NRC FORM 173 (2-78) U.S. NUCLEAR REGULATORY COMMISSION

STANDARD ORDER FOR DOE WORK

ORDER NUMBER: 10-79-68

DATE: AUG 28 1979

ISSUED TO: (DOE Office)	ISSUED BY: (NRC Office)
Chicago Operations Office	Office of Standards Development

ACCOUNTING CITATION

APPROPRIATION SYMBOL:

B&R NUMBER: 10-19-03-06-3

FIN NUMBER: A 20679

PERFORMING ORGANIZATION AND LOCATION: Argonne National Laboratory

FIN TITLE: Reanalysis of the Tri- State Leukemia Survey Data

WORK PERIOD - THIS ORDER

FIXED ☐	ESTIMATED ☒
FROM: 9-1-79	TO: 9-30-80

OBLIGATION AVAILABILITY PROVIDED BY:

A. THIS ORDER	$ 67,000
B. TOTAL OF ORDERS PLACED PRIOR TO THIS DATE WITH THE PERFORMING ORGANIZATION UNDER THE SAME "APPROPRIATION SYMBOL" AND THE FIRST FOUR DIGITS OF THE "B&R NUMBER" CITED ABOVE.	$ 518,000
C. TOTAL ORDERS TO DATE (TOTAL A & B)	$ 585,000
D. AMOUNT INCLUDED IN "C" APPLICABLE TO THE "FIN NUMBER" CITED IN THIS ORDER.	$ 67,000

FINANCIAL FLEXIBILITY:

☐ FUNDS WILL NOT BE REPROGRAMMED BETWEEN FINS. LINE D CONSTITUTES A LIMITATION ON OBLIGATIONS AUTHORIZED.

☒ FUNDS MAY BE REPROGRAMMED NOT TO EXCEED ± 10% OF FIN LEVEL UP TO $50K. LINE C CONSTITUTES A LIMITATION ON OBLIGATIONS AUTHORIZED.

STANDARD TERMS AND CONDITIONS PROVIDED DOE ARE CONSIDERED PART OF THIS ORDER UNLESS OTHERWISE NOTED.

ATTACHMENTS:
THE FOLLOWING ATTACHMENTS ARE HEREBY MADE A PART OF THIS ORDER:

☒ STATEMENT OF WORK
☐ ADDITIONAL TERMS AND CONDITIONS
☐ OTHER

SECURITY:

☒ WORK ON THIS ORDER IS NOT CLASSIFIED.
☐ WORK ON THIS ORDER INVOLVES CLASSIFIED INFORMATION. NRC FORM 187 IS ATTACHED.

REMARKS:

Reference: Form 189, submitted 8-9-79 for $67,000.

NOTE: SD cannot fund capital equipment costs.

ISSUING AUTHORITY	ACCEPTING ORGANIZATION
SIGNATURE: Robert B. Minogue 8/29/79	SIGNATURE:
TITLE: Director, Office of Standards Development	TITLE:
NRC FORM 173 (2-78)	DATE:

8105050291

STATEMENT OF WORK

REANALYSIS OF THE TRI-STATE LEUKEMIA SURVEY DATA WITH SPECIAL REFERENCE TO THE LEUKEMOGENIC POTENTIAL OF DIAGNOSTIC X-RAYS

FIN: A20679, B&R: 10-19-03-06-3

1.0 BACKGROUND

The present controversy surrounding the magnitude and extent of human health effects from low-levels of ionizing radiation necessitates continued research efforts in this area. Of particular interest, are data regarding populations exposed to low and/or chronic levels of low LET ionizing radiation, such as is reflected in the Tri-state data base, the subject of the presently proposed reanalysis.

The objectives of this project are to produce testable theories and hypotheses regarding the leukemogenic potential of diagnostic x-rays and to identify or reject some of the less plausible models proposed by other workers.

