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CANCER INCREASE STUDY METHODOLOGY: A REVIEW AND DISCUSSION OF THE "SOUTHEASTERN MASSACHUSETTS HEALTH STUDY 1978-1986"

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SUMMARY

In October 1990 the Massachusetts Department of Public Health released a report of an epidemiologic study of adult leukemia occurring in the vicinity of the Pilgrim 1 Nuclear Power Plant near Plymouth, Massachusetts. The study used a case-control design in which adult leukemia cases occurring between 1978 and 1986 in 22 towns were compared with persons without leukemia (controls) selected from the same study population. Exposure scores, used to estimate potential for exposure to radioactive emissions from Pilgrim, were calculated for all cases and controls. When the exposure scores of cases were compared with those of controls, the analyses showed the scores to be higher for the leukemia cases, suggesting that individuals with the highest potential for exposure to Pilgrim emissions had a significantly increased risk of leukemia. This association was found only for cases diagnosed before 1984; for cases diagnosed during 1984, 1985, or 1986, no association was observed between leukemia case status and potential for exposure to emissions from the plant.

Our review of the report and supporting documents shows no major methodologic problems that would account for the finding of an association between leukemia risk and the Pilgrim plant. Examination of the study findings in relation to what is known about leukemia risks associated with radiation exposure, however, indicates that the results of the Southeastern Massachusetts Health Study are inconsistent with a large body of evidence from a number of other studies.

We examine the findings of the study in the light of other epidemiologic studies. The absence of an association during the latter years of the study (1984-1986) is inconsistent with data from a number of other studies that have examined temporal relationships between radiation exposure and leukemia risks. These risks continue well past the maximum latent period of 11 years suggested by the Southeastern Massachusetts Health Study. On the basis of emissions data from Pilgrim, the leukemia risks suggested to be associated with Pilgrim are orders of magnitude greater than estimates based on a number of other studies. Finally, if the leukemia risks are as great as the study suggests,

the number of leukemia cases in the study area should be far greater than is found. Leukemia rates are not elevated in the study area.

We do not interpret the findings of the Southeastern Massachusetts Health Study as indicating a causal association between emissions from the Pilgrim nuclear power plant and leukemia. We do not believe that the findings of the study require a revision of estimates of leukemia risk associated with nuclear plant emissions. At the same time, the findings of the study cannot be readily dismissed on the basis of its design or conduct, indicating the possible need for additional studies of leukemia in Southeastern Massachusetts.

CONTENTS

1.0 INTRODUCTION

In response to reports of increased rates of leukemia in the area around the Pilgrim 1 Nuclear Power Plant (subsequently referred to as Pilgrim or the Pilgrim plant) near Plymouth, Massachusetts, the Massachusetts Department of Public Health (MDPH) conducted an epidemiologic case-control study of adult leukemia in 22 towns in southeastern Massachusetts. This study resulted in a report entitled "Southeastern Massachusetts Health Study 1978-1986" (SMHS) released by the MDPH in October 1990. The report noted an association between risk of leukemia and proximity to the Pilgrim plant.

Questions have been raised regarding methods employed in the SMHS and interpretation of findings. Thus, a bipartisan review committee was established by the MDPH and Boston Edison Company. The committee issued a report (Hoffman et al. 1992) in October 1992 that considered the study's design and conduct and interpreted results in terms of existing knowledge regarding radiation and cancer risks. Other reviews have also been conducted during the 2 years since the report was issued (Congel and Willis 1992; Poole 1991a, 1991b; Poole, Rothman, and Dreyer 1990).

In this report, we review the SMHS and related documents. We consider the design and key findings of the study. We examine these findings in the context of other epidemiologic studies of leukemia risks associated with radiation exposure. Our conclusion is that, although the SMHS demonstrated an association between leukemia risk and indices of exposure to releases from Pilgrim, this association can not realistically be interpreted as causal. This conclusion is based primarily on three factors: 1) incongruent temporal relationships between measured Pilgrim releases and increased risk, 2) a lack of consistency with estimates of risk from other epidemiologic studies, and 3) discrepancies between actual mortality rates and numbers of cases and those projected to occur in the vicinity based on the risks estimated by the SMHS. However, there are no obvious methodologic problems with study design or conduct that provide an answer for the study's inconsistent findings.

2.0 BACKGROUND

Pilgrim began operations in late 1972. Due to fuel rod problems, radioactive emissions in the mid-1970's were above currently accepted EPA guidelines. Concerns about potential health effects associated with the Pilgrim plant arose in the early 1980s.

Initial analysis of leukemia mortality ratios and ... idence ratios by the MDPH, using data from vital records for the years 1969-1983 and cancer registry data from 1982-1984, suggested increased rates of leukemia. Increases were observed for the time period 1979-1983 among costal census tracts and in specific towns, including Plymouth. These findings led to discussion and additional analyses of readily available data to examine the association. Importantly, these early studies also led to a decision by the MDPH to conduct a major epidemiological study to examine the hypothesis that the observed elevated occurrence of leukemia in this area was related to Pilgrim emissions. This study was conducted by the MDPH and is referred to as the Southeastern Massachusetts Health Study.

3.0 THE SOUTHEASTERN MASSACHUSETTS HEALTH STUDY

The SMHS was a matched case-control study of adult leukemia. In a case-control study, exposure histories of a group of persons with a disease of interest (cases) are compared with the exposure histories of a group of persons from the same population who do not have the disease (controls). Key steps include definition of the study population, definition and identification (ascertainment) of cases (case finding), selection of controls, measurement or estimation of exposure or surrogates for exposure, and statistical analyses that compare exposures of concern between cases and controls. If exposures are greater for cases than for controls, then an association may be inferred between the exposure and disease under study.

3.1 STUDY POPULATION

The study population for the SMHS was adult residents of 22 towns in Southeastern Massachusetts. These towns constitute a large part of Plymouth county and have most of their area within 20 miles of Pilgrim.

Cases for the study included all persons who were diagnosed with a form of leukemia, except chronic lymphocytic leukemia, between 1978 and 1986 at age 13 and older. Cases were ascertained using multiple sources, including hospital medical records and the Massachusetts Cancer Registry.

