A REVIEW OF THE SOUTHEASTERN MASSACHUSETTS HEALTH STUDY

By

Daniel Hoffman, Ph.D.

Joseph L. Lyon, M.D.

Frank Masse, B.S., C.H.P., C.M.P.

Harris Pastides, Ph.D

Dale Sandler, Ph.D.

Dimitrios Trichopoulos, M.D.

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EXECUTIVE SUMMARY

The Southeastern Massachusetts Health Study (SMHS) was conducted by investigators from the Massachusetts Department of Public Health to determine if communities near the Pilgrim nuclear power plant in Plymouth, Massachusetts had elevated leukemia mortality rates associated with radioactive plant discharges. The final report, released to the public in October 1990, found a two to four fold increase in the risk of leukemia among residents of certain towns within a 20 mile radius from the plant. A review committee of six public health professionals with expertise in the design and conduct of epidemiologic studies, the epidemiology of leukemia, and radiation physics, was jointly appointed by the State Health Department and the Boston Edison Company in the summer of 1991. The committee was asked to review the study's design and implementation, critique its findings, and interpret the findings in light of existing knowledge concerning the health effects of ionizing radiation. The committee requested additional information from the SMHS investigators and this was factored into its deliberations. This report presents the opinions of the review committee. The committee's conclusions are as follows:

1. The study team adhered to generally accepted epidemiologic principles of study design, data collection and data analysis.

2. Potential problems that may have affected the results of the study were identified in three general areas: the method used to identify the leukemia cases; the selection of the subjects who served as controls; and the methods used to determine the study subjects exposure to ionizing radiation. The exact impact of these potential problems on the study's conclusions was difficult to estimate.

3. The review committee used information from several expert bodies about the amount of radiation required to cause leukemia and estimates of the radiation exposure to the people living within 20 miles of the Pilgrim plant, to evaluate the biological plausibility of the study's findings. The committee determined that the study's estimate of the number of excess leukemia deaths, over a ten year time period was approximately 90 greater than that predicted by data from other radiation studies.

   The leukemia mortality rates for this area have remained close to the state average throughout the period. This finding contradicts the substantial increase in leukemia risk found by SMSH. The committee was, therefore, concerned about the biological plausibility of the study's findings. The strength of the association between leukemia and proximity to the Pilgrim power plant

was unexpected based on previous studies of the leukemogenic effects of low dose radiation. Furthermore the specific problems mentioned above make it difficult to conclude that the observed association is real and related to nuclear power plant emissions.

However, there have been other instances of observed cancer increases that are inconsistent with predictions based on mathematical modeling of radiobiology theory. Because the findings of the SMSH cannot be readily dismissed on the basis of methodological errors or proven biases, further attention to the possible risks associated with power plant may be warrented.

4. The review committee recommends that additional research be considered that addresses numerous questions raised by this report. Specifically a new study should:

   A. Include the Cape Cod towns that were excluded by the original study.

   B. Include cases of childhood leukemia.

   C. Establish a uniform system of case finding.

   D. Extend the time period of the study and consider including populations living around other nuclear power plants in the New England area.

   E. Consider alternative radiation exposure estimation models.

   F. Form an independent advisory committee that includes both scientists and citizens.

Introduction

The Southeastern Massachusetts Health Study represents an ambitious effort by investigators from the Massachusetts Department of Public Health Environmental Epidemiology (MDPH) group to address an important concern, namely, whether residents of certain communities proximal to the Pilgrim nuclear power plant had an increased risk of leukemia possibly associated with radioactive discharges from the plant. The investigators designed, conducted and analyzed a complex study in a very short time and with limited resources. A preliminary analysis of this study was completed in early 1990.

Because of the state health officials concern about the association found by the study, in early 1990, the MDPH investigators invited four outside experts (Drs Cobb, Hoffman, Lyon and Sandler) with expertise in the epidemiology of leukemia to evaluate the study design for any flaws, and to recommend further analyses that might be performed. Three of the four advisers (Dr Cobb excepted) had not been involved with the development of study design and protocol, the phase of an epidemiologic study where expert review and critique are especially important and helpful to the investigators. This meant that three of the external advisers could only comment about decisions affecting study design and data collection that had already been made and implemented.

This committee met with the MDPH investigators on June 25, 1990, and reviewed the study design, data collection methods, and

preliminary analysis of the data. (Their recommendations to the MDPH investigators are attached in Appendix 1.)

