

Review of “Development of a CLL Risk Model for NIOSH-IREP”

David Richardson

Department of Epidemiology, School of Public Health,  
University of North Carolina at Chapel Hill

August 25, 2009

## BACKGROUND

The Energy Employees Occupational Illness Compensation Program Act of 2000 (EEOICPA) is a compensation program for current and former employees in the U.S. nuclear weapons complex who developed cancer as a result of their occupational exposure to ionizing radiation. Under the EEOICPA, chronic lymphocytic leukemia (CLL) currently is regarded as a non-radiogenic form of cancer.

NIOSH is reconsidering this classification of CLL as a non-radiogenic disease. SENES Oak Ridge, Inc., in collaboration with NIOSH, developed a prototype risk model for CLL that allows for non-zero calculations of probability of causation (Trabalka and Apostoaei, Development of a CLL Risk Model for NIOSH-IREP, June 30, 2009). This review comments on the proposed risk model for CLL, proposed radiation risk coefficients, and proposed latency assumption.

### Proposed Risk Model for CLL

Analyses of associations between estimated radiation doses and cancer incidence among Japanese atomic-bomb survivors in the Life Span Study (LSS) provide estimates of the excess relative risk (ERR) for most cancer types in NIOSH-IREP. Given the small number of CLL cases in this atomic bomb survivor cohort (reflecting the fact that CLL is very uncommon in the Japanese population), the draft report titled “Development of a CLL Risk Model for NIOSH-IREP” proposes using a broader group of malignant diseases for development of a CLL risk model. Specifically, the draft report proposes a risk model for CLL derived by modifying the current NIOSH-IREP risk model for the group of non-Hodgkin’s lymphoma (NHL), Hodgkin’s

disease, and multiple myeloma (MM). The draft report asserts that “Based on the information reviewed to date ... we think that the risk model in IREP for NHL, Hodgkin’s disease (lymphoma), and multiple myeloma (lymphoma and multiple myeloma grouping; ICD-9 codes 200–203) (Preston et al. 1994; Land et al. 2003) could be a reasonable surrogate for a CLL risk model.”

As the draft report notes, there are major differences between NHL, Hodgkin’s disease, and MM; and, the argument for inclusion of Hodgkin’s disease in this group of diseases which are intended to serve as a “surrogate” for CLL is not compelling (pages 15-16). Contemporary lymphoma classification schemes consider B-cell CLL and small lymphocytic lymphoma to be a single disease entity, and a sub-type of non-Hodgkin’s lymphoma, in recognition of the biological and clinical similarities between these B-lymphocyte malignancies (1). The Life Span Study data encompass an adequate number of NHL cases with which to support a separate analysis of radiation-dose response associations for NHL. NIOSH should revise the proposed model for CLL to draw upon information derived from an analysis of the association between radiation dose and NHL in the LSS cohort.

The draft report further contends that the proposed grouping of NHL, Hodgkin’s disease, and MM is justified given the obstacles to developing a new risk model based on analysis of incidence of NHL. This is an argument for doing what is convenient, rather than logical. The report notes that an analysis of NHL would require data access, use of specialized software, and an independent regression analysis of these data. These are relatively modest obstacles to the proper conduct of this federal compensation program.

### Proposed Radiation Risk Coefficients

The radiation risk estimates for NHL, Hodgkin's, and MM in IREP that are proposed for application to CLL analyses are derived via a model in which the ERR/Sv is time-constant for exposure ages greater than or equal to 30 years and attained ages greater than or equal to 50 years (ERR/Sv=0.178; 95%CI: <0, 0.9465). Given that CLL is a disease of older ages and very rarely occurs at ages < 50 years, the modeled variation in ERR/Sv with attained age is of little consequence for claimants (i.e., terms in the expression shown on page 15 of the draft report for the modifier involving  $g(a)$  have little consequence since the attained age of CLL cases is typically greater than 50 years). In fact, for simplicity, a CLL model might be simplified by striking attained age effect modification. Similarly, given that few workers were exposed at ages <18 years, and the modeled variation in ERR/Sv is modest over the age range 18-<30 years, the proposed model may largely behave as a time-constant model for the ERR/Sv (with an ERR coefficient of approximately 0.18 per Sv).

The radiation risk estimates for NHL, Hodgkin's, and MM in IREP that are proposed for application to CLL analyses (i.e., an ERR/Sv=0.178 for exposure ages greater than or equal to 30 years and attained ages greater than or equal to 50 years) is substantially smaller than the radiation risk estimate in Table 2 (page 16) for NHL among men (ERR/Sv=0.91). Moreover, Richardson et al. (2009) reported on the association between DS02 radiation dose estimates and mortality due to non-Hodgkin's lymphoma among males aged 15-65 years in the Life Span Study cohort with mortality follow-up through 2000 (2). The estimated ERR/Sv (ERR/Sv=0.86; 90%CI: 0.13, 2.03 under a minimal 5-year lag and ERR/Sv=1.12; 90%CI: 0.26, 2.51 under a 10-year lag) is larger in magnitude than the time-constant ERR/Sv proposed for exposure ages