Controls for the study were matched to cases on the basis of age, within five years, sex, vital status, year of death, and residence in one of the 22 towns at the time of the matched case's diagnosis. Controls for deceased cases were selected from lists of deaths of permanent residents of the towns who had died from causes not thought to be related to leukemia or to exposures from Pilgrim plant emissions. Causes of death which were excluded from the controls included death from pancreatic cancer, kidney cancer, lung cancer, cancer of the mouth, larynx, pharynx, esophagus, and bladder, and chronic obstructive lung disease. Controls for living cases were selected from current residents of the 22 towns by random sampling from town directories for 1987 or 1988. The control selection procedure was designed to provide two controls matched to each case.

Information was collected from cases and controls, or their proxy (typically a spouse or relative) in the case of deceased individuals, via telephone interviews. Interviewers collected residential and occupational data for the 40-year period prior to diagnosis for cases and for 40 years prior to a case's diagnosis for the matched controls. This information was used to assess potential for exposure to radioactivity from Pilgrim.

One hundred fifteen leukemia cases meeting the case definition were identified in the 22-town study area. Approximately 91% of the cases, 105 cases, participated in the study. The participation rate for controls was 66%, but a number of individuals were contacted to achieve the desired two controls for each case. As noted above, the controls were matched to the cases on age (within five years), sex, vital status, year of death, and residence in one of the 22 study towns at the time of the corresponding case's diagnosis.

3.2 Estimation of Exposure

As a surrogate for measuring exposure, each subject's residential and worksite history, along with meteorologic data, was used to calculate an exposure score. The score was based on measurements of distances and direction from Pilgrim of all residential and occupational addresses occupied by the subject for 3 months or more between 1972 and the fifth year prior to leukemia diagnosis. Wind direction data were used to estimate the frequency that a particular address was downwind of Pilgrim. Thus, potential for exposure was based on scores derived from the proximity of subject's home to Pilgrim, length of residence at that address, proximity of subject's job site to Pilgrim, length of employment at that job location, and frequency downwind from Pilgrim of each residence and job location.

Exposure estimates (scores) excluded residences and jobs within 5 years of diagnosis. This was because the MDPH investigators assumed a 5-year latency for leukemia. Latency is a measure of the time between exposure to a potential cause (agent) and appearance of manifestations of disease.

Exposure scores were determined by a distance-duration-wind frequency score and by distance-from-the-plant measurements. Exposure scores accounted

for latency, duration of exposure, and inability of a single address to characterize exposures for most people. Exposure scores were grouped into three categories: low, medium, or high. It is important to note that these scores are useful only for relative assignment of exposure and not as an absolute measure of exposure on a quantitative scale.

3.3 Potential Confounding Factors

In addition, data were collected on potential confounders. Confounders are factors thought to be related to both the exposure of interest, in this case "exposure" to Pilgrim emissions, and to the outcome of concern, in this case leukemia. Controls were matched to cases on the basis of potential confounders such as age and sex. In the questionnaire, information was collected from the subjects on social factors, workplace exposures, and other environmental contaminants that were potential confounders.

Workplace exposures were dealt with by examining the occupations of subjects and the industries in which they were employed. In the initial report occupations and industries were grouped by potential for similar exposures and "high risk" occupations were established. This approach was expanded and modified in a later report. Other environmental contaminants were evaluated by considering distance from the coast and population density. Considerable attention was also paid to smoking history and medical radiation exposure.

3.4 Statistical Analyses

Analyses conducted included descriptive statistics and analyses of associations between exposure to radioactivity from Pilgrim (as estimated both by exposure scores and by distance from the plant) and case or control status. Analyses of associations were based on estimates of the relative risk of leukemia associated with various exposure groups compared to the group with the lowest level of exposure. Relative risk estimates reflect the magnitude of an association between exposure and disease and the likelihood (risk) of developing the disease in the exposed group relative to the unexposed. Relative risk is calculated as the ratio of the risk of disease among the exposed to the risk among the unexposed.

In a case-control study such as the SMHS where subjects (cases and controls) are selected on the basis of disease status (cases = disease, controls = absence of disease), it is impossible to directly calculate the relative risk of disease. Relative risk can be estimated in a case-control study by calculating the ratio of the odds of exposure among cases to that among controls. This is referred to as an odds ratio. The odds ratio is considered to be a valid estimate of relative risk when the disease is infrequent and cases are newly diagnosed, when prevalent cases are not included in the control group, and when selection of cases and controls is not based on exposure status.

In the SMHS, odds ratios were calculated and used as estimates of relative risk. Tables in the SMHS report presenting analysis results have titles referring to "estimated relative risk," but results are in a column labeled "O.R." (odds ratio). Statistical methods were used which enabled investigators to control for (or take into account) effects of potential confounders on the calculated relative risks. Such control can, however, have limitations, and must be applied and interpreted to avoid biasing results.

Statistical methods used were appropriate for the design and type of data dealt with. The statistical analyses included conditional logistic regression, which was used to estimate relative risks and to compare the fit of various models. Some analyses were carried out which controlled for potential confounders in the regression model, while others stratified subjects on the basis of confounders, such as smoking level.

3.5 SMHS Report

The report from the SMHS includes extensive tables that present both descriptive and analytic statistics. We will focus on results of analytic analyses that suggested an increased risk of leukemia associated with the exposure score and with distance from Pilgrim. The score generated higher relative risks than did distance alone. In the view of the MDPH investigators, this reflected the relative inferiority of distance as a measure of exposure.

Key findings of the SMHS are as follows:

- Subjects with the highest potential for exposure to Pilgrim emissions had almost four times the risk of leukemia as those having the lowest potential for exposure.

- Associations between leukemia risk and exposure scores and distance from Pilgrim were found only among those cases diagnosed before 1984.

- Among those cases diagnosed before 1984, a dose-response relationship was observed; that is, the relative risk of leukemia increased as potential for exposure to plant emissions also increased.

- No apparent dose-response relationship was observed for cases diagnosed between 1984 and 1986.