The MDPH staff prepared additional analyses at the request of the advisory committee and replied to some of the committee's recommendations. Unfortunately the final report was released to the public in October 1990 before all the committee's recommendations were addressed, and before the changes to the final report could be reviewed by these external advisers.

After the release of the study findings the Boston Edison Company requested that a review committee be jointly appointed, three members to be nominated by the Boston Edison Company and three by the Massachusetts Department of Public Health. This committee's charge was to review the study's design and implementation, critique its findings, and interpret these findings in the context of the larger body of knowledge concerning the health effects of exposure to ionizing radiation. The MDPH accepted this proposal and a six member review committee was constituted. The MDPH nominated three of the four members who had served on its earlier advisory committee, and the Boston Edison Company nominated three individuals affiliated with academic institutions in Massachusetts. All committee members agreed to serve without any compensation (except for travel expenses).

The review committee met for the first time on July 8, 1991, to be given its charge, and to discuss the study. The attached letter, contained in Appendix 2, summarizing the review committee's recommendations at the conclusion of this meeting, contains many of

the same recommendations made by the earlier advisory committee at the June 25, 1990, meeting (See Appendix 1).

Additional data responding to some of the 1990 advisor's committee and 1991 review committee requests were provided by the staff of the MDPH in November 1991, and February and July 1992. The committee held a public hearing in Boston on Friday, June 26, 1992, and has also received and reviewed written material submitted by interested citizens and other groups. On the basis of all the information provided us, we have reached the consensus presented in this report.

COMMITTEE FINDINGS

The MDPH investigators adhered to generally accepted epidemiologic principles of study design, participant selection, data collection and analysis. They did, however, experience problems in case ascertainment, control selection, and exposure ascertainment. It is difficult to determine, retrospectively, the specific impact of these problems. Nevertheless, the committee considered problems that might have led to a spurious positive association between adult leukemia and residence near the Pilgrim nuclear power plant. These included:

1. The selection of the specific townships and individuals included in the study.

2. The possibility of enhanced ascertainment of leukemia cases in areas closer to Pilgrim Station.

3. The method of selection of controls.

4. The method of exposure classification.

The committee also considered the study findings in the context of other such studies that have examined the health effects of exposure to ionizing radiation. A more detailed consideration of these potential problems is presented below.

1. Study Populations

A. Exclusion of Cape Cod Towns

The committee believes that all towns within the 20-mile radius, including those on Cape Cod, should have been studied. That the Health Commissioner, at the time of the study's inception, did not grant approval for this additional effort is extremely unfortunate. These towns should be included in any new study.

The supplemental report of the MDPH (November 21, 1991) presents certain ecological, or group, comparisons that imply that the effect of the exclusion of these towns would not be large. The committee, however, had difficulty determining precisely how these group effects would apply to individual cases and controls; this problem is acknowledged by the MDPH authors in the supplemental report. If a new study is undertaken, it should be designed to collect primary information from all residents of a carefully defined population based exclusively on geographic considerations.

B. Exclusion of Children

The MDPH researchers did not include children in the original study due to the small number of cases of childhood leukemia expected during the study period. While the committee does not view their omission as a flaw that compromised the study's internal validity, there was complete agreement that, given their known susceptibility to ionizing radiation, the inclusion of children would have provided additional useful information about any possible leukemia risk associated with the Pilgrim plant.

C. The exclusion of cases of chronic lymphocytic leukemia (CLL)

Cases of CLL were excluded from the analysis, and this decision was based on the known difficulty of ascertaining newly diagnosed CLL cases. The committee acknowledges this difficulty, nevertheless, a new study should consider a more extensive case finding mechanism that might include cases of chronic lymphocytic leukemia because of the additional knowledge that may be contributed.

2. Cases Studied

A. Case Ascertainment

Eligible cases for this study were identified from area hospitals as well as from the Massachusetts Cancer Registry (MCR). Leukemia cases of age 13 and older at diagnosis whose dates of diagnosis were between 1978-1986 were included in the study. Because some hospitals would not cooperate by reporting cases to the investigators that were already reported to the MCR, the investigators had to rely exclusively on the MCR for some geographic areas. While this mixed-mode ascertainment was reasonable, the possibility of biased case-finding and case-reporting to the MCR exists. It is possible that the case reporting to the MCR was more complete in towns closer to Pilgrim Station, because of community concerns about the health risk associated with living near the plant, or that cases farther from the Pilgrim plant were diagnosed in hospitals well outside the region. If this differential reporting occurred the result would

be an overestimation of risk associated with residence close to the power plant.

