

Centers for Disease Control and Prevention (CDC)
NIOSH/Office of Compensation Analysis and Support (OCAS)
4676 Columbia Pkwy., Mailstop C-46
Cincinnati, OH 45226

Dear Sir,

Thank you for the opportunity to comment on this fascinating problem.

My Background as it is relevant to this project

To establish my credentials, I am an Associate Professor of Medicine at McMaster University in Hamilton, Ontario. I hold a Career Investigator Award from the Heart and Stroke Foundation of Canada, and I have a Master's Degree in Clinical Epidemiology/Health Services Research from McMaster University. I hold Board Certifications in Internal Medicine and Hematology. My position at McMaster requires me to have clinical, administrative and research roles; these are delineated in my curriculum vitae of which I believe you have a copy. I have published about 65 peer-reviewed scientific articles, and about 25 book chapters.

My current clinical practice does not include treatment of patients with CLL, however, I do follow a number of patients with early stage CLL; furthermore, when newly diagnosed patients with advanced stage CLL are admitted to the hospital I am expected to provide their clinical care until referral to an outpatient Hematological Malignancy clinic can be obtained.

I have extensive experience in literature review and population epidemiology; I have participated in a number of large meta-analyses as delineated in my CV. My current research fellow (Dr Wendy Lim) is taking advanced training in population epidemiology and cumulative analyses, under the tutelage of Dr Deborah Cook at McMaster. Dr Cook is a leading expert in cumulative analyses.

My understanding of the background to this problem

1. Patients with CLL known to have been exposed to radiation as a component of their work for the United States Government are currently excluded from compensation because it has been concluded that there is no association between radiation exposure and CLL.
 - a. This conclusion is based upon the observation of a low, and not increased

risk of CLL in atomic bomb survivors and upon epidemiological studies in nuclear workers and patients exposed to therapeutic radiation

Comment: As is spelled out clearly in the bibliographic material the low rates of CLL in Asians, systematic misclassification of indolent hematological malignancies (prior to the advent of advanced diagnostic techniques such as flow-cytometry), short follow-up periods and the likelihood that patients will die with (and thus not of) CLL make scientific interpretation of the current literature difficult or impossible. In the absence of randomized trials within which patients were, or were not, exposed to relevant doses of radiation and were followed for long periods of time (30 years or more) it is unlikely that the relationship between CLL and radiation will be able to be definitively answered.

Perhaps the most important observation from the reviewed literature is the lack of sufficient follow-up to observe an increased risk of CLL; thus, although most acute leukemias occur with a short latency after radiation exposure, radiation associated changes leading to genetic alterations which might produce CLL are likely to require many decades to produce clinical evidence of CLL.

It must be noted, however, that the papers included in the annotated bibliography did generally report that monitored *workers* exposed to usual workplace doses of radiation tended to have lower all-cause SMRs than expected; although rates vary widely between studies this observation was attributed to a "healthy worker effect". Similarly, although variable rates are reported there is little evidence of a strong (defined by large odds ratios or high relative risks) association between other hematological cancers, such as acute and chronic myeloid leukemias and chronic lymphocytic leukemias and usual workplace doses of radiation. This supports that the contention that any such association with CLL will be difficult to "tease out".

2. CLL is the only form of cancer that is automatically excluded from compensation, implying
 - a. that all other cancers may be caused by radiation
 - b. that CLL is therefore systematically different from these cancers
 - c. that good quality evidence exists for an association between other cancers and radiation exposure

Comment: This series of conclusions lack face validity. CLL is clearly not different from other forms of cancer; as noted in the bibliographic material it is caused by a deficit of programmed cell death, rather than excess proliferation. However this characteristic is shared with other cancers currently considered compensatable. CLL is associated with (and likely due to) specific genetic mutations (in particular in the *P53* and *bcl2* gene); specific genetic mutations are one of the consequences of exposure to radiation. Finally, although I am not a content expert, I cannot imagine that good quality data has established reliable links between radiation exposure and all other forms of cancer. Therefore, it seems unusual that in the face of similarly poor data more confidence has been attached to the lack of an association between CLL and radiation exposure, when compared with the *positive* association for all other cancers.

3. Current organizational regulations require that compensation be provided if there is a lack of clear evidence that it should not be

Comment: In my opinion 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

Materials reviewed:

1. CHRONIC LYMPHOCYTIC LEUKEMIA
Annotated Bibliography
This draft annotated bibliography is the result of an initial attempt to identify relevant literature on CLL. The draft bibliography includes annotations of the relevant literature published through July 1, 2004.
2. Ionizing Radiation and Chronic Lymphocytic Leukemia
David B. Richardson, Steve Wing, Jane Schroeder, Inge Schmitz-Fuerhake, and Wolfgang Hoffmann
doi:10.1289/ehp.7433 (available at <http://dx.doi.org/>)
3. Federal Register, May 2 2002: Part IV Department of Health and Human Services

42 CFR Parts 81 and 82
Guidelines for Determining the Probability of Causation and Methods for
Radiation Dose Reconstruction Under the Employees Occupational Illness
Compensation Program Act of 2000; Final Rules