DEVELOPMENT OF A RISK MODEL FOR CHRONIC LYMPHOCYTIC LEUKEMIA FOR NIOSH-IREP

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1. PURPOSE AND APPROACH

SENES Oak Ridge, Inc. was asked by the Office of Compensation Analysis and Support (OCAS) of the National Institute of Occupational Safety and Health (NIOSH) to investigate the possibility of developing a radiogenic risk model for chronic lymphocytic leukemia (CLL) for potential inclusion in the computer program NIOSH-IREP. Adaptation of the risk model for the lymphoma and multiple myeloma grouping in NIOSH-IREP was considered to be an option for a CLL risk model because CLL is now classified as a form of non-Hodgkin's lymphoma (NHL). The lymphoma and multiple myeloma model in NIOSH-IREP is based primarily on Japanese atomic-bomb survivor data for non-Hodgkin's Lymphoma (NHL), but also on data for Hodgkin's disease (also a lymphoma) and multiple myeloma (ICD-9 codes 200−203) (Land et al. 2003; UNSCEAR 2008).

This model has been used by the Veteran's Administration (VA) under the atomic veterans compensation program to assess the probability of causation (PC) of CLL occurring in military personnel who were exposed to radiation during tests or uses of atmospheric nuclear weapons. Currently, the PC of CLL occurring in these military personnel is estimated using the highest of the reconstructed doses to one of three organs: red bone marrow, spleen, or thymus. The rationale behind the VA's approach is that since CLL is now considered to be a form of NHL, red bone marrow is not the sole target organ (see more below).

We reviewed key papers on the epidemiological, molecular, and clinical basis of CLL, including, but not limited to those cited by Richardson et al. (2005), by John Boice (in his January 7, 2005, response to NIOSH/OCAS on reconsideration of CLL for purposes of compensation; Boice 2005), in the draft NIOSH Annotated Bibliography for CLL (NIOSH 2004), Silver et al. (2007), the CLL Issue of the British Journal of Haematology (Volume **135**, No. 5, 2007), and by the BEIR VII committee (NRC 2006). The latter included an additional paper (Hall et al. 1992) that examined dose-responses and latency for CLL in patients exposed to I-131 in diagnostic or therapeutic procedures. We also compiled information on sex and age-specific background incidence rates for CLL from the SEER registry for the U.S. population (SEER 2005) and from the IARC data bases for the Japanese populations (Parkin et al. 1997) (Appendix A). We also evaluated data potentially bearing on the issue of latency of radiogenic CLL from epidemiological studies.

The evaluated data was used to create a risk model for CLL by modifying the risk model for lymphoma and multiple myeloma obtained from an evaluation of the Japanese atomic-bomb survivor data from the Life-Span Study (LSS) cohort by Land et al. (2003) to include an extended latency period with greater uncertainty than that currently used in IREP. Alternatives to the risk transfer module used for lymphoma and multiple myeloma in IREP were considered but rejected because of limitations of extant epidemiological studies. This risk model is proposed to be used on an interim basis, at least until a model based on DS02 data for incidence of NHL in the LSS cohort becomes available.

2. BACKGROUND

The occurrence of lymphomas, and of CLL in particular, has not been convincingly linked to radiation exposure (see, e.g., IARC 2000; Preston et al. 1994; Boice 2002, 2005; NIOSH 2004; NRC 2006; Cardis et al. 2007; Schubauer-Berigan et al. 2007; Silver et al. 2007; Hamblin 2008; UNSCEAR 2008; Vrijheid et al. 2008; El Ghissassi et al. 2009). An inability to discern a statistically significant increased risk for CLL from radioepidemiological studies had led to the widespread conclusion that CLL is not radiogenic (Boice 2002, 2005). However, it has been argued that a number of factors (including diagnostic misclassification; see Sect. 4), coupled with limited follow-up periods in epidemiological studies and the possibility of an extended latency period for induction of CLL, have confounded previous attempts to determine whether CLL is radiogenic (Crowther 2004; Richardson 2004; Richardson et al. 2005; Schubauer-Berigan et al. 2007; Silver et al. 2007; Hamblin 2008). In addition, others have argued that, despite the current lack of evidence from epidemiological studies, mechanistic evidence from genetic and molecular studies indicates that CLL should, in principle, be inducible by radiation exposure (Crowther 2004; Richardson 2004; Richardson et al. 2005; Zablotska 2004; Rai 2007a).

These arguments appear to be supported by a variety of new information, including the recent demonstration by Richardson et al. (2009) of a significant positive association between NHL and ionizing radiation in the Japanese atomic bomb survivors based on extended follow-up. 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 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."

Data on cancer incidence in the LSS cohort from 1950 through 1987 (Preston et al. 1994) provided the basis for development of risk models for leukemia, lymphomas, and multiple myeloma used in IREP (Land et al. 2003). However, only 4 cases of CLL were reported in the exposed and unexposed groups combined; this number was too small to develop a meaningful risk model for CLL.

The incidence of CLL in the Japanese population is very low and CLL is primarily a disease of old age in both the U.S. and Japan (Appendix A). Using the age- and sex-specific incidence rates for CLL in the Japanese population as a whole in Table A.1, combined with information on age at exposure, sex, vital status, and overall population size for the LSS cohort from Fig.1 in Preston et al. (1994), we estimated that about one case of CLL (0.76; 95% C.I. 0.60, 0.93) might have been expected in the LSS cohort over the 37-y period from 1950−1987, in the absence of radiation exposure. A similar estimate based on cancer incidence data for Hiroshima and Nagasaki in Table A.2 was slightly higher (1.2 cases; 95% C.I. 0.78, 1.76). Our estimate of the expected number of cases of CLL in unexposed persons is thus about one-fourth of the number observed in the LSS cohort as a whole.

Although this comparison suggests that there could be a positive association between radiation and incidence of CLL in the LSS cohort, despite the small number of cases involved, the published information on the LSS cohort does not provide data on radiation doses or characteristics of the exposed individuals (gender, age at exposure, or attained age) who developed CLL. Thus, we are prevented from drawing conclusions about the radiogenicity of CLL from this comparison. From an epidemiological perspective, we can only conclude that we currently do not have scientific evidence from the LSS data to say that CLL is radiogenic, not that there is no risk of radiation-induced CLL in the LSS cohort or in occupationally exposed persons (also see Zablotska 2004; Rai 2007a; Hamblin 2008).

3. CHARACTERISTICS, CLINICAL FEATURES, AND ORIGINS OF CLL

3.1 What is CLL?

Chronic lymphocytic leukemia is a disorder of morphologically mature but less immunologically mature lymphocytes and is manifested by progressive accumulation of these cells in the blood, bone marrow, and lymphatic tissues (Chiorazzi et al. 2005; NCI 2009b). It appears etiologically and clinically to be a lymphoma and thus differs from other forms of leukemia (Harris et al. 1999; Boice 2005; NCI 2009a). Despite its name, it is considered to be a form of NHL by the U.S. National Cancer Institute (NCI 2009a) and the World Health Organization (Harris et al. 1999).

The NHLs are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment. They can be divided into two prognostic groups: the indolent lymphomas and the aggressive lymphomas. Indolent types have a relatively good prognosis, with median survival times post-diagnosis as long as 10 years (e.g., most cases of CLL), but they are usually not curable in advanced clinical stages. In contrast, the aggressive types of NHL have a shorter natural history, but a significant number of patients can be cured with intensive combination chemotherapy regimens (NCI 2009a).

3.2 Origins and Etiology

CLL is now viewed as a disease originating from antigen-stimulated, mature B lymphocytes, which either avoid death through the intercession of external signals or die by apoptosis, only to be replenished by proliferating precursor cells (Keating et al. 2003; Stevenson and Caligaris-Cappio 2004; Chiorazzi et al. 2005; Rai 2007b; Zent 2007; Table 1).

Although the weight of evidence points to disruption of apoptosis (programmed cell death) as an early initiating event in some lymphomas (e.g., Voutsadakis 2000), the genes responsible for the origin and progression of the *majority* of cases of CLL remain unknown (Voutsadakis 2000; Stilgenbauer et al. 2002; Dewald et al. 2003) and the current view is that an inherent apoptotic defect is not the initiating lesion in CLL (Table 1; also see Rai 2007b).

Table 1. Comparison of Historical and Current Views of CLL

Historical view	Current view[a]
Clinically heterogeneous disease with homogeneous cellular origin	Clinically heterogeneous disease originating from B lymphocytes that may differ in activation, maturation state, or cellular subgroup
Disease derived from naive B lymphocytes	Disease derived from antigen-experienced B lymphocytes that differ in level of immunoglobulin V-gene mutation
Leukemic-cell accumulation occurs because of inherent apoptotic defect involving entire mass of leukemic cells.	Inherent apoptotic defect involving entire mass of leukemic cells is unlikely at the outset. Leukemic-cell accumulation occurs because of survival signals delivered to subgroup of cells from external environment through variety of receptors (e.g., B-cell receptors and chemokine and cytokine receptors) and their cell-bound and soluble ligands.
Disease of accumulation	Disease of accumulation with a higher level of cell proliferation than previously recognized
Prognostic markers identify patients at various risk levels (e.g., low, intermediate, or high in Rai staging categories) with acknowledged heterogeneity in clinical outcomes among patients in low- and intermediate risk categories.	New molecular and protein markers identify patients within low- and intermediate risk categories who follow different clinical courses.
Therapy is based largely on clinical observations and trial-and-error methods.	New findings provide clues to discrete targets for developing hypothesis-driven and effective therapeutic agents.