4.0 ISSUES REGARDING THE SOUTHEASTERN MASSACHUSETTS HEALTH STUDY AND ITS FINDINGS

A committee comprised of members appointed by the MDPH and by Boston Edison was established to review the SMHS. This bipartisan review committee reviewed the SMHS design and implementation, critiqued its findings, and interpreted findings in light of existing knowledge concerning health effects of ionizing radiation (Hoffman et al. 1992). Other major reviews of the SMHS and its findings were conducted by Dr. Charles Poole, an epidemiologist with Epidemiology Resources Inc. in Massachusetts. Copies of reports and memoranda prepared by Dr. Poole (Poole, Rothman, and Dreyer 1990; Poole 1991a, 1991b) were reviewed in developing this report.

In addition to the reports by Dr. Poole and the bipartisan review committee, we obtained copies of two memoranda that were sent to the review committee by the investigators of the SMHS (Knorr and Morris 1991, 1992). These memoranda addressed issues raised by the review committee during their review (Knorr and Morris 1991) and by Poole (Knorr and Morris 1992).

In preparing this report, we examined the MDPH final report and the documents described above. We analyzed and interpreted these reports, memoranda, and reviews with regard to what we considered to be the major issues concerning the SMHS and its findings. Below we identify specific questions regarding the study and provide our summary assessment of the issues. For many of the questions, more extensive technical discussion that reflects our assessment and supports our interpretation of the issue is included in the appendix.

Questions raised regarding the conduct of the SMHS and interpretation of the findings include the following:

- Is the study population representative of the exposed and non-exposed areas in the region around Pilgrim?
- Is identification of cases (ascertainment) complete and comparable across towns?
- Was the control group representative of the population in the area around Pilgrim who do not have leukemia?

- Is it possible to determine the relationship between exposure scores used in the study and radiation doses received?
- Did investigators examine the effects of statistical analysis decisions, such as cutpoints for exposure scores and biases possibly created by confounders?
- What is the temporal relationship between releases from Pilgrim and the occurrence of leukemia cases?
- What do the findings mean when interpreted in light of other epidemiologic studies that estimate risks of leukemia associated with ionizing radiation exposure?
- What dose levels and risks would be required to produce the suggested observed excess of leukemia cases?

Each bullet is addressed in the sections that follow. The summary assessment of these issues is presented in two sections: one that addresses questions concerned with the design and conduct of the study and one that addresses questions related to the interpretation of the findings. Detailed discussions that support the summary statements are included as a technical appendix.

4.1 DESIGN AND CONDUCT OF THE STUDY

4.1.1 Is the Study Population Representative of the Exposed and Non-exposed Areas in the Region Around Pilgrim?

Questions have been raised about the exclusion of portions of the northern area of Cape Cod (the Upper Cape), which lie within 20 miles of Pilgrim, from the study population. It does not appear that this biased the findings of the study, but it has been suggested (Hoffman et al. 1992) that if additional studies are done in the area around Pilgrim they should include the Upper Cape.

4.1.2 Is Identification of Cases (Ascertainment) Complete and Comparable Across Towns?

Differences from town to town in the completeness of the identification of leukemia cases could bias the study's results. Suggestions that case finding was more complete near Pilgrim, and that there was an under identification of cases in some areas more distant from the facility, are supported by an assessment of different methods of case identification. This does not appear to have significantly affected the findings of the study.

4.1.3 Was the Control Group Representative of the Population Around Pilgrim Who Did Not Have Leukemia?

In a case-control study, it is important that the control population be selected in such a way that their exposure to a suspected agent be representative of the exposure of the general population. There is a strong possibility that the control group for the SMHS was not representative, and suggestions have been made that this issue be evaluated further. For example, the bipartisan review committee (Hoffman et al. 1992) noted that there might be important socioeconomic differences between cases and controls and that participation by potential controls based on distance from Pilgrim was not adequately accounted for. Poole et al. (1990) questioned the representativeness of the dead controls. While there may be some bias resulting from the controls used, this does not account for the association between exposure score and leukemia.

4.1.4 Is it Possible to Determine the Relationship Between Exposure Scores Used in the Study and Radiation Doses Received?

The exposure model used by the MDPH in this study seems reasonable and should suffice for this type of investigation. A more complex model for estimating atmospheric diffusion could have been used, but results would not likely change greatly. This is particularly the case since exposure scores were used for ranking and were not used as a quantitative value.

While it is not possible to estimate radiation doses using the methods of the SMHS, the approach used does allow for a relative ranking of potential for exposure. It would be possible to carry out a dose reconstruction project using emissions data and detailed information on meteorological conditions and residence and activity patterns, but such a project is not called for on the basis of the emissions data.

4.1.5 Did Investigators Examine the Effects of Statistical Analysis Decisions, such as Cutpoints for Exposure Scores and Biases Possibly Created by Confounders?

The statistical methods used in the study are generally appropriate. In the report (MDPH 1990) and in a subsequent memorandum to the bipartisan review committee (Knorr and Morris 1992) attention was paid to a variety of potential confounders. Control of confounders, variables associated with both an

exposure and a health endpoint, is often a problem in epidemiologic studies. It is not clear in the MDPH study whether alternative approaches to analyses would have had an effect on the results. In addition, there is no consideration of the use of the exposure score as a continuous variable. It is possible that the use of other cutpoints -- grouping levels -- for the exposure scores would have led to different results.

4.2 INTERPRETATION OF STUDY FINDINGS

4.2.1 What is the Temporal Relationship Between Releases from Pilgrim and the Occurrence of Leukemia Cases?

The association between Pilgrim and leukemia risk was not observed in the last three years of the study period, 1984-1986. This finding is not consistent with what is known about the time relationship between radiation exposure and leukemia risk. The time between exposure and the development of disease, known as the latent period, for leukemia is much longer than what was observed in the SMHS. On the basis of studies of leukemia risk among atomic bomb survivors and other groups exposed to ionizing radiation, increased risk would be expected to continue for at least 20 years after exposure. Since maximum emissions from Pilgrim occurred in 1974-1977, the association observed in the SMHS apparently lasted only 8 years following maximal potential exposure. The temporal relationships between Pilgrim emissions and leukemia risks are not consistent with other larger and well conducted studies.

We do not consider the question of time relationships to be the most significant inconsistency of the SMHS with regard to other studies of leukemia risk. Nonetheless, it is still important in the overall assessment of the meaningfulness of the reported association between Pilgrim emissions and leukemia.

