Environmental Epidemiology:
Risk Assessment

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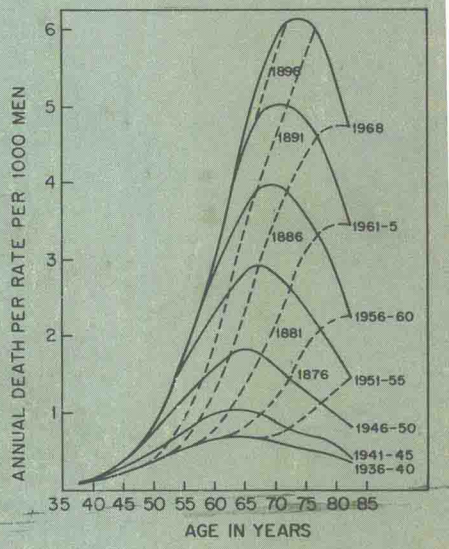

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Environmental Epidemiology: Risk Assessment

Ross L. Prentice and
Alice S. Whittemore, *editors*

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PREFACE

In 1974 SIMS embarked on a series of five-day Research Application Conferences (RAC's) at Alta, Utah, for the purpose of probing in depth selected societal fields in light of their susceptibility to mathematical analysis and their concern to society. The first seven conferences dealt with ecosystems, epidemiology, energy, environmental health, time series and ecological processes, energy and health, and energy conversion and fluid mechanics.

These proceedings are a result of the eighth conference, on environmental epidemiology - risk assessment, which was held in 1982. The twenty-five speakers and observers contributed their expertise in such disciplines as biometry, environmental medicine, epidemiology, mathematics and statistics. Considerable attention was given to assessing risk due to environmental agents, particularly those known or suspected to be carcinogenic; both the complex medical issues involved and the mathematical and statistical methodologies used in analysis were presented. Ross L. Prentice of the University of Washington (Seattle) and Alice S. Whittemore of Stanford University co-chaired the Conference. Donald R. Snow of Brigham Young University was Local Coordinator.

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D. L. Thomsen, Jr.
President, SIMS

September 1982

INTRODUCTION

Risk to health from environmental toxicants is a subject of intense public concern. Within this century, technological advances and energy needs in the industrialized world have reaped an unwelcome harvest of real and potential harm to man. The types of harm are well-known and dreaded: cancer, birth defects, chronic lung disease, growth disturbances, chromosomal abnormalities. Most of these effects take decades to manifest themselves, and most are irreversible. Consequently public health emphasis has increasingly focused on preventive medicine. Essential to sound decisions in the control of toxic exposures is accurate assessment of human risks through environmental epidemiology.

Few endeavors are more problematic and subject to controversy than is health risk assessment based on human data. Such assessment must cope with a number of formidable obstacles. Mechanisms for disease causation are poorly understood. Most toxic exposures occur chronically and at low and variable levels. These exposures are measured with substantial error. Monitoring populations for disease is time-consuming, expensive, and vulnerable to serious bias. Comparisons between exposed and unexposed populations are confounded by differences in smoking and other determinants of health. To obtain valid estimates of risk in the face of these and other obstacles, one needs sensitive, robust and sophisticated methods for the design and analysis of epidemiological studies. In June 1982, SIMS held a conference on the development and application of such methods, and the Proceedings of this Conference are presented here.

The new discipline of environmental risk assessment has grown rapidly within the past two decades, and this growth is reflected by powerful new methodological tools. Progress in methodology has been charted in a series of SIMS Conferences. A Conference in 1976 (1) discussed the use of new statistical models (e.g., the proportional hazards model, the logistic model, and loglinear models) that have proved useful in circumventing some of the above obstacles. These models were applied to study cancer and pulmonary disease associated with environmental exposures. A related Conference in 1978 (2) continued this theme, but focused specifically on methodologies for determining the health risks associated with alternative energy sources. The present Conference, and the papers in this volume which record it, indicate the broad utility of the new methods, as well as alternatives, improvements and refinements that have developed within the last few years.