[a] The current view refers to understanding of CLL as it has evolved during the past 10 years (Source: Chiorazzi et al. 2005; Rai 2007b).

The developmental history of CLL (e.g., the stage in B-cell development in which malignant transformation occurred) is informative both for predicting the course of the disease and for defining the appropriate target organ for dose reconstructions (see Appendix B).

CLL cases can be divided into two groups, depending on the degree of somatic hypermutation of the immunoglobulin V_H genes. Cases from the "unmutated" group (defined as having B-CLL cells with V_H gene sequences with <2% differences from the germ line cells) have a much more aggressive disease course than those from the mutated group, and represent about 40% of the cases reported in most Western countries (Chiorazzi et al. 2005; Hamblin 2008). Interestingly, however, gene-expression profiling studies (Klein et al. 2001; Rosenwald et al. 2001) indicate that unmutated CLL cells do not differ from mutated CLL cells in a large number of differentially expressed genes, suggesting the possibility of a common origin for both.

3.3 Characteristics and Relationship to SLL

CLL results in a clonal expansion of mature-appearing B lymphocytes involving lymph nodes and other lymphoid tissues with progressive infiltration of bone marrow and circulation in blood (Berkow 1992). The compartments in which CLL proliferates are termed pseudofollicles, vaguely nodular areas without mantles that are observed in lymph nodes and bone marrow (Stevenson and Caligaris-Cappio 2004). The pathological features of the lymph node in which CLL develops are those of a small lymphocytic lymphoma (SLL) (Chiorazzi et al. 2005); SLL and CLL are characterized as a single disease entity in the primary extant classification of hematopoietic and lymphoid diseases used currently (see Section 4). As lymphocytes progressively infiltrate the bone marrow, abnormal hematopoiesis leads to anemia and immune dysfunction develops, resulting in increased susceptibility to a variety of infections (Berkow 1992; Keating et al. 2003).

As noted earlier, not all cases of CLL are "indolent;" they represent about 60% of the cases reported in most Western countries (Chiorazzi et al. 2005; Hamblin 2008). Even within this "indolent" group, those that are first diagnosed in later stages (e.g., stage IV in the Rai staging system or stage C in the Binet classification system) progress much more rapidly toward a fatal outcome, because current therapies are less effective than for other aggressive forms of NHL (Keating et al. 2003).

Patients with indolent (i.e., mutated) CLL (or SLL) often can survive for long periods with no or minimal therapy. Because these diseases are often asymptomatic, they are typically identified in individuals undergoing routine medical examinations or seeking treatment for other

diseases (Berkow 1992). The median survival time for patients dying from B-cell CLL or its complications is now about 10 years (Berkow 1992; Keating et al. 2003; NCI 2009b).

Patients with these forms of lymphoma can die as a result of (1) conversion to a more malignant form (such as large B-cell lymphoma or Hodgkin's disease; Kyasa et al. 2004), (2) an increased rate of other malignancies (Kyasa et al. 2004), or (3) complications of treatment, rather than from the initially diagnosed form of the disease (Magrath 1992). Those patients who experience progression of their CLL predominantly die of complications of the disease itself, primarily from infections (Keating et al. 2003). In a study of a well-defined CLL/SLL population of predominantly older male smokers, second malignancy was the most common cause of death (34%), followed by progressive CLL (18%) and infection (16%) (Kyasa et al. 2004). Because the majority of second malignancies in this group were those of the lung and prostate, the contribution to mortality from second cancers suggested by these results is undoubtedly an overestimate.

CLL affects older persons primarily, with 75% of CLL patients diagnosed at an average age of 60 in the U.S. population. It is about 2−3 times more common in men than in women (Keating et al. 2003; Dores et al. 2007; Appendix A).

3.4 Implications for Assigning a Target Organ for Dose Reconstruction

The evidence that CLL cells *emerge* from a population of antigen-selected, mature, immunocompetent B-lymphocytes that have carried out typical functions of normal B-cells currently seems compelling (Keating et al. 2003; Stevenson and Caligaris-Cappio 2004; Chiorazzi et al. 2005; Caligaris-Cappio and Ghia 2007; Ghia et al. 2007; Linet et al. 2007; Rai2007b; Appendix B). Activated B cells leave the lymph node (or other site of activation) in the efferent lymph, return to the blood and seed the spleen, bone marrow, lymph nodes, mucosal associated lymphatic tissue, Peyer's patches, tonsils, and/or sites of inflammation (Anderson 2002). Thus, these cells could potentially undergo transformation to CLL clones anywhere in the haematopoietic or lymphatic systems.

It therefore follows that the bone marrow cannot be designated as the sole target organ for induction of CLL by radiation exposure, as is often assumed.[1] It would appear that the defining lesion for CLL could be initiated anywhere the mature B-lymphocyte precursor might be located, i.e., potentially in most tissues of the body, including the bone marrow, but also in the lymph nodes, spleen, and mucosa-associated lymphoid tissues.[2] Thus, the number of potential target organs/tissues needs to be expanded well beyond the three sites (red bone marrow, spleen, or thymus) that have been used in estimating PC for CLL (see Section 5.2).

There are several reasons why the bone marrow cannot be excluded as a potential target organ, however. First, after encountering antigen, human equivalents of B-2 cells[3] migrate to solid lymphoid organs to undergo the germinal center reaction, where they can become memory cells, which often migrate to the bone marrow, lying dormant until a repeat antigen exposure triggers a similar migration to the lymphoid follicles (Chiorazzi 2007). In addition, some T-cell-dependent B-cells that become memory or plasma cells via the germinal center reaction migrate to the bone marrow where they may persist for many months (Angelin-Duclos et al. 2000) or even for a person's lifetime (McHeyzer-Williams and McHeyzer-Williams 2005). *Long-lived* plasma cells preferentially home to the bone marrow (McHeyzer-Williams and McHeyzer-

[1] NHL, Hodgkin's lymphoma, and multiple myeloma also originate from mature B cells (Stevenson et al. 1998), for which the bone marrow appears not to be the most appropriate target organ. For example, the precursor cell in multiple myeloma is thought to arise from the action of one or more exogenous stimuli while the B-cell is resident in a lymph node (Bakkus et al. 1994). The precursor then circulates to the bone marrow where it establishes itself by adhering to the stromal cells and inhibiting osteoblastic activity and osteocalcin production (Teoh and Anderson 1997).

[2] The immune system operates like a single organ but its lymphatic components are located in every part of the body other than the central nervous system. Except for lymphocytes, which are present in most tissues, lymphatic tissue is present in the red bone marrow and the thymus (primary lymphoid organs) and the secondary lymphoid organs: lymph nodes, spleen, mucus membranes (including tens of thousands of isolated lymphoid follicles in the large and small intestines; Brandtzaeg and Johansen 2005; Brandtzaeg et al. 2008), tonsils, adenoids, Peyer's patches, and the vermiform appendix. Integration of this system is effected through lymphocyte recirculation, a process by which lymphocytes leave the blood, cross tissues, and return to the blood via efferent lymph. Approximately 1−2% of the lymphocyte pool recirculates each hour, optimizing the opportunities for antigen-specific lymphocytes to come into contact with antigen in secondary lymphoid tissues (Anderson 2002; Bowers and Hunt 2007). As a result, the total circulating pool of lymphocytes in blood is turned over about 50 times a day (Pabst 1988; Westermann and Pabst 1992). In normal subjects, about 70−80% of blood lymphocytes are T cells and 10−20% are B cells (Westermann and Pabst 1992; Mellors 2002). However, T-lymphocytes circulate more readily than B-lymphocytes, whose movements are more restricted both inside and outside the confines of the blood and lymphatic systems. Unlike the B cells, which tend to remain in lymphoid tissue, T cells constantly recirculate between the peripheral blood and lymph in their search for antigen. In addition, the migratory capabilities of specific B lymphocytes may be quite different, depending on the B cell subset or lineage from which they derive (Young et al. 1997; Andrade et al. 1998; Montoya et al. 1999; Young 1999; Chiorazzi 2007).

[3] B-1 and B-2 cell lineages have been described in the mouse, but this type of lineage discrimination is not as clear in humans (Meffre et al.; 2004; Chiorazzi 2007).