2.0 WORK REQUIRED

Perform a re-analysis of the adult portion of the Tri-state data, accomplishing the following specific tasks:

a) calculate age-standardized relative risks of adult leukemia for non-overlapping x-ray exposure categories-develop absolute risk estimates which can be related to existing absolute risk estimates for low-level low-LET radiation leukemogenesis

b) investigate possible relationships between radiation exposure, disease, and leukemogenesis in adults - discuss these findings in the context of susceptible subgroups for radiation leukemogenesis

c) investigate the possible influence of other variables e.g., temporal aspects of exposure, ethnic, socioeconomic on the relationship between diagnostic x-ray exposure and leukemogenesis

d) develop explanatory models and generate testable hypotheses to account for the Tri-state data

3.0 REPORTING REQUIREMENTS

3.1 MONTHLY LETTER STATUS REPORT

Each month the performing organization shall submit a brief letter status report which summarizes: the work performed during the previous month, personnel time expenditures during the previous month, and costs generated against the work effort. Any change to cost projections should be indicated.

3.2 QUARTERLY AND FINAL TECHNICAL REPORTS

Each quarter the performing organization shall submit a report which describes the work performed - the final report shall be submitted for NRC staff review in draft form for NRC policy, management, regulatory, and legal issues.

4.0 MEETINGS AND TRAVEL

As deemed necessary to keep fully abreast of progress of the contract, and to gather and disseminate information relating to the completion of the contract.

5.0 NRC FURNISHED MATERIAL

None.

6.0 PERIOD OF PERFORMANCE

Performance under this contract will commence on the effective date of this contract and will be completed, including the final report, within a period of one year.

7.0 TECHNICAL DIRECTION

Mr. Stephen C. Whitfield (301) 443-5860 has been designated as the NRC technical monitor for this effort.

8.0 DISPOSAL OF PROPERTY

N/A.

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PROGRAM BUDGET

IDENT. NO.

1. TITLE

"Reanalysis of the Tri-state Leukemia Survey Data with Special Reference to the Leukemogenic Potential of Diagnostic X-rays"

ARGONNE NATIONAL LABORATORY
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2. BUDGET ACTIVITY NO.
DOE 40-10-01-01 NRC 10-19-03-06-3
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3. SCIENTIST RESPONSIBLE
M. E. Ginevan/D. Grahn

4. WORK STARTED
FY 1979

5. RELATED WORK (With Same Contractor or Others)
DOE GK-01-02-01-1, Human Health Effects from Energy Generation
NRC 60-19-30-01 (A2059/8M419) Projection Models for Health Effects Assessment

6. PERSON POWER AND COST DATA

	FY 1979	FY 1980 PRESIDENT'S BUDGET	FY 1980 INCREM. REQUIRE.	FY 1981
6a. DIRECT PERSON POWER (Person Years)				
SCIENTIFIC				
REGULAR	0.1	0.9	-	1.0
TEMP. PAID BY ANL	-	-	-	-
TOTAL SCIENTIFIC	0.1	0.9	-	1.0
OTHER TECHNICAL				
REGULAR	-	-	-	-
TEMP. PAID BY ANL	-	-	-	-
TOTAL OTHER TECHNICAL	-	-	-	-
TOTAL PERSON YEARS	0.1	0.9	-	1.0
6b. OPERATING COSTS (In Thousands)				
DIRECT SALARIES	$ 3	$30	-	$36
MATERIALS AND SERVICES	1	5	-	6
MAJOR PROCUREMENTS	0	0	-	0
INDIRECT COSTS	2	26	-	30
TOTAL COST	$ 6	$61*	-	$72
6c. CAPITAL EQUIPMENT (In Thousands)	$ 5	$ 0	$ 0	$ 0

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*FY1979 Carryover

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6d. MAJOR PROCUREMENTS (In Thousands)

None

6e. COST (RECAP OF SUBACTIVITIES) (In Thousands)

Not Applicable

7. EXPLANATION OF MAJOR PROCUREMENTS

Not Applicable

8. EXPLANATION OF CAPITAL EQUIPMENT

The requested $5,000 for capital equipment in FY 1979 is to cover the cost of a desired purchase of a 1200 baud CRT/hard copy work station, at an estimated cost of $5,000. Since the proposed study involves data analysis and mathematical modeling almost exclusively, an additional modern high speed work station is required. The terminals which we have at present were acquired for and are fully utilized by ongoing projects. Further, existing terminals are rather slow (300 baud) and thus ill suited to large scale data analysis and modeling applications.