B. Missed Cases

In response to the review committee's request, the MDPH reviewed vital records and identified an additional 48 subjects who potentially qualified for the study but were not included. The committee considered this evidence of underascertainment of cases to be important. The committee requested additional information about these cases, including diagnosis listed on the death certificate, age, date and residence at death. It was reported that 14 of these would not have qualified because they had chronic lymphocytic leukemia (CLL) or were diagnosed outside the period of interest.

Using the more detailed data provided to the review committee by Dr Martha Morris, in her memorandum dated July 1, 1992, and the data in Table 35 of the original report, the following unmatched odds ratios were calculated.

Table 1. Comparison of the original odds ratios, and the new odds ratios after the additional 34 cases are added to the original 105 cases. (The odds ratios are calculated assuming that any new controls selected for the 34 new cases would have had the same geographic distribution as the cases.)

Original Odds Ratios (See Table 35)

DISTANCE	CASES	CONTROLS	ODDS RATIOS
20.2+	33	82	1.00
10-20.2	47	92	1.27
<10	25	34	1.83

New Odds Ratios Based on the Original Plus the 34 Newly Identified Cases.

DISTANCE	CASES	CONTROLS[1]	ODDS RATIOS
20.2+	42	82	1.00
10-20.2	65	92	1.38
<10	32	34	1.84

Based on these data it appears that the failure to ascertain the 34 potential leukemias did not substantively affect the study's conclusions.

C. Case Distribution by Cell Type.

In response to another request by the committee, the MDPH report presented data indicating that potential exposure was inversely related to chronic myelogenous leukemia (CML); while the numbers are relatively small and the committee does not feel that this affects the conclusions about other cell types, it is noted as a curious observation.

From data presented in Table 4 of the MDPH report it is noted that there is a greater proportion of chronic lymphocytic leukemia (CLL) cases, a cancer not usually believed to vary with ionizing radiation exposure, in the 22 towns studied than in the SEER (Surveillance, Epidemiology and End Results program of the U.S. National Cancer Institute) populations (40% vs. 34.9% among males; 40% vs.29.7% among females). The reasons for this excess are not clear, but may be related to the more intense case ascertainment employed by the study or to differential reporting of this disease in the study area. It is difficult to reliably identify new cases of CLL but this excess might also point to some other cause of leukemia operating in this area.

3. Control Selection

It is important to control for differences in socio-economic status in studies of leukemia because the disease incidence varies with socio-economic status. An additional problem in case control studies is that individuals of lower socio-economic status may be less likely than those of higher socio-economic status to participate in a study as controls; this could result in a biased

association. For example if people living in the area closest to the Pilgrim nuclear power plant (the area with the highest exposure) were of higher socio-economic status, compared to those living farther inland, and the proportion of eligible control subjects willing to participate decreased with socio-economic status, then the study would include fewer controls living near the power plant, irrespective of any untoward health effects or power plant exposure; this would result in a spurious positive association. Other examples could be constructed that would produce bias in a different direction.

The report prepared by the MDPH investigators does not adequately account for participation by potential controls by distance from the plant. This makes any evaluation of potential bias introduced by the processes used to select controls difficult.

4. Exposure Assessment

The committee recognizes the complexity of this issue and understands the reasons for the investigators using an exposure marker that accounted for subjects' locations both at home and at work. The investigators chose a model that suggests that airborne particulate exposure decreases as the inverse of the square of the distance from the plant. This rule generally holds for known airborne particulate pollution. It was reasonable to use the rule for this application, but this model does have the effect of overemphasizing radiation exposure closer to a point source.

While there is little monitoring information on the plant

emission's dose contribution to the specific areas in the region of interest, there are data on the radioactive material released. The speculation that long lived nuclides may have been released from plant effluent points that were not routinely monitored can be reasonably discounted based on the routine whole body counting of the plant workers. These workers are also neighbors and representative of the general community when they are not on duty. The whole body counting sensitivity is such that long lived radionuclides are measured at 0.1% of the permissible continuous body burden of the workers, 1% of the maximum continuous level for the general public. There was no evidence of unmonitored releases of radioactive material in these data. Our findings, concerning radiation releases, are consistent with the findings of State and Federal regulatory agencies throughout the same period. Had radiation releases of the magnitude required to produce the reported excess leukemia in the area surrounding the plant occurred, these releases also would have been detected by the large number of radiation monitors in use by businesses and universities throughout Eastern Massachusetts. After reviewing the available monitoring data throughout the period covered by the study, including a review of emissions monitoring techniques, the committee concluded that radiation releases from the Pilgrim plant were probably not significantly higher than reported. The committee also believes that the larger source of exposure to the bone marrow, the only important exposure for induction of leukemia, to the population living near the Pilgrim plant or anywhere would

be the natural background radiation.