Williams 2005), and these authors consider such cells to belong to the memory cell compartment.[4]

Second, an inherited familial predisposition to CLL has been documented (Keating et al. 2003; Chiorazzi et al. 2005; Linet et al. 2007; Rai 2007a) and genetic differences in immunoglobulin genes considered relevant to CLL are observed in populations at low risk for developing CLL (e.g., persons of far East Asian ancestry; Keating et al. 2003). Low incidence rates for CLL persist in individuals migrating to the U.S. from Asian countries and in their descendants (Fig. A.1; Dores et al. 2007; Linet et al. 2007), suggesting that a genetic factor may be involved in the reduced levels of CLL observed in Asian populations. Thus, it is conceivable that irradiation could produce genetic changes in bone marrow stem cells that could result in increased susceptibility to development of CLL that might only be manifested at later stages of lymphocyte development. A counter-argument is as follows: One of the reasons CLL appears non-radiogenic is that only those (relatively few) persons with an inherited predisposition to CLL[5] are affected by radiation exposure, and that radiation acts primarily as a weak promoter, e.g., on a B-cell in a later stage of development, rather than as an initiator, acting directly on a bone marrow stem cell. Schubauer-Berigan et al. (2007) concluded that a 10-y latency period for radiogenic CLL (also see Sect. 5.3) would indicate that radiation acts primarily as a promoter for CLL development. Thus, because of current uncertainty about both the lymphocyte precursor for CLL and the role of genetic background in induction of radiogenic CLL, the bone marrow should be included as *one* of the potential target organs for development of radiogenic CLL.

4. CLASSIFICATION AND DIAGNOSIS OF CLL

As pointed out earlier, diagnostic misclassification is one of the factors that have confounded previous attempts to determine whether CLL is radiogenic. Although effective diagnosis is now a routine matter for CLL (NCI 2009b), diagnostic classification has long been marked by a lack of consistency. Because of the typically old age at onset, many patients die

[4] Rai (2007c) suggested that the B cell leading to CLL was transformed at a stage just prior to that which would produce a plasma cell (the last and final stage of a normal lymphocyte's differentiation). This stage would include most memory cells but would rule out the long-lived plasma cells identified by McHeyzer-Williams and McHeyzer-Williams (2005).
[5] Potentially associated with mutations in the ATM gene in some cases (see Caligaris-Cappio 2000).

with these diseases, but not as a consequence of them. Thus, death certificate information provides a very poor indication of the prevalence of CLL/SLL (Richardson et al. 2005).

B-cell CLL and small lymphocytic lymphoma (SLL) are currently classified as a single disease entity in the World Health Organization modification of the Revised European American Lymphoma (REAL) Classification (Harris et al. 1999; NCI 2009a). In this classification, lymphomas and lymphoid leukemias of the same cell type are considered one disease with different clinical presentations or stages, i.e., with the principal distinction between the two being the extent of solid tissue or peripheral blood involvement, respectively (Harris et al. 1999; Richardson et al. 2005). Put another way, B-cell CLL and SLL may simply be different manifestations of the same disease (NCI 2009a). Although CLL/SLL patients in some locations may be seen by different physicians based on their presentation [e.g., patients with peripheral blood involvement (CLL) are typically seen by hematologists and those with tissue involvement (SLL) are seen by oncologists], there is a consensus that the two diseases are biologically the same (Harris et al. 1999).

They are closely affiliated with hairy cell leukemia (HCL), another slowly progressing disease of mature B cells. It appears that the prevalence of cases that present as "SLL" may be much lower than that of CLL (Dores et al. 2007); it reportedly made up <10% of CLL/SLL cases in one major study (Kyasa et al. 2004). All of these forms now fall into the broader category of NHL, as noted earlier (Harris et al. 1999; NCI 2009a).

Although the modified REAL classification has been adopted by the World Health Organization and CLL is considered to be an indolent form of NHL by the NCI (2009a), it is not the only system in use currently. CLL is classified as a leukemia and both SLL and HCL are classified as lymphomas in the International Classification of Diseases (ICD)-9-CM 2001 system (AMA 2001).

Papers on radioepidemiological studies involving CLL referenced by Richardson et al. (2005) and Boice (2005) indicate that most of the previous studies (i.e., pre-1996) were conducted using the ICD-8 system as the primary classification scheme. 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. Epidemiological studies of the Japanese atomic-bomb survivors have utilized previous iterations of the ICD classification system (Preston et al. 1994; Thompson et al. 1994), and the most recent studies were based on the ICD-9 system (Preston et al. 2004). 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.[6]

5. DEVELOPMENT OF A RISK MODEL FOR CLL

5.1 Selection of Risk Coefficients

Based on the information reviewed to date, and on the risk models currently developed for IREP, 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 serve as the basis for a CLL risk model. This model is based on the incidence of 117 cancers of these types observed through the year 1987 in the Japanese A-bomb survivors exposed to doses ≥0.01 Sv: 76 cases of NHL, 10 cases of Hodgkin's lymphoma, and 31 cases of multiple myeloma (Preston et al. 1994; UNSCEAR 2008; Land et al. 2003; Table 2).

Although the risk model in IREP is based on data for all three types of cancers, UNSCEAR has derived risk estimates for each cancer type individually (Table 2). Point estimates for the ERRs for males for NHL and multiple myeloma were positive, while those for females were negative. Data for Hodgkin's lymphoma were not extensive enough to attempt analyses by gender or age at exposure.

The 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

[6] A T-cell form of CLL reportedly made up about 5% of CLL cases diagnosed in the past. Although T-cell CLL and prolymphocytic leukemia are grouped together under peripheral T-cell and NK-cell neoplasms in the updated REAL/WHO classification, it appears that CLL is currently considered a disease of exclusively B-cell origin (see Chiorazzi et al. 2005; Chiorazzi 2007; Rai 2007b, Rai 2007c; Zent 2007; NCI 2009a; NCI 2009b). Further, Rai (2007b) indicates that the ratio of T cells to B cells in peripheral blood is reversed in CLL, with over 90% of circulating lymphocytes being *B-CLL* cells.

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.

negative. For the IREP model, it was assumed that the ERRs for the two sexes 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 (Land et al. 2003).

The risk model for lymphoma and multiple myeloma in IREP is defined as follows:

- For exposure ages $e \geq 30$ and attained ages $a \geq 50$, the ERR at 1 Sv = 0.178 (95% C.I. <0, 0.9465);
- For exposure ages $e < 30$ and attained ages $a < 50$, the ERR at 1 Sv is multiplied by a modifier with a *geometric mean* = $\exp\{-0.05255\, f(e) - 1.626\, g(a)\}$, and a *geometric standard deviation* = $\exp\{[0.0003261\, f(e)^2 - 0.014594\, f(e)\, g(a) + 0.5648\, g(a)^2]^{1/2}\}$, where
  - $f(e) = -15$ for ages at exposure ≤15, increasing monotonically as (e-30) from the value at age 15 to a value of 0 at age 30; after age at exposure 30, it remains equal to zero.
  - $g(a) = \ln(a/50)$ for attained ages <50, and 0 for attained ages ≥50.

The risk models in NIOSH-IREP are not used to perform risk calculations for persons who are <15 y old. The variation of ERR at 1 Sv with attained age is shown in Fig. 1 for selected ages at time of exposure.

For low acute and fractionated exposures and for chronic exposures, the dose and dose rate reduction factor (DDREF) for solid tumors is applied to these risk estimates. The DDREF is phased in at doses <0.2 Gy for acute and fractionated acute exposures (Land et al. 2003).

5.2 Concerns Associated with Use of the Lymphoma and Multiple Myeloma Model

Application of the lymphoma and multiple myeloma risk model as the basis for CLL is subject to a number of issues and caveats. The first issue is whether a risk model for CLL should be based on data for NHL alone, i.e., by reanalyzing the data after excluding Hodgkins lymphoma and multiple myeloma. There are major differences in etiology and effects of Hodgkins lymphoma and multiple myeloma compared to NHL (NCI 2009a). One potential argument in favor of inclusion of multiple myeloma is that, like CLL, it too is a disease of old

