Response to Review Comments on the Draft Report

***Development of a CLL Risk Model for NIOSH-IREP*[1]**

December 1, 2009

The reviewers of the draft report were:

- David Richardson, Ph.D., Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill
- Mary Schubauer-Berigan, Ph.D., Division of Surveillance, Hazard Evaluation and Field Studies, NIOSH, Cincinnati, Ohio
- Richard Wakeford, Ph.D., Dalton Nuclear Institute, University of Manchester, UK
- Lydia Zablotska, Ph.D., Department of Epidemiology and Biostatistics, School of Medicine, University of California San Francisco.

Note: The reviewers' opinions do not necessarily represent those of their organization or university. Affiliations are provided as information only.

The review comments have been grouped into eight general categories:

- Need to include newer epidemiological findings
- Potential radiogenicity of chronic lymphocytic leukemia (CLL)
- CLL incidence rates in the U.S. and Japanese populations
- Appropriateness of current IREP lymphoma and multiple myeloma model for CLL
- Alternative models
- Appropriateness of extended latency for CLL
- Background information on CLL, including implications of reclassification as an NHL
- Internal dosimetry for CLL
- Specific editorial/technical suggestions

Need to Include Newer Epidemiological Findings

One reviewer (Mary Schubauer-Berigan) noted that the list of key references on page 3 of our CLL risk model report appeared to be "slightly outdated." Although Silver et al. (2007) and publications from the 2007 workshop on CLL that were published in the British Journal of

[1] Responses were prepared by J. R. Trabalka and A. I. Apostoaei of SENES Oak Ridge, Inc., under contract 200-2006-18097

Haematology were cited in our draft report, she suggested adding them to the list of key references on page 3. We have done so.

Lydia Zablotska and David Richardson each identified other recent epidemiological studies that they felt merited inclusion and that could influence development of a CLL risk model. The most extensive listing was provided in Zablotska's review. The papers by Linet et al. (2005) and Rericha et al. (2006) on CLL in radiological technologists and Czech uranium miners, respectively, were reviewed by Silver et al. (2007) and Schubauer-Berigan et al. (2007), both of which we cited. The studies by Rericha et al. (2006) and Abramenko et al. (2008) were reviewed in the paper by Hamblin (2008), which we also cited, and the latter two papers were cited in our draft report on internal dosimetry for assessment of radiogenic risks from CLL (Apostoaei and Trabalka 2009).

Our report was drafted in 2007, and amended only slightly in January 2009, primarily to reflect information obtained during work on the draft CLL dosimetry report. We had previously accumulated and reviewed all but one of the papers cited by Zablotska and Richardson. However, there was no pressing need to include them in the report because we had already noted that CLL was potentially radiogenic and none of them provided risk models that were appropriate substitutes for the lymphoma and multiple myeloma models in IREP (see below). All of the relevant epidemiological papers identified by Zablotska and Richardson have now been cited in the revised report.

Potential Radiogenicity of CLL

The reviewers did not disagree with our basic conclusion, namely that CLL could be radiogenic, and that, from an epidemiological perspective, we can only conclude that we currently do not have solid scientific evidence of a well-defined dose-response from the LSS data, but not that there is no risk of CLL due to occupational radiation exposure.

The BEIR VII committee (NRC 2006) conducted an exhaustive review of radio-epidemiological studies. They pointed out that the variability inherent in all epidemiological studies requires that the entire body of relevant literature be evaluated in order to assess possible associations between radiation and cancer induction, be they positive or negative. On this basis, it is the current judgment of all expert groups, including the BEIR VII committee, UNSCEAR,

and IARC, that the occurrence of lymphomas, and of CLL in particular, has not been convincingly linked to radiation exposure (also see Hamblin 2008; El Ghissassi et al. 2009). These conclusions are supported by the results of recent comprehensive studies of CLL in occupational workers (Cardis et al. 2007; Vrijheid et al. 2008; Muirhead et al. 2009).

However, Zablotska countered that studies of CLL incidence in Czech uranium miners (i.e., Rericha et al. 2006) and in radiological technologists (both reviewed in Silver et al. 2007 and Schubauer-Berigan et al. 2007) and three recent case-control studies of Chornobyl (Chernobyl) remediation workers (one of which was the aforementioned study by Abramenko et al. 2008) indicate that CLL is not only associated with radiation exposure (also see Richardson's comments in paragraph 3 on page 7 of his review) but also that its risk profile may be similar to that of other types of leukemia. Relying on one study by Abramenko et al. (2008), Zablotska also suggests that cases of CLL in radiation workers occurred at younger ages, were more advanced when identified clinically, and showed faster progression. These last conclusions are inconsistent with the findings from other occupational studies cited above and previous studies of medically exposed individuals, which had a similar level of follow-up (see Fig. 2 in the draft report; Inskip et al. 1993; Weiss et al. 1995; Wick et al. 1999).

Both Silver et al. (2007) and Schubauer-Berigan et al. (2007) concluded that the case both for and against CLL as a radiogenic disease is still to be proven. The papers by Rericha et al. (2006) and Abramenko et al. (2008) specifically were evaluated by Hamblin (2008), who concluded that these "new data"…certainly do not establish that CLL may be caused or even made worse by ionizing radiation." Thus, the burden of proof for a different perspective on CLL appears to fall on the results from the other two studies of CLL in Chornobyl remediation workers (Kesminiene et al. 2008; Romanenko et al. 2008).