The papers are arranged in five sections of two to five papers per section. Section One contains four papers concerned with risk assessment among populations whose exposure varies geographically. Two of the papers discuss the analysis of cancer incidence and mortality among Japanese atomic bomb survivors. A third paper reports on a study of cancer incidence and water pollutants, while the final paper describes

the problems in searching for reproductive hazards associated with aerial pesticide spraying. All of these papers grapple with exposure errors and difficulties in effectively monitoring populations at risk.

Cancer risk assessment among occupationally exposed populations is addressed by the five papers in Section Two. The occupational exposures are radiation (two papers), asbestos fibers (two papers), and arsenic (one paper). These papers have several features in common. All rely on an internal control within the exposed group instead of a general population control. Several use mechanistic carcinogenesis models to help interpret estimated exposure-response relationships. All face the issue of which exposure index to use when searching for relationships to disease.

The two papers in Section Three deal with risk assessment in populations screened for cancer. The first describes methods for estimating characteristics of the disease process and of the screening program effectiveness. The second addresses issues that arise in the conduct of case-control studies if cases are identified through a screening program. Both papers contend with limitations on the generalizability of results obtained using special populations.

A key ingredient of the papers in Sections One to Three is the use of standard cohort or (possibly synthetic) case-control study designs. The papers in Section Four elucidate issues confronted when departing from these standard designs by using data from vital statistics publications or from cooperative clinical trials in cancer therapy. The first paper considers advantages and disadvantages in the use of aggregate cancer mortality data in relation to aggregate data on average cigarette consumption. The second paper describes a variant of the case-control study in which disease-free control selection is replaced by selection of other case series. The two papers discuss the difficulties encountered when using relatively inexpensive existing disease data.

The final section contains two papers with a predominantly methodological flavor. The first discusses the flexibility of the logistic regression model for environmental risk assessment. The second discusses alternatives to the proportional hazards model that may be useful in the analysis of certain types of environmental data.

The presentations in this Proceedings indicate definite progress in the quantification of human risk from toxic exposures even in the relatively short time span since the 1976 SIMS Conference. Many of the obstacles in environmental epidemiology remain large and intractable. Nevertheless, improved study design and analysis can curb the limitations imposed by these obstacles, and provide a framework for more accurate and precise assessment of human risk. Continued progress toward this goal is essential for rational societal decisions concerning exposure to environmental toxicants.

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CONTENTS

SECTION ONE
Risk Assessment Among Geographically Exposed Populations

Papers in this section are concerned with assessment of the health consequences of geographically determined exposures. In the atomic bomb survivor studies discussed by Beebe and by Prentice radiation exposures were essentially instantaneous. Health consequences of interest range from cancer incidence and mortality, to chromosomal abnormalities to birth and growth abnormalities. In the studies of Iowa water quality and water treatment procedures discussed by Wallace the 'exposures' of interest are essentially continuous while elevated cancer incidence is the primary potential health concern. Chemical (malathion) exposures associated with aerial spraying for the medfly are discussed by Pettiti, along with issues that would arise in a study to identify reproductive risks associated with such spraying.

Limitations on the quality of individual subject exposure histories are an important consideration in such risk assessment efforts. Usually it will be necessary to impute such histories from the individual's recall of his location and environment during times of exposure. In the case of the radiation or chemical exposures mentioned above these data then need to be combined with information or assumption concerning dose levels as a function of distance from point sources and as a function of shielding by natural barriers or by buildings, in order to estimate exposure histories. In the case of the water quality data the individual's residential history needs to be combined with information or assumption on water intake levels and on dietary intakes. Exposure history levels in such studies are thereby subject to substantial random variation and may also involve important systematic bias. Data collection and analysis efforts need to address this important limitation, particularly for the production of quantitative dose-response estimates.