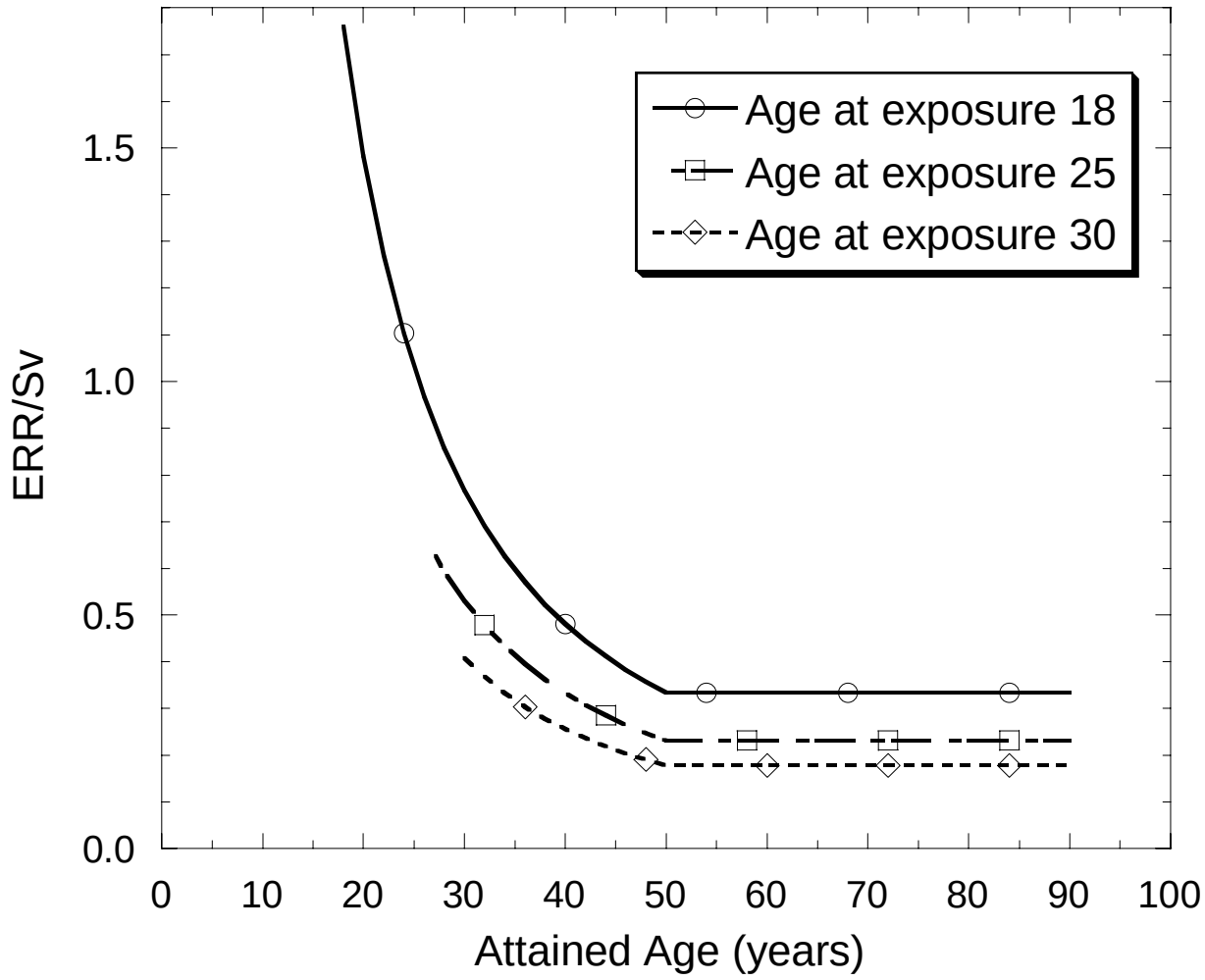

Fig. 1. Variation of the ERR at 1 Sv with attained age for selected ages at exposure in the lymphoma and multiple myeloma model in IREP, which is used as a surrogate for a risk model for CLL in this report.

age (Preston et al. 1994), and some aspects of its causation may be similar to some types of CLL (Lonial 2005). However, the median survival time for patients diagnosed with multiple myeloma is about three years (George and Sadovsky 1999), as compared to ~10 years for CLL. Arguments for inclusion of Hodgkins lymphoma seem less compelling, even though the estimated median survival post-diagnosis is about the same as that for CLL (~10 y; Grund 2004; NCI 2009c).

Use of data for NHL alone reportedly results in a similarly low risk coefficient, comparable to that for the grouping, but with somewhat tighter confidence limits than if the other two diseases are included (see Table 2 and text describing the model for the lymphoma and multiple

myeloma grouping). One concern is that, although both indolent and aggressive forms of lymphoma are included in the definition of NHL, when CLL is excluded (as in the Japanese atomic bomb survivor data) more cases of NHL may fall into the "aggressive" category than for CLL or for an NHL grouping that includes CLL (NCI 2009a, 2009b). Another is that the grouping of cancers in the current "NHL" data set is incomplete. It excludes, in addition to CLL, HCL, and possibly other conditions (discussed earlier) that are included in the current definition of NHL by the NCI (2009a). These types of cancers are included in a grouping called "other leukemias" by Preston et al. (2004) (see Appendix B).

Thus, the possibility exists that even NHL as defined in the questionable ICD classification system used in analyses of dose-responses in the LSS cohort might not be a good surrogate for CLL. However, since some, perhaps many, cases of CLL in former nuclear weapons workers covered under the EEOICPA were undoubtedly diagnosed in the past using a variety of classification schemes, use of a blanket category such as NHL (or the entire lymphoma plus multiple myeloma grouping) to develop a risk model for CLL may be the only interim option at present.

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 significantly reduced the pool of CLL (and NHL) precursors in which malignancies could have been initiated, resulting in a potential depression of the dose-response as a "cell-killing" effect. 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 (2007) obtained a marginally significant dose-response (ERR/10 mSv: 0.20; 95% C.I. -0.035, 0.96) in a study of mortality from CLL in a case-control study involving workers from six U.S. nuclear facilities when workers with doses >0.1 Sv were excluded. However, this observation could simply be a result of data selection and/or the small numbers of individuals with higher doses.

Development of a completely new risk model, e.g., based solely on incidence of NHL or some plausible combination of NHL with a lymphoma considered similar to CLL, such as HCL, that has not heretofore been included in the NHL category in previous analyses of data for the

LSS cohort, would require: (1) full access to relevant DS02 dose-response data currently being analyzed by the Radiation Effects Research Foundation (RERF), (2) an independent Poisson regression analysis of these data leading to a unique risk model and associated parameter set, and (3) access to a specialized software package (e.g., AMFIT module of the software package EPICURE; Preston et al. 1998) for such an analysis. Alternatively, the NCI staff members who developed the current risk models in IREP could be asked to perform the required analyses. One obvious disadvantage of performing such analyses at the current time is that extended information on the LSS cohort, i.e., dose responses for lymphoma and leukemia incidence based on the new DS02 dosimetry system are yet to be published and thus are not generally available.

Another issue is that the risk model in IREP was based on Japanese atomic-bomb survivor data that were analyzed assuming that the bone marrow dose was the appropriate reference (Preston et al. 1994). However, as discussed above, newer information on the origins of all of the diseases covered by the lymphoma plus multiple myeloma grouping indicate that use of a bone marrow dose is not appropriate, and that a whole-body dose should be more representative of the exposure conditions of the precursors of these diseases if induced under conditions of uniform external exposure (as in the LSS cohort). We would expect that, all else being equal, use of a bone marrow dose could yield somewhat lower risk coefficients than use of a whole-body dose (perhaps ~5% lower; see dose adjustment factors given in Walsh et al. 2004).

When and if these data are reanalyzed in future (i.e., after DS02-based dose-response information is made available), an appropriate surrogate for a whole-body dose should be used instead of the bone marrow dose alone, e.g., perhaps by an appropriate combination of the esophageal, colon, and bone marrow doses, because most of the lymphatic system, like the esophagus, lies close to the surface of the body, while the circulating blood is more uniformly distributed the throughout the tissue volume. An alternative to a whole-body dose that could provide a more representative dose to the potential lymphocyte precursors of CLL would be a weighted average. It could be estimated by applying relative weights to doses to the different lymphocyte-containing organs/tissues based on distributions of lymphocytes in the human body (e.g., Trepel 1974; Ganusov and De Boer 2007; Blum and Pabst 2007). Unfortunately, however, these distributions, which are based partly on extrapolations of data on laboratory animals (mainly rodents) to humans, do not provide information for the individual categories of lymphocytes. This is problematic because T lymphocytes outnumber B lymphocytes by about 2

to 1 in the human body as a whole (Westermann and Pabst 1992; Young 1999; Mellors 2002), and constitute >95% of the lymphocytes in some tissues and organs (Westermann and Pabst 1992).

Because lymphocytes, as well as the lymphatic organs and tissues, are distributed widely in the human body, but the exact proportions of B-lymphocyte precursors for CLL (or ratios of B cells to T cells) within any of the regions are not known precisely, making such fine distinctions does not appear to be justified when estimating a whole-body dose at the present time (Section 6; also see Apostoaei and Trabalka 2009).[7]

5.3 Handling of Risk Transfer between Populations

Because of the very large difference in baseline risks for CLL between the Japanese A-bomb survivors and the U.S. population (Appendix A), the issue of risk transfer also required special consideration. The risk transfer refers to whether a multiplicative or additive risk model for the Japanese population should be given higher weight when applied to the U.S. population. In IREP, equal weights are given to these models (Land et al. 2003).

One could argue, for example, that if the interaction between CLL and radiation was more multiplicative than additive, a higher incidence might have been observed in epidemiological studies of radiation workers and medically exposed groups. However, the NIOSH review of epidemiological studies related to CLL (Silver et al. 2007) reinforces the point that the follow-up periods in such studies were probably too limited to permit detection of a dose-response for CLL because of an extended latency period (see Fig. 2). In addition, most studies were focused on mortality rather than incidence as an endpoint, which, as noted earlier, may have significantly underestimated the occurrence of CLL.

The potentially weak radiogenicity of CLL, combined with inadequate follow-up, inconsistent diagnosis and classification of CLL, and a questionable endpoint (mortality) in

[7] The distribution of lymphocytes in the human body given in ICRP Report 89 (ICRP 2002): 0.2% in blood, 7% in red marrow, 7% in lymphatic tissues, and about 86% elsewhere, suggests that most lymphocytes are located outside the bone marrow, circulatory, and lymphatic systems at any given time. However, this information was based on a now-discredited reference (see Trepel 1974). A more credible distribution is as follows: 2% in blood, 10% in red marrow, 80+% in lymphatic tissues, and <8% in other tissues (Blum and Pabst 2006). In addition, much of the information on the lymph nodes in the 2002 ICRP report is derived from outdated material (dates of references ranging from 1885−1926) originally included in its 1975 report on reference man (ICRP Publication 23).