However, none of the studies of Chornobyl remediation workers provided risk coefficients for CLL alone that were significantly different from zero at the 95% level of confidence. The BEIR VII committee concluded that studies of Chornobyl remediators did not provide reliable risk estimates because of difficulties in follow-up and the lack of validated dose estimates (NRC 2006). For the majority of these workers, individual doses were often monitored inadequately or were not monitored at all (Kryuchkov et al. 2009). The risk estimate in the study by Romanenko et al. (2008) does not reflect effects of the very large dosimetric uncertainty, and the study by Kesminiene et al. (2008) did not examine the effect of dosimetric uncertainty on the dose-

response for CLL in isolation from other forms of leukemia. Hamblin (2008) suggested that the differences in clinical characteristics and mutational status reported in the study by Abramenko et al. (2008) were probably explained by "less assiduous screening" of the control populations, because the incidence of CLL with unmutated IgVH genes (indicating a more aggressive form of the disease) in remediation workers was not significantly greater than that in the controls, and both were much higher than the figure of 40% of cases reported in most Western countries.

The results reported in Chornobyl remediation workers, including a minimum deviance for both CLL and non-CLL leukemia using a latency of 2 years in one study (Romanenko et al. 2008), are seemingly diametrically opposed to those reported in the majority of epidemiological studies and deserve considerable additional follow-up before being accepted as valid representations of the radiogenicity of CLL.

Nonetheless, the reviewers' points are well taken. Based on an evaluation of all of the newer information, a new paragraph was inserted in Section 2, as follows:

> ***Suggestive but as yet inconclusive findings in a number of recent epidemiological studies indicate that the evidence for CLL as a radiogenic disease is growing (see, e.g., Linet et al. 2005; Rericha et al. 2006; Schubauer-Berigan et al. 2007; Abramenko et al. 2008; Hamblin 2008; Kesminiene et al. 2008; Romanenko et al. 2008). Although these studies do not currently provide the basis for a radiation risk model for CLL, and contrary findings (i.e., no significant association between radiation and CLL) have been reported from recent comprehensive studies of radiation workers (Vrijheid et al. 2008; Muirhead et al. 2009), we fully agree with Hamblin's (2008) conclusion that "[i]rradiation may have been given a clean bill of health with respect to CLL with less than adequate evidence."***

Finally, we have modified the text in the last two paragraphs of Section 2 in an attempt to address what may have been a source of confusion for two reviewers (Richardson and Zablotska) about the information on potential radiogenicity of CLL that we tried to extract from the limited information available to us from the LSS data. Since our purpose was not to conduct an epidemiological study for CLL in the LSS cohort and since the breakdown of cases between the exposed and non-exposed members of the cohort is unavailable (total was only 4!), we could not carry out a formal calculation of standardized incidence ratios (SIRs) for CLL and associated statistical confidence intervals, as suggested by Richardson. Thus, our point was that because the

expected background incidence of CLL in the LSS cohort was so low (~1 case), the available information did not allow us to conclude that CLL was not radiogenic in the LSS cohort despite the low number of cases observed. Because the material in these two paragraphs now seems superfluous, we deleted most of it.

CLL Incidence Rates in the U.S. and Japanese Populations

We have revised the calculations based on the incidence rates presented in Appendix A to reflect the more appropriate 1950−1987 time frame covered by the LSS data for CLL and have added 95% confidence limits to our estimates of the background incidence of CLL in the Japanese populations as recommended by both Richardson and Zablotska. However, neither of these revisions had a significant impact on the estimated baseline incidence of CLL.

Zablotska recommended that we revise our data for the baseline incidence of CLL in Japan to reflect the updated information available in IARC Vol. VIII (Parkin et al. 2003). However, these data are less relevant for the period of CLL ascertainment in the LSS cohort (1950−1987), because the updated information covers a different (i.e., more recent) period. No action is needed in response to this comment.

Referring to our analysis of CLL incidence in the U.S. population, Zablotska said that rates can be affected by reporting delay, and that it would be advisable to combine incidence rates of CLL and SLL, citing the study of Dores et al. (2007), who describe the effects of reporting delay and provide age-adjusted rates of CLL + SLL that are about twice the incidence rates presented in Fig. A.1 in our report.

The purpose for including the CLL incidence rates in the U.S. and Japan in our report was to highlight that fact that Asians who live in the U.S. retain a background incidence that is similar to that in Asia but which is significantly lower than in other population sub-groups who live in the U.S. The differences suggest a strong influence of genetic background as opposed to environmental effects on the incidence of CLL. This conclusion is fully supported by the data provided by Dores et al., which account for reporting delays and the effects of combining CLL with SLL.

We arrived at the same conclusions as Dores et al. (2007) because delays in reporting of CLL cases affect all populations and sub-groups in Japan and the U.S. Thus, the issue of potential

effects of reporting delays on CLL studies, raised by Zablotska based on the paper by Dores et al. (2007), is not germane to comparisons between non-Asian and Asian populations in the U.S. (Fig. A.1) or between non-exposed and exposed populations in Japan. The paper by Dores et al. (2007) also confirms that the differences between the Asian and non-Asian populations exist whether one uses data for CLL alone or for CLL + SLL. Thus, we recommend keeping Fig. A.1, which compares age-dependent rates of CLL incidence in the Japanese population and in different ethnic groups in the U.S. population. However, we will include information from the paper by Dores et al. (2007) on effects of reporting delays and of inclusion of SLL in the discussion of information on baseline risks of CLL in Appendix A.

