

August 19, 2005

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): RECONSIDERATION OF EXCLUSION FROM ELIGIBILITY FOR COMPENSATION UNDER EEOICPA

I. Background

The Energy Employees Occupational Illness Compensation Program Act of 2000 (EEOICPA) provides a lump sum payment of \$150,000 plus medical benefits to any covered former U.S. nuclear weapons worker diagnosed with cancer, if that cancer was judged to be “as least as likely as not” (a 50% or greater probability) caused by occupational exposure to ionizing radiation. The Department of Health and Human Services (HHS) is charged with developing and updating, as needed, the scientific guidelines for assessing eligibility for compensation. The Office of Compensation Analysis and Support (OCAS) of the National Institute for Occupational Safety and Health (NIOSH) performs this function for HHS.

Each EEOICPA cancer claim is individually evaluated according to the claimant’s radiation dose, type of cancer, and other relevant factors by means of a computerized set of quantitative risk assessment models. These computerized models provide “probability of causation” estimates for radiation-exposed individuals. Probability of causation is defined as the likelihood, expressed as a percentage, that a worker’s cancer was caused by occupational exposure to ionizing radiation.

The amount and type of radiation exposure incurred by a claimant is established by a process called “dose reconstruction.” Dose reconstruction consists of systematic research and analysis leading to a quantitative estimate of radiation exposure. The reconstructed radiation dose, type of cancer, and related factors determine probability of causation and, in turn, the success or failure of a claim. A probability of causation of 50% or greater means that the cancer was at least as likely as not induced by radiation and, thus, that it merits compensation.

II. Treatment of chronic lymphocytic leukemia under EEOICPA

Chronic lymphocytic leukemia (CLL) is currently regarded as a non-radiogenic cancer under the regulations (DHHS, 2002) that established the guidelines for determining probability of causation under EEOICPA. CLL is the only type of cancer assigned, a priori, a probability of causation of zero.

NIOSH excluded CLL from coverage primarily because no elevation in CLL incidence had been observed among the Japanese World War II atomic bomb survivors, the data source from which most cancer risk models used under EEOICPA were derived. In addition, in NIOSH’s judgment, other epidemiological evidence available at the time the guidelines were promulgated did not convincingly demonstrate an association between

ionizing radiation and increased risk of CLL. Moreover, the National Cancer Institute (NCI) had specifically excluded CLL from radiation risk calculations in a set of radio-epidemiologic tables used in adjudicating cancer claims filed by radiation-exposed military veterans. (NCI, 2000.) In addition, NIOSH observed that CLL was not covered by any other radiation compensation program.

III. Why NIOSH is reconsidering CLL

Although CLL was designated non-radiogenic for compensation purposes, other types of cancer lacking compelling evidence of radiogenicity (e.g., prostate cancer, non-Hodgkin's lymphoma, hairy cell leukemia, etc.) were not excluded from eligibility for compensation. For those cancers, NIOSH judged that the evidence, even though in some instances marginal, was nonetheless sufficient to err on the side of eligibility. Further, NIOSH's cancer designations were consistent with NCI's position. NIOSH noted at the time, however, that the designation of CLL as non-radiogenic would be revisited in the future (NIOSH, 2002.) In the interim, this perceived disparity in the treatment of cancers with questionable evidence of radiogenicity has generated concern among EEOICPA claimants and other stakeholders.

Proponents of including CLL for compensation have advanced the following arguments:

1. There are hundreds of different types and sub-types of cancer, including many with sparse evidence of radiogenicity, yet only CLL is specifically excluded from compensation under EEOICPA. It is not plausible that CLL could be the only type of cancer that can not possibly be induced by radiation. Moreover, there is no scientific evidence that convincingly demonstrates it is non-radiogenic.

NIOSH comment: NIOSH did not assert that evidence proves CLL is non-radiogenic, only that evidence had not supported the case for radiogenicity.

2. A major reason for excluding CLL was the apparent absence of excess risk among the Japanese A-bomb survivor cohort. However, the reported incidence of CLL varies widely among populations throughout the world. In fact, CLL is rare among the Japanese population and extremely rare among Japanese females (the majority of the A-bomb cohort) prior to age 70. Thus, the ability to detect excess CLL risk due to radiation exposure from atomic bombs is poor.

NIOSH comment: NIOSH agrees that the statistical power to detect excess CLL risk among the Japanese survivor cohort was limited.