4.2.2 What do the Findings Mean When Interpreted in Light of Other Epidemiologic Studies that Estimate Risks of Leukemia Associated with Ionizing Radiation Exposures?

Epidemiologic studies must be interpreted in the light of other relevant data. Earlier studies do not support an association between adult leukemia and proximity to nuclear facilities (National Research Council 1990). More importantly, studies that include risk estimates based on a quantitative

assessment of radiation dose and leukemia risk do not support a causal association between the maximal population- and individual-doses, based on Pilgrim emissions data, and leukemia risk. This conclusion is supported both by studies of worker populations with low-dose exposure and by studies that extrapolate from high- to low-dose estimates of risk. Even using very conservative estimates, less than one additional leukemia case over a 10 year period would be expected to be associated with Pilgrim emissions. The SMHS projects at least 90 times more leukemia cases associated with Pilgrim than would be predicted using data from other radiation studies. Because the estimates of risk from the SMHS are so out of line with estimates from other studies that were based on better information regarding exposure, the Pilgrim findings can not reasonably be considered to support a causal association.

4.2.3 Are Rates of Leukemia in the Area Around Pilgrim Consistent with the Risks Estimated by the SMHS?

The study by MDPH suggests that at least 54 leukemias diagnosed from 1978-1983 were attributable to radioactive emissions from the plant, a result that is scientifically implausible. These 54 cases constitute two-thirds of all cases diagnosed in the study area. On this basis, the total number of cases that occurred in the population should have been about 3 times higher than normal levels. This was not the case; observed numbers of cases were slightly lower than normal compared with any of 10 different areas in the United States where cancer incidence is monitored routinely.

During the time period when the 54 cases of leukemia attributable to Pilgrim occurred (1978-1983), Plymouth County residents experienced fewer leukemia deaths than expected. On the basis of routinely collected data on leukemia deaths, leukemia mortality rates for the study area before, during, and after the study period have remained close to the state average.

5.0 CONCLUSIONS

The observed strength of the association between leukemia and potential for exposure to emissions from the Pilgrim plant was unexpected based on previous studies. It is difficult to conclude that the observed association is real and related to nuclear power plant emissions. The SMHS is neither of sufficiently unique quality or size so as to override the large body of scientific evidence concerning dose-dependent effects of ionizing radiation.

We do not believe that results of the SMHS can logically be interpreted as suggesting a causal relationship between emissions from the Pilgrim plant and leukemia risk. We base this conclusion on discussion presented above with regard to the temporal relationship between emissions and leukemia risk, the lack of congruence between the SMHS and other studies of leukemia and radiation exposure, and the estimated numbers of leukemia cases that would be expected to occur if risks were as great as estimated.

Results of the SMHS do not indicate a need for concern about leukemia risks in the vicinity of other nuclear power plants with comparable levels of emissions. We did not, however, find major flaws in the design, conduct, or analysis of the study that explain its findings.

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TECHNICAL APPENDIX

Detailed discussions of each of the questions raised in this review are contained in this appendix. The first section addresses questions related to design and conduct of the Southeastern Massachusetts Health Study, and the second section addresses questions related to interpretation of study findings.

A.1 DESIGN AND CONDUCT OF THE STUDY

A.1.1 Is identification of cases (ascertainment) complete and comparable across towns?

It was suggested that lists of towns and zip codes sent to hospitals by the MDPH were incomplete and would bias towards spuriously elevated relative risks because omitted areas lie more than 15 miles from Pilgrim. According to the MDPH, listings of towns, villages, and zip codes sent to hospitals were complete (Knorr and Morris 1992).

Questions were raised relating to the completeness of case identification. Poole, Rothman and Dreyer (1991) suggested that a review of study methods should include a case-by-case comparison with cases in the Massachusetts Cancer Registry (MCR). However, sources of case ascertainment used were not independent, so this was not possible. Case finding could not be kept independent of MCR because some hospitals refused to search for cases already reported to the MCR.

Poole (1991b) has also suggested that use of the MRC as a primary means of case finding leads to bias resulting from incorporating confirmed information from residents who were looking only for under-ascertainment of cases near Pilgrim. Between 1988 and 1990, the number of cases diagnosed in the years 1982-1986 increased by only 4% state-wide. However, for Plymouth and the other four coastal towns on which the MDPH ecological analysis focused, the number increased by 18% and for Plymouth itself, by 42%. This suggests that there was more intensive reporting of cancer cases in the vicinity of Pilgrim than in other areas.

On the basis of the above, it is possible that case reporting to the MCR was more complete in towns closer to Pilgrim or that cases farther from the plant were diagnosed in hospitals well outside the region. Risks would be overestimated if these possibilities occurred.

Identification of cases in hospitals without tumor registries was done through a review of medical records' by hospital staff. A standardized review of individual charts by data collection staff would have been advisable.

According to Poole (1991b) there were 48 leukemia deaths identified on death certificates that were not ascertained for the MDPH study. The investigators in the SMHS (Knorr and Morris 1991) note that "this is probably largely explained by the fact that many people who died of leukemia in the area during those years would not have been eligible for inclusion." No information was provided for the basis of this assumption. How was it determined that they were ineligible?

Initial review of these 48 leukemia deaths by MDPH (Knorr and Morris 1991) excluded 14 cases on the basis of known information, leaving 34 potentially missed cases. MDPH requested hospital discharge data on cases, but they are excluded from any of published analyses. The additional subjects (34 of 48) who potentially qualified for the study were included in a recalculated odds ratio. The failure to ascertain these potential cases did not substantively affect conclusions.

Poole (1991b) had information from 25 hospitals not used for case finding in the SMHS. These data apparently included 75 individuals who gave addresses in the study area. MDPH reviewed these cases (Knorr and Morris 1992) and, based on discharge diagnosis, only 18 were non-chronic lymphatic leukemia cases, and 6 had been included in the study. MDPH believed that 7 of the remaining 12 cases might have been diagnosed outside the study time period.