Proposed Risk Model

(1) Appropriateness of Current IREP Lymphoma and Multiple Myeloma Model for CLL

Two reviewers (Schubauer-Berigan and Richard Wakeford) agreed with the proposal to use the proposed lymphoma and multiple myeloma model for estimating the PC of CLL claims, and as discussed in the draft report, the VA has set a precedent by using this same model under the atomic veterans compensation program to PC of CLL occurring in military personnel who were exposed to radiation during tests or uses of atmospheric nuclear weapons.

The other two reviewers (Zablotska and Richardson) did not agree with the use of the lymphoma and multiple myeloma model as a surrogate for CLL. They also objected to our use of an extended latency with this model. Our response to their concerns about latency is covered in a later section devoted to this issue. However, it should be recognized that questions about latency affect judgments about the appropriateness of the risk model, and the two issues cannot be completely separated (see section entitled Appropriateness of Extended Latency for CLL below).

Zablotska's questions about appropriate target organs are also covered in a separate section below. Because our discussion of risk transport between populations (Section 5.2) was confusing to her and to Schubauer-Berigan, and we recommended adopting the status quo in IREP, we have deleted the problematical text and included some of the points she made as justification for our choice (see response to Schubauer-Berigan's specific comment # 12 on page 16).

Schubauer- Berigan's comments about discontinuing the use of a DDREF in IREP are duly noted, but they may have been based on a misconception, namely that the DDREF distribution currently in use always reduces the probability of causation (PC) for a claimant. This is not the case because values from the lower end of the DDREF distribution (i.e., <1) drive PC estimates at the 99th percentile, the decision criterion used in evaluating compensation claims. In addition, the technical basis for the risk estimates in the 15-country study to which she referred in support of her argument has been challenged because of concerns about data for the Canadian cohort (see Wakeford 2005; UNSCEAR 2008; Jacob et al. 2009). Further, the more recent results from the epidemiological study of the U.K. cohort by Muirhead et al. (2009), which were based on cancer incidence data, support the use of a DDREF similar in magnitude to that currently used in IREP. Thus, although we agree that the DDREF distributions in IREP should be reevaluated, based on the full range of information that has become available since they were developed, we don't currently see a justification for deleting them in their entirety.

Zablotska raised issues similar to those we have already discussed regarding the inclusion of multiple myeloma cases in the CLL model. She also suggested that the characteristics of radiogenic CLL might be different than those in an unexposed population, a conclusion that was countered by Hamblin's review of the paper by Abramenko et al. (2008).

She also suggested, again based on the responses in the Chornobyl clean-up workers, that the risks of CLL may be comparable to the risks of non-CLL leukemia, and that consideration should be given to using current ***leukemia*** models to predict the risks of CLL, a conclusion with which we strongly disagree.

Richardson argued that because "CLL is a disease of older ages and very rarely occurs at ages <50 years," that the modeled variation in age at exposure in the IREP lymphoma and multiple myeloma model is of little consequence. He suggested that, for simplicity, that the attained-age effect could be eliminated. In addition, he stated that since few workers were exposed at ages <18 years and the age-at-exposure influence is modest over the 18−30 year age range, a plausible model may behave as a time-constant ERR/Sv of 0.18: the point estimate for a person who is ≥30 years old at time of exposure and attained age ≥50 years.

While we agree that the variation of ERR/Sv with age at exposure between ages 18-30 may be considered modest, it is not negligible. A model like that proposed by Richardson would penalize those workers who were exposed at younger ages or workers who might develop CLL

within a relatively short time after exposure. The current model in IREP with a fully described age-at-exposure and attained-age dependency does not pose any computational challenges. Thus, we believe that simplifying the model in IREP as proposed by Richardson is unnecessary.

Richardson then pointed to an apparent discrepancy, stating that the value of ERR/Sv from the IREP model for lymphoma and multiple myeloma ***incidence in both men and women*** is lower than estimates of ERR/Sv modeled by his team for NHL ***mortality in men*** in the LSS cohort (see Richardson et al. 2009). We do not think that this was an appropriate comparison.

The rationale and approach used by Land et al. to develop the model currently used in IREP to estimate ERR/Sv for lymphoma and multiple myeloma was described in Section 5.1 of the draft report:

> "[As for NHL or multiple myeloma individually, t]he central value of the point estimate of the ERR for males in the model for the lymphoma and multiple myeloma grouping used in IREP was also positive, while that for females was negative. For the IREP model, it was assumed that the ERRs for the two genders were the same, although there reportedly was suggestive evidence that they differed ($p = 0.09$). The age parameters used were derived from an analysis of the incidence of solid cancers other than digestive cancers, female stomach cancer, liver cancer, female breast cancer, thyroid cancer, and non-melanoma skin cancer. The common age parameters derived from this analysis were reportedly used for the lymphoma and multiple myeloma model because there was little evidence of departure from them in the grouped data for the latter."

It should be noted that the decision to pool these data was driven in large part by the recommendation of the NAS/NRC that individual models not be developed for those cases where fewer than 50 cancers were observed in the LSS cohort.

Counter to Richardson's assertion that the number of cases of NHL in the LSS data is adequate to support a separate analysis of the dose-response for CLL, it is clear from Table 2 in the draft report that the NAS/NRC criteria would argue against separate models for NHL, Hodgkins lymphoma, or multiple myeloma or for males and females for NHL alone.

