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UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D. C. 20555

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MEMORANDUM FOR: (See Attached List)

FROM: Robert E. Alexander, Chief
Health Effects and Occupational
Radiation Protection Branch, RES

SUBJECT: INFORMATION PAPER ON RADIATION EPIDEMIOLOGY

The attached information paper was prepared by Dr. Michael E. Ginevan, who is a biostatistician in my branch. It has been presented to the Commission as part of an answer to questions regarding epidemiologic issues which arose in a Commission briefing on the proposed revision of 10 CFR Part 20. I think that Dr. Ginevan's paper provides an easily-understood, non-technical treatment of many of the important issues concerning radiation epidemiology studies. I hope you find it useful.

Robert E. Alexander, Chief
Health Effects and Occupational Radiation
Protection Branch, RES

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Answers to Common Questions Regarding
Radiation Epidemiology
by
Michael E. Ginevan

In 1980 the Nuclear Regulatory Commission issued NUREG/CR-1728, "The Feasibility of Epidemiologic Investigations of the Health Effects of Low Level Ionizing Radiation," which as its title implies, evaluated the potential for further epidemiologic studies of health effects of ionizing radiation. In the same year, the National Academy of Sciences issued the report "The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980" which is commonly referred to as the "BEIR III Report." Authoritative answers to many questions regarding radioepidemiology and radioepidemiologic studies can be found in these two documents. However, since the combined length of these documents approaches 1000 pages, they are hardly a handy reference. Further, both publications are oriented toward a technical audience, and thus may omit answers to elementary questions which nonetheless are repeatedly asked. The following material was prepared as a "quick reference" for questions and issues regarding radioepidemiologic studies. It is presented in question and answer format. The questions addressed are those which experience suggests arise most often. The tone of the answers is deliberately nontechnical and is meant to provide an aid to answering questions from nonspecialists.

Question #1: What is epidemiology?

Answer #1: Epidemiology is the study of the distribution and determinants of disease frequency in man. Two basic types of study are generally pursued. In the first (prospective), a group of persons who have received some unusual exposure, such as the survivors of the atomic bombings of Hiroshima and Nagasaki, are followed through time to determine what, if any, diseases might show excess incidence and thus be caused by this exposure. The second study type (retrospective) examines persons with a specific disease to determine what, if any, exposures they might have experienced with unusual frequency and which thus might have caused their disease. In either case, disease incidence or exposure excesses are determined by comparing the study group to a group of controls consisting of an unexposed or healthy population which is comparable in terms of age structure, sex ratio, and other relevant characteristics such as proportion of cigarette smokers. In such comparisons, the criteria for making conclusions whether excesses are present are statistical. That is, one makes conclusions based on whether the probability that the study and control populations have the same disease incidence experience (prospective study) or exposure experience (retrospective study) is large or small.

Question #2: Do epidemiologic studies settle questions of disease causation in a definitive manner?

Answer #2: Generally no. All that an epidemiologic study can do is suggest the nature and magnitude of disease-cause association. For example, there are

those who still argue that it has not been proven that cigarettes cause heart disease or even lung cancer, despite the existence of a large body of positive epidemiologic studies.

It should also be noted that epidemiologic studies cannot prove safety. This is because "no significant increase" may still be statistically compatible with some effect. However, large studies can rule out all but very small health effects.

Question #3: Why perform radiation epidemiology studies?

Answer #3: It has been suggested that if real health effects are caused by exposure to low levels of ionizing radiation, they should be obvious without elaborate epidemiologic studies. This is not true. None of the health effects expected are unique to radiation exposure (radiogenic cancers, for example, are not distinguishable from cancers caused by other agents), and the projected excess of adverse health effects is small in relation to "normal" levels. Only a careful study, with sound statistical design, excellent dosimetry, and good worker records can reasonably be expected to detect and define radiation health effects.

Question #4: Of what relevance to radiation protection criteria are the results of epidemiology studies?

