not known to be exposed in the studied occupational groups.

In a cohort study groups of exposed persons are followed to obtain outcome risks, as has been done in the main body of the present radium project studies. The description of the present retrospective study refers to expected numbers of cases in the known occupationally exposed groups, a statistic that would be appropriate for a cohort study. If a cohort study were intended, however, the newly described retrospective study would not be a new study but would simply be a new case-finding activity of the present occupational group studies. In that circumstance only cases identified in persons already on lists of exposed persons would be of interest. Indeed it is understood that such a death certificate search of listed persons is already in progress or contemplated as part of the analysis of bias.

If a general population or case-control study is envisaged using only the already available exposure information, then any exhumed cases with radium burden but not on previously obtained lists will not be admissible patients for analysis, since they will imply an exposure of this population that has not been included in the prior exposure studies. If all exhumed cases are to be used, a comparison group of cases of non-tumor deaths must similarly be exhumed, or some other procedure must be used to determine the radium burden of the general population of the two cities.

The chief goal of the retrospective study is to improve the estimate of tumor risk in the dose range of 10 to 1000 rads. As indicated above, it is doubtful that any useful information on this question would be obtained from exhumed cases not already on exposure lists unless exposure frequency for the entire populations of the two cities is determined. If a substantial number (perhaps 3 or more) of tumors with doses in the range of 10 to 1000

were found, this would constitute a major new piece of information on risk. If fewer cases or no cases were found, the problem of incompleteness of follow-up would have a major bearing on interpretation of the finding.

The study described plus an additional survey of radium burden in some comparison sample in the two cities is a major new proposal, and the study description given suggests only preliminary planning. Any decision to move ahead with the retrospective study will presumably not be considered without extensive further planning.

6. Personnel.

The personnel associated with the radium project are clearly highly competent in their specialty areas of radiobiology, radiation physics, and radiation medicine. The organization of the case finding and follow-up activities is highly effective.

An important deficiency exists in epidemiologic expertise. There is no professional epidemiologist on the project staff or associated with the project for a major commitment of time and effort. This deficiency is indicated in the Plan of the Radium Project in both general and specific ways. In general, the language of the project is unfamiliar to epidemiologist reviewers and appears to dwell at unnecessary length on basic epidemiologic concepts. It is stated that the investigators do not view the project as a conventional epidemiologic study (Foreward, page i), and it is felt that they do not consider the project to have major epidemiologic components. In specific, the discussion of bias is inadequate, as described above, and it is suggested that the investigators do not understand the severe limitations of this body of material, given optimal analysis. The description of the retrospective study indicates an unfamiliarity with traditional features of epidemiologic study design.

7. Recommendations

a. It is recommended that the Center for Human Radiobiology obtain professional epidemiologic assistance in study design and analysis. A number of methods of accomplishing this recommendation are suggested below, and the Ad Hoc Committee does not make an exclusive recommendation of any one of these but suggests that they be considered as indicative of the degree of assistance that should be obtained.

(1) The comments of the peer review group of November, 1973, recommended "an ad hoc committee of epidemiologists who would work with the Laboratory Director or Associate Director for Biomedical and Environmental Research to establish rigorously formulated objectives and biometrical methods...." This recommendation deserves further consideration. A committee which would simply establish objectives and methods, however, would probably have insufficient long-term commitment to the study to give needed assistance in the long run.

(2) A senior epidemiologist might be appointed to the research group on a part time basis. This person would have an on-going responsibility, as a member of the group of investigators, for the epidemiologic aspects of research design and execution and for data analysis.

(3) A junior epidemiologist, at the level of Assistant Professor or of

similar seniority, might be appointed on a part time basis as described above. An investigator at this level would establish a continuing consultant relation with a senior epidemiologist or with an advisory group of epidemiologists.

(4) A relationship might be established on a permanent basis with other units of the Atomic Energy Commission where epidemiologic studies are being conducted. A suitable person or committee from such other unit might be named as permanent collaborator in epidemiologic methods and become part of the research group of the Center for Human Radiobiology.

b. A general protocol for the radium project should be drawn up along the lines of the present Plan of the Radium Project but conceived only with broad objectives and a broad outline of the study plan.

