Comments on the arguments for covering chronic lymphocytic leukemia under the Energy Employees Occupational Illness Compensation Program Act of 2000 (EEOICPA) advanced by its stakeholders in the "Chronic Lymphocytic Leukemia: Reconsideration of Exclusion from Eligibility for Compensation under EEOICPA."

Currently, the eligibility for compensation for work-related diseases is under the provisions of the EEOICPA. The second argument of the EEOICPA's stakeholders stated that the major reason for excluding chronic lymphocytic leukemia (CLL) from compensation was based on the absence of excess risk of CLL in the cohort of the survivors of atomic bombings in Japan. Indeed, the Office of Compensation Analysis and Support of the NIOSH uses Radio-Epidemiological Tables (1985) to assign to CLL the probability of causation equal to zero, i.e., a priori rejecting any association of CLL with radiation exposure. These Tables are based on the study of the survivors of atomic bombings in Japan (A-bomb studies) and are being continually updated by the National Cancer Institute. Upon review of the relevant materials, the arguments advanced by the EEOICPA stakeholders could be answered by addressing the following three issues:

(i) judgment about radiogenicity of CLL is based on the study of subjects exposed to high-dose high dose-rate exposures while the majority of U.S. nuclear weapons workers were exposed to low doses of radiation at low-dose rates;

(ii) judgment about radiogenicity of CLL is based on the study of the homogeneous Japanese population whose genetic make-up, lifestyle habits, and background mortality rates differ from the North American population;

(iii) judgment about radiogenicity of CLL is based on the mortality studies while for chronic lymphocytic leukemia incidence studies would be more appropriate.

(i) The A-bomb studies are extremely important to our understanding of the radiation-associated leukemia risks and have become "the authoritative standard to which all findings from epidemiological studies on other exposed populations, such as nuclear workers, have been compared" ((1), p.658). The first issues is concerned with the fact that the findings of the A-bomb studies are limited because they are based on the high-dose high-dose-rate exposure of the homogeneous Japanese population and do not provide information on the effects of protracted low-dose exposures such as experienced in occupational settings. Thus, the question can be re-structured as one of extrapolation from the range where convincing data are available to the range where they are lacking.

It has been shown that quantitative evaluation of epidemiologic data allows extrapolation of risk estimates beyond the range where data are available, though it must be recognized that there is uncertainty in making such extrapolations (2). The body of evidence considered as a whole shows that the positive association between radiation exposure and incidence and mortality from various cancers is comparable between high-dose high-dose-rate studies and low-dose low-dose-rate studies (3). Therefore, extrapolations from high-dose studies to low doses continue to be used by the international regulatory committees for setting standards of radiation exposure limits for occupationally exposed workers and for the general population.

It would clearly be desirable to measure risks directly in populations exposed to low doses of radiation at low dose-rates and this, to date, has primarily been done among nuclear workers. Individual occupational studies lack power to produce stable risk estimates. For example, recent analyses of mortality of nuclear power industry workers from the U.S. (4) and Canada (5) looked at the follow-up of approximately 100,000 workers. Yet, only 7 cases of CLL have been identified among 51 cases of leukemia in both studies. Combining low-dose and low-dose-rate studies both increases the statistical power and allows researchers to examine the consistency of findings across studies. The most convincing results on the associations between occupational exposures and subsequent radiation-related mortality to date come from the combined study of nuclear workers from the three countries (6). In this study, significant increases in the risk of

leukemia excluding CLL have been estimated. The fact that the upper 90 percent confidence bound was 5.7 per Sv, provides some confirmation that leukemia risks based on extrapolations from high-dose studies have not been seriously underestimated. While almost 20 percent of all leukemia cases in this study were classified as CLL, no increase in risk for this type of leukemia was shown.

(ii) The second question pertains to the problem of extrapolations to populations with different genetic make-up, lifestyle habits, and background mortality rates. The problem is not severe for leukemia and for all solid tumors combined because their baseline rates are similar across countries. CLL, on the other hand, shows great variability in mortality rates in the general population among different populations (7).

The models predicting leukemia risk used to assist national and international authorities in making risk assessments and in formulating decisions concerning permissible levels of exposure have been proposed by the Committee on the Biological Effects of Ionizing Radiations (BEIR V Committee) (2). BEIR V based its conclusion on the absence of an association between radiation exposure and CLL primarily on the three large studies which include both Japanese and Western populations:

1. mortality from leukemia in the cohort of survivors of atomic bombings in Japan (8);
2. mortality from leukemia in the cohort of British patients treated with a single course of x-ray therapy for ankylosing spondylitis (9);
3. incident cases of leukemia among patients from North American and European countries who were treated with fractionated doses of ionizing radiation for carcinoma of the uterine cervix (10, 11).