greater than or equal to 30 years and attained ages greater than or equal to 50 years, and similar in magnitude to the estimate reported for NHL among males in Table 2 of the report. Richardson et al. (2009) also noted that when the LSS data were limited to survivors with doses in the range 0-<0.5 Sv (a dose range most comparable to the worker claimants in this compensation program) estimates of radiation-lymphoma mortality associations were of greater magnitude than when estimated over the entire dose range. Under a 5-year lag assumption (i.e., events occurring over the period 1950-2000), the estimated ERR/Sv for NHL was 2.86 (90% CI: 0.10, 7.24). This value is of much larger magnitude than the proposed time-constant ERR/Sv for exposure ages greater than or equal to 30 years and attained ages greater than or equal to 50 years.

#### Proposed Latency Assumption

The preferred model for NHL, Hodgkin's disease and MM used in the draft report allows the ERR/Sv to vary as a function of age at exposure, attained age, and their joint effect. Jointly these parameters describe the effect of time-since-exposure in the LSS cohort. It is therefore unclear what basis there would be for imposing a latency distribution that spans the period when there is empirical (i.e., observed) data on the evolution of lymphoma risk following irradiation in the LSS population. The draft report proposes allowing for age at exposure and attained age effects (and their interaction) as well as imposing a distribution of latency effects that only reaches its maximum approximately 25 years after exposure. The preferred LSS model for the grouping of lymphomas (as implied by its use in NIOSH IREP), allows for a time-constant ERR/Sv for exposure ages greater than or equal to 30 years and attained ages greater than or equal to 50 years (once the interval between exposure and start of follow-up has transpired). This would imply that for exposure ages greater than or equal to 30 years and attained ages greater than or

equal to 50 years the exposure effect should be at its maximum once cancer incidence follow-up of the LSS cohort commences (approximately 13 years after exposure) and persist at that magnitude thereafter. Under the proposed model, the ERR/Sv only reaches its maximum value approximately 25 yr after exposure.

Under the proposed prototype model for CLL, the latency function is notably different from that used for other cancers (including the current model for lymphoma and multiple myeloma). Data collection for incident cancers for the atomic bomb survivor studies commenced 13 years after the bombings (with a special leukemia registry providing leukemia incidence data commencing in 1950). The LSS risk models describe the temporal evolution of the ERR/Sv (with age at exposure and attained age) in the period 1958 forwards (1950 forwards for leukemia). Rather than allow an abrupt transition from 0 excess risk to the modeled ERR/Sv in the LSS for a given attained age and age at exposure (or, extrapolating using the exponential age functions that are modeled), a smooth latency function is used in NIOSH-IREP. Under the current IREP model, for lymphoma and multiple myeloma (and all solid cancers except thyroid and bone cancer), an S-shaped (sigmoid) function was used to describe a smooth transition in the ERR/Sv over the latent interval. The nominal value of the midpoint of the sigmoid latency function is assumed to be 7.5 yrs, and the shape parameter for this function is set so that the latency adjustment attains values of approximately 0.01 and 0.99 at 4 and 11 yrs, respectively. Given empirical data for lymphomas in the period approximately 13 years or more after exposure, it would make sense to employ a model that gives full weight to fitted ERR/Sv estimates in the period when there is empirical data available. As noted above, the inclusion of model terms for effect modification

by attained age, age at exposure, and their joint effect, is used to describe variation in effect with time since exposure in the period where empirical data are available.

#### Epidemiological findings not covered in the draft report

Richardson et al. (2009) reports on estimated radiation dose-lymphoma mortality associations among male workers at the SRS. Positive associations between radiation dose and NHL mortality were observed in that cohort as well under 5- and 10-year lag assumptions (ERR/Sv=6.45; 90%CI: 0.48, 17.95; and, ERR/Sv=7.62; 90%CI: 0.93, 20.77).

Given that CLL cases may be asymptomatic for many years, and that incidence data may have greater diagnostic accuracy than mortality data, there has been interest in results of incidence studies of CLL following radiation exposures. Some recent incidence studies of CLL among radiation workers have noted positive associations, including a study reporting an increase in CLL among Czech uranium miners who had gamma radiation exposures (3), and studies reporting positive associations between estimated radiation dose and CLL incidence in the Ukrainian-American study of leukemia and related disorders among Chernobyl recovery workers (ERR/Gy = 4.09; 95% CI < 0-14.41) (4), and in the study of hematological malignancies was conducted among Chernobyl liquidators (accident recovery workers) from Belarus, Russia and Baltic countries (ERR/100 mGy= 0.47; 90%CI: nd, 7.61)(5). In contrast, Muirhead et al. reported no evidence of an association between radiation dose under a 10 year lag and CLL incidence (ERR per Sv=-0.337, 90% CI: -1.72, 3.1) in their analysis of workers in the National Registry for Radiation Workers (6).