The overall variation in total bone marrow exposure due to natural background radiation plus emissions from the Pilgrim plant are likely to be much less than a factor of two during the period of interest. The increased bone marrow exposure to residents of the study region due to the operation of the plant was likely comparable to the increases to residents of Denver, Colorado, who receive a higher radiation dose than residents of Boston, due to Denver's higher altitude. Therefore it is difficult to reconcile this small increase in potential radiation exposure with the reported large increase in leukemia risk found by the study.

The committee was informed of an isolated elevated Cesium 137 observation in a milk sample taken at a farm more than ten miles from the Pilgrim plant in June 1982 that appeared to be inconsistent with plant release data. This observation was reviewed by the radiation safety staff for the Pilgrim plant and they concluded that the Cesium 137 was probably due to fallout radiation from open air nuclear weapons testing in China.

The committee reviewed the more wide spread data of the contractor responsible for the environmental monitoring that resulted in this observation and found similar unexplained relatively isolated elevated Cesium 137 observations in monitoring data at other nuclear power plants during the same period. Similar observations were also found in U.S. Environmental Protection Agency monitoring data in others parts of the country, supporting the conclusion by the Pilgrim plant radiation safety staff that the

unexplained increase in Cesium 137 was probably due to radioactive fallout from Chinese nuclear weapons testing.

The committee agreed that any future study should review emission data from Pilgrim Station with the view of developing an alternative exposure model. The committee recognizes that the available data are imperfect, nevertheless, some useful quantification may emerge.

5. Coherence of the Study Findings in Relationship to Present Knowledge.

A. Routinely Collected Data on Leukemia Deaths.

At the review committee's request the investigators calculated leukemia death rates before, during, and after the study period (1973-1986). The leukemia mortality rates for this area have remained close to the state average throughout the period. This finding contradicts the substantial increase in leukemia risk found by the SMSH. Any future study will need to reconcile these morality rates with the study's findings.

B. Estimating Potential Radiation Exposure to Produce the Excess Leukemia Found.

For the purposes of radiation risk assessment, we usually extrapolate from the effects observed at high radiation doses to estimate the effects at low doses, but this process has many uncertainties. Consequently, biologic plausibility in the low dose range is not only uncertain, but effects in this dose range are very difficult to detect, if they exist, using standard

epidemiologic techniques. A better estimate of what effects might occur at low dose, chronic exposures can be found in the studies of the US Department of Energy nuclear weapons production workers exposed to low cumulative radiation doses over a period of several years. A recent report in the Journal of the American Medical Association by Wing et al., (Volume 265, 1991, pages 1397-1402) that analyzed long term mortality data from this cohort, reported an increased risk of leukemia among white males that was greater than the risk predicted by using the linear extrapolation model. Similarly, a review of current studies by Wilkinson and Dreyer (Epidemiology 1991; 2:305-309) found a significant summary risk estimate or 1.8 associated with employment in the nuclear industry.

While no estimates of a specific radiation dose were available for the SMSH study there are several studies that have sufficient data to predict the number of new cases of leukemia that occur per unit of radiation exposure. Using data from these studies we prepared an estimate of the range of doses necessary to produce the effect seen by the MDPH study. These results are presented in the next section.

C. Biologic Plausibility

Epidemiologic studies have often identified exposure-disease relationships well before evidence of a biologically plausible mechanism, the work of John Snow on Cholera in 1854 being the classic example; nevertheless the committee was troubled by the lack of any evidence of exposure to the bone marrow of the population living in the areas surrounding the Pilgrim plant. The

main radiation releases were noble gases that do not enter the human food chain and accumulate in the human body. The radioiodines released by the plant, if ingested, are likely to deliver a very low dose of radiation to the bone marrow. The committee could find no other radioactive substances released by the Pilgrim plant that accumulate in the bone marrow, or give off large amounts of gamma radiation.