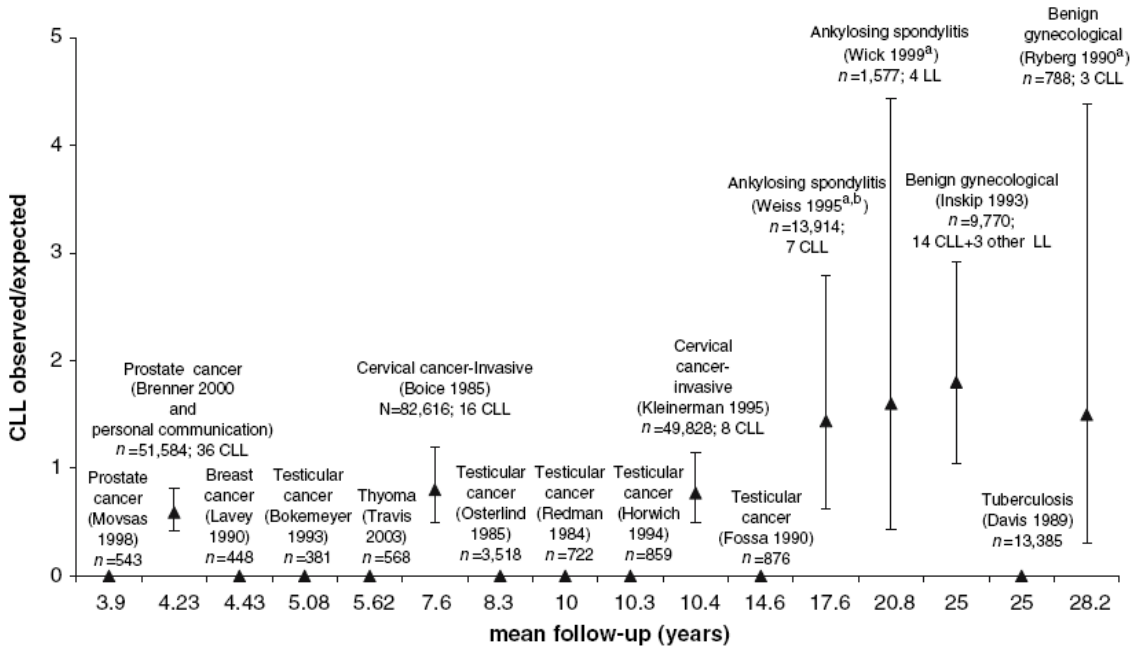

Fig. 2. Results from medical cohort studies and clinical trials suggesting a latency for incidence of radiogenic CLL of about 15 y or more, based on an analysis of mean follow-up time. Outcome is CLL mortality, except where noted. [a]Incidence studies. [b]Risk estimate for patients who received radiotherapy was lower than for patients who were not irradiated. Source: Silver et al. (2007).

epidemiological studies, appears to make any judgment about the relative contributions of alternative representations of excess radiogenic risk inappropriate. Thus, it is concluded that the "uninformed" risk transfer module (as described on page 35 and in Fig. IV.G.1 of Land et al. 2003), which is used for the bulk of solid tumors in IREP, as well as lymphoma and multiple myeloma, is a more appropriate choice for the CLL model, based on current information.

5.4 Latency

Our review of the epidemiological data indicated that the extended latency period (~20−30 years) for *mortality* from CLL suggested by Richardson et al. (2005) would not be applicable to a risk model for incidence of CLL (i.e., as in IREP). One reason is that the post-diagnosis survival times for CLL patients are highly uncertain, potentially ranging from a few months to a normal life expectancy (NCI 2008b). Another is that it is questionable whether existing

epidemiological data on CLL induction by radiation are capable of providing useful information on an extended latency period (Appendix C).

Beyond the obvious concerns about potential for misdiagnoses and classification of CLL, all of the studies of medically exposed persons that we examined are potentially limited by the (1) confounding effects of prior disease on CLL incidence, (2) uncertainties in diagnosis and classification of CLL, (3) limited statistical power, particularly in one study of the consequences of diagnostic or therapeutic uses of ^{131}I for thyroid diseases because of the relatively low doses involved, and, to a lesser extent, (4) meaningfulness of bone marrow doses for lymphoma induction.

If we subtract an estimated median post-diagnosis survival time of ~10 y from the estimate of Richardson et al., the resulting estimate of latency of ~15 y for incidence of CLL is consistent with that suggested by the analysis of Silver et al. (2007) based on an examination of mean follow-up time in medical cohort studies, in which the risk of CLL "is elevated, though non-significantly, in almost all studies with more than 15 years average follow-up" (see Fig. 2) and our own admittedly crude point estimate (see Appendix C).

However, recent time window analyses within epidemiological studies highlight the uncertainty in potential latency periods for both CLL and NHL. A case-control study of mortality from CLL in occupationally exposed persons by Schubauer-Berigan et al. (2007) yielded marginally significant estimates of risk with a time lag of ≥10 years when workers with doses >100 mSv were excluded, suggesting that a lag period of 10 years was appropriate for this group. The study by Romanenko et al. (2008), which did not examine the effects of the very large uncertainty in doses for Chornobyl remediation workers (see Kryuchkov et al. 2009), reported a minimum deviance for the risk estimate for both CLL and non-CLL leukemia using a time lag of only 2 years. In contrast, although Richardson et al. (2009) obtained significant dose-responses ($p \leq 0.05$) for mortality from NHL in both the LSS cohort and workers at the Savannah River Site using a time lag of 10 years, their study did not show evidence of a significant risk until a period of 35+ years had elapsed following irradiation. "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). Such contrasting results indicate that the issue of a suitable estimate of latency for modeling risks of radiogenic CLL or NHL is far from resolved.

The results of our evaluation of information from medical cohort studies bearing on latency of multiple myeloma and NHL are similar to those for CLL (Appendix C), i.e., an uncertainty band of ±5 y around a point estimate of latency for CLL or NHL of ~10−15 y. Because of current uncertainty in the value for the central estimate of a latency period, we have elected to use a point estimate of 10 y with an uncertainty band of ±5 y. The characteristics of the resulting latency distribution are described in the next section.

5.4.1 Handling of Latency in the CLL Model

As with other neoplasms in the IREP model, the risk of CLL should be very low for short times after exposure due the existence of a minimum latency period (here assumed to be 5 y). For longer times after exposure the magnitude of risk is adjusted by a factor which is phased in using an S-shaped function, as described on pages 95−96 of Land et al. (2003). For the CLL risk model, the midpoint of the S-shaped function for latency was set at 10 y. At the midpoint, the ERR/Sv is half the maximum ERR/Sv, which is attained at about 20 y. Figure 3 shows the ERR at 1 Sv for CLL adjusted by an S-shaped function with a mid-point of 10 y, to account for the effect of the minimum latency period.

Because precise knowledge about the onset of radiogenic CLL is lacking, an additional random linear translation of the S-shaped curve is introduced by letting the midpoint vary around the nominal value of 10 y. The uncertain midpoint is assumed to be distributed according to a triangular distribution with minimum 5 y, mode 10 y, and maximum 15 y. The effect of this uncertainty is an increase of assigned share for malignancies diagnosed within a shorter time following exposure (Fig. 4).

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 0.01 and 0.99 at 4 y and 11 y, respectively. The addition of a triangular distribution (with extremes at 5 and 10 years) about the midpoint extends the points at which the 99th percentile of the latency adjustment reaches 0.01 and 0.99 to approximately 1.5 y and 9 y, respectively (Land et al. 2003).

In contrast, the latency adjustment represented by the central curve in Fig. 4 reaches 0.99 of the maximum at 17 y after exposure. When the uncertainty in the mid-point of the S-shaped function is included, the point at which the 99th percentile of the latency adjustment reaches 0.99

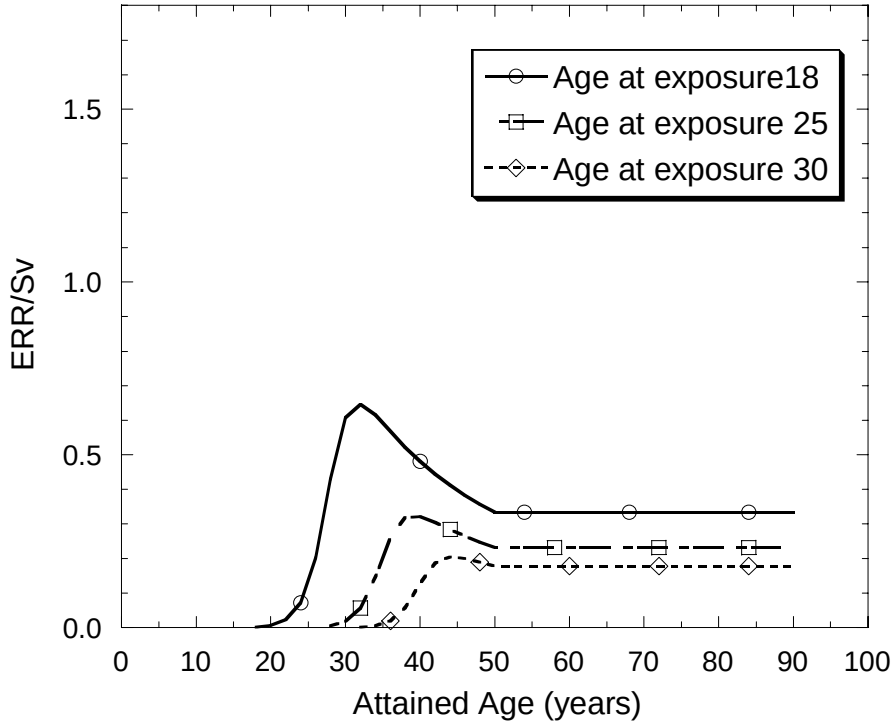

Fig. 3. Risk model for CLL, adjusted for the effect of minimum latency period, depicted as the variation of the ERR at 1 Sv with attained age, for ages selected ages at exposure.

is extended to 12-13 y. As a result, the 99th percentile of PC for CLL should be based on values for latency of about 12-13 years.