No excess cases of CLL have been observed in the first two cohort studies. However, the observed numbers in each of them were very small (less than five). In addition, the average age of subjects in these studies was relatively young at the time of analysis, while CLL is known as the leukemia of older age, usually appearing in those 65 years or older.

The third study used by the BEIR V Committee, on the other hand, was a case-control study based on a relatively large number of CLL cases (52), which did not show any risk of CLL associated with exposure to ionizing radiation (RR=1.03, 90% confidence interval (CI): 0.3, 3.9). Risks of other types of leukemia were increased, albeit non-significantly.

A review of the most recent updates from the three studies used by the Committee in its estimation of the leukemia risk model yielded the following results:

Study	Reference	Outcome	Number of CLL cases (% of the total number of leukemia cases)
A-bomb survivors	Preston 2004 (12)	Mortality	6 (2%)
Ankylosing spondylitis patients	Weiss 1995 (13)	Mortality	7 (12%)
Cervical cancer patients	Kleinerman 1995 (14)	Incidence	35 (20%)

No excess cases of CLL have been observed in the updated analyses from the two cohort studies. Thus, although the average age of the subjects in these two studies has increased along with the number of CLL cases, the risks have remained unchanged. In fact, the patterns of mortality in these cohorts resemble the patterns of leukemia mortality in these populations in general, with less than 5% of all leukemias being CLL in Asian populations, and 20-25% in Western populations (7).

A case-control study (14) based on the extended follow-up of some of the cohorts analyzed by Boice et al. (11) showed no increased risk of CLL, while the risk for other types of leukemia (acute and non-lymphocytic leukemia combined) was significantly increased (RR=1.38, 95% CI: 1.10, 1.72).

In summary, even after extended follow-up of the cohorts which were used by the BEIR V Committee as the basis for leukemia risk models, there appears to be no association between exposures to ionizing radiation and chronic lymphocytic leukemia either in Asian or Western populations.

(iii) The third question is related to the fact that the majority of epidemiological studies are based on leukemia mortality. Ron et al. showed that incidence and mortality of radiosensitive tumors in the cohort of A-bomb survivors were generally comparable (15). However, incidence data were shown to have greater diagnostic accuracy and an ability to capture information about radiosensitive but relatively nonfatal cancers more accurately than the mortality data. Finch and Linet have suggested that over a quarter of all cases of CLL may be asymptomatic for many years, and even after diagnosis survival is significantly longer compared to other types of leukemia (7). Thus, it is possible that mortality data based on death certificates leads to considerable under-diagnosis of CLL. Those who die younger from other causes may not live long enough to develop CLL, while those who survive into old age could develop several diseases in addition to CLL. If CLL is mild or asymptomatic, it would not be recorded as the primary cause of death on the death certificate.

To date, one of the largest incidence studies of CLL was conducted by Boivin et al. in 1986 (16). This case-control study was based on four population-based tumor registries and looked at the leukemia incidence after radiotherapy for a first primary cancer. No risk was shown for CLL (OR=0.8) while risk for all other leukemias combined was increased (OR=1.4, 95% CI: 1.0, 2.4).

The largest study of incidence in the cohort of occupationally exposed workers in Canada showed that although there was a significant number of incident cases of CLL (20% from the total number of 98), the radiation-related risks could not be estimated because the majority of cases occurred in the no-dose or very low-dose group (<5mSv) (17).

To summarize, the A-bomb studies have been used as the basis of excluding CLL from compensation. The three major drawbacks of these studies have been addressed above. Additional evidence from incidence studies, studies of occupationally exposed workers, and studies based on the Western populations was used to address most of these drawbacks. From the scientific point of view, this evidence could be interpreted as the absence of a convincing association between radiation exposure and subsequent CLL. If risks are present, but, are not identified in epidemiological studies, then they are certainly much smaller than the risks estimated for other types of leukemia.

CLL remains one of the most controversial issues in radiation epidemiology. Though in the past it was thought to be definitely non-radiogenic, recent discoveries, particularly from genetic and molecular studies, provide evidence that lymphatic cancers may differ to a great degree from other types of leukemia (18). If risks are present, they are probably so small as to render them virtually undetectable in individual studies under currently available scientific epidemiological methods. Meta-analysis of existing studies would increase statistical power and improve our understanding of the issue.

In conclusion, from an epidemiological point of view it is not possible to prove that there is no risk of CLL due to occupational radiation exposure. It is only possible to say that currently we do not have solid scientific evidence to say that CLL is radiogenic.

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