There have been several recent studies suggesting that the leukemogenic potential of alpha irradiation may be greater than has been appreciated. For example Kadhim and colleagues (Nature 1992; 355: 738-740) reported the transmission of chromosomal instability in progeny of alpha irradiated stem cells, suggesting that there may be unanticipated risks associated with alpha irradiation. Henshaw et al. (Lancet 1990; 1:1008-1012) and others (Peto, Nature 1990; 345:389-391) reported unexpectedly strong correlations between residential exposure to radon and leukemia risk. Henshaw et al. noted that alpha radiation from radon is accompanied by gamma radiation, and that there is increased solubility of radon and radon daughters such as polonium in fat cells found in bone marrow. Both of these factors could contribute to a higher than currently believed bone marrow dose from alpha irradiation.

The committee also reviewed other studies that have estimated radiation dose to the bone marrow sufficient to produce excess leukemia cases similar to the SMHS. These studies include the Japanese atomic bomb survivors and persons exposed to medical X-radiation. Data from these studies has been used to develop "data

driven" relative risk models for radiation induced leukemias. These models incorporate factors for uncertainties of the data and predict the lifetime risk of dying of leukemia based on either a single or continuous exposure to a specific level of radiation. Such risk factors are not usually calculated until the dose exceed 0.1 Sv (10 rem) single dose of low dose, low dose rate (low LET) radiation, or to a continuous lifetime exposure to 1 mSv (0.1 rem) per year. For example in a population of 100,000 males exposed to a single 10 rem exposure, 110 excess leukemia deaths would be expected among this cohort (90% CI= 50, 280). This is an increase of 15% above leukemia cases expected from all other causes in a group of males of this size during their lifetime (BEIR V). The excess for females under similar assumptions about radiation dose would be 80 leukemia deaths (90% CI = 30,190), and represents 14% above that expected during the life of this cohort.

Other expert bodies (UNSCEAR 1988, and ICRP 1990) have developed similar models using slightly different assumptions. Pooling these leukemia risk estimates with that from the BEIR V report gives an estimate of lifetime risk for leukemia mortality of 0.0005 excess deaths for low dose, low dose rate exposure to 10 rem of low LET radiation. This estimate incorporates a Dose Reduction Effectiveness Factor of 2 for low dose, low dose rate radiation exposure. Risk estimates for other levels of radiation can be derived on the basis of proportionality of effect with dose, assuming a linear dose-response model in the low dose range. While this model assumes an acute one time exposure to ionizing

radiation, currently accepted models based on continuous, protracted exposures to low dose radiation, such as might have been the case for those living near the Pilgrim plant, predict fewer excess leukemia due to cell repair mechanisms after radiation damage. So the selection of the acute radiation coefficients to estimate excess deaths, may overstate the number of deaths expected around the Pilgrim plant.

We applied the above risk estimates to the population covered by the SMHS to determine how many excess leukemia cases would be expected using the radiation release data reported to the U.S. Nuclear Regulatory Commission (NRC) by the Boston Edison Company for the Pilgrim plant. We recognize that there is a substantial amount of uncertainty about the actual radiation dose received by the SMSH study population, but felt these estimates were worthwhile to put the study in the context of other studies of leukemia associated with low dose radiation exposure.

The U.S. Nuclear Regulatory Commission estimated the total population dose to the surrounding population from the start of the Pilgrim plant in 1972 to 1981 at 120 person-rems, with a hypothetical maximum annual individual dose of 34 millirem to those nearest the plant. The committee used the pooled estimate of lifetime leukemia risk from the BEIR V report, the UNSCEAR report and ICRP report, of 0.00005 excess lifetime leukemia deaths per rem of radiation. (This is for a one time radiation exposure and may overestimate the risk of subsequent leukemia from chronic low level exposure.)

We estimated the population in the 22 towns around the Pilgrim plant at 203,898 (U.S. 1980 Census) and that the study covered ten years. The U.S. Nuclear Regulatory Commission (NRCP) estimated the hypothetical maximum annual dose received at 34 millirem during the time period when the defective fuel rods were in place. That dose affected only those living close to the Pilgrim plant, estimated at 640 people by the NRCP. We used this value as the upper limit of a radiation dose that might have been received. We also assumed the population at highest risk to be 1000 in number and that this group received 34 millirem each year for ten years rather than the four years the defect fuel rods were actually in place.

We assumed that the population outside the area closest to the plant, estimated at 202,898, received an average bone marrow dose from the defective fuel rods of no more than 5 millirem, and this also occurred over 10 years. We then estimated the number of excess cases of leukemia that would have occurred, using the pooled estimate of excess risk from the BEIR and UNSCEAR reports. These numbers are given in Table 2.