The ability to effectively monitor the health consequences of interest is an essential ingredient of this type of risk assessment effort. The definition of the cohort to be monitored may require care since geographical exposures may not adhere naturally to any administrative unit with an available census. Migration may complicate health effects monitoring in long-term follow-up studies. For example, it is the availability of a Japanese national family registration system that permits quality monitoring of cancer mortality among atomic bomb survivors and the availability of a population based cancer registry that permits quality monitoring of cancer incidence in Iowa.

The papers in this section provide a valuable record of approaches to address these and other methodolgic issues among three diverse geographically exposed populations.

Assessment of Health Risks from Exposure to Ionizing Radiation

Gilbert W. Beebe *

Abstract. Rapid development in the assessment of health risks from exposure to ionizing radiation has produced an impressive array of risk differentials of presumed biologic significance. In the human data these differentials involve: (A) the variety of cancer, especially its site; (B) host factors, especially age; (C) time following exposure; (D) magnitude of dose; and (E) type of radiation. From experimental work we may presume that dose-rate also plays a role, especially for sparsely ionizing radiation. Current research is extending the scope of differentials with respect to these and other variables, including cell type and concomitant environmental risk factors, and testing dose-response models suggested by experimental and theoretical work. As facts to be explained, differentials in risk may lead to hypotheses to be explored experimentally and improve our understanding of how ionizing radiation causes cancer.

1. Introduction. The health effects of ionizing radiation are of different kinds (1). There is every reason to believe that there are genetic effects in man even though they have not yet been demonstrated (2). And in addition to cancer there are non-carcinogenic effects, i.e., infertility, birth defects, cataracts, impaired growth, and chromosomal aberrations. Different end-points may require different measures of risk.

How the radiogenic excess is distributed in time varies among the somatic end-points of interest. Particular attention attaches to the cancers that are superimposed on natural incidence in a fairly characteristic pattern. That is, it is only some years after exposure that the excess will even begin to appear, following which it may peak

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or plateau, and then, as in the case of leukemia, fade out. Excess solid tumors may continue to appear to the end of life. In contrast, small head size induced by radiation is evident at birth and persists throughout life. Cataracts induced by ionizing radiation differ only in not being so immediately evident. For these two effects one would generally estimate risk as the number of excess events per individual exposed to a given dose. Chromosomal aberrations are somewhat different in that many forms are unstable and tend to disappear in time while other forms tend to persist for decades. When the sampling is performed, therefore, may influence the level and the variety of the radiation-induced changes that can be observed. Infertility risk estimates present special problems with respect to time. We may have an immediate, permanent sterility or a lowering of fertility that is merely temporary. Finally, although growth only takes place in time, the detection and measurement of impaired growth may depend on the observation of a deficit at a fixed point in time or at a fixed age, or on the calculation of a growth rate.

The consideration of how radiation-induced events are distributed in time leads to a series of risk measures that may be broadly classified as prevalence measures or incidence measures. Greatest interest attaches to the estimation of the risk of radiogenic cancer, which depends on incidence measures.

2. Risk Estimates for Radiogenic Cancer. The form of the UNSCEAR (3) and BEIR I (4) estimates for cancer will serve as a convenient basis for discussing incidence measures of risk, and much of this will also be relevant to the prevalence measures:

$$\text{Radiogenic cancer risk} = \frac{\text{(Observed - Expected) Cancers}}{\text{Millions of Person-years x Mean Dose}}$$

Regression methods require the same elements except for the explicit representation of the expected number of cancers.

2.1 The Cancers To Be Observed. The observed cancers may be of all sites, a single site, or some presumably meaningful subset of sites. And within a single site we may distinguish histologic subtypes. For leukemia we must distinguish cell-types since it is well established that chronic lymphocytic leukemia is not radiogenic and it may have a high natural incidence in the later decades of life (5).