Answer #4: In the 1930's and 40's results of several epidemiologic studies suggested that exposure to fairly high levels (greater than 100 rems) of ionizing radiation could cause leukemia. Subsequent observations have shown that ionizing radiation can cause a broad range of other human cancers, including lung, digestive tract, breast, thyroid, bone, pancreas, and liver. These epidemiologic studies, some of which are ongoing, form much of the principal basis for radiation protection criteria used by the NRC and others and are thus of critical interest. The extent to which epidemiologic studies form the basis of modern risk-based radiation protection standards cannot be overstressed. Two other major areas of inquiry in radiation biology, dosimetric modeling and animal studies, do provide a body of information which is useful for evaluating such factors as human risk versus dose curve shapes (linear versus linear-quadratic) at low doses and the relative effectiveness of exposure to internal alpha emitters versus external gamma rays. The primary value of this information is, however, in guiding extrapolation from human risks, known from epidemiology studies, to areas where data are lacking, not in establishing human risk directly. A good example of this is the recently completed Radioepidemiologic Tables which define the probability that radiation caused specific cancers. These are based, almost entirely, on human epidemiologic studies, but do utilize animal studies to justify decisions such as the use of a linear-quadratic, as opposed to linear, model.

Question #5: What major radiation epidemiology studies have been or are presently being pursued?

Answer #5: The premier study, on which much of our radiation risk estimates are based, is the epidemiology study of the population exposed to radiation in the atomic bombing of Hiroshima and Nagasaki. This large study (of the prospective type) is following the morbidity and mortality experience of more than 82,000 individuals who were in the cities when the bombs fell. Of these,

more than half (54,808) received less than 10 rems, and less than 10 percent (6084) received more than 100 rems. This latter group is most important in estimating health effects because it is only at these relatively higher doses that definite increases in cancer rates are observable. The exposed people are followed through time, and their causes of disease or death are determined. Cause-specific morbidity or mortality rates are then calculated and comparisons are made among the dose categories, from these come crude (although the best available) estimates of dose response.

A recent study, conducted on persons who were exposed in utero (as fetuses) during weeks 10-17 of pregnancy when the atomic bombs were dropped, suggests that exposure to low levels of ionizing radiation (less than 20 rems) can also cause severe mental retardation. This, however, is a preliminary finding which needs corroboration.

It also seems likely that radiation would cause an excess of genetic disease in the descendants of exposed persons, because animal studies have consistently demonstrated that radiation exposure increases mutation rates. However, no definitive increases in genetic diseases have been demonstrated by epidemiology studies of the bomb survivors. Thus, the exact magnitude of such effects is rather uncertain.

Several other prospective type studies have yielded useful information on radiogenic cancer risks. These include men who received x-ray therapy for ankylosing spondilitus (arthritis of the spine), children who received x-ray therapy for ringworm of the scalp (these studies have been particularly useful in the assessment of thyroid cancer risks), women who received x-ray exposure to the breast (breast cancer), radium dial painters (our principal source of information on bone cancer risk), and uranium miners (our principal source of risk estimates for lung cancer risk from inhaled radon progeny). Few of these studies are as statistically "clean" as the atom bomb survivor study. This is because several study populations involve special groups of persons such as those undergoing radiation therapy, or occupational exposures. In contrast, the bomb survivors are a cross section of society. Statistically, the best of these studies is probably the radium dial painters. This is because the natural incidence of the cancer involved, osteosarcoma, is nearly zero. Thus, almost all cases can reasonably be attributed to radium exposure. The least definitive study is that of the uranium miners. Many of these men were heavy smokers, many suffered from silicosis, and mining often involved exposure to other carcinogens such as diesel exhaust. Therefore, exactly how much excess lung cancer one should attribute to radon daughter exposure is highly uncertain. Nonetheless, all of these studies provided some useful insights as to the cancer risk of human radiation exposure.

Retrospective type studies can also be useful in determining radiation health effects. One such study, of the effects of x-rays on the embryo/fetus, is the Oxford Survey of Childhood Cancers. This study considered a group of 7649 children who died of childhood cancer (before age 10) between 1953 and 1965, and an equal number of controls, matched on age and sex. This study suggested that exposure in utero raised the risk of childhood cancer by about 40%. This finding was subsequently replicated by a large prospective study conducted at Harvard. This study, which followed up some 1.4 million children born between 1947 and 1960, suggests a 30% increase in the risk of childhood cancer attributable to in utero x-ray exposure. Neither of these studies had really

good dosimetry. Exposure is usually expressed in either numbers of x-ray films, or simply x-rayed, versus not x-rayed. It is known, however, that doses were low, between 1 and 10 rems.

Question #6: What epidemiology studies of particular relevance to the health effects of relatively low level (less than 100 rems) radiation are being planned or done?