We recently discovered that the UNSCEAR has reanalyzed the data for NHL alone, significantly lowering the estimates of ERR/Sv in the process (see hi-lited data in revised Table 2 below). Although the point estimate for NHL incidence in males is still positive, it is less than half the previous estimate and is not significantly different from zero even at the 90% level of

confidence. When the cases of NHL in males and females are considered together, the pooled risk estimate (ERR/Sv 0.08; see Table 2) is even smaller than that for the IREP lymphoma and

Table 2. Risk estimates for incidence of non-Hodgkin's lymphoma, Hodgkin's lymphoma, and multiple myeloma in the Japanese atomic-bomb survivors at doses ≥0.01 Sv

Cancer site	Internal grouping		Number of cases	Average ERR at 1 Sv[a]	Source
Non-Hodgkin's lymphoma	***Gender***	***Male***	***41***	***0.44 (−0.16, 1.42)***	Table 41 in UNSCEAR (2008), based on data in Preston et al. (1994)
		Female	***35***	***−0.22 (<−0.22, 0.40)***	
	Age at exposure	***<20 y***	***17***	***0.45 (<0, 2.16)***	
		20−40 y	***34***	***−0.12 (<−0.12, 0.73)***	
		>40y	***25***	***0.09 (<0, 1.04)***	
	Time since exposure	***12−15 y***	***7***	***0.33 (<0, 2.14)***	
		15−30 y	***34***	***0.33 (<0, 1.44)***	
		>30 y	***35***	***−0.22 (<−0.22, 0.45)***	
	All		***76***	***0.08 (<0, 0.62)***	
Hodgkin's lymphoma	All		10	0.43 (-1.6, 3.5)	Table 42 in UNSCEAR (2008), based on data in Preston et al. (1994)
Multiple myeloma	Gender	Male	12	0.17	Table 43 in UNSCEAR (2008), based on data in Preston et al. (1994)
		Female	18	−0.28	
	Age at exposure	<20 y	4	1.07	
		>20y	26	0.09	
	All		30	0.20 (<-0.2, 1.7)	
Multiple myeloma	All		31[b]	0.26 (0, 1.85)[c]	Land (2000)

[a]90% C.I. in parentheses, except where noted.

[b]Includes one additional case of multiple myeloma not originally included in the analysis by Preston et al. (1994).

[c]95% C.I. in parentheses.

multiple myeloma model (0.178). As is the case for the individual estimates of ERR/Sv for both males and females, it is not significantly different from zero at the 90% level of confidence.

Thus, in light of the latest analysis by UNSCEAR, many of the comments and recommendations made by Richardson and Zablotska may no longer be relevant.

Because the last data set for NHL in the LSS cohort was defined by the ICD-9 classification rather than the most current classification adopted by the WHO and the NCI, it still does not include CLL, HCL, Sezary's disease, and a variety of other conditions now included under the NHL umbrella, which, if included, could conceivably lower the ERR/Sv even further.

Finally, in her specific comment No. 2, Schubauer-Berigan noted that IARC recently excluded CLL along with NHL and multiple myeloma from its list of cancer types having sufficient evidence of radiogenicity (see El Ghissassi et al. 2009). [Hodgkins lymphoma was also excluded by IARC, and, it, along with CLL, is excluded from the U.K. compensation program, per Richard Wakeford.] She concluded that consistent treatment of these three types of cancers within a compensation program made sense from a scientific and epidemiological perspective, if the sole barrier to inclusion of CLL has been the lack of an available dose-response model from the LSS cohort. Richard Wakeford made essentially the same point in his review.

(2) Alternative Models

Richardson contends that we argued for use of the current lymphoma and multiple myeloma model and against development of a new risk model based on NHL alone out of convenience. In point of fact, we simply pointed out what we thought it would take to conduct such an analysis, and he apparently does not disagree with our enumeration of the steps required, which were detailed in Section 5.1 of the draft report. He considered these steps to be modest obstacles to proper conduct of the EEOICPA program.

However, he did not acknowledge a major disadvantage of performing such analyses at the current time, namely that extended information on the LSS cohort, i.e., dose responses for lymphoma and leukemia incidence that are based on DS02 dosimetry and significantly extended follow-up, are yet to be published.

Zablotska "strongly advocate[ed]" that NCI (specifically Charles Land) be asked to develop a new risk model from the DS02-based LSS data when they become available, by combining the NHL and CLL cases and by "careful consideration of the newly published Chornobyl studies."

Wakeford also suggested that it might be prudent to await the upcoming analysis of the DS02-based data for lymphatic and hematopoietic cancers by the staff from the RERF and NCI before making any decisions about CLL and the applicability of the current lymphoma and multiple myeloma model.

As a fall-back position, Zablotska recommended adoption of "the NHL-alone model" rather than use of the lymphoma and multiple myeloma model. Her recommendations in this regard echo those of David Richardson.

Unfortunately, no such model currently exists, as discussed above, and there are good arguments against reanalysis of the existing NHL data set because of the relatively small numbers of cases available and the lower revised risk estimates for NHL developed by UNSCEAR. The existing LSS data for NHL were also based on an older disease classification system and are thus incomplete for reasons previously given. It seems unlikely that the disadvantages of using data based on an outmoded classification system could be fully overcome or that the results would be materially different from those based on the current IREP model for lymphoma and multiple myeloma.

The decision to proceed with an existing model, that is acknowledged at the outset to be imperfect, or to await development of a more refined model based on the new DS02-based LSS data is a policy decision and not a technical one (see discussion of unresolved issues and caveats in Section 5.1 of the draft report).