One of the most interesting aspects of the cancers themselves is the hierarchy of risk into which the various organs and tissues fall, with breast, thyroid, and bone marrow at the top whether absolute or relative measures of risk are used. The order among them depends only on which measure is used. One remarkable feature of the hierarchical sequence of risk by target tissue is that it bears no relation to natural incidence. Leukemia and thyroid cancer are relatively

uncommon forms of cancer, breast the most common in women. Lung cancer, the most common cancer in men, occupies an intermediate position in the hierarchy. Next to lung cancer prostate cancer is the most common in US males, but is at the low end of the radiogenic risk scale. The uterus (corpus) and cervix are next to the breast in frequency of involvement in women, but are also found at the low end of the scale of radiogenic risk. The fact that absolute risk estimates vary so markedly among the various organs and tissues of the body also suggests that our risk estimates may be too crude, e.g., that more account needs to be taken of the identity and number of vulnerable cells, or of mitotic activity or some other cellular characteristic.

2.2 Derivation of Expected Numbers. Since the radiogenic tumors cannot be identified individually but only estimated as an excess number, the basis for calculating expected numbers becomes very important. In planning the mortality studies of the A-bomb survivors in Japan, for example, it was decided that a comparison group be formed of individuals who were not in the city (NIC) at the time of the bomb but who met the requirements as to 1950 residence in Hiroshima or Nagasaki (6). Although these were the cities of longest residence for about half of the NIC group, about half had resided overseas for some years and 20 percent for nine or more years before 1950 (7). Whatever may have been the selective factors involved in their post-war migration, the NIC group as a whole had a different health history from the A-bomb survivors and in the early years of the study (1950-1954) a very favorable mortality in relation to the nation as a whole, not merely to the A-bomb survivors (8). In the second half of the decade, however, the standard mortality ratios (SMR's) for the NIC group were relatively normal for all diseases combined and for all malignant neoplasms as a class, so that, in analyses that do not include the first five years of the follow-up period (which starts in 1950), the NIC group may be combined with the 0-rad dose group as a comparison or baseline group.

Court-Brown, Doll, and Smith (9-13) have always used British national mortality rates as their basis of expectation for the mortality of the ankylosing spondylitis patients treated by x-ray. Individuals suffering from this disease are known to have excess mortality, and in their reports the investigators have dealt separately with causes of death known to be associated with the disease, so that the contribution of the radiation to excess mortality might be more precisely assessed. Fortunately, there is now in the literature a report by Smith et al (14) on a follow-up study of ankylosing spondylitis patients from the same source as the x-ray series but not treated by x-ray. Although the latter series is much smaller, it supports the interpretation that excess cancer (except colon) in the x-ray series is radiogenic.

The SMR approach presents particular difficulties in studying occupational exposure, but nice alternatives are hard to find. Although Court-Brown and Doll employed the SMR approach in their study of British radiologists (15-16), they were able to refine the comparisons with cause-specific expectations based on men in social class I as the closest approximation to medical practitioners as a class.

In planning the Hopkins study of US radiologists, Seltser and Sartwell selected other medical specialists for comparison with radiologists who were members of the Radiological Society of North America (17). They chose other societies of specialists thought to have minimal occupational exposure to ionizing radiation. Even so, in addition to the finding of differential mortality rates for cancer as expected, the investigators have found excess mortality for many other causes and have argued that the results are consistent with the hypothesis of radiation-accelerated aging (17-18). No other major study presenting human evidence on this point gives diseases other than cancer as the cause of radiation-induced life-shortening (14,16,19,20).

Sibling controls have been used in several major studies, one by Hempelmann et al on thyroid cancer following irradiation of the thymus in infancy (21), one by Modan et al on cancer following epilating doses of x-ray to the scalp for tinea capitis (22-23), and another by Shore et al on breast cancer following x-ray therapy for acute postpartum mastitis (24). The tinea capitis study, performed in Israel, employed a second, general population, control matched on sex, age (within 2 years), country of origin, and year of immigration. The two control groups were quite homogeneous as to cancer incidence and their use led to similar risk estimates. In the mastitis study the sampling plan included 3 control groups devised to rule out alternative explanations for any apparent excess in breast cancer associated with x-ray therapy. The three control groups were so similar as to breast cancer incidence that they were combined in the analysis.