TABLE 2 Estimates of Cases of Leukemia Expected among the Population of the 22 Town Near the Pilgrim Plant Compared to Those Found by the SMSH.[1]

Dose Millirem	Population	Person-rem	Predicted Leukemia Cases
5[2]	202,898	10,145	0.507
34[2]	1,000	340	0.017
TOTAL	203,898	10,485[3]	0.524

Excess Leukemia Cases Divided by Predicted Excess Leukemia Cases

$$47/0.524 = 89.7$$

1. The SMHS reported an excess of 47 leukemia cases. The excess leukemia cases predicted by the committee are based on a risk factor of 0.00005 excess leukemia cases per rem.
2. The dose was multiplied by ten to take into account a ten year period of observation.
3. This estimate of population-dose is much larger than that estimated by the NRC, and reflects a worst case scenario for radiation around the Pilgrim plant.

We therefore calculated a maximum excess number of leukemia

cases in the area around the Pilgrim plant attributable to plant released radiation of 0.524 over the ten year time period. Or phrased another way there were at least 89.7 times more leukemia cases reported by the SMHS as predicted using data from the other radiation studies.

The disparity between the number of excess leukemia cases reported by the SMHS and that predicted by other radiation studies was a concern to the committee. The committee was also concerned with the failure of the SMHS to document, from vital records, any excess leukemia deaths in the study area during the 10 years of the study compared to leukemia mortality in the same area before the Pilgrim plant opened.

D. Time limited Association of Exposure to Leukemia

One of the most intriguing findings of the study is the time limited association between distance from the plant and risk of leukemia. The excess of leukemia cases was found among those who lived near the plant when it was first put into operation, but not in those who moved in after the defective fuel rods were replaced (allowing for a lag time of five years from exposure to onset of disease). Most of the potential biases discussed in this report would have had to be present throughout the period studied, and not just during a certain period that corresponded with high plant emissions. From this perspective, the time limited association in the MDPH study suggests increased risk corresponding to some peak radiation exposure at a specific time in the past, accounting for the latency of the leukemia seen. But it is also possible that

this finding reflects a random increase in leukemia cases not associated with radiation, yet inadequately explained by any environmental factors studied in this report.

The strength of the association between leukemia and proximity to the Pilgrim power plant was unexpected based on previous studies of the leukemogenic effects of low dose radiation. Furthermore the specific problems mentioned above make it difficult to conclude that the observed association is real and related to nuclear power plant emissions.

DISCUSSION AND RECOMMENDATIONS

The SMHS Review Committee attempted to identify the strengths and weaknesses of this important study and to provide a basis for better understanding of any potential health risks to the communities of Southeastern Massachusetts. While numerous limitations of the study were identified and explored in this report, the committee's statement should not be interpreted as suggesting that the study was undertaken in an unprofessional or careless manner. On the contrary, this study met several standards of proper epidemiology practice and was performed in an objective manner, despite the limited resources and the emotional climate that prevailed in the potentially affected communities.

However, the committee does not believe that the SMHS is neither of sufficiently unique quality or size so as to override the large body of scientific evidence concerning the dose-dependent effects of ionizing radiation. In particular the lack of

information on specific radiation doses to individuals (and use of surrogate information on distance), problems with selection of the cases and controls for the study, and hypothesized levels of radiation exposure required to have caused the observed increased rates of leukemia, were of concern to the committee. The possibility that the study's findings may be attributed to chance should also be kept in mind. It has been pointed out by a group of highly regarded statisticians and epidemiologists that, in small or low power studies, a "statistically significant" result is more frequently generated by chance than by genuine difference in the risk of disease between the groups. (Peto, R., Pike, M.C., Armitage P., Breslow N.E., Cox D.R., Howard S.V., Mantel, N., McPherson, V., Peto, J., Smith, P.G. British Journal of Cancer 1976; Volume 34:585-612.)

The committee, in quantitative terms where possible, examined each identifiable methodological problem and its likely impact on the study results. In the end, it was the committee's decision that additional extensive analyses of the current study's data would not serve to diminish the current controversy.

A carefully designed new study that addresses the concerns expressed in this report should be able to contribute to a resolution of the issues that led to the initiation of the SMHS. If further research is pursued the Review Committee offers the following recommendations.

RECOMMENDATIONS FOR ADDITIONAL RESEARCH

If further research of those living/working near the Pilgrim plant and subsequent risk of leukemia is contemplated, the committee offers the following suggestions.

1. That a carefully defined study area be selected, and that this area includes those towns on Cape Cod that were excluded in the original study.