Nonetheless, based on the newer information on CLL incidence in recent epidemiological studies and the increased estimates of ERR/Sv for NHL mortality in male atomic-bomb survivors reported by Richardson et al. (2009), we agree that the IREP lymphoma and multiple myeloma model should be used only as an interim solution, and that a high priority be assigned to development of a new CLL model based on the updated DS02 data on NHL (including CLL and other diseases now included in the revised definition of NHL) after the RERF-NCI team publishes the new LSS data. In retrospect, we should have strengthened the point that the lymphoma and multiple myeloma model was only a surrogate for CLL, and should be replaced as soon as new data from the LSS cohort became available.

Whereas neither the earlier analysis of mortality from malignant lymphoma in the LSS cohort by Pierce et al. (1996) based on follow-up through 1990 nor the UNSCEAR analysis of LSS data on CLL incidence based on follow-up through 1987 showed a significant dose-response in males or females, the updated analysis of mortality from NHL by Richardson et al. (2009), which was based on 10 years of additional follow-up, now shows a highly significant response in males. Thus, it is conceivable that the DS02 data for lymphoma incidence, which will have an even longer follow-up when published,could show significantly higher risks for both males and females.

Another concern that appears to have been overlooked is the potential for confounding of dose-responses for CLL and lymphomas associated with a "cell-killing" effect. Because of the very high radiosensitivity of lymphocytes, especially B lymphocytes, an artificially lower ERR/Gy could have resulted from studies of acute exposures some of which were delivered at high doses. The effect could have been manifested at lower doses than for solid tumors or leukemia.

Significant depressions in human lymphocyte populations have been observed in blood and other lymphoid tissues at doses ≥0.25 Gy. Killing of highly radiosensitive B-lymphocytes in persons who received acute doses ≥1 Gy (e.g., some members of the LSS cohort and medically exposed groups) (Mettler and Upton 1995; Waselenko et al. 2004) would have drastically reduced the pool of CLL (and NHL) precursors in which malignancies could have been initiated, potentially resulting in a depression of the dose-response if analyzed over the full dose range (up to 4 Sv). Such "cell-killing" effects have been observed for other types of malignancies, but occur at higher doses consistent with the lower sensitivity of the precursor cells (e.g., from solid tissues).

The ERR/Sv reported by Richardson et al. (2009) for NHL mortality in the LSS cohort when survivor doses were limited to <0.5 Sv (4.24; 90% C.I. 0.83, 9.76) was about *four times* greater than the ERR/Sv based on the full dose range (1.12; 90% C.I. 0.26, 2.51). These results are suggestive of an effect of cell-killing at higher doses. Intriguingly, Schubauer-Berigan et al. (2007) obtained a marginally significant dose-response (ERR/10 mSv: 0.20; 95% C.I. -0.035, 0.96) in a case-control study of mortality from CLL involving workers from six U.S. nuclear facilities when workers with doses >0.1 Sv were excluded. In the latter case, however, the ERR

estimate translates to an ERR/Sv of 20, i.e., high enough to suggest a potential artifact, a common concern about such studies.

We think that the results obtained over the lower dose range from the study by Richardson et al. (2009) provide additional support for our recommendation to implement the IREP lymphoma and multiple myeloma model for CLL only on an interim basis. Dose-responses for CLL and lymphomas appear to be less well-understood than formerly thought.

Appropriateness of Extended Latency for CLL

Two reviewers (Schubauer-Berigan and Wakeford) agreed with our proposal to use the IREP lymphoma model with an extended latency period and two (Richardson and Zablotska) did not.

Based on the information available in 2007 when the model report was initially drafted, it was being argued that an extended latency period for induction of CLL was a major factor confounding previous attempts to determine whether CLL was radiogenic (Crowther 2004; Richardson 2004; Richardson et al. 2005; Schubauer-Berigan et al. 2007; Silver et al. 2007; also see Hamblin 2008). The available information pointed to a central estimate of latency (15 years) that was twice as long as that used in IREP for other cancers, albeit with a very high uncertainty (see Figs. 1 and 2 in the draft report).

The midpoint of the S-shaped latency function used in IREP for the bulk of solid tumors, including the lymphoma and multiple myeloma grouping, is 7.5 years, and reaches 0.99 at 11 years, a full 6 years beyond the point in time when data from the LSS cohort become available. The addition of a triangular distribution (with extremes at 5 and 10 years) about the midpoint extends the points at which the latency correction reaches 0.01 and 0.99 to 1.5 and 9 years, respectively. In contrast, the triangular distribution we recommended had extremes at 10 years and 20 years.

Using the distribution we recommended, the 99th percentile estimate of PC for CLL in former atomic energy workers are based on values for latency sampled from near the upper bound of the leftmost curve in the latency distribution in Fig. 2. In this region of the distribution, the latency correction reaches 0.99 between 17 and 18 years. Thus, PC estimates at the 99th percentile were driven by values of latency that are about 4−5 years longer than in the latency distribution that is currently used in IREP.

Application of an extended latency appeared to be justifiable, given clinical information indicating a long lag between initiation and diagnosis of CLL, the lack of evidence of radiogenicity of CLL in 2007, and questions about whether the modeled estimates of ERR/Sv for lymphomas and multiple myelomas might indicate a higher risk than that for CLL because of differences in the diseases, including the relative distributions of indolent and aggressive forms. However, the growing evidence for radiogenicity of CLL and recent information from the study of lymphoma mortality in the LSS cohort by Richardson et al. (2009) suggest that an extended latency may not be justified.

Both Richardson and Zablotska challenged the used of an extended latency for CLL, even with explicit consideration of its uncertainty as in Fig. 2, albeit for slightly different reasons. [Zablotska appears to suggest that we assume a point estimate of 15 years for latency (see bullet at the bottom of page 8 in her review), as opposed to the wide distribution shown in Fig. 2.]