3. Hairy cell leukemia (HCL) is a slowly progressing lymphocytic leukemia. Because its symptoms are similar to CLL, it has sometimes been misdiagnosed as CLL. In fact, it has been regarded by some as a sub-type of CLL. Misdiagnoses of cancers of the blood and bone marrow were more common when many EEOICPA claimants were diagnosed with cancer, before improvements in

diagnostic techniques had been achieved. Thus, it's likely that medical records for some claimants may contain inaccurate diagnoses. Despite the similarities between HCL and CLL and the diagnostic problems associated with those similarities, HCL is eligible for compensation under EEOICPA, but CLL is not. The disparity in treatment of these diseases is neither fair nor justified.

NIOSH comment: NIOSH generally defers to NCI for expertise in the classification of cancers, and NCI has consistently regarded HCL and CLL as separate diseases. On the other hand, this distinction is not universal; for example, the United Kingdom's radiation compensation program excludes both CLL and HCL from compensation eligibility.

4. NIOSH convened a public meeting in Washington, DC in July 2004 to seek input on gaps in CLL research. That meeting featured a panel discussion of experts from the fields of epidemiology, medicine, radiobiology, and related health sciences. A consensus seemed to emerge among this NIOSH-convened panel that scientific evidence is inconclusive with respect to CLL's etiology and to its association with ionizing radiation. The intent of EEOICPA, and the often stated intention of NIOSH in carrying out its mandate under EEOICPA, is to err on the side of the claimant whenever scientific evidence is lacking. The arbitrary exclusion of CLL, without regard to an individual's degree of radiation exposure or to the stochastic nature of cancer risk, is clearly contrary to that intent.

NIOSH comment: The public meeting referred to above was convened on July 21, 2004 by NIOSH's Health-Related Energy Research Branch (HERB) as part of an ongoing effort to investigate the possible relationship between ionizing radiation and CLL. HERB has not yet published a report of that meeting. However, NIOSH/OCAS reaffirms its commitment to err on the side of the claimant whenever the state of scientific knowledge is lacking.

NIOSH is sensitive to the perception of disparate categorization of radiogenic cancers. Moreover, as noted earlier, it was stated when EEOICPA program guidelines were first published in 2002 that CLL would be revisited at a later date. Thus, NIOSH/OCAS determined in 2004 that it would be appropriate to reconsider the 2002 exclusion of CLL from eligibility for compensation.

IV. Solicitation of expert opinion

As part of the process of reconsidering CLL for EEOICPA compensation purposes, NIOSH/OCAS in October-November 2004 solicited the independent opinions of five experts otherwise unaffiliated with NIOSH, each of whom was selected based on his or her experience and expertise in the field of epidemiology, medicine, and/or radiation carcinogenesis.

Each expert was asked, separately, to (1) review a document outlining the CLL issue as it pertains to EEOICPA (NIOSH/OCAS, 2004), (2) respond in writing to the question

reprinted below, and (3) provide a rationale for his or her conclusion. In addition, each expert was provided with the program guidelines for determining compensation (DHHS, 2002) and a draft bibliography of relevant CLL literature, the latter prepared by NIOSH's Health-related Energy Research Branch (NIOSH/HERB, 2004.) However, reviewers were invited to base their professional conclusions on any combination of personal expertise, NIOSH-provided documents, or reference materials of their own choosing.

The question posed to each contributor was: *“In your expert judgment, is the evidence of an association, or lack thereof, between radiation exposure and the risk of developing CLL sufficient to continue to regard CLL as a non-radiogenic cancer and to continue to exclude it, a priori, from eligibility for compensation under EEOICPA?”*

Note that the above question was intentionally framed within the narrow context of compensation policy. NIOSH/OCAS does not seek nor presume to resolve the scientific controversy surrounding CLL and radiation, nor should any policy decision that may arise from the current reconsideration of CLL for compensation purposes be construed as NIOSH's position on CLL's radiogenic properties or lack thereof.

Given the above caveat, expert opinions were obtained from five individuals. They are listed below in alphabetical order (titles and affiliations provided for information only), followed by their respective conclusions and (capsule) rationales.

1. John D. Boice, Jr., ScD

Scientific Director
International Epidemiology Institute
Rockville, MD
&
Professor of Medicine
Vanderbilt University School of Medicine
Nashville, TN

Boice's conclusion: "...CLL should not be considered a radiation-inducible cancer."