Specific protocols should be prepared for limited projects within the total study. These protocols should include detailed plans of data collection and analysis. In the case of projects that have already accumulated substantial data, specific plans for preliminary or final reports should be incorporated in the present plan.

c. A special plan of analysis of problems associated with incomplete data should be prepared. This plan might include the concepts presented in the document Calculation of tumor incidence from an incompletely-measured sample. Further comments on this document are enclosed and further considerations relative to problems of incompleteness and bias are included as section 1 of this Review. This plan should indicate the analyses to be carried out to achieve the maximum information from the radium project and should also indicate necessary limitations imposed by the nature of the data.

d. It is recommended that the retrospective study (pages 29, 30 of the Plan) be reconsidered. If it is ultimately decided to carry out this study, involving a major expansion of the exhumation activity, a detailed study protocol should be developed and discussed with appropriate epidemiologic staff or consultants.

e. It is recommended that one or more preliminary reports of the radium project be prepared for publication in scientific journals in the near future. These should be substantial reports with extensive display of data and with detailed treatment of problems of incompleteness of data and of limitations imposed by this incompleteness.

Encl. Comments on: Calculation of tumor incidence from an incompletely-measured sample.

Comments on: Calculation of tumor incidence from an incompletely - measured sample using death certificates from the unmeasured cases.

An analytic procedure is presented for evaluating the effect of bias in the estimate of tumor incidence as derived from studies of the radium burden cases.

The procedure considers an objective list of radium burden cases to be composed of 3 sub - groups -

- a, Cases measured and followed for tumor incidence
- b, Cases not measured and followed but dead and located in death search
- c. All other (i.e. not measured and followed but either surviving or dead and not traced)

Tumor rates in group a, are determined and assumed to be free of misclassification error. Rate = J

Tumor rates in group b, are determined and corrected for misclassification using published estimates of errors of misclassification. Corrected rate = K.

No rates are available for group c, but it is assumed that groups b and c have similar rates. Rate = K.

The tumor rate for the total objective list is then estimated to be -

$$I = JM + K (1 - M)$$

where M is the fraction measured and followed.

Bias is taken to refer to selection of the sub - group a, from

the total list and is defined quantitatively as

$$\text{Bias} = B = J/K,$$

so that the null condition is $B = 1$; when the sub - groups a. and b. have the same tumor rates.

The total tumor rate is then estimated in terms of B as -

$$I = JM + J (1 - M)/B = J[M + (1 - M)/B] = Jp$$

For fixed values of M and B it is clear that the standard error of I is proportional to the standard error of J, with constant of proportionality p -

$$p = M + (1 - M)/B$$

The investigators have made a different estimate of the standard error of I, using the relationship -

$$I = \frac{N_1}{L} + \frac{N_2 F}{LDC} + \frac{N_3 G}{LDC}$$

where N_1 , N_2 , and N_3 are numbers of tumors or numbers of non - tumors in sub - groups; F and G are measures of misclassification error; and L, D, and C are constants defining the size of the population and sub - groups. An estimate of standard error is obtained under the assumption that N_1 , N_2 , and N_3 are independent variables, each with a Poisson distribution. The Poisson parameters are functions of the quantities J, L, M, D, C, B, F, and G. Assuming a variety of values for these quantities, the ratio of the standard error of I given non-null values of B to the standard error of I given the null value of B ($B = 1$) is computed. This ratio ranges from .89 to 1.3. The quantity p, above, ranges from .79 to 1.39 under the same assumed values for M and B, so it may be assumed that, within the ranges

studied, the assumptions of independent Poisson variables lead to estimates of standard error in an acceptable range.

The investigators conclude that "the total error in our estimate of the tumor incidence for a listed population should be about equal to the error which arises solely from the statistics of small numbers even if follow-up is only 50% complete."

Discussion

The above analysis does not adequately treat the serious problems of potential bias involved in the studies of the radium burden cases.