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9. INTRODUCTION

Several recent papers (Bross et al., 1979; Bross and Natarajan, 1972, 1977; Bertell, 1977), based on the Tri-state leukemia survey data (Graham et al., 1963), have suggested that low-level exposure to diagnostic X-rays may pose a greater hazard to human health than previously thought. These conclusions are far from universally accepted (Boice and Land, 1979; Ginevan, 1979), and indeed are contradicted in part by the original Tri-state studies (Graham et al., 1966; Gibson et al., 1972). However, they do raise some questions as to the appropriate interpretation of these data which can only be resolved by extensive reanalysis.

We have a complete copy of the Tri-state data base, and propose to perform such a reanalysis. The questions to be addressed fall into two major areas, the shape of the adult dose-response function (that is, to what extent does increasing X-ray exposure to adults increase adult leukemia risk), and the degree to which preconception, intrauterine, and postnatal exposure of children increases their leukemia risk.

10. ADULT STUDIES

The original Tri-state analysis, a retrospective case control study, which included 1414 leukemia cases and 1370 controls matched for age and sex, attempted to determine the effect of adult X-ray exposure on adult leukemia risk. This investigation showed an apparent increasing risk of nonlymphatic leukemia with X-ray dose in males, but no effect in females (Gibson et al., 1972). The analysis suffers from two main defects. First, leukemia risks were calculated for overlapping exposure categories. That is, risks for persons exposed to 11 or more, 16 or more, 21 or more, and 41 or more X-ray films were calculated. The problem with this approach is that the highest exposure is contained in all lower categories. Since the individuals in this category do, for nonlymphatic leukemia in males, show elevated leukemia risks, this tends to inflate the risk for all other categories (Ginevan, 1979).

The second major shortcoming of the original Tri-state analysis is that all X-ray exposures up to 1 year prior to leukemia diagnosis were considered. This could be a source of bias for two reasons: (1) Studies of the Hiroshima-Nagasaki survivors (Land and Norman, 1978) suggest that there is a latent period of 5 years or more between radiation exposure and onset of leukemia, and that the latent period increases with decreasing dose. While one may argue that complete correspondence between the case of the atomic bomb victims and the case of very low-level X-ray exposures is not to be expected, the fact remains that the temporal aspects of the X-ray exposures in the Tri-state survey have not been considered in any detail. (2) This first source of bias is complicated by the fact that leukemics may exhibit heightened sensitivity to pneumonia and other infectious disease prior to showing definite symptoms of leukemia

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Kneale, 1971; Stewart and Kneale, 1969). Since sick people are often X-rayed, it may be that excess X-ray exposures occurring within a few years of diagnosis are caused by leukemia rather than vice versa. It may also be that this is not the case in the Tri-state data. To date, the question has not been considered.

The studies of Bross et al. (1979) and Bertell (1977) also examine the Tri-state adult X-ray exposure data, with the thesis that X-rays, in very small doses, cause large increases in leukemia risks. The shortcomings of these studies, which are numerous, are considered in detail by Boice and Land (1979) and Ginevan (1979). One major problem is that the authors use specially developed statistical procedures that bear little correspondence to conventional analyses and which have not been subject to adequate peer review. Thus, the value of these studies is problematical. A further difficulty is that each paper restricts its attention to a subset of the Tri-state data (all males with nonlymphatic leukemia and males 45-65 years of age with nonlymphatic leukemia, respectively) that best illustrates the authors' contentions, and gives no attention to the rest of the Tri-state data or, indeed, to other relevant leukemia studies (i.e., Stewart et al., 1962; Gunz and Atkinson, 1964).