Rationale given: (Excerpted) “The body of scientific evidence indicates that CLL is not caused by exposure to ionizing radiation at any level of dose. Not one of the major epidemiologic studies of (exposed patients or workers) has reported a statistically significant increase in CLL. Authoritative committees...have concluded that CLL is not caused by ionizing radiation. CLL appears etiologically and clinically a lymphoma and differs from the other forms of leukemia. Lymphomas have also not been convincingly linked to ionizing radiation. In the same epidemiologic studies that find significant increases in myeloid leukemia, no increases in CLL are found despite CLL being the most frequent leukemia among adult Western populations. The etiologic factors that cause CLL are not well defined but are different from those factors that cause other forms of leukemia. (Note: Dr. Boice lists benzene, cigarette smoking, and alkylating agents as examples of agents that cause myeloid leukemia but not CLL.) Thus based on epidemiologic studies of radiation finding no evidence for an association with CLL, coupled with the etiologic and clinical differences between CLL and the other forms of

leukemia that are caused by radiation, CLL should not be considered a radiation-inducible cancer.” (Boice, 2005)

2. Mark A. Crowther, MD, MSc, FRCPC

Associate Professor of Medicine

Hematology Residency Program Director & Head of Service, Hematology

McMaster University & St. Joseph’s Hospital

Hamilton, Ontario, CA

Crowther’s conclusion: “...the available evidence is insufficient to rule out an association between ionizing radiation and CLL; in this case my interpretation of the current standards is that compensation should be provided.”

Rationale given: (Paraphrased/excerpted) Although an association between radiation and CLL has not been established through epidemiology, this can be explained by the low rates of CLL among Asian populations, the misclassification of hematological cancers prior to improved diagnostic techniques, the relatively short follow-up periods of most studies, and a lack of randomized clinical trials. “CLL is clearly not different from other forms of cancer...it is caused by a deficit of programmed cell death, rather than excess proliferation. However, this characteristic is shared with other cancers currently considered compensable. CLL is associated with (and likely due to) specific genetic mutations...specific genetic mutations are one of the consequences of exposure to radiation.” Given the lack of compelling evidence that CLL cannot be caused by radiation, it should be eligible for compensation. (Crowther, 2004)

3. David M. Ozonoff, MD, MPH

Professor of Environmental Health

Boston University School of Public Health

Boston, MA

Ozonoff’s conclusion: “In summary, my expert opinion supports including CLL as a radiogenic cancer and against the continuing, and it seems to me, arbitrary practice of exclusion.”

Rationale given: (Excerpted) “The arguments for continued exclusion are not only weak, but lacking in foundation. Considering that all blood cells come from a common progenitor stem cell it has always seemed plausible to me that any cancer of the blood system could be radiation related. This is now generally accepted as true for benzene, which also affects progenitor stem cells. ... We tend to forget that the four ‘forms’ of leukemia (ALL, AML, CML and CLL) are designations made on clinical grounds and are related to prognosis and management rather than etiology. Indeed if one wanted to employ cell surface markers, there could be hundreds or even thousands of ‘different’ types of leukemia. ... Thus while the type of leukemia is very important if one wants to treat the disease it is incorrect to assume this is related to etiology. Just as the difference between a fracture of the thigh bone and the wrist bone is extremely important for treatment and management of a fracture, it says nothing about the etiology of either.” (Ozonoff, 2004)

4. David B. Richardson, PhD

Assistant Professor of Epidemiology
University of North Carolina School of Public Health
Chapel Hill, NC

Richardson’s conclusion: “Available scientific evidence does not provide sufficient grounds for continuing to regard chronic lymphocytic leukemia (CLL) as a non-radiogenic form of cancer.”

Rationale given: (Excerpted/paraphrased) “...conclusions regarding ionizing radiation as a cause of human cancer are based upon a synthesis of evidence from molecular and cytogenetic research, experimental studies in radiobiology, epidemiology, and theoretical work on cancer causation.” With regard to CLL pathogenesis, NIOSH appears to have granted insufficient weight to mechanistic evidence and too much weight to observational epidemiology. Epidemiological evidence for radiation-induced CLL is limited due to factors such as relatively long latency and unreliable case ascertainment. “This is an inappropriate weighting of evidence for the evaluation of whether ionizing radiation exposure is a cause of CLL. ...the scientific evidence pertaining to the molecular mechanisms of CLL induction weighs heavily towards the conclusion that CLL is similar to other hematological malignancies... The weight of this scientific evidence is in support of the conclusion that the somatic mutations that contribute to the genesis of CLL can be produced by ionizing radiation exposure. ... Available scientific evidence suggests that CLL incidence will be increased by exposure to ionizing radiation. Scientific evidence does not provide a sufficient basis for regarding CLL as non-radiogenic.” (Richardson, 2004)

5. Lydia B. Zablotska, MD, PhD

Assistant Professor of Clinical Epidemiology
Columbia University School of Public Health
New York, NY

Zablotska’s 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.”