Although as indicated above, chronic lymphocytic leukemia was excluded from the SMHS, there is a greater proportion of chronic lymphocytic leukemia cases in the 22 towns studied than in populations included in the national cancer Surveillance, Epidemiology, and End Results (SEER) Program (Poole 1991a). This form of leukemia is not associated with ionizing radiation

exposure and the excess may be related to the intensive case ascertainment employed by the MDPH. It has been suggested that if further studies of leukemia are conducted in this area that cases of chronic lymphocytic leukemia be included. If similar patterns are found for chronic lymphocytic leukemia as for other leukemias this would strongly suggest methodologic bias.

A.1.2 Was the control group representative of the population around Pilgrim who did not have leukemia?

There were differences between cases and controls in tracing. Cases were dropped if a traceable relative would not participate in the study. Similar controls were replaced.

With regard to diagnoses of deceased controls, are the proportions of various causes of death among controls similar to those for the population, with the exclusions removed? It would be interesting to know how the distribution of causes of deaths for deceased controls (MDPH 1990 Table 14) relates to the distribution of causes of death (for all non-excluded causes) for Plymouth county and for Massachusetts as a whole. Death rates throughout the study area should be examined to see if the deaths used as controls adequately represented the geographic distribution of the population of living persons that give risk to the cases. Such a procedure relies on an assumption that death rates from selected causes of death were equal throughout the study area.

It is stated in the SMHS that "control volunteers are most likely to be biased towards high exposure. Whereas cases may agree to participate because they suspect the disease they have is of interest, controls, who usually have been healthy, are more likely to be motivated by the suspicion that they have been exposed." (p.70) It would be interesting to know what evidence supports this statement. In addition, this would seem to be of less potential importance if live controls were used. In addition, it is unclear that dead controls were "healthy" based on their causes of death in Table 14.

Cases tended to have been more likely than controls to have occupied one or two residences (versus three or more) from 1972 to the diagnosis year. This means that there were differences in mobility. Since controls were more

likely than cases to have occupied multiple residences, this raises a serious question about the representativeness of the control selection procedure.

If people living in the area closest to Pilgrim were of higher socioeconomic status than those living further away, and there was an inverse relationship between participation and socioeconomic status, then there would be fewer controls living near the plant. The report does not account adequately for control participation by distance from the plant.

A.1.3 Is it possible to determine the relationship between exposure scores used in the study and radiation doses received?

The exposure model used by the MDPH in this study seems reasonable and should suffice for this type of investigation. A more complex model for estimating atmospheric diffusion could have been used, but results would not likely change greatly. This is particularly the case since exposure scores were used for ranking and were not used as a quantitative value.

The method used for determining location of subjects is potentially inaccurate. Questioning a relative or friend about where a subject lived or worked may not produce valid information. Types of respondents were similar in general categories for cases and controls (Table 17), but the distribution of specific responses for cases and controls could differ importantly between "spouse or parent" and "sibling or child".

The MDPH authors state (p.77) that one strength of their methodology was "the evaluation of exposure on an individual basis." While they did develop individual exposure "scores," based on five variables related to time and proximity to Pilgrim and its emissions, it is an overstatement that this surrogate is really a measure of exposure. In the executive summary, the authors themselves place exposure in quotation marks and note that exposure was "estimated by quantifying the potential for exposure." The exposure score was not meant to be a quantitative measure of dose but, rather, a means for ranking subjects.

Poole (1991b) has suggested that the analyses which examined cases and controls by the proximity of their residences to the coast were made questionable by use of closest residence. All years were weighed equally for exposure. Use of a single five-year minimum induction time assumption is not

realistic. In response, MDPH investigators pointed out (Knorr and Morris 1992) that the "closest" residence was used only in the analysis of distance from the residence to the coast, not in all distance-based analyses. The five-year latent period was assumed for all other analyses and 93% of subjects had resided at the same distance from the plant during the fifth year prior to diagnosis.

The question was raised regarding equal treatment of all years, i.e., quantification of radiation from Pilgrim. MDPH showed that when using a more reasonable definition of a potentially exposed population, allowing for a latent period, and controlling for potential confounders at the individual level, an association remains (Knorr and Morris 1992). When a exposure-potential scoring system was used that weighted exposures based on temporal variation in the emission of radioactive noble gasses, results were similar to those without weighting. This was attributed to the fact that subjects who were in the area during low-emissions years were also there during high-emissions years.

A suggestion was made that individual reconstruction of radiation doses, using all available emissions and monitoring data, should be performed for all cases and controls in the study. Should a dose-reconstruction project be undertaken, there needs to be assurance that emissions data accurately reflect actual releases. It would be possible to estimate doses using radionuclide release data from both stack and building vent, along with joint frequency data of wind speed, direction, and stability for the site for quarterly or even monthly time periods. A possible future study could include a mini-dose reconstruction project. However, from data now in hand and with the conservative dose assessments done to date which show a dose that could not possibly cause the excess leukemias as indicated in the study, an extensive dose reconstruction study would not appear to be cost effective.

The distribution of doses from effluents assumed by MDPH is inconsistent with actual calculated doses (Congel and Willis 1992). The "potential exposure" scores are not interpretable as estimates of ionizing radiation doses. However, from what is known about leukemia risks associated with radiation exposure, it is possible to estimate levels of exposure required to produce the suggested number of excess cases.

The speculation that long-lived nuclides may have been released and not monitored can be discounted based on routine whole body counting of plant workers. There was no evidence of unmonitored releases in these data. If releases of the magnitude required to produce the reported excess of leukemia had occurred, they would have been detected by the large number of radiation monitors in Eastern Massachusetts.

The average annual effective dose to the maximally exposed individual member of the public due to airborne radioactive releases from nuclear power plants with a boiling water reactor, such as Pilgrim, is 0.001 mSv (0.1 mrem). This small increase in potential radiation exposure is difficult to reconcile with the reported large increase in leukemia risk.

A.1.4 Did investigators examine effects of statistical analysis decisions, such as cutpoints for exposure scores and biases possibly created by confounders?

The statistical methods used in the study are generally appropriate, and it is highly unlikely that observed results came about because of inappropriate statistical analyses. There are, however, several possible problems that might have affected results at least slightly. It is stated that analyses were controlled for age, sex, vital status, year of death, socioeconomic status, smoking status, occupation, and industry. With so many factors, it is likely that information on some cases and controls was lost because there were no other individuals with similar values for the controlling variables. It is also unclear how continuous variables were handled. It would have been informative to see alternative results presented with adjustment only for the matching variables (age, sex, vital status, and year of death).