Whatever the cause of this oversight, the fact remains that the omitted data appear to support the general conclusion that small doses of diagnostic X-rays in adults are relatively harmless (Ginevan, 1979), rather than supporting the central argument of Bross et al. (1979) and Bertell (1977). Finally, as in the original Tri-state study, neither of these investigations considers the possibility of a latent period, or the possibility that apparent excess diagnostic X-ray exposures were the result of a preleukemic condition.

11. STUDIES OF PRECONCEPTION, PRENATAL, AND POSTNATAL X-RAY EXPOSURES OF CHILDREN

Three investigations have dealt extensively with the prenatal exposure portion of the Tri-state leukemia data (Graham et al., 1966; Bross and Natarajan, 1972, 1977). The original Tri-state case control analysis, which included 139 cases and 844 controls (Graham et al., 1966), considered preconception irradiation of parents and postnatal X-ray exposures of the children as well.

In the original Tri-state analysis of children's exposures (Graham et al., 1966) it was estimated that children exposed *in utero* experienced a relative leukemia risk of 1.40. This is in reasonable agreement with some other studies of the effect of intrauterine X-ray exposure (MacMahon, 1962; Stewart et al., 1958; Stewart, 1973). Their overall conclusions, however, are far from unequivocal for several reasons.

First, not all studies of intrauterine radiation have found excess leukemia risk. Court Brown et al. (1960), for example, followed about 40,000 children who had received intrauterine X-ray exposure. Nine leukemia cases were observed as opposed to 10.5 expected. On the basis of this observation, it is unlikely ($p < 0.05$) that the relative risk in the exposed group could have been as large as 1.5.

There are also some rather peculiar features in the intrauterine exposure portion of the Tri-state data. For example, only 27 cases and 54 controls actually received intrauterine radiation in the sense that the mother received an abdominal exposure. Another subset was comprised of 67 cases and 137 controls whose mothers had received nonabdominal exposure. When these two subsets were combined, and all cases of irradiation during pregnancy were considered (many presumably involving little fetal exposure) - a total of 94 cases and 191 controls - the relative risk of leukemia was approximately 1.40, or the same risk as that of those who had actually received abdominal exposure. Put another way, the presumptive X-ray dosage to the child seemed less important than whether or not the mother had been X-rayed.

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This impression is reinforced by the observation that those children whose mothers had reported preconception X-ray exposure to any site showed an even higher relative risk than those children who had received actual intrauterine exposure (1.59 vs. 1.4). Even more perplexing is the observation that children whose fathers had preconception irradiation (to any site) showed a relative risk of 1.3.. A final odd feature of the data is that the form of postnatal irradiation most strongly associated with increased leukemia risk is dental X-rays. As noted by Miller (1969), many of these results are biologically implausible.

The papers of Bross and Natarajan (1972, 1977) are interesting in that they suggest the existence of a small subgroup in the population that is particularly prone to leukemia and which is also particularly sensitive to radiation. The problem with their approach is, first, that all of the analyses presented ignore the fact that much of the intrauterine "exposure" considered consists of nonabdominal X-rays. A disturbing aspect of their second paper (Bross and Natarajan, 1977) is that of the original Tri-state data of 319 cases and 884 controls (Graham et al., 1966), only 138 cases and 393 controls are considered. No discussion of potential bias generated by discarding over half the data is provided. Finally, the second paper attempts to "prove" hypotheses generated in the first using the same data, or at least part of them and, further, utilizing the same sort of idiosyncratic statistical methodology found in Bross et al. (1979) which, as mentioned earlier, has not been subject to adequate peer review. Thus, these studies are of questionable value.

Clearly, in view of the many anomalous findings generated in the original Tri-state analysis of the child X-ray exposure data (Graham et al., 1966), and the suspect nature of the subsequent analyses of subsets of these data (Bross and Natarajan, 1972, 1977), a careful re-examination of these data is needed.