The differences between the revised latency adjustment proposed for the CLL risk model and the existing latency adjustment in IREP are introduced by the assumption of a slightly longer but more uncertain minimum latency period (10 y with a range of 5 to 15 y for the CLL model versus 7.5 y with a range of 5 to 10 y used in IREP). Despite the differences in the two distributions, 99th percentile estimates of PC made using the revised distribution should be rather similar to those made with the existing latency distribution in IREP, all else being equal, with the revised distribution expected to produce lower 99th percentiles of PC at 5 to 20 y after exposure, but possibly producing higher 99th percentile of PC at 2−5 years after exposure—the latter effect being caused by the larger uncertainty in the revised latency adjustment proposed for the CLL model.

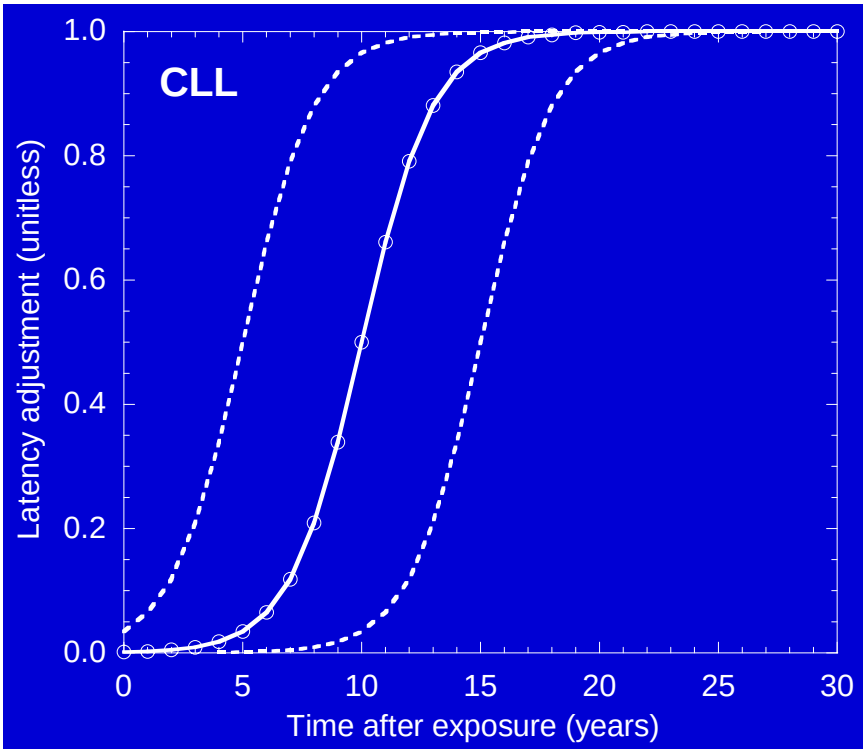

Fig.4. Adjustment factor accounting for the uncertainty in the minimum latency period.

5.5 Sample Results from the Proposed CLL Model

Representative estimates of PC from the CLL model are given in Table 3 for an acute exposure of 1 Sv to high-energy gamma radiation. Although results are restricted to exposures to males, the 99th percentile of PC for females is similar to that obtained for males because the same risk coefficients are used and because the upper bound of PC is given by the multiplicative risk projection to the U.S. population, provided that the Japan to U.S ratios of age-adjusted incidence rates in males and females are significantly lower than 1 (Appendix A). As shown in Table 3, the PC exceeds 50% at the 99th percentile for times since exposure greater than 10 y for men aged 20 y at the time of exposure, and for times since exposure between 10 and 20 y for men aged 25 y at the time of exposure. For age at exposure 20, the 95th percentile of PC also exceeds 50% for cancers diagnosed 15 and 20 y after exposure. Doses higher than 1 Sv will be required to produce 99th percentile values of PC that equal or exceed a value of 50% for older ages at time of exposure or for older ages at time of diagnosis when age at exposure is greater or equal to 25 y.

Table 3. Probability of causation (PC in %) of CLL in males acutely exposed to 1 Sv of high-energy gamma radiation

Age at exposure (y)	PC[a] (percentile)	Time since exposure (y)					
		5	10	15	20	25	≥30
20	50th	0.80	7.84	13.8	12.2	10.4	8.88
	95th	16.7	48.4	54.2	50.1	45.4	41.3
	99th	**35.0**	**65.0**	**67.6**	**63.2**	**58.6**	**54.6**
25	50th	0.46	4.88	9.07	8.16	6.99	6.99
	95th	9.91	35.4	41.9	38.7	34.8	34.8
	99th	**22.5**	**51.0**	**55.3**	**51.3**	**47.2**	**47.2**
30	50th	0.28	3.09	5.98	5.48	5.49	5.49
	95th	6.04	24.9	31.2	28.9	28.9	28.9
	99th	**14.4**	**38.3**	**43.3**	**40.1**	**40.2**	**40.2**
35	50th	0.23	2.56	5.10	5.48	5.49	5.49
	95th	4.85	21.2	27.5	28.9	28.9	28.9
	99th	**11.5**	**33.4**	**38.6**	**40.1**	**40.2**	**40.2**
40	50th	0.19	2.16	5.10	5.48	5.49	5.49
	95th	4.01	18.4	27.5	28.9	28.9	28.9
	99th	**9.50**	**29.5**	**38.6**	**40.1**	**40.2**	**40.2**

[a] PC were obtained using a modified version of NIOSH-IREP v.5.6 in which the "Lymphoma and Multiple Myeloma (200-203)" model was adapted to represent CLL. The PC values were obtained based on 30 runs with 2000 iterations each.

For testing purposes, the proposed CLL model was also applied to seventeen claimants selected by NIOSH/OCAS (*Development of a CLL Risk Model for NIOSH-IREP − Revised Addendum*, dated December 10, 2009). These claimants had diseases with ICD-9 codes 202.2x (Sezary's disease) or 202.4x (hairy cell leukemia), which have been described in the literature as clinically resembling CLL. The PC values at the 99th percentile obtained using the proposed CLL

model were compared to the PC values at the 99th percentile obtained using the "Lymphoma and Multiple Myeloma (200-203)" model in NIOSH-IREP v.5.6. All PC values for these claimants were lower than 50% regardless of the model used. The PC values produced by the proposed CLL model are always lower (sometimes significantly lower) than the values obtained using the current Lymphoma and Multiple Myeloma model in NIOSH-IREP. The reason for the lower PC values at the 99th percentile is the longer latency used in the proposed CLL model.

6. DOSE RECONSTRUCTIONS FOR NUCLEAR ENERGY WORKERS FOR USE WITH THE CLL MODEL

6.1 Background

As discussed earlier, estimates of *external* doses for use in modeling the radiological risk of CLL appear to be well represented by *whole-body doses*, but not by bone marrow doses. For purposes of dose reconstruction made in conjunction with risk estimates based on IREP, information from existing personal dosimeter or film badge records for doses from penetrating radiation should probably suffice in most instances.

For *internal* exposures or for *non-uniform external* exposures to former radiation workers, however, the situation is much more complex. The target organ or tissue is the irradiated site in which a normal stem or stem-like cell undergoes transformation to a cancerous clone. The leukemias *per se* (as distinguished from diseases such as CLL and HCL) are monoclonal diseases that arise from hematopoietic stem and progenitor cells located in the red bone marrow. Thus, the red bone marrow is considered both the sole target organ for radiogenic leukemias and the site in which the pathological effects of the leukemic clones develop.

For CLL, the precursor cell is a mature, likely antigen-experienced lymphocyte of currently uncertain lineage or subtype (among the known subsets of normal B cells) and of unknown location in the body when it was transformed to a B-CLL cell (by radiation or some other stimulus). Thus, the appropriate target organ is unclear (Schubauer-Berigan et al. 2007). The residence times of potential lymphocyte precursors at given locations within the body prior to transformation, which normally would be used to estimate the potential dose received, and their effective lifespan, which should limit the time during which they could have been irradiated, are

also essentially unknowable. Under these conditions, the risk from radiation exposure cannot be estimated from radiation doses reconstructed using a conventional "target organ" approach.