Zablotska contended that at "the time when all solid cancers are assigned a 10-year latency period, it is hard to defend the notion that CLL is different from other cancers." However, NHL, Hodgkins disease, and multiple myeloma are hematopoietic cancers, and our review of information on the etiology of CLL indicates that it may be quite unique—and unquestionably different from that of "solid" cancers.

She noted that "a strategy of separating CLL from other radiation-related leukemias has been challenged recently and that one should be cautious about introducing new 'exceptional' approaches to modeling CLL risks." However, the revised approach she suggests is driven by the studies of CLL in Chornobyl workers, which have a number of limitations, as discussed earlier. It is clear that the etiology of CLL, which is now classified as an NHL, is very different from that of the "true" leukemias. We also note that the most recent review by IARC still excludes CLL, NHL, and multiple myeloma from its list of cancer types having sufficient evidence of radiogenicity (El Ghissassi et al. 2009).

Zablotska also suggested that a 10-year lag has become a standard in CLL/NHL studies in the last decade, noting that Richardson et al. (2009) found significant increases in the risk of mortality from NHL in men in the LSS cohort under both 5- and 10-year lag assumptions, based on DS02 data that cover the period from 1950−2000. In addition, she cited an observation of a minimum deviance for both CLL and non-CLL leukemia in one study of Chornobyl remediation workers (Romanenko et al. 2008) using a latency of only 2 years, a value that we questioned

earlier in the section on Potential Radiogenicity of CLL. However, studies of CLL by Schubauer-Berigan (2009) and of NHL by Richardson et al. (2009) devoted considerable effort to investigation of the effects of varying lag times and extended times since exposure on the ERR/Sv, suggesting that there is as yet no standard for latency in epidemiological studies of either CLL or NHL.

In the study by Richardson et al. (2009), a better fit (P = 0.02) was obtained using a 10-year lag than with a 5-year lag. They did not evaluate the use of longer lag periods. However, they observed the highest values of ERR/Sv for *mortality* in males from NHL (and the lowest P values) when time since exposure exceeded 36 years in both the LSS cohort and in Savannah River Site workers.

Time window analyses showed that positive associations between radiation dose and lymphoma mortality among male atomic bomb survivors *have only been observed since 1980*, i.e., 30 years after follow-up began in 1950. "In each cohort, evidence of a dose-response association was primarily observed more than 35 years after irradiation. Such findings indicate a protracted induction and latency period" (Richardson et al. 2009). These findings suggest that the issue of latency for NHL is still not fully resolved.

Richardson's own specific arguments against an extended latency for use with the lymphoma and multiple myeloma model—or an alternative NHL-based model, based on cancer incidence rather than cancer mortality, appear to be based on the fact that the age-related parameters were based on data for solid tumors rather than lymphoma and multiple myeloma. He contended that a 13-year lag period, not far different from the central estimate of 15 years that we employed in our latency function, is already inherent in the LSS data for solid cancer *incidence* because follow-up did not begin until 1958. Because there is empirical data in the period beginning about 13 years after exposure, he argued that it would make sense to employ a model that gives full weight to the fitted ERR/Sv values during this period, i.e., to allow the age effects in the model to determine the outcome after 13 years.

However, as noted earlier, Land et al. (2003) elected to use age-related parameters based on solid tumors because there was little evidence that the patterns in data for the lymphoma and multiple myeloma grouping differed significantly, even though data on incidence of CLL, NHL, Hodgkins lymphoma, and multiple myeloma were available beginning in 1950, about 5 years

after the bombings. In addition, the 10-year time lag he used in his study of lymphoma mortality in the LSS cohort extends a full 5 years into the region in which empirical data are available.

Despite our serious reservations about some of the specific arguments made by Zablotska and Richardson, we think that there is enough information currently to warrant reducing the latency period for use with the lymphoma and multiple myeloma model in IREP. Thus, the midpoint of the function shown in Fig. 2 of the draft report will be reduced from 15 years to 10 years, while maintaining the uncertainty in the midpoint at ± 5 years. This change would shift each point in the curves shown in Fig. 2 to the left by 5 years. The net result should be that the 99th percentile estimate of the latency correction will typically be based on values for a time since exposure of about 12−13 years rather than at about 17−18 years, as in the distribution shown in Fig. 2.

This change in latency is being made, even though there is still major uncertainty about the appropriate latency period for CLL and lymphomas that could justify a longer period, and about the effects of assumptions about latency on risk estimates for CLL simulated with the lymphoma and multiple myeloma model.

Background Information on CLL, Including Implications of Reclassification as an NHL

One reviewer (Schubauer-Berigan) recommended that the extensive discussion in Section 3 be moved to an appendix and retain a brief summary in the main text because she thought there was too much detail on the natural history of CLL and the important information was not readily extractable by the reader. We think that most of the material is relevant to understanding why the bone marrow cannot be the sole target organ and why previous studies of CLL may have been uninformative. To address her concerns, however, some of the material has been moved to an appendix, subheadings have been added, and the material in Section 3 has been reorganized.

Internal Dosimetry for CLL

The subject of internal dosimetry for CLL was sufficiently complex that a separate study was undertaken to deal with the question of what constitutes an appropriate target organ for CLL (Apostoaei and Trabalka 2009). Zablotska did not have access to our CLL dosimetry report and

thus she may not have fully appreciated the complexity of this issue, even for whole-body external exposures (see paragraph 3 on page 9 in her review). Similar concerns apply to NHL (see NIOSH/OCAS 2005; ORAU 2006).