Answer #6: There are two prospective studies of groups of radiation workers currently being performed which may provide some information on the health effects of low level ionizing radiation. The first is the followup of workers who received more than 5 rems in a given year while working in DOE laboratories (the so called "5 rem study") which is being conducted by Oak Ridge Associated Universities. No conclusions can be drawn at this time because most of these men (over 85%) are still alive.

The second occupational group, being studied by John Hopkins University, consists of 33,000 shipyard workers who received some radiation exposure in the course of working on nuclear submarines. While this cohort is larger than the "5 rem study," doses are lower, generally less than 5 rems, so this study may not yield any more definitive information than the "5 rem study." Again, no real conclusions can be drawn at present because most workers are still alive.

A third occupational study, being considered by the National Cancer Institute (NCI), is at the feasibility study stage. The feasibility study, to begin in 1986, will look at worker records and worker followup for past and present employees of the Calvert Cliffs nuclear power plant. If the feasibility study gives promising results, the epidemiology study may be expanded, and may eventually include all nuclear power plant workers.

There are some current studies of populations exposed to elevated levels of background radiation (see for example: "Health Survey in High Background Radiation Areas in China" by the High Background Radiation Research Group, China, Science 209, 877-880 (1982) and "Evaluation of the Long-Term Effects of High Background Radiation on Selected Population Groups on the Kerala Coast" by A. R. Gopal-Ayengal et al., In: Peaceful Uses of Atomic Energy, Vol. II, pp. 31-51, United Nations, Vienna (1972)), but these are not likely to be highly informative. For one thing, these areas (in India, China, and South America) are, unfortunately, relatively undeveloped by western standards. Thus they do not have modern health care or good reporting of causes of death. Moreover, really high background radiation areas such as the Kerala Sands in India are rather limited in area and have rather small (less than 10,000) populations. It is also rather difficult to identify appropriate control groups for these populations, and dosimetry is poor (doses can vary substantially over short distances). Finally, the average dose differential between very high and normal background areas is, at most, 0.3 rem per year. For a population of 10,000 persons, this would correspond to a lifetime risk of 5 excess leukemia cases as compared to 98 expected and 35 excess other cancers as compared to 1,600 cases expected. The corresponding relative risks, 1.05 for leukemia and 1.02 for other cancers, would be difficult to detect under any circumstances, and given the other deficiencies of the exposed populations, are virtually impossible to detect.

Studies of background radiation and cancer mortality have also been carried out in the United States (see for example "Low-Level Ionizing Radiation and Human Mortality: Multi-Regional Epidemiological Studies. A Preliminary Report" by R. J. Hickey et al., Health Physics 40, 625-641 (1981)) but these too have problems. Though our vital statistics data is much better here than in India or China, the differential in radiation dose between high and low exposure populations is much less, so the effects are still too small to detect.

A worthwhile epidemiology study of the health effects of environmental radioactivity will begin in 1986 in western Pennsylvania. Many residents in this area are exposed to exceptionally high levels of radon and radon progeny emanating from the bedrock in that area. Evaluation of lung cancer risk as a function of radon exposure is to be performed via a large-scale retrospective study. The results of this study, which is being funded by the Department of Energy, could provide definitive information on the health risks of environmental radon.

Question #7: What populations could be studied to get direct estimates of health effects due to exposure to relatively low (less than 100 rems lifetime dose) levels of ionizing radiation?

Answer #7: It is easy to enumerate study populations which, superficially, seem worthy of study, but it is exceedingly difficult to identify populations which are actually worthy of study. One group often brought forward as a potential source of useful information is the persons in the Southwest who were exposed to fallout as a result of atom bomb tests. There are two major problems associated with this study group. First, the bomb tests were conducted in the Southwest because it was sparsely populated. Thus, the potentially exposed population is small. Second, there is essentially no dosimetry, so we don't know who received what dose. The severity of the problem may be illustrated by comparing this situation with that of the survivers of the atomic bombings of Hiroshima and Nagasaki. Here, much better dosimetry is available, and a rather large population is at risk, but what would be the case if the better dosimetry were not available? For leukemia we would still have strong evidence for radiation health effects; 180 cases were observed versus only about 90 expected. But, for all other tumors we would have 4576 observed and 4416 expected, which is a barely significant excess. Thus, without good dosimetry, even the best data available (a large population exposed to high radiation levels) offers only weak evidence for adverse health effects of radiation exposure. That is why populations such as the relatively small group exposed to much lower doses from fallout are not attractive condidates for epidemiology studies.