### Comment on the calculation of expected CLL counts for the LSS population

It is unclear what contribution to this report is made by the calculation of the expected incidence of CLL in the LSS cohort (and Appendix A). The interpretation of the findings appears one-sided; the authors contend that clear interpretation of the findings is only possible if the evidence suggests that ionizing radiation is protective for CLL. “If the estimated number of CLL cases in the absence of exposure had been greater than 4 [the observed number] then we might have been able to conclude that the dose-response for CLL in the LSS cohort should be negative.”

The authors should clarify why they have tabulated the expected count over the period 1945-1987 (rather than over the period Oct 1, 1950-1987). The report currently includes “estimates for the number of cases of CLL expected in the LSS cohort over the 42-y period from 1945–1987.” In contrast, the cited LSS analysis spans the period Oct 1, 1950-1987; it is unclear why the report includes expected counts spanning a non-comparable period (and longer period). In Preston et al. (1994) cancer cases ascertained by the Leukemia registry prior to Oct 1, 1950 were excluded. The estimated number of expected cases should be somewhat reduced when re-tabulated over the period Oct 1, 1950-1987.

The observed number of CLL cases (4 cases observed) is 4.44 times the number expected based on the Japanese population (0.9 cases expected) and 3.33 times the number expected based on incidence rates for Hiroshima and Nagasaki (1.5 cases expected), leaving aside the problem in derivation of the expected counts noted above. The report should revise the calculations of expected counts to correspond to the period of CLL ascertainment in the cited LSS report,

include an estimate of the ratios of observed to expected counts (i.e., SIRs), and report associated 90% confidence intervals for these ratios.

### Conclusion

This report provides a useful starting point for consideration of a risk model for CLL to apply via NIOSH-IREP. This model may be strengthened by several suggested revisions, described below.

Firstly, NIOSH should revise the proposed model for CLL to draw solely upon information for NHL.

Secondly, the proposed ERR/Sv for exposure ages greater than or equal to 30 years and attained ages greater than or equal to 50 years (ERR/Sv=0.178; 95%CI: <0, 0.9465) is substantially smaller than the radiation risk estimate in Table 2 (page 16) for NHL among men (ERR/Sv=0.91) and substantially smaller than values reported for the association between radiation dose and mortality due to non-Hodgkin's lymphoma among males aged 15-65 years in the Life Span Study cohort with mortality follow-up through 2000 (ERR/Sv=0.86; 90%CI: 0.13, 2.03 under a minimal 5-year lag and ERR/Sv=1.12; 90%CI: 0.26, 2.51 under a 10-year lag).

Given that the LSS data suggests a significant excess risk for males (2, 7), sex-averaged estimates of association may understate the excess risk for male claimants. The revised NIOSH model should incorporate information regarding the magnitudes of radiation-lymphoma associations observed in these analyses of male LSS survivors.

Thirdly, the proposed risk model allows ERR/Sv to vary as a function of age at exposure, attained age, and their joint effect. However, the model in the draft report further includes a distribution of latency intervals. Under the proposed model the ERR/Sv reaches 0.999 of the maximum 25 years after exposure. The revised NIOSH model should follow the current IREP model for lymphoma and multiple myeloma by employing a sigmoid latency function with a midpoint of the sigmoid latency function at 7.5 yrs and shape parameter set so that the latency adjustment attains values of approximately 0.01 and 0.99 at 4 and 11 yrs, respectively. Such a model would allow the terms for effect modification by attained age and age at exposure to describe latency functions in the period for which there is empirical data.

The general approach for evaluation of compensation claims for CLL described in the report “Development of a CLL Risk Model for NIOSH-IREP” fits well within the approach currently implemented under the EEOICPA. However, workers would be better served, in terms of fairness and in terms of the soundness of the scientific basis for evaluating CLL claims, by addressing the issues raised above.

## REFERENCES

- Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997.[see comment]. *Journal of Clinical Oncology* 1999;17:3835-49.
- Richardson DB, Sugiyama H, Wing S, et al. Positive associations between ionizing radiation and lymphoma mortality among men. *American journal of epidemiology* 2009;169:969-76.
- Rericha V, Kulich M, Rericha R, et al. Incidence of leukemia, lymphoma, and multiple myeloma in Czech uranium miners: a case-cohort study. *Environmental health perspectives* 2006;114:818-22.
- Romanenko AY, Finch SC, Hatch M, et al. The Ukrainian-American study of leukemia and related disorders among Chernobyl cleanup workers from Ukraine: III. Radiation risks. *Radiation research* 2008;170:711-20.
- Kesminiene A, Evrard AS, Ivanov VK, et al. Risk of hematological malignancies among Chernobyl liquidators. *Radiation research* 2008;170:721-35.
- Muirhead CR, O'Hagan JA, Haylock RG, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *British journal of cancer* 2009;100:206-12.
- Preston DL, Kusumi S, Tomonaga M, et al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987 [published erratum appears in *Radiat Res* 1994 Jul;139(1):129]. *Radiation research* 1994;137:S68-97.