For both CLL and NHL, and unlike the situation for most primary solid tumors, where the tumor results from the interaction of radiation with immobile cells, radiation could have interacted with the lymphocyte precursors anywhere in the lymphatic or circulatory system, and then formed the cancerous lesion elsewhere. Using NHL as the example, because the site of origin cannot be determined with any confidence—and data on the inventories and distributions of lymphocytes in the human body is quite uncertain, NIOSH modified the selection of target organs so that the dose to the organ/tissue receiving the highest dose is used in the dose reconstruction. For internal dose, the thoracic lymph nodes were selected because the dose to these tissues from exposure via inhalation of insoluble radioactive material is always higher than the dose to other organs/tissues. For external dose, the lungs were selected for B-cell lymphomas and the thymus for T-cell lymphomas.

Although most epidemiological studies of CLL/NHL reportedly used either the whole-body doses based on film badge readings or doses to bone marrow, neither approach gives an exact measure of the organ/tissue weighted dose that would be considered representative for estimating radiogenic risk. For cases involving uniform external exposures to the whole body, the errors introduced by use of whole-body doses or bone marrow doses would be quite small, amounting to a few percent, as discussed in the draft report. However, the issue is thus not whether use of whole-body or bone marrow doses compromised past epidemiological studies but rather what dose is most appropriate for developing risk coefficients for use in IREP.

For internal exposures, the uncertainties in doses could amount to several orders of magnitude, depending on the radionuclide and route of entry. To address one of Schubauer-Berigan's questions, the dose to the thoracic lymph nodes could be used for dose reconstruction purposes, but could be considered overly conservative for CLL, for which the level of radiogenicity has not been firmly established. Thus, as noted above, the issue of an appropriate approach for estimating internal doses for dose reconstruction was considered by NIOSH to be worthy of further investigation. However, because the draft report on this subject is still undergoing technical review, it is inappropriate to make the formal recommendations on how to

estimate an appropriate dose from internal exposure that she requested. We have moved the discussion on this topic from Appendix C (back) into the main text as she recommended.

Specific Editorial/Technical Suggestions by Zablotska and Schubauer-Berigan

Lydia Zablotska

- First bulleted item on page 11 of her review was addressed earlier.
- Several mistakes in referencing various tables on pages 14−15 were alleged:
  - Tables 18, 19, and 20 in UNSCEAR (2000)
  - Table IV.C.2 in Land et al. (2003)

Response: We found no mistakes in our references. The reference to UNSCEAR (2000) was correct. Dr. Zablotska evidently wanted us to add the specific references to tables in UNSCEAR (2000) from which the data were obtained. We have added table references, but these now refer to UNSCEAR (2008), which provides revised risk estimates for NHL and more detailed information on the effects of age at exposure and time since exposure on the risk estimates.

The reference to Land et al. (2003) she proposed was incorrect. The correct reference is to Land (2000) (see Table 2).

- She suggested that there were several direct quotes from Land et al. (2003) on p. 15 that were not properly referenced.

Response: There were no direct quotes from Land et al. (2003) on page 15.

- Section 5 would benefit from a more structured approach with separate subtitles for each.

Response: We agree with her suggestion. The material in Section 5 has been revised accordingly.

- Figure 1 is missing Boivin et al. (1986) with 166 CLL cases.

Response: There is no missing information in the figure. It was obtained from the systematic review of material on the radiogenicity of CLL by Silver et al. (2007). They did not include data from this study in the figure, evidently because it did not merit inclusion. They noted that "[this] study of radiotherapy for various [primary cancers] had no dosimetry data, and only evaluated incident CLL risk as a check against study bias."

- Her comment on the application of weights to different target organs on page 18 was addressed in the previous section.
- In view of the recently published epidemiological studies, she disagreed with the statement on page 19 about "week [sic] radiogenicity" of CLL, citing improved study methods and diagnostic procedures in recent studies as providing substantial evidence of radiation-related risks of CLL.

Response: We disagree; see earlier discussion on this topic.

Mary Schubauer-Berigan

The first three of her specific recommendation have been addressed previously.

4. She asked why there was no mention of T-CLL, which comprises 5% of the cases.

Response: This was explained in footnote 7 of the draft report. CLL is now defined as an exclusively B-cell disease in the current NCI-WHO disease classification.

5. She requested that the implications of the discussion on B-cell maturation on page 7 be made more explicit, namely to show that lymph nodes could be target organs for CLL.

Response: The material to which she refers is part of Section 3. The location in which B-cell maturation takes place is not necessarily the place where transformation to a CLL clone takes place, which could be almost anywhere in the hematopoietic or lymphatic systems because of

post-maturation migration. Thus, the lymph nodes are one of the potential locations where transformation could take place. We have added material to strengthen this point.

6. She pointed out an error in the fifth sentence in the first paragraph on page 11, where we misinterpreted a statement about the implications of the latency period that was made in Schubauer-Berigan et al. (2007), namely that we should have specified a period of 10 y.

Response: We have replaced the words "an extended latency" to "a 10-y latency" in the offending sentence.

7. She thought that the second full paragraph on page 11 was repetitive and confusing, and also objected to the wording in the first sentence, asking what we meant by: "75% diagnosed at an average age of 60" and asking that it indicate a median age at diagnosis or other meaningful fractile.

Response: Some of the material on the influence of genetic factors on CLL incidence was repetitive. We have deleted part of it and moved the remainder to support the prior discussion where this issue was addressed. To address her specific question, we have inserted the words "***of CLL patients***" after "75%" in the first sentence. We think the use of "an average age of 60," as previously given, is reasonable.