2. Those leukemia cases occurring in children be included in the study, even though their numbers may be small.
3. That a uniform system of case finding be established, and applied throughout the study area. The decision to include or exclude cases of chronic lymphocytic leukemia needs to be carefully considered before cases identification is begun.
4. That the time period of the study be extended to include additional years.
5. That a different mechanism of control selection not based on the vital status of the case be used. This mechanism should try to reconstruct the source population that gave rise to the cases as accurately as possible.
6. That an independent evaluation of the potential radiation exposure from the Pilgrim plant, and from other sources, including background radiation, be used to construct the study's exposure measure.
7. That other potential causes of leukemia such as chemical exposure be evaluated.
8. That an independent scientific advisory committee be

established to review the study design and protocols before it is implemented.

9. That a citizen's advisory committee also be established. This committee would review the study design and the study progress.

10. That an expanded study area, including other nuclear power plants in or near Massachusetts be considered to enhance the power of the study to detect any associated risks.

APPENDIX 1

APPENDIX 1

RECOMMENDATIONS OF PEER REVIEW COMMITTEE SOUTHEASTERN MASSACHUSETTS HEALTH STUDY

July 25, 1990

ADDITIONAL ANALYSES

Need to hire an experienced statistical consultant to assist with reviewing and implementing the committee's recommendations.

CASE SELECTION/ASCERTAINMENT

1) Compute and compare incidence and mortality rates from 1978-1986 in study areas. Present by age, sex, and cell type, when possible. Compute incidence/mortality ratios by year and compare with SEER data (eg., Connecticut Cancer Registry rates). Compute ratios by year, age, sex and cell type. This may help to address changes in leukemia ascertainment since 1982.

2) Develop a table on sources of diagnostic confirmation of leukemia cases, at least from 1982 onward. Compare the distribution of these sources with those used in the Connecticut Cancer Registry to identify differences if they exist.

CONTROL SELECTION

1) Analyze, through stratification, the effects of differential cause of death among the controls. Exclude cancers, then cardiovascular disease, then accidents to examine the effects on the odds ratios.

2) For proxy respondents, develop a table indicating among cases and controls, the source of proxy information (eg., spouse, child, etc.) Compute point estimates or the odds ratios by each type os respondent.

3) Develop a table on the issue of control replacement. For example, the numbers of case-control pairs with no replacement, with 1 replacement, etc., to address the magnitude of possible effect of control replacement.

4) Select a sample of cases and controls residing in the study area in 1975-75 and validate addresses using various sources. Also, validate for the same sample, that the individuals actually lived in that residence for the claimed duration.

EXPOSURE ASSESSMENT

1) Need to more clearly define and explain how the exposure index was developed.

2) Need to examine the components of the exposure model separately; eg., duration of residence independant of distance, proximity to the plant, and both factors together.

3) Analyze the residential exposures separately from occupational exposures (in the ratio of 2/3 residential, 1/3 occupational). Also, if possible, factor in outdoor occupation apart from indoor occupation.

4) Compute sex-specific exposure-response odds ratios.

5) Put radiation exposures to populations into and understandable context. For example, the estimated gamma dose to individuals under various conditions (wind direction, time of year, plant release data, duration of residence, etc.)

6) Based on the estimated leukemia excess in your study and the estimated radiation doses, calculate a radiation risk estimate for this study (eg., excess leukemia case per year per rad of radiation).

7) Need to quantify high, medium, and low exposure scores. Also, analyze exposure data using a distribution-dependent cutpoint for these values. Analyze exposure-response using exposure as a continuous variable.

8) Conduct an analysis restricted to cases and controls who lived in the study area from 1974-75. Also select the 1973-78 period based on the observation that this was the time of increased emissions from the plant. Finally, restrict your analysis to persons residing in the area 10 years prior to diagnosis of leukemia.

9) Add a variable to the exposure index to indicate straight-line distance to the seacoast.

DATA ANALYSIS

1) Conduct a separate analysis by sex and age as variables in logistic regression. Add matching factors for the analytic variables.

2) Analyze education separately as an indicator of socio-economic status and re-do the analysis on this basis.

3) Analyze risk as a function of age at first exposure.

4) Conduct separate analyses for each leukemia cell-type by sex and age at first exposure.

5) Derive point estimates of the odds ratio by date of diagnosis, by date of first residence in the study area, and by actual year of first residence in the study area.

RECOMMENDED ADDITIONAL STUDIES

1) Conduct a case-control study of childhood leukemia in same study area, going back to 1972. Collect data on paternal occupation.