Questions that immediately arise include: If the dose to a mature B lymphocyte determines the biological response to radiation exposure, but that B cell potentially could have arisen at any time during the life of an individual diagnosed with CLL, does the term "radiation dose" as it is normally used in conjunction with a specific population of cells within a target organ or tissue have any meaning? How does one define "age at exposure" or "time since exposure" under such conditions? To what extent does irradiation of stem and progenitor cells of the lymphocytes *in the bone marrow* influence later development of CLL, even though the event that transforms the normal B cell to a CLL clone occurs at a later time and most probably in a different location? Is it possible to develop an aggregated estimate of internal dose incorporating appropriate uncertainties to cover the range of behaviors, locales inhabited, residence times, and lifespan typical of the half-dozen types of mature B cells that are currently considered to be potential CLL precursors? To what extent does such an estimate have to be tailored to account for the route of entry of a radionuclide and internal kinetics and partitioning specific to a given radionuclide? Given the paucity of relevant information, would such an aggregated estimate be a case of "garbage in," "garbage out?"

Under ideal conditions, dose estimates would be made considering the potential routes of entry (e.g., inhalation vs wounds) and radionuclide-specific patterns of transport and accumulation. For inhaled plutonium, for example, highest doses might accrue to the lymph nodes associated with the lung. However, transfers via the circulatory system to other organs and tissues, including the bone marrow, from the lung, extrathoracic regions of the respiratory tract, and their associated lymph nodes will result in additional doses to circulating lymphocytes while in blood and to circulating and sedentary lymphocytes while transiting or residing in the bone marrow and lymphatic system.

Since a fraction of B lymphocytes spend some of their time outside the blood, lymph, bone marrow, and lymphatic tissues *per se*, plutonium taken up by organs and tissues such as liver and skeleton could represent another important source of exposure. For example, the liver contains a large resident and migratory population of lymphocytes and macrophages that provide immune surveillance against foreign antigen (Lalor and Adams 2002). Unfortunately, the exact proportions of the pools of the half-dozen CLL precursors—or of the total pool of B

lymphocytes—in specific regions of the human body, such as the liver, are not currently known. Since mass distributions of lymphocytes are based primarily on information that does not distinguish among B, T, or natural killer cells, and as such are dominated by the more abundant T cells, performing a mass balance for B cells carries with it high uncertainty and limits the use of data in some of the published sources (e.g., ICRP 1994, 2002).

The situation for CLL is analogous to that for NHL, in which radiation could have interacted with the lymphocyte precursors anywhere in the lymphatic or circulatory systems, and then formed the cancerous lesion elsewhere. Because the site of origin for NHL could not be determined with any confidence—and data on the inventories and distributions of lymphocytes in the human body are quite uncertain, the dose to the organ/tissue receiving the highest dose is used in dose reconstructions for NHL (ORAU 2006). For both B-cell and T-cell lymphomas, the thoracic lymph nodes were selected as the target organ because the dose to these tissues from exposure via inhalation of insoluble radioactive material is always higher than the dose to other organs/tissues. Thus, a similar approach could be applied to CLL if a more scientifically acceptable alternative cannot be developed.

For radionuclides that are more uniformly distributed in the body, such as tritium and ^{137}Cs, estimates of whole-body doses based on concentrations and the effective half-lives of the radioactive materials should be sufficient. For other radionuclides with non-uniform deposition patterns in the body (e.g., ^{131}I), doses to components of the lymphatic system and to the circulating blood would have to be estimated on a case-by-case basis, as for plutonium.

How to aggregate doses to individual components of the lymphatic and circulatory systems for purposes of developing the input to IREP is an issue that would have to be evaluated carefully. One potential way to accomplish this is to estimate dose rates to circulating lymphocytes based on the estimated fraction of the time that they spend while in blood or lymph and in tissues outside and inside the lymphatic and hematopoietic systems, e.g., based on residence times of and dose rates from radionuclides within these compartments or on dose rates to lymphatic components or bone marrow from nearby organs of accumulation (such as the thyroid, which can irradiate nearby lymph nodes following uptake of ^{131}I).[8]

[8] Lymphocytes *as a group* spend about 0.5 h in the bloodstream, after which ~45% move into the spleen, where they spend several h, ~42% get into the lymph nodes, where they spend about 12 h, and ~10% cross the endothelial cells lining the capillaries and move into other body tissues. Details on the fractional distributions of B, T, and natural killer lymphocytes in each of these fluxes are currently lacking.

ICRP dose models all contain a blood compartment that can be used to calculate dose rates for lymphocytes in circulating blood and organs and tissues of accumulation, but it appears that information on transfers to the lymphatic compartments is very limited, except for inhaled materials, for which information on transfers to the lymph nodes associated with the lungs and extrathoracic regions of the respiratory tract is available (ICRP 1994). Thus, obtaining meaningful dose estimates to use as input for IREP for former radiation workers could be a significant challenge, depending on the nature of the exposure and the specific radionuclides involved.

If, as expected, this challenge proves to too daunting for some combinations of exposure type and radionuclide, an alternative would be to estimate the maximum dose to a lymphocyte in any component of the circulatory, lymphatic, or blood-forming systems or in any other organ or tissue through which they circulate or in which they reside—as is currently done using the thoracic lymph nodes as the target organ for NHL. However, there are also significant challenges associated with making such an estimate and serious questions about whether use of such an estimate would even be justified—particularly in the case of CLL, for which an association with radiation exposure is still in doubt. We will use the example of inhaled plutonium again to illustrate the associated technical questions and concerns.

6.2 Challenges in Estimating Meaningful Doses for Use with the IREP CLL Model

Cells in the thoracic lymph nodes are expected to experience the highest dose *rate* following inhalation of plutonium (ICRP 1994). Under these conditions, is it reasonable to use a conservative estimate of dose referenced to the thoracic lymph nodes to estimate the probability of causation of CLL using IREP? The argument in favor of this approach is that uncertainties about the nature of the CLL precursor, including its homing/migratory behavior, cannot rule out the possibility that such a cell could have spent most of its lifetime in the thoracic lymph nodes. If one gives the benefit of the doubt to the claimant, as has been done for other B-cell lymphomas (ORAU 2006), shouldn't the organ potentially receiving the highest dose be the target organ for dose reconstruction?

The counter-argument is that a conservative estimate may be difficult to justify on technical grounds, given the weak evidence for radiogenicity of CLL. Even if a lymphocyte is periodically

irradiated by α particles in these lymph nodes at a high dose rate while it is passing through or temporarily resident in the lymph node, the probability that it will receive a significant *dose* from plutonium *could be* quite low because some lymphocytes can spend a significant part of their time outside the lymphatic system (e.g., while circulating in blood) or could be localized for long periods in lymphoid tissues remote from the thoracic lymph nodes.

As an alternative to an assumption of total residence in the thoracic lymph nodes, one could attempt to estimate a dose to a lymphocyte precursor for CLL based on the ratio of the mass (volume) of the thoracic lymph nodes to those of the circulating blood, lymphatic system, bone marrow, or the body mass through which lymphocytes circulate. The mass of the thoracic lymph nodes in adults (15 g) is about 2−2.5% of that of the mass of the lymphatic system as a whole (600−730 g, depending on gender) and about 0.025−0.04% of the lean body mass (ICRP 1994, 2002). Thus, the probability that a lymphocyte might be in the thoracic lymph nodes at any given point in time could range from about 2% for the hypothetical case of a B-lymphocyte restricted to but circulating within the lymphatic system alone and as low as about 0.03% for the highly unlikely case of a B-lymphocyte circulating freely into and out of extra-lymphoid organs and tissues.

In the case of a B-lymphocyte able to circulate freely through only the blood and lymphatic systems (e.g., antigen-naïve mature B cells, some types of memory cells), the probability would be reduced by about an order of magnitude, i.e., from about 2% to about 0.2−0.3%, when compared to that of a B-lymphocyte restricted to the lymphatic system alone because of the extra volume (and mass) contributed by the blood (4.50−6.03 L; specific gravity about 1.05; ICRP 2002).[9] Multiplying these probabilities by the expected dose rate in the thoracic lymph nodes and the estimated lifetime of the lymphocyte precursors for CLL could yield an estimate of dose because some lymphocytes spend only part of their time at any one place, either inside or outside the lymphatic system.

However, as previously discussed, there are large uncertainties involving the characterization of the lymphocyte precursor for CLL/SLL, the degree to which precursors circulate or are localized in the blood and lymphatic systems or other organs and tissues at the point in time when they undergo transformation to become CLL clones, and the nature of post-

[9] A large fraction of B lymphocytes in the peripheral blood do not recirculate, but tend to remain in the blood (Young 1999). Thus, the cases described are oversimplifications of what actually happens in the human body.

transformation transfers of the clones to regions where the disease manifests itself (e.g., bone marrow, lymphatic components, or other organs and tissues). All of these factors affect our ability to estimate the probability that the dose associated with a given locale is representative of that which produced the ensuing cancerous lesion.