12. PROPOSED STUDIES

The overall goals of the proposed studies are to produce testable theories and hypotheses regarding the leukemogenic potential of diagnostic X-rays and to identify or reject some of the less plausible models proposed by other workers.

The first priority in our reanalysis of the Tri-state data will be calculation of age standardized relative risks of adult leukemia for non-overlapping X-ray exposure categories, for both sexes, and for all leukemia types considered in the original Tri-state study (acute lymphatic, chronic lymphatic, acute myelogenous, chronic myelogenous). As in the original study, statistical procedures involving the relative risk statistic or odds ratio discussed by Wolf (1955), Haldane (1956), Sheehe (1966), and Fleiss (1973) will be employed. In these calculations the size of the age strata used will be minimized as much as possible. In at least two studies (Bross et al,

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1979; Burtell, 1977) age strata 20 years wide were used. Such broad categories, especially in a disease like leukemia, whose incidence increases greatly with age (Doll, 1965) provide inadequate standardization. That is, leukemia risk increases with age and, if X-ray exposure tends to either increase or decrease with age (most likely the former), a positive or negative association might well result from inappropriate standardization.

In addition to age, sex, and X-ray exposure history, the adult portion of the Tri-state data includes information on disease history. This variable will receive particular scrutiny because, as mentioned earlier, some studies have suggested that persons with undiagnosed leukemia are particularly vulnerable to infectious diseases such as pneumonia (Kneale, 1971; Stewart and Kneale, 1969). We will determine if these observations are supported by the Tri-state data.

Information on the temporal aspects of X-ray exposure is also available. This will be utilized to examine the question of whether the pattern of X-ray exposure shown by the cases in the Tri-state study is consistent with a latency period hypothesis (Land and Norman, 1978). In both the disease history and temporal exposure history investigations, conventional relative risk analyses will be used (Wolf, 1955; Haldane, 1956; Sheehe, 1966; Fleiss, 1973).

The Tri-state data also contain information on such factors as ethnicity, education, occupation, and religion.

While there seems little a priori reason to think that such variables would greatly influence X-ray/leukemia relationships, it seems best to have considered all possibilities. We will therefore use either the stratification by multivariate confounder score methodology suggested by Miettinen (1976) together with discriminant function methodology (Lachenbruch and Goldstein, 1979), or the multivariate log linear methods discussed by Bishop et al. (1975) and Fienberg (1977) to consider the possibility that some multivariable function may, in fact, be responsible for observed X-ray/leukemia associations. The choice of the first or second approach will be dictated by examination of the data. These last analyses should be taken to be wholly exploratory, but might be valuable aids in hypothesis generation.

The final phase in the reanalysis of the adult portion of the Tri-state data will be devoted to construction of mathematical and verbal models which, based on the foregoing analyses, best describe the Tri-state data. In this last phase and throughout our studies considerable emphasis will be placed on integration of our findings with the results of other adult leukemia surveys (Gunz and Atkinson, 1964; Stewart et al., 1962; Stewart and Kneale, 1969; Kneale, 1971; Bross et al., 1979; Bertell, 1977) to provide the most complete picture possible of the relationship between adult leukemias and diagnostic X-rays.

Some progress in re-evaluation of the adult portion of the Tri-state data has already been made. The resulting paper, which has been accepted for publication in Health Physics (Ginevan, 1979), is included as Appendix I in the copies sent to NRC.

Re-evaluation of the child portion of the Tri-state data will address the many anomalous features of the original analysis. As in the adult data, conventional relative risk analyses will be used for the most part.

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First of all, it is of importance to determine the degree to which preconception, intrauterine (used here in the sense that the mother received any X-ray exposure during pregnancy), and postconception X-ray exposures are confounded. That is, it is not made clear in the original study the degree to which the elevated risk seen in children who received preconception irradiation may be a result of subsequent intrauterine or postnatal exposure or, similarly, the degree to which preconception irradiation may inflate observed risks of postnatal or intrauterine radiation. It seems reasonable to hypothesize that, especially in the era of the general practitioner (almost half the cases were born between 1945 and 1954), certain doctors would be more likely to order X-rays, which would in turn be reflected as large numbers of children showing all three types of exposure. It may be that the data will not allow the independent effects of the three sorts of irradiation to be sorted out, but the attempt should be made and the results should be clearly stated.