2.3 The Subjects at Risk. Selection of the persons for whom risk is to be estimated poses interesting and complex issues for the statistician, basically because radiation-induced risks vary so greatly with host factors and perhaps with other environmental factors. Unfortunately these factors have not been completely identified and the influence of none of them has been fully determined. We have only just begun to understand the role of age at exposure, for example, and are learning that its influence may vary from tumor to tumor (5). In leukemia, the highest risks, whether they be relative or absolute in form, are for individuals exposed either early in life or late in life (12,25). Mortality from all radiogenic solid tumors combined is greatest in A-bomb survivors who were 50 or older at exposure in 1945 if risk is measured in absolute terms, e.g.,

as excess cancers per million persons per year per rad, but the relative risk estimate is highest for those in the first decade of life at exposure, although the latter is based on few deaths (13 in the 100+ rads group through 1978) (26). For lung cancer both absolute and relative risk estimates are highest for those aged 50 or older in 1945, and no excess risk is as yet evident among those under 10 in 1945 (26). For breast cancer the influence of age is still different, those at highest risk thus far being women who were 10-19 in 1945, and no excess cancers having been seen among those who were under 10 in 1945 until 1980 (27). Goals of the work on breast cancer include a description of the age variation in risk and some determination of its basis. Because the structure and composition of breast tissue undergo great changes over the life cycle, there is reason to hope that the investigation of the carcinogenic risk in relation not only to age but also to such signal events as menarche, pregnancy, and menopause may be informative. Since breast tissue is highly sensitive to the carcinogenic action of ionizing radiation, and many characteristics of reproductive life are associated with the risk of breast cancer normally, there is also interest in learning whether any of those factors interact with radiation to enhance or reduce combined effects. Thus far preliminary reports have been largely negative (28-30). The risk of thyroid cancer may be greater in individuals exposed in the first two decades of life (31), but the statistical evidence is far from conclusive and the recent BEIR III report gives only a single estimate for all ages at exposure (5).

There is much less information on the role of sex in risk estimation. Apart from differences associated with sex-specific organs, the known sex differences in risk involve only leukemia and thyroid cancer. Males have higher absolute risk estimates for leukemia but the lower values for thyroid cancer. Do these differences merely reflect differences in natural incidence and mortality? The only hard data on this point are for leukemia among the Japanese A-bomb survivors in which males also have a higher relative risk than females (5). For thyroid cancer the male:female ratio of the absolute risks is 1:2.6 (5), but this is close to the ratio of the natural incidence rates, 1:2 in the Third National Cancer Survey by NCI in 1969-1971 (32). Sex differences merit more attention than they have received.

There must be other host factors that influence radiation-induced cancer risks. Differences between risk estimates for the Japanese and those for the population of North America and UK have attracted attention, particularly for breast cancer, but age-specific analyses have shown little or no difference when risk estimates are expressed in absolute terms (33). But relative risks, of course, are very different, since breast cancer is very much less common among Japanese women in Japan; among second-generation Japanese in the US, breast cancer incidence approaches that of the US population generally (34). In the New York Bellevue Hospital series of tinea capitis patients treated by x-ray, basal cell carcinomas are observed in white patients

but not in black (35). Hempelmann et al have reported that the risk of thyroid cancer among Jews following x-ray of the thymus in infancy is three times that among non-Jews (21).

Discussions of other host factors of potential significance include immune competence, hormonal status, and capacity for DNA repair. Individual susceptability to radiation at the level of cell-killing is well known, e.g., in patients with ataxia-telangiectasia (AT) (36). But such sensitivity has not been shown to be expressed in the form of cancer. The concern is, of course, that there may be subsets of the population of sufficient size and sensitivity to the carcinogenic action of ionizing radiation to influence the shape of the dose-response curves for cancer in the low-dose region (37). For example, heterozygotes for AT are thought to comprise one percent of the population and there are other genetic defects affecting DNA repair mechanisms.