2) Need to collect additional data on radiation releases. Ideally, a dose-reconstruction study should be implemented using data from the plant, EPA, and the NRC, along with meteorological data during the particular periods of interest. Individual dose algorithms should be computed using the dose-reconstruction data and information on residencies and activities from the case-control study.

3) Develop a "living at the time a case diagnosis" control group to address the issue of residential history.

PEER REVIEW COMMITTEE

Daniel A. Hoffman, Ph.D., Chairman

Sidney Cobb, M.D.

Joseph L. Lyon, M.D., M.P.H.

Dale P. Sandler, Ph.D.

APPENDIX 2

Summary of Advisory Committee Recommendations

July 1991

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Robert S. Knorr, Ph.D.
Deputy Director
Division of Environmental Health Assessment
Massachusetts Department of Public Health
7th Floor
150 Tremont Street
Boston, Massachusetts 02111

Dear Bob,

I was writing a brief report of our recommendations to you about further analyses of your study, and realized that some of these ideas might be of immediate use to you, so I decided to send them along. I realize that Harris will send you written comments that summarize much of our conversation, but I thought these might be helpful also.

The committee made recommendation for additional analyses and review on the following points:

1. Obtain leukemia mortality rates for Plymouth County, or each township, covering the time period before and after the opening of the plant. These rates will establish a baseline for leukemia occurrence in this area before, during and after exposure. Any information about cell and clinical type of leukemia will help.

2. Obtain "all causes mortality rates" and numbers of deaths for each township in the affected area for the time period of the study. This data should be stratified by age and sex within each township. The data should also be divided by those towns that are on the seacoast, and those towns that are inland.

   We are trying to rule out a systematic bias in control selection. Our assumption is that the inland townships had a much higher all causes mortality rate than the seacoast towns, thus leading to a systematic bias in control selection.

3. Using township mortality data check to see if there are deficits or excesses of leukemia cases in any township during the study period. The purpose of this exercise is to test the completeness of leukemia ascertainment for each of the townships to see if there was a systematic bias in case selection that might explain the findings.

4. Provide more detail on the confirmation of the leukemia cases. The leukemia cases were said to be histologically confirmed in 90% of the cases, but such a statement is too imprecise for such an important study. Is histologically confirmed a bone marrow diagnosis, or does it also include cases based on peripheral blood? For a densely populated state like Massachusetts, 10% of cases without histologic confirmation is also alarming. It should be more like 1-2%. What was used to make the diagnosis in those cases where there was no histologic confirmation?

5. The data on the confirmation of addresses given by respondents needs to be put in tabular form, divided by case-control status. Since there may be more than one address during the exposure period the table also needs to show the proportion of all potential addresses confirmed.

6. The table showing the number and proportion of individuals who refused to participate needs to be divided by case-control status, and percents calculated for cases and controls separately. (As an addendum, it might be useful to also calculate a refusal rate by case control status for seacoast versus inland communities.

7. The data on smoking needs to be broken down by clinical and cell type, age, and pack-years smoked. The association has been seen in those with acute myelogenous leukemia, who are older, and who have accumulated a high number of pack-years. Odds ratios should be calculated for these subgroups.

8. The occupational groupings used to define high risk needs to be stated explicitly.

9. Analyses by broad categories of cell type and age at first exposure should also be done. Acute versus chronic is the most obvious disease breakdown, and ages 13 to 44 and 45+ are the best ages. The data on the latency periods of leukemia after radiation needs to be cited. The original paper was authored by Ichimaru and Ishimaru, Journal of Radiation Research, 1976, 16 (supplement):89-96, and was summarized by Land in Radiation Carcinogenesis, Epidemiology and Biological Significance: Progress in Cancer Research and Therapy, Volume 26, New York: Raven Press, 1984, see pages 421-436. Latency should then be examined using groups similar to the ones they used in the Hiroshima and Nagasaki cohorts. I have enclosed a figure from the article by Land that summarizes the different latency periods.

10. Dr. Masse will review the data on radioactive releases from the plant, the adequacy of monitoring, and amounts measured during the study period. He should attempt to reconcile this with data obtained from citizens' groups.

11. The exposure score should be recomputed, using the term for distance from the plant as linear, rather than squared term. Odds ratios should then be recomputed.

12. A study of leukemia in children in the same area needs to be conducted immediately.

13. The exclusion of the towns on Cape Cod needs to be justified.

Best Wishes