1. The population sub - group c., patients not measured and followed and not found in a death certificate search is large. Table 4 (Plan of Radium Project, page 19) shows 258 patients not studied and living plus 261 patients not located among 1,338 patients on objective lists of the major radium dial companies. It is possible that an additional number of patients "located and studied" are not currently traceable, and a number of patients not studied and dead may not be locatable in death certificate search. Uncertainties of this sub - group c. relate to the possibility that inability to be studied, inability to be followed, likelihood of survival, and inability to be traced after death in death certificate search are all correlated with either degree of radium exposure or with tumor development. There seems to be no basis for the assumption that the tumor rate in the group b. is similar to that in group c.

2. In the numerical analysis the quantity B, bias, is assigned the values 1.3, 1.0, and 0.7, implying 30% variation above or below the

null value. No justification is given for assuming that the bias lies within this range. The assumption of a bias within this range leads directly to the conclusion of a satisfactorily small error in the total tumor rate I.

3. The "total error in estimate of tumor incidence" apparently refers to the quantity $I - J$, the difference between the tumor rate I for the total population and the rate J for the sub - group a. measured and followed. Employing the relationship $I = Jp$, this total error, TE, may be given as -

$$TE = I - J = Jp - J = J (p - 1) = \frac{N_1}{LM} (p - 1)$$

where N_1 is the number of tumors in the measured sub - group of size LM. The standard error I, SE (I), is -

$$SE (I) = SE (Jp) = SE \left(\frac{N_1}{LM} p \right) = SE (N_1) \frac{p}{LM} = \frac{p}{\sqrt{N_1}} \frac{p}{LM},$$

assuming Poisson distribution.

The total error is then related to the standard error by the ratio r, such that

$$r = \frac{TE}{SE} = \frac{N_1 (p - 1)}{\sqrt{N_1} p} = \sqrt{N_1} \frac{p - 1}{p}$$

where $p = M + \frac{1 - M}{B}$ and has the range M to ∞ as B ranges from ∞ to 0. The null value of p is 1, when B = 1. The quantity $\frac{p - 1}{p}$ has the range $\frac{M - 1}{M}$ to 1 with null value 0.

In the present study the total number of tumors, N_1 , in the measured population is about 40, and the proportion of the population measured, M, is about 0.5. Therefore the quantity r has the range

$$- 6.3 < r < 6.3, \text{ with a null value } r = 0. \text{ That is,}$$

the total error can be no greater than 6.3 times the standard error, and for values of p near the null value the error will be very small relative to the standard error.

This relationship is cited by the investigators as if giving assurance that the estimate of I will be good. Unfortunately, in the absence of information about K , the tumor rate in the sub - groups b. and c. not measured and followed, the estimate of I may be unacceptable. Assume, for example, that $J = .07$ and $K = .21$ and that the death certificate search yields an estimate $K' = .07$. That is, the death certificate cases may be similar to the measured cases, while the group c., not measured, surviving or dead and untraced, have a relatively high tumor rate. If the proportion measured and followed, m , is 0.5, then I is estimated as $I' = .07 \pm .01$ while the true value of I is $\frac{1}{2} (.07 + .21) = .14 \pm .02$. Here the total error is .07 which is 3.5 times the standard error of I . This total error, however, is 7.0 times the standard error of I' . That is, the known quantities I' and $SE(I')$ give no indication that the estimate is only one - half the true value.

By selecting estimates of bias B in the range 0.7 to 1.3 the investigators suggest that the bias of 0.33 implied in the above example is improbable. As noted in section 2, above, no justification is given for this assumption.

4. The analysis given by the investigators assumes that sub - groups of the population defined by completeness of measurement and follow - up are comparable in number of years of risk at various intervals

since beginning and since ending accumulation of radium burden. Information on this question will presumably be available for patients on objective lists, and suitable modifications in analysis will be possible.

The analysis concerns total exposed groups, as, for example, employees of specified companies. Rates of interest, however, are rates for sub - groups with radium burdens in specified ranges. In general, estimates of burdens are available only for the measured sub - groups, so that the size of the unmeasured sub - groups in limited ranges of burden will not be known. The analysis does not consider the question of estimates of error due to bias within such sub - groups.