An examination of possible models of leukemia inheritance (i.e., through a single dominant or recessive gene, through the interaction of several genes, etc.) would also be of interest. These models would be used in examining the increase in leukemia incidence in children whose parents had been irradiated prior to conception and in determining whether this increased leukemia risk can be explained by a population genetic model and the available data on radiation effects on mutation rates (UNSCEAR, 1977). Such models could also be useful in sorting out the question of possibly confounded prenatal, intrauterine, and postnatal X-ray exposures. That is, for the confounded case, the genetic model could furnish at least an upper bound on the possible effect of prenatal exposure.

A third area which deserves close attention is the question of the association of children's disease history with leukemia risk and X-ray exposure. As noted above, it has been claimed that there is a subgroup of children who are particularly likely to contract leukemia and who are particularly sensitive to leukemia induction by diagnostic X-rays (Bross and Natarajan, 1972, 1977). This claim, which is based largely on disease history data, deserves re-examination within the context of the complete data set. Such a re-analysis would also have considerable bearing on the question of whether or not undiagnosed leukemics are particularly prone to bacterial diseases such as pneumonia (Kneale, 1971; Stewart and Kneale, 1969).

A fourth worthwhile area of inquiry concerning the child portion of the Tri-state data involves recalculation of risks of leukemia given different radiation exposures using multivariate confounder scores (Miettinen, 1976). This method is preferred because the large number of potentially important variables [year of birth, age at diagnosis (case) or interview (control), parity number, presence/absence of previous miscarriages or stillbirths, mother's age, father's age, father's education and/or occupation, ethnicity, etc.], together with the somewhat small

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number of cases (319) renders a multivariate log linear analysis (Bishop et al., 1975; Fienberg, 1977) difficult if not impossible. As in the adult data the confounder variables would be generated using discriminant analysis procedures (Lachenbruch and Goldstein, 1979).

As in the adult data considerable emphasis will be placed on the last phase which will consist of construction of verbal and mathematical models which will provide an integrated description of what the Tri-state data show concerning the effects of prenatal, intrauterine, and postnatal X-ray exposure on children's risk of contracting leukemia. In this phase particular attention will be focused on integrating the results of our analyses of the Tri-state data with the findings of other workers (MacMahon, 1962; Stewart et al., 1958; Stewart, 1973; Court Brown et al., 1960; Graham et al., 1966; Bross and Natarajan, 1972,1979).

The most direct result of the proposed research will be a better understanding of what the Tri-state data really say about the leukemogenic potential of diagnostic X-rays, both in the area of dose response relationships and in identifying factors other than X-rays that may influence an individual's risk of contracting leukemia. We hope this understanding will shed light on the relevance of other studies of leukemia and diagnostic X-rays and more general questions of radiation carcinogenesis as well.

13. PROPOSED SCHEDULE OF EFFORT

The proposed schedule of effort is shown in Figure 1. The analyses of the adult and child data form two non-overlapping but related one year projects. Each analysis is presently conceived as having four major, overlapping, related phases, each of about three months duration. Toward the end of the data analysis effort, a seven-month period will be devoted to model building and integration of our findings with those of other workers.

The last six months of effort is devoted exclusively to this last task because it is our view that a coherent synthesis is perhaps the most valuable contribution this sort of study can make, and is at the same time the most difficult task to do well.

Results of our studies will be published in the open literature. Such publications, often out of necessity, place a premium on brevity. Nonetheless, it is our belief that details, particularly in the context of standard setting, regarding the exact analyses employed and results obtained are of great importance. Therefore, to make comprehensive accounts of our studies generally available, details will be presented in the form of Argonne reports.

