DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

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Subject Comments on "Development of a CLL Risk Model for NIOSH-IREP"
Trabalka and Apostoaei, Draft July 2009

To James Neton, Ph.D.
Associate Director for Science, Office of Compensation Analysis and Support

General comments:

The document describes the development of a risk model from the Japanese Life Span Study (LSS) cohort of atomic bomb survivors to be applied to the compensation of cases of chronic lymphocytic leukemia (CLL) among U.S. nuclear workers. In general, I believe that the proposed model to be used from the LSS cohort [non-Hodgkin lymphoma (NHL) combined with Hodgkin lymphoma and multiple myeloma] is appropriate. I also concur with the dose metric to be used in estimating risk from the LSS cohort. A much more difficult issue is the selection of the appropriate organ or tissue for which dose should be calculated in consideration of the nuclear worker claimant's compensation case. This issue, unfortunately, is not discussed adequately in the document; it is virtually unmentioned outside of Appendix C, and no ultimate recommendation is given. This very important topic should be moved from the Appendix to the main body of the document and some firmer recommendations made on how to estimate an appropriate dose from internal exposure. With no accounting for the contribution to risk from internal dose, it is unlikely that claims for compensation will be successful (since a very high external dose is required to meet the benchmark of a 50% or greater assigned share at the upper 99% confidence limit). Because CLL is a form of NHL, it is not clear why a similar approach could not be used to estimate a target organ for CLL. Lastly, to reduce the main body length as a result of this change and to increase overall clarity and focus for the document, I recommend moving the very lengthy section 3 (Origins, Characteristics, and Clinical Features of CLL) to an Appendix. Other comments and suggestions are detailed below.

Specific comments:

1. The list of key references on p. 3 appears slightly outdated. I suggest adding Silver et al. (2007) and the publications in the 2007 Br J Haematol related to the workshop on CLL held earlier that year. These references, cited extensively later in this document, formed part of the justification for the decisions made in producing risk models.

2. In formulating the arguments about the radiogenicity (or lack thereof) of CLL, it may be of interest to note that the International Agency for Research on Cancer recently excluded CLL along with other non-Hodgkin lymphoma and multiple myeloma from its list of cancer types having sufficient evidence of radiogenicity (El Ghissasi F, et al. 2009 Lancet Oncol 10:751-752). Consistent treatment of these three types of cancer within a compensation program therefore makes sense from a scientific and epidemiologic perspective, if the sole barrier to the inclusion of CLL has been lack of an available dose-response model from the LSS cohort.

3. As indicated in the General Comments, I suggest moving Section 3 to an appendix and only briefly summarizing it in the main body of the text. While it is important information to illustrate the complexity of the natural history of CLL and its relation to NHL, the material is described in far too much detail for this document, and the important information is not readily extractable by the reader.

4. Section 3 and the rest of the document describe B-lymphocyte CLL very well, but I saw no mention of T-lymphocyte CLL, which comprises 5% of all CLL. Will all forms of CLL use the same models and assumptions? It would be good to have this mentioned explicitly.

5. The implications of the lengthy exposition on B-lymphocyte maturation on p. 7 could be made more explicit. For example, the second paragraph mentions germinal cell division in lymph node follicles, but doesn't state that this implies lymph node could be a target organ for the development of the earliest events causing CLL.

6. The first paragraph on p. 11 misinterprets a statement by Schubauer-Berigan et al. (2007). This statement was not that an extended latency period suggests radiation is a promoter for CLL, but rather that a latency of 10 years does so. Considering CLL's long pre-clinical and clinical phase, a latency of 10 years would be very short for CLL mortality, which is what the study was based upon. Indeed, the research presented elsewhere in the reviewed document also would lead to such a conclusion. Please correct the misinterpretation of the reference.

7. The second full paragraph on p. 11 is repetitive and confusing. What does "75% diagnosed at an average age of 60" mean? If this sentence is retained it should be re-written to indicate the median age at diagnosis or some other meaningful fractile.

8. The first full paragraph on p. 13 contains some confusing information about CLL coding in ICD-8. There is a unique code for CLL in that revision, 204.1 (the same as ICD-9). I think the paragraph is trying to state that this code was lumped in with other codes. This is not a problem stemming from the ICD coding per se, but rather with how the investigators chose to group CLL.

9. The relevance of the first full paragraph on p. 14 is unclear. I would retain it only if it sheds light on the appropriate target organ for CLL or is otherwise directly relevant to the questions at hand about deriving an appropriate risk assessment model for compensation.

10. Use of a pooled estimate for NHL, Hodgkin lymphoma, and multiple myeloma is described in the text (p. 14) but is not shown in Table 2. Please provide these estimates in Table 2 or in the text.

11. The effects of attained age and age at exposure would be more easily understandable if there were a verbal description of their net effect on p. 15.

12. I would not argue that there is much support for a risk transport model like that used for breast cancer. The latter's departure from the standard risk transport model employed for other cancers in IREP derives from the very comprehensive epidemiologic studies that have been able to answer this question directly for breast cancer. Such evidence is simply not available for CLL. Occupational studies have exposures that are too low to permit discrimination between multiplicative and additive interaction with other risk factors (which are not even generally understood for CLL). For this reason, I support the use of the "uninformed" transport model.

13. The discussion of latency on p. 20 does not mention the recent paper by Schubauer-Berigan et al. (2007), which explored the latency question through use of time windows. An overall dose-response was seen for exposures less than 100 mSv. The time windows analysis for this group suggested that a latency of 10 years was appropriate (no evidence of risk was seen in shorter time windows). And, this was for a mortality study. Latency for CLL incidence would be expected to be shorter still.

14. The sample results in Table 3 on p. 23 appear to be given as percentages, not probabilities, though they are not labeled that way. Please clarify the labels on this table so that the results are more easily comprehended.

15. The document ends rather abruptly on p. 24, with no discussion of the very important material in Appendix C. I suggest that this Appendix be incorporated into the document, as the target organ for which doses should be estimated is very important for compensation purposes.

16. Appendix B, p. 39: suggest incorporating information from the third column of Table III of Schubauer-Berigan et al. (2007), as mentioned in comment 13 above.

17. Tables B.9 and B.10 are not really relevant for a discussion of CLL latency without an appropriate denominator.

18. Appendix C, while providing a very useful discussion of the complex issues involved, ultimately does not provide a firm recommendation on the target organ for which dose should be estimated. It is not clear why this issue is substantively more challenging for CLL than for other forms of NHL, for which a model and a dose assessment program already exists in NIOSH-IREP.

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cc: Douglas Trout, M.D.