8. She pointed out another misinterpretation in the first full paragraph on page 13, where we mistakenly attributed some of the problems in changes in CLL classification to changes in classification of CLL in the series of ICD reports, when, in fact, the problem was that investigators inappropriately lumped lymphoproliferative diseases with other ICD codes with CLL.

Response: We have revised the material in this paragraph as follows (changes hi-lited):

… ***However, investigators often combined several ICD codes to create their own definitions of CLL or other types of leukemia. For example, Weiss et al. (1995) lumped***

CLL *per se* (i.e., as then defined to include diseases of both B- and T-cell origin; ICD-9 code 204.1) with unspecified lymphocytic leukemias (ICD-9 code 207.8), while HCL (a lymphoma in the ICD-9 scheme; code 202.4) was lumped with acute myeloid leukemia… Other chronic leukemic patterns that have been ***categorized as "CLL" in clinical practice*** include: prolymphocytic leukemia, HCL, lymphoma leukemia, and Sézary syndrome (Berkow 1992). Thus, the effects of changing ***definitions***, which likely increased the potential for misdiagnoses ***or mischaracterizations*** of CLL, must be carefully considered in interpreting the results of epidemiological studies involving CLL.

9. She recommended deleting the first full paragraph on page 14 because of uncertain relevance to the issue of target organ.

Response: Although we think this material is germane to the issue of a target organ for CLL, it is not critical to this discussion. Thus, we have deleted it in order to reduce the length of Section 3.

10. She stated that we referenced a pooled estimate for NHL, Hodgkins lymphoma, and multiple myeloma on page 14 but did not include it in Table 2. She asked that we include it in the table or in the text.

Response: She apparently misinterpreted the following sentence: "Although the risk model in IREP is based on the pooled data set, UNSCEAR has [only] derived risk estimates for each cancer type individually (Table 2)." We have added the word "only" to the cited sentence to prevent misunderstandings on the part of other readers.

11. She suggested that the effects of attained age and age at exposure in the IREP model would be more easily understandable if there were a verbal description of their net effect on page 15.

Response: This is a good suggestion. We plan to add a figure and text to do what she asked.

12. She suggested that we eliminate the discussion about having considered—and rejected—an additive risk transport model. [Zablotska also reacted negatively to this discussion (see second paragraph on page 10 in her review).]

Response: Our recommendation was to adopt the current approach to risk transport in IREP, using a function which assigns equal probabilities to multiplicative and additive models. As noted on page 6, we have deleted the problematic text while including some of the points Zablotska made as justification for our choice of the current approach used in IREP.

13. She thought that the discussion of latency on page 20 should mention the results of the time windows analysis in her recent paper (Schubauer-Berigan et al, 2007), in which a significant dose-response for mortality from CLL was seen at doses <100 mSv but not when higher doses were included. The former suggested that a latency of 10 years was appropriate and that latency for an incidence study would be shorter still.

Response: We do not plan to add the detailed material she suggested because the investigators did not provide a scientific justification for excluding the results associated with higher doses. The results at lower doses could represent an artifact of data selection. It seems implausible that they could be explained by a cell-killing effect, because the dose-ranges involved (~100 mSv or less) are well below those where significant killing of lymphocytes has been observed. The suggested latency period of 10 years is at odds with the results in Fig. 1 reported by Silver et al. (2007) and other statements in the paper she referenced. However, we will reference results from her paper, along with several others, in the discussion associated with justifying an extension of the centroid of the latency function used with the lymphoma and multiple myeloma model from 7.5 years to 10 years.

14. She noted that the results in Table 3 appear to be percentages not probabilities, and recommends clarifying the labels.

Response: She is correct. We have revised the table legend to reflect this. If, as recommended, we reduce the length of the latency period, as proposed above, the PC calculations in Table 3

will also have to be rerun because these calculations were made with a risk model which included the 15-y latency function.

15. This item was dealt with earlier in the section on Internal Dosimetry for CLL.

16. She suggested including information from the third column of Table III of Schubauer-Berigan et al. (2007) in Appendix B.

Response: We do not plan to do so, for reasons that were discussed in our response to item 13. These were the selected data to which we objected. However, we will reference her paper as part of the revised discussion on the latency period.

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

Response: We do not understand the comment. These tables have the same format as all of the other tables in the appendix, with numbers of cancers and time since exposure being the key information presented. We think that they are useful and should remain in the section.

18. This item was dealt with earlier in the section on Internal Dosimetry for CLL.

Summary and Conclusions

We very much appreciated the thoughtful and constructive comments of the reviewers. We think that the changes that we have made—or have recommended—in response to their comments will significantly improve the approach to estimating risks of CLL as well as the clarity of the final report. We agree that evidence for CLL as a radiogenic disease is growing. We reiterate that the absence of a well-defined dose-response for CLL in the LSS data does not mean that there is no risk of CLL due to occupational radiation exposure.

Although we do not think that a suitable alternative to the lymphoma and multiple myeloma risk model currently exists for estimating the PC of CLL, we agree that the model proposed in

our report should be used only as an interim solution, and that a high priority be assigned to development of a new CLL model based on the updated DS02 data on NHL (including CLL and other diseases now included in the revised definition of NHL) after the RERF-NCI team publishes the new LSS data. We also think that there is enough information currently to warrant reducing the midpoint of the proposed latency period for use with the lymphoma and multiple myeloma model from 15 years to 10 years, while maintaining the uncertainty in the midpoint at ± 5 years.

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