There are also no analyses treating exposure as a continuous variable. It is unclear from the report how the cutpoints for exposure scores were established. It is possible that the three exposure categories chosen could have maximized the association with case or control status. Other cutpoints would have clarified the effect of the reported cutpoints.

It is important to recognize that chance variation could have contributed to the identified association; confidence intervals around the relative risks are very broad. It is doubtful that chance accounts entirely

for the observed association, but chance fluctuation combined with a modest amount of bias from other sources could explain the findings.

According to Tables 21 and 22 in a MDPH November 21, 1991, memorandum to the bipartisan review committee (Knorr and Morris 1991), the standardized mortality ratio (SMR) for females in the 22 towns was highest during the time period 1969-1973 (prior to any potential impact from Pilgrim, which started operation in late 1972). Similarly, in the six towns closest to Pilgrim, the SMR for females is also highest during the 1969-1973 period and the total SMRs for the time period 1969-1973 and 1979-1983 are elevated due to the elevation of the female SMRs. The "excess" seems to be restricted to females.

The SMR is the ratio of the number of deaths observed in a population to the number of deaths expected. The number of expected deaths is based on the population at risk and the expected rate of death from a specific cause from a referent or standard population.

The time periods in Tables 21 and 22 in a MDPH memorandum of November 21, 1991 (Knorr and Morris 1991), differ from those used in Tables 32-34 of the report, where "exposure scores" were used to calculate odds ratios (1969-73, 74-78, 79-83, and 84-86 vs. 78-81, 82-83, and 84-86). There is no explanation as to why these different time periods were used. SMRs used are for all leukemias. It is unclear what proportion of all leukemia deaths would be attributed to non-chronic lymphocytic leukemias.

Leukemia incidence rates should be computed using the study's cases and population figures from the U.S. Census Bureau. Leukemia incidence for the low exposure group was well below the state average. This would increase the odds ratios (relative risks) for the medium and high exposure groups.

A.2 INTERPRETATION OF STUDY FINDINGS

A.2.1 What is the temporal relationship between releases from Pilgrim and the occurrence of leukemia cases?

According to the bipartisan review committee, one of the most intriguing findings of the study is the time-limited association between distance from the plant and risk of leukemia. The time-limited association suggests

increased risk corresponding to some peak radiation exposure at a specific time in the past, accounting for the observed latency of leukemia.

The association between leukemia and the study's measure of "potential exposure" to emissions from the plant abruptly disappeared among cases diagnosed in the years 1984-1986. The association, therefore, apparently ceased only 11 years from plant start up and 8 years from the maximum releases that occurred in 1974-77 (MDPH 1990 Fig. 2). This does not appear to be consistent with what is known about time relationships between radiation exposure and leukemia risks.

Is it reasonable to expect a maximum empirical induction time of only 11 years? Certainly not on the basis of other studies of leukemia and radiation, in which increased leukemia risk declined over many years after peaking between 5 and 10 years after radiation exposure.

The short duration of the increased risk of leukemia is inconsistent with being causally associated with Pilgrim releases. The increase disappeared when it would have been reaching its maximum if it were radiogenic. Importantly, among adults ages 45+, excess deaths increase rapidly for up to 16 years after exposure. With regard to ages of cases in the SMHS, over 70% of study cases were over 45 at diagnosis and 55% of cases were above age 60 at the time of diagnosis (mean age at diagnosis was 58.8). Based on studies of Japanese atomic bomb survivors, acute leukemias occurred early among youngest survivors and risk returned to normal within about 15 years after exposure. Importantly, with regard to the SMHS, with increasing age at the time of exposure, the peak incidence occurred later and the period of excess risk was longer. For the age group 45 and older at exposure, the peak incidence may not have occurred until 20 years after exposure and there was no evidence of a rapid decline thereafter. According to BEIR V (National Research Council 1990), among males 60 or greater at time of exposure, excess deaths are twice as great at 15 years following exposure as they are at 5 years and almost half again as high as they are at 10 years. This illustrates the fact that risks continue to increase for many years following exposure.

The MDPH authors (MDPH 1990) note that "the disappearance of an association with the plant when only cases diagnosed after 1983 were examined

suggests that the higher emissions during the 1970s rather than the emissions from normal routine plant operations might have been the cause of the increased leukemia risk." This requires a short latency period and does not fit with what is known regarding leukemia risk. From the perspective of latency, Dousset (1989) used a 2-year latent period for leukemia in their study of deaths around a reprocessing plant in France (La Hague). There were no statistically significant differences in leukemia rates between the area around the facility and a comparison population.

Based on data from the atomic bomb survivor studies, while excess deaths for childhood leukemias appear to be relatively constant for the first 15 years following exposure, excess deaths among adult males increased for up to 25 years after exposure. Thus, it is not logical that if there was an increased risk of leukemia associated with Pilgrim emissions from the period 1974-1977, it would disappear by 1984 (MDPH 1990 Table 34).

Maximum releases occurred in 1974-1977. If the maximum risk is within 5 years following exposure (National Research Council 1990), then there should be a peak of risk between 1979 and 1982. In the report, the cases from 1978-81 showed a different pattern of relative risks than did those for 1982-83; in 1978-81 the odds ratio for the medium exposure group was significantly elevated while that for the highest group was not, a situation that was reversed in the 1982-83 data.

For chronic granulocytic leukemia, the only chronic form associated with radiation, excess risk among atomic bomb survivors was essentially restricted to the period 5 to 20 years after exposure. In the SMHS, 16% of cases were chronic myelogenous (granulocytic) leukemia. In the report, there was no discussion of the distribution of cases by diagnosis by time. Based on the Japanese data, we would expect cases of chronic myelogenous leukemia, among adults, to occur earlier in time following exposure than cases of acute leukemia.

A.2.2 What do findings mean when interpreted in light of other epidemiologic studies that estimate risks of leukemia associated with ionizing radiation exposure?