The most promising occupational group, and probably the most promising study group in general, is that of radiation workers. The advantages and disadvantages of studying this group are addressed in the answer to Question #8 below.

Other occupational groups, such as airline pilots and hostesses, have been suggested as providing a basis for epidemiology studies. This assumes that high doses are accumulated by these workers. In fact, a worst-case scenario of a 10 hour polar flight from, for example, California to Europe, would result in a dose of only 0.01 rem. A pilot making 200 such flights per year would get

only 2 rems, and most airline personnel would receive much less dose because short distance domestic flights are at lower altitude and cosmic radiation is less intense away from polar latitudes. Add to this the fact that airline personnel have an effective working life of less than 20 years and it becomes clear that the projected career doses for this relatively small occupational group are not sufficiently high to be useful in evaluating radiation health effects.

Question #8: Could one obtain useful estimates of health effects due to low level radiation from studies of radiation workers?

Answer #8: Possibly. Radiation workers were recognized as the best available study population by the Congressionally mandated NRC study of the feasibility of epidemiologic investigations of the health effects of low levels of ionizing radiation (NUREG/CR-1728). This is true because these populations are fairly large, have good dosimetry and health records, and moderate levels (0-80 rems) of lifetime radiation exposure. However, although the Interagency Scientific Review Group for this study concluded that a worker registry "particularly for those workers employed in nuclear work, is worthy of serious consideration," it did not endorse the desirability of new epidemiology studies of nuclear workers from a scientific point of view.

A number of factors entered into this decision. First, as noted above, two large populations of nuclear workers, the DOE "5 rem study" and the nuclear shipyard workers, are already being followed. Second, the results of a study of, for example, nuclear power plant workers, would not begin to be useful until about the year 2010. This is because most workers have been hired as fairly young men in the 1960's and 1970's, and even early hires will not begin to develop cancer or die in appreciable numbers until the mid-1990's. This is important because until appreciable numbers of health effects have occurred, it is difficult to estimate excess risks. The NRC sponsored feasibility study for epidemiological investigations of the health effects of low level ionizing radiation (NUREG/CR-1728) concluded that, if 20,000 nuclear power plant workers were followed for their lifetime, 26-45 excess incident cancers would be expected, and that these cancers (which constitute an increase of 0.95-1.6% above background) would yield a significant result only 18% of the time.

Such a study might still be desirable from a societal standpoint. The excess cancers predicted by the NRC sponsored feasibility study is based on the BEIR report, and it has been stated by some that these estimates are low (by as much as a factor of 10). If the projected excess were really 9.5-16% the chances of detecting it would be very good indeed, more than 99%. Therefore, if a study detected no such high excess health effects it could be useful in rejecting high estimates of risk.

Further, such a study could provide information which could be combined with the results of other studies to refine estimates of low level radiation health effects. For example, as discussed under question #9 below, other countries are following up their nuclear worker populations. These studies could be combined with the results of further studies of U.S. workers to provide fairly tight upper bounds on low level radiation health effects.

It can be questioned, however, whether somewhat better bounds would be worth the high cost of such a study. The feasibility study conducted by NRC (NUREG/CR-1728) concluded that a 40-year followup of 20,000 nuclear workers would cost 4.5 million (1980) dollars. However, a complete registry would include more than 20,000 workers, and some inflation has occurred since 1980, so the actual costs would probably be even higher.

The question of whether to start further studies of nuclear workers is a policy decision which is not a purely scientific issue. There does seem to be a consensus that a worker registry is a good idea because it would provide not only the basis for epidemiology studies, should they be indicated in the future, but also, in the words of the Scientific Review Group, "is worthy of serious consideration in the interests of occupational protection." However, the scientific arguments for immediately instituting a large scale epidemiologic study of nuclear worker populations are not compelling. This conclusion may appear to contradict the NCI feasibility study mentioned in question 6. However, this is not really the case. The present NCI study is limited in scope and may not lead to a study of all nuclear workers. Moreover, even if such a study were pursued by NCI it would, of necessity, last 40-50 years and be quite costly. NCI, as a pure research organization, can afford to take a long term view. NRC, as a regulatory agency, cannot.

Question #9: What are other countries doing in the way of surveillance of nuclear worker populations?

Answer #9: Canada, England, and Japan all have worker registries which collect comprehensive dose data. In each case epidemiologic followup of exposed individuals is underway.