14. LITERATURE CITED

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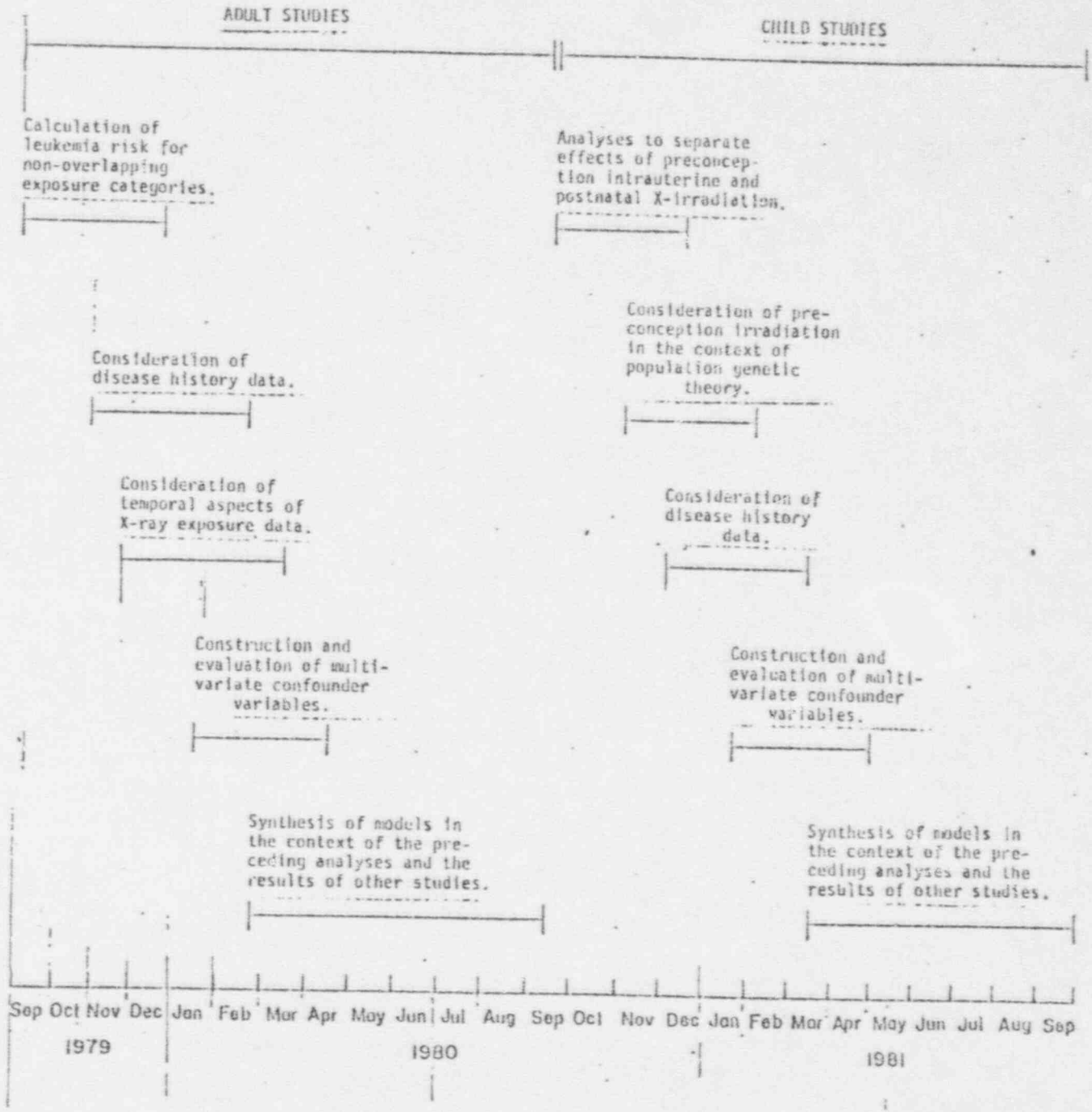

Figure 1. Proposed schedule of effort.