An outstanding controversy in radiation epidemiology concerns the possibly much greater sensitivity of the fetus to the carcinogenic action of ionizing radiation. In 1956 Stewart and her associates began publishing data from the Oxford Childhood Cancer Survey (38) suggesting that doses of x-ray on the order of a few rads delivered to the fetus during pelvimetry were associated with an increased risk of cancer in the first decade of life. MacMahon confirmed the finding in the US in 1962 (39) but many, including MacMahon in 1980 (40), have not accepted the causal nature of the association (41-43). If, indeed, a few rads to the fetus increase the risk of childhood cancer by 50 percent or more, then fetal tissue is very much more sensitive than that of children in the initial years of life.

Other risk factors for cancer, e.g., occupational exposures, may interact with ionizing radiation to enhance the combined risk, but such studies are difficult and there is as yet no real evidence on the issue. Smoking has been studied together with radiation as to their joint effect on lung cancer, but without clear-cut results. A small study of A-bomb survivors provides no evidence of interaction (44). Early studies of uranium miners (45) suggested that radiation from radon and radon daughters interacted with cigarette smoking to enhance their joint effect on lung cancer. Subsequent papers (46,47) have considered the possibility that the effect of smoking was mainly to accelerate the appearance of excess lung cancer rather than to interact with ionizing radiation in some multiplicative way.

2.4 The Role of Calendar Time. Radiogenic cancer has a fairly characteristic temporal pattern: subsequent to exposure there is an initial latent period of some years, followed by a long interval of expression, perhaps with a peak, and then subsidence, at least for leukemia and bone cancer. There is not much precision to our knowledge of this pattern except for leukemia, where relative risks are high, and in at least two series there is clear evidence that the

period of expression is not indefinitely long (12,26). The upswing in leukemia among A-bomb survivors began in 1947 or 1948, two or three years after exposure (48) and long before 1978 it was clear that the excess had ceased in Nagasaki and was approaching zero in Hiroshima (26). In the ankylosing spondylitis series the beginning of expression is less readily identified, as the observed deaths in the first 2.5 years after x-ray include three deaths in the same year as the treatment, and it is thought that the leukemia in those several cases was the cause of the symptoms that led to treatment (12). In both series there is a marked peak in radiogenic leukemia when the temporal distribution is examined, at 4-5 years in the ankylosing spondylitis patients (12), and 5-7 years in the A-bomb survivors (48). Thereafter the excess pursues a rapidly downhill course.

For solid tumors, where relative risks are much lower, it is more difficult to demonstrate the end of the minimal latent period following exposure. But it is clear that the latent periods are longer for solid tumors than for the leukemias, on the order of ten years rather than two or three. In their recent analysis of the ankylosing spondylitis series Smith and Doll suggest that excess cancer mortality from solid tumors of the heavily irradiated sites began about 9 years after exposure (12). A numerical excess in the first five years is ascribed to diagnostic error. The interval 9-11 years after treatment was also the period of peak expression, following which relative risks declined progressively. Among the A-bomb survivors there was significant excess mortality from solid tumors in the interval 1950-1954 that has never been fully explained. In the next 4 years, 1955-1958, the linear regression coefficient for the dependence of cancer deaths on dose was negative. Thereafter, however, and through 1978 (the last year of observation), regression coefficients were significantly above zero and rose steadily. The highest absolute risk coefficient is that for the most recent period, 1975-1978 (26). Relative risk ratios, however, show no clearly rising pattern over time.

Whether the latent period is shorter for high-dose exposure remains an unsettled issue. In their age-specific analysis of leukemia, lung cancer, and breast cancer, Land and Norman showed that the temporal distribution of radiogenic cancers of the lung and breast is probably unrelated to dose and suggested that relative measures of risk may be more appropriate than absolute measures for these tumors (49). Radiogenic leukemias, however, with their sharp early peak incidence following exposure, are distributed quite differently from normally occurring leukemias, and since the peaks are higher for high-dose cases proportionately more of them do occur earlier (50).

The temporal distribution of radiogenic tumors depends heavily on age at exposure. In A-bomb survivors under age 15 in 1945 excess mortality from acute leukemia began promptly at a high level, but disappeared by 1960. In those 15-29 in 1945, excess mortality also