Epidemiologic studies must be interpreted in light of other relevant data. One strongest source of information for direct assessment of effects of

exposure to radiation at low doses and dose rates are studies of workers who have been exposed occupationally. The comments on worker studies included in the MDPH (1990) report on p. 5-8 do not provide an adequate description or summary of the studies and their findings. The MDPH authors' position on risk estimates associated with radiation is illustrated clearly in their statement: "demonstration of extraordinarily high releases is not absolutely essential for serious consideration of a hypothesized link between Pilgrim releases and cancer; the questionable validity of currently accepted risk estimates would seem sufficient to generate interest in the relationship between even normal nuclear power plant operation and cancer."

The authors (MDPH 1990) cite "many reports of high leukemia incidence near nuclear facilities" as strengthening the hypothesis of a causal association between Pilgrim and leukemia. The authors themselves note, however, that studies of leukemia and nuclear facilities in the United Kingdom found that "children and not adults living near nuclear facilities were at increased risk of leukemia." Since adult and childhood leukemias may be etiologically distinct, this does not provide strong support for their hypothesis. The studies reviewed in Appendix XII (of the MDPH report) do not support an association between adult leukemia and proximity to nuclear facilities.

Several studies have shown that the likelihood of developing leukemia is greatest among those who are young at the time of exposure (Citations in McLaughlin et al. 1992). The studies in the vicinities of nuclear facilities that have examined adult leukemias have not demonstrated associations; the exception to this is the MDPH study (Shleien, Ruttenber and Sage 1991).

Understanding risks is based in large part on extrapolating from high dose to low dose exposures and, to a lesser degree, on studies of populations with low dose exposures. MDPH authors suggest that low-dose observational studies have been discouraged in favor of extrapolation from high-dose exposures. It is not that studies of persons exposed at low doses have been discouraged, rather, risk estimates based on these exposures are far less precise than those obtained from high dose studies. While the process of high dose to low dose extrapolation is often problematic, information regarding risks at high doses certainly establishes limits for reasonable (and

unreasonable) low dose estimates. If a study shows risks at low doses that are incompatible with what is known about risks at high doses, then there are reasons to be particularly concerned about the study and its methods.

In their closing statements the MDPH authors (MDPH 1990) wrote that "supposedly, there should be no detectable elevation in risk from this source." They go on to suggest that their results support "a number of occupational studies which have found elevated rates of various types of cancers among workers exposed to relatively low levels of ionizing radiation." Their conclusion is that concepts of risks based on unusual populations exposed to high doses are questionable. It is not logical, however, that risks at low levels of exposure are greater than at higher levels.

The MDPH authors state that studies show cancer occurring more frequently among radiation workers than other workers. In the studies cited as being conducted in the last two decades, results are interpreted by the authors of the individual reports as being consistent with those expected based on linear extrapolation from high dose data.

Most occupational studies have shown strong healthy worker effects (death rates lower than those of the general population), and little evidence of dose-response associations between radiation and cancer risk when internally based comparisons are conducted. Dose-response analyses in worker studies have generally been based on internal comparisons among workers with different levels of radiation dose, and the general population has not been used in these comparisons. Although there is always potential for bias in epidemiologic analyses, it is not likely to be as bad as conveyed by the authors of the MDPH report.

The MDPH authors (MDPH 1990) state "occupational studies considered as a unit represent the strongest evidence that exists indicating that estimates of the risks associated with exposure to low levels of ionizing radiation have been underestimated." This statement certainly is not in agreement with the interpretation most scientists (including the authors of the papers cited in the MDPH report) have given these studies. For example, both the BEIR III and BEIR V committees reviewed low dose studies, and did not find reason to modify risk estimates obtained through extrapolation from high dose data. The BEIR V

model was based on a risk coefficient of 2.6% per 10 mSv for exposure in adulthood for the time period 2-25 years after exposure. This included a reduction in the linear risk estimate by a factor of two to allow for reduced effects at low doses (National Research Council 1990).

The MDPH authors (MDPH 1990) note that some of more recent studies of radiation workers have revealed dose-response relationships for leukemia. In studies they cite, the Beral et al. (1985) and Inskip et al. (1987) analyses of the United Kingdom Atomic Energy Authority (UKAEA) data found a leukemia trend in the positive direction, but not close to statistical significance. Smith and Douglas (1986) did find a significant correlation for Sellafield workers when doses were lagged for 15 years (not found with a 0 year lag); however, this correlation came about because of deaths in workers with fairly substantial cumulative doses (20+ rem), and the result was consistent with predictions from currently accepted risk estimates.

Probably the best currently available summary of the worker study data from the United Kingdom is that provided by the National Registry of Radiation Worker (NRRW) study (Kendall et al. 1992). This study includes most of the workers in the UKAEA, Atomic Weapons Establishment (AWE), and Sellafield populations, for whom separate results have been published. The leukemia risk estimate (with 90% confidence limits) from this study was 4.3% per 10 mSv (0.4%, 14%). For comparison, the 1988 UNSCEAR (UNSCEAR 1988) report presents an estimate of 3.8% based on males exposed in adulthood. Also, the latest Hanford analyses (Gilbert, accepted for publication) yield a leukemia risk estimate of -1.1% per 10 mSv with 90% confidence interval (<0, 1.9%).

The results of the case-control study are irreconcilable with all established predictions of risk from low doses of ionizing radiation. To produce 54 leukemias would require a population dose of 350,000 to 750,000 person-rem (Poole 1991a). The estimated population dose from Pilgrim plant emissions during the study was less than 200 person-rem. This dose was 30 to 100 times lower than would be necessary to cause one case of leukemia and several thousand times lower than the dose required to produce 54 leukemias.

In a population of 100,000 males exposed to a single 10 rem exposure, 100 excess leukemia deaths would be expected, an increase of 15% above

expected cases from all other causes. The excess for females under similar assumptions would be 80 leukemia deaths, which represents an excess of 14%. [As noted earlier, on the basis of these estimates one would expect more male than female cases with a given exposure but the odds ratio in the SMHS is higher among females (Tables 29-30)]. The selection of this acute radiation coefficient to estimate deaths may overstate the number of deaths expected around the Pilgrim plant.