For example, the percentage of total lymphocytes represented by B lymphocytes within the various body compartments ranges from ≤1% in skin, thymus, and the epithelium of the lung or digestive tract, to ≥50% in the spleen, tonsils, red bone marrow, and greater omentum. There is also a wide variation in the distributions of specific types of lymphocytes within different microenvironments of lymphoid organs or tissues (Westermann and Pabst 1992). There are 5 or more subsets of B cells, including several different types of memory cells, in human blood (Klein et al. 1998; van Zelm et al. 2007). Likewise, there are 5−7 different subtypes of B cells, including several different types of memory cells, in human tonsils (Liu et al. 1997; van Zelm et al. 2007). About 50−90% of the intraepithelial lymphocytes in the palatine tonsils are B cells, while the majority of the B cells in the crypt epithelium are mature memory B cells (Nave et al. 2001).

The extent to which lymphocytes are localized within the lymphatic system, and even within a given lymph node, thus depends on the type of lymphocyte (e.g., B- or T-cell) and its specific origin (see footnotes and associated text in Appendix B) and its experience with antigen, including involvement of the germinal center reaction. Some memory B-cells tend to remain in the lymph nodes while activated T-cells usually leave the lymph nodes via the efferent lymph and circulate more freely. However, T-cell-dependent B-cells that become memory cells via the germinal center reaction often migrate to sites other than the lymph nodes, including the bone marrow and antigen-draining sites in mucosal associated lymphatic tissue, Peyer's patches, the subepithelial region of the tonsils, and splenic marginal zones, where they may persist for a considerable period of time (months or more) (Liu and Arpin 1997; Paramithiotis and Cooper 1997; Hay and Andrade 1998; Angelin-Duclos et al. 2000; Chiorazzi 2007).

Thus, how often lymphocytes might be exposed to plutonium α particles in the thoracic lymph nodes, for example, could vary significantly depending on the type of lymphocyte

precursor, the level of "antigen experience," and whether it was activated with T-cell help in the germinal center.[10]

In addition, the doses from plutonium α particles to each of the lymphocyte precursors for CLL in the groups identified above would depend on their effective lifespan. Estimated mean lifespan for lymphocytes is about 4−6 months, but individual lifetimes can range from a few days to several months for some B cells and from several years to a human lifetime for memory cells (Chiorazzi 2007; Rai 2007c). Marginal zone B cells are predominantly memory cells, and most are long-lived, with some expected to survive as long as their host (Boyd 2007). The lifespan is again determined by the type of lymphocyte involved, its temporal pattern of exposure to antigen, and nature of involvement of the germinal center reaction (Angelin-Duclos et al. 2000; Chiorazzi 2007).

Uncertainty about the influence of each of these factors on a given lymphocyte and about the lymphocyte precursor for CLL makes it difficult to choose which estimate of lifespan would be most appropriate to apply in a dose reconstruction effort. For example, active suppression of terminal differentiation gives the memory lymphocyte a self-renewing capability like that of stem cells in other organ systems (Fearon et al. 2001) and thus makes it a seemingly good candidate for a CLL precursor. Under these conditions, an assumption of a lymphocyte lifespan as long as a human lifetime might be a technically defensible choice. Unfortunately, there is not yet a consensus on whether the memory cell is the most likely precursor for CLL (Keating et al. 2003; Stevenson and Caligaris-Cappio 2004; Chiorazzi et al. 2005; Hervé et al. 2005; Caligaris-Cappio and Ghia 2007; Chiorazzi 2007; Ghia et al. 2007; Zent 2007). Even if agreement could be reached on this point, uncertainties of the types described in the previous paragraph limit the estimation of a meaningful dose for use in IREP with the proposed CLL model.

Finally, only those lymphatic cells or CLL precursors (see footnote 10) located within the thoracic lymph nodes would be exposed at a high dose rate over the entire lifetime of an exposed person. Although the structural cells of the lymph nodes themselves are not expected to be precursors for CLL, radiogenic changes in these cells, including induction of senescence,[11] could

[10] A possible but seemingly low probability scenario could involve a mature B-lymphocyte (e.g., a memory cell) that localized in one of the thoracic lymph nodes for an entire human lifetime. Unfortunately, it is not currently possible to estimate the probability of such a scenario based on current limited information.

[11] It is more likely that such changes would result from buildup of senescent cells as part of the aging process rather than as an effect of radiation exposure. This could explain in part why CLL is primarily a disease of old age.

potentially affect the tissue microenvironment in a manner that would promote development of CLL, e.g., by rescuing CLL cells from apoptosis or supporting the expansion of CLL clones (Table 1; Stevenson and Caligaris-Cappio 2004; Chiorazzi et al. 2005).[12, 13]

However, even under such assumptions, the dose rate to this restricted part of the lymphatic system (i.e., the thoracic lymph nodes) is not necessarily meaningful for estimating the risk of developing CLL (or other types of NHL, for that matter). The reason is that a substantial body of research indicates that the mass of the whole organ or tissue is the appropriate reference to be considered in calculating radiation dose and estimating radiation risk. The problem in the case of CLL is to ascertain just what constitutes the "whole organ or tissue" (see footnote 2).

The frequency of chromosome aberrations and induction of liver cancer was not affected by spatial inhomogeneity in the dose delivered to Chinese hamster liver cells by plutonium α particles (Brooks et al. 1974, 1983). Based on a wide range of information, including results from studies of the effects of variations in spatial distribution of doses from plutonium deposited in the lungs of dogs, hamsters, and rats (Bair et al. 1974), the NCRP (1975) concluded that "particulate plutonium in the lung is no greater hazard than the same amount of plutonium more uniformly distributed throughout the lung." Brooks (2003) has recently concluded that bystander effects make the organ or tissue respond as a whole and thus indicate that radiation effects may be related to organized responses at the level of the organ or tissue rather than to alterations induced in single cells. Thus, it is not clear that the dose within an individual component of the lymphatic system, as opposed to an estimate of the dose to the entire "system"—assuming a meaningful definition of the term is possible for CLL—would necessarily be a meaningful quantity with respect to induction of CLL (or other types of NHL).

[12] All experts contacted by NIOSH/OCAS (Chiorazzi 2007; Kay 2007; Rai 2007; Zent 2007) agreed that CLL cells are sustained and stimulated to proliferate by external signals from other cell types (stromal cells in bone marrow, T cells in lymph nodes, and nurse-like cells in peripheral blood—or perhaps elsewhere; see footnote 13) or soluble factors (cytokines, chemokines, and/or antigens). CLL B cells seem to need close or intimate contact with the cell types just mentioned and are drawn to them by chemokines. Although there is extensive current research in this area, including that by one of the experts (Kay), it is not possible to assess which signals are most important or how many are needed to sustain a CLL clone. Chiorazzi and Kay seem to agree that a multiplicity of such signals is probably needed. Kay also pointed out that it is not currently known whether genetic or cytogenetic alterations in these other cell types play a role in the etiology of CLL.

[13] Nurse-like cells were first recognized *in situ* in the thymus, where they form characteristic complexes with immature T cells and play an important role in T-cell maturation and differentiation. Mature counterparts of blood-derived nurse-like cells are likely to play a role in protecting CLL B cells from apoptosis in distinct lymphoid (and non-lymphoid) microenvironments rather than in the bloodstream (Burger et al. 2000).

It currently appears that reconstructing internal doses or external non-uniform doses for claimants with CLL (and related cancers) represents a major technical challenge given current uncertainties of the types just discussed. Effective implementation of the CLL model in cases in which claimants received non-uniform internal or external exposures hinges on whether meaningful estimates of dose can be reconstructed and appears to require a significant research effort, outside the scope of this report. An analysis of several approaches to determine a meaningful dose from non-uniform exposures for the purpose of assessing the risk of CLL (Apostoaei and Trabalka 2009) has recently been completed.

7. CONCLUSIONS

Based on the most recent information on CLL incidence reported in epidemiological studies and the latest estimates of ERR/Sv for NHL mortality in male atomic-bomb survivors reported by Richardson et al. (2009), it is concluded that the IREP lymphoma and multiple myeloma model should be used for CLL, but only as an interim solution because of the concerns enumerated in Section 5.2. 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 by Richardson et al. (2009), which was based on 10 years of additional follow-up, now shows a highly significant response for mortality from NHL in males. Thus, we think 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.

Therefore, a high priority will be assigned to development of a new NHL model to cover CLL, and other diseases now included in the revised definition of NHL, after the RERF-NCI team publishes the new LSS data. Reanalysis of the Japanese A-bomb survivor data for NHL (or, barring that, for the lymphoma and multiple myeloma grouping), using an appropriate surrogate for whole-body dose, and with a focus on deriving age-at-exposure and attained-age dependencies that are independent of those derived for solid tumors, could potentially result in significant changes to the risk coefficients in the proposed CLL model.

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APPENDIX A

AGE AND GENDER DEPENDENCE OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) INCIDENCE RATES IN U.S. AND JAPANESE POPULATIONS

This appendix summarizes age-dependent and age-adjusted incidence rates of CLL (ICD-9 204.1) in the United States (SEER 2005), in Japan, and in a combined population from Hiroshima and Nagasaki (from the IARC; Parkin et al. 1997). The age-adjusted rates are normalized to the