Rationale given: (Excerpted) “...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. ... From the scientific point of view, this (epidemiological) evidence could be interpreted as the absence of a convincing association between radiation exposure and subsequent CLL. ... 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. If risks are present, they are probably so small as to render them virtually undetectable in individual studies under currently available scientific epidemiological methods.” (Zablotska, 2004)

V. Summary

Boice argues strongly that little if any evidence supports the contention that CLL can be induced by ionizing radiation, even at minimal exposure levels, a position supported by authoritative committees. In fact, numerous epidemiologic studies of varied populations have consistently demonstrated a lack of association between CLL and ionizing radiation. Further, he notes that significant differences exist between CLL and other types of leukemia. CLL is etiologically and clinically more akin to a lymphoma, and evidence associating lymphomas with ionizing radiation is weak at best. Finally, the fact that other types of cancers weakly (if at all) associated with radiation are (mistakenly) eligible for compensation does not justify adding CLL. CLL presents the weakest case for radiation induction of all cancers.

Zablotska seems to concur with Boice on most points, but she also notes that recent genetic and molecular evidence casts some doubt on the traditional notion that CLL is non-radiogenic. While thus conceding the possibility that CLL may be induced by radiation, she adds that the risk, if any, would likely be so small as to be undetectable by epidemiological studies. Her conclusion is much more cautious than Boice's. While evidence for an association between ionizing radiation and CLL is weak, it cannot be demonstrated that the risk is zero.

Crowther, Ozonoff, and Richardson maintain that it is scientifically illogical to presume that CLL is not radiogenic, each citing various (and often similar) biologic and mechanistic constructs in support of radiation induction. In fact, they maintain, cellular and other non-epidemiologic evidence tends to support the case for radiation induction; thus, it is much more plausible to assume that CLL, like other forms of cancer, is radiogenic. All agree that available scientific evidence does not support the continued exclusion of CLL from compensation. Moreover, given that NIOSH's stated policy is to err on the side of claimants if scientific evidence is inconclusive, it is thus arbitrary, inconsistent, and unfair to regard CLL as non-radiogenic.

VI. Recommendation

Three of the five expert consultants (Crowther, Ozonoff, Richardson) maintain unequivocally that CLL is radiogenic and that it should not be excluded from compensation. Only one (Boice) of the five experts concludes that CLL should absolutely not be regarded as a radiation-inducible cancer under EEOICPA. Another (Zablotska) takes a position that could be categorized as cautious.

The issue hinges on how NIOSH should proceed in the absence of conclusive scientific evidence. Although epidemiological evidence appears to offer little support for concluding that CLL is a radiogenic cancer, a small positive risk cannot be excluded. Furthermore, objections have been raised with regard to the power and methodology used

to address CLL in past epidemiologic studies. The biological, mechanistic evidence lends somewhat more support for the plausibility of CLL as a radiogenic cancer, but is far from conclusive. The differences in the expert opinions solicited by NIOSH appear to stem from the relative weight given to the epidemiologic and mechanistic evidence. Given the direction, as set forth in EEOICPA, to side with the claimants in the face of scientific uncertainty, NIOSH proposes to (1) now regard CLL as a possibly radiogenic cancer for purposes of compensation eligibility and to cease excluding it from compensation under EEOICPA, and (2) to create a new risk model for CLL, incorporating risk coefficients consistent with those assigned to other cancer risk models of similarly weak evidence for radiation induction.

NIOSH notes that this action should be regarded as a policy decision which applies only to compensation eligibility under EEOICPA. It is not intended to apply, nor should it be construed as applying, to other compensation programs or to regulatory issues outside of EEOICPA, nor should it be interpreted as official NIOSH policy regarding the radiogenic nature or lack thereof of chronic lymphocytic leukemia.

VII. References

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