The bipartisan review committee report (Hoffman et al. 1992) notes that the U.S. Nuclear Regulatory Commission estimated the total population dose to the surrounding population at 120 person-rem (1972-1981) with a hypothetical maximum individual dose of 34 mrem to those nearest the plant. The estimated population in the 22 towns was 203,898. These are very conservative estimates and would tend to exaggerate risks. The maximum number of excess leukemia cases attributable to plant releases was 0.524 over the 10 year time period. There were at least 90 times more leukemia cases reported by the SMHS than would be predicted using data from other radiation studies.

We have also carried out calculations of dose estimates and cancer risks using information on the population and plant releases to estimate total-body doses for both the population residing within 2-80 kilometers of the site and a maximally exposed individual (MI) residing 0.5 mile southeast of the site. Our estimates are based on less conservative assumptions regarding emission levels and population doses than the estimates used by the bipartisan review committee. The population assumed exposed was 4,400,000 people (1980 census). Plant releases for the 6 years of greatest airborne emissions (1973 to 1978) were derived from Nuclear Regulatory Commission reports. These data are presented as an Appendix Table.

The total doses for the 6 years considered are estimated to be 200-300 man-rem. If we assume for conservatism that this dose was received at one time instead of over a 6-year period, we can use the single-exposure excess cancer mortality estimate for leukemia of 110 per 100,000 males per 10 rem (the female value is somewhat smaller: 80) as given in the BEIR V report (National Research Council 1990). By this we mean that for every 100,000 males exposed to 10 rem of radiation we would expect 110 excess leukemia

deaths. Using the higher male value, we can calculate the individual risk value of:

110 male leukemias / 100,000 / 10 rem = 0.0001 leukemias per man-rem

The individual female leukemia risk would be 0.00008 per woman-rem, essentially the same for this type of discussion.

To estimate the expected number of leukemia deaths associated with Pilgrim emissions, we will assume the higher male value for risk and the higher release value for dose. For the 2-80-km population, the risk is:

0.0001 leukemia/man-rem x 300 man-rem = 0.03 leukemia

If we are more conservative and assume that 1000 people (males) resided at or near the point of maximum individual exposure of 1.5 rem, then the risk for this group would be:

0.0001 leukemia/man-rem x 1000 men x 1.5 rem = 0.15 leukemia

Thus, even for the highly conservative assumptions on the dose to the maximally exposed individual, the possibility for a single leukemia death to be attributable to Pilgrim airborne effluents during the 6-year period of concern is highly unlikely. Stated another way, to get a likelihood of at least one leukemia death we would have to assume that:

1 / (0.0001 x 1.5) = 7000

Approximately 7,000 persons (male and female) residing in the vicinity of the Pilgrim site would have to receive a dose of 1.5 rem to result in one leukemia death.

An important summary consideration comes from Shleien, Ruttenber and Sage (1991). They note that "cancer risks from exposure to ionizing radiation have been estimated in a number of studies that have related quantified doses to disease rates, and risks estimates from these studies are fairly consistent with one another. For results of a new study to alter these estimates, it must be at least as methodologically sound as the one it challenges."

The calculated dose-response relationships are totally inconsistent with what is known about leukemia risks associated with radiation exposure. The total calculated population dose from Pilgrim effluents has been estimated as less than 200 person-rem (Poole 1991a) or 260 person-rem (Congel and Willis

1992) or between 200 and 300 person-rem from our estimates. Based on BEIR V risk estimates, this would be expected to cause a total of from 0 to 0.05 cancer deaths.

Leukemia is more frequent in males than females. The case population of the SMHS included 64 males and 41 females. In an earlier study in 1982-84, myelogenous leukemia was elevated in males and females but only the male risk was statistically significant. Thus, in the present study, why did females exhibit a stronger association than males? According to the MDPH investigators, the male-female difference in high-exposure category was probably not due to chance; the p value for the sex-exposure interaction term was 0.07. What would explain sex-specific risks? The finding are opposite to what would be expected on the basis of leukemia risks reported in BEIR V and indicates potential for sex-specific confounders. According to BEIR V, the risk of leukemia following radiation exposure is higher for males than for females. The estimate of excess leukemia mortality per 100,000 males per 10 rem exposure is 110 cases whereas for a comparable population and exposure for females, the estimate is 80 cases (National Research Council 1990). The sex ratio was 1.5 males:1 female which is similar to population incidence. Also, as noted, in the earlier study only male risk was significantly elevated. Is it possible that exposure scores for females are based more highly on residence than are males' scores? Are there differences in terms of location of employment? Do women tend to work nearer their residence than males?

APPENDIX TABLE - EMISSIONS AND DOSE DATA FOR PILGRIM 1

Year	1973	1974	1975	1976	1977	1978	Total over 6 yr
Noble-gas releases (Ci):							
Kr-88	65,000	91,000	8,000	23,000	85,000	13,000	
Xe-133	58,000	81,000	2,300	30,000	150,000	4,300	
Xe-135	110,000	150,000	8,000	11,000	20,000	2,800	
Population Dose (person-rem)							
20 m release	49	76	6	14	53	7	200
Ground release	68	99	6	24	100	8	300
Max. Individual Dose (rem)							
20 m release	0.020	0.039	0.0038	0.0071	0.026	0.0039	0.1
Ground release	0.34	0.56	0.046	0.11	0.42	0.061	1.5

Notes:

Noble-gas releases are from the NRC series of reports on "Radioactive Materials Released From Nuclear Power Plants." 1973 through 1978. NUREG-75/001, NUREG-0077, NUREG-0218, NUREG-0367, NUREG-0521, and NUREG/CR-1497. Only total noble-gas release is given in 1973 document so krypton and xenon release amounts distributed the same as for the 1974 distribution.

Population doses include direct, inhalation, and ingestion pathways from all radionuclides reported released for persons residing between 2 and 80 km of the Pilgrim site: approximately 4,400,000 persons. The doses represent estimates assuming two release levels: 20 meters and ground.

Maximum Individual (MI) doses include only direct dose to total body from noble gases. The doses are to an individual residing 0.5 mile southeast of the site. As with the population dose estimates, the MI doses represent estimates assuming two release levels: 20 meters and ground.

Meteorology used for the elevated release dose estimates was from 1974-1975.

For ground release, site meteorology from a 10-m level for 1989 was used.

Actual releases come from a building vent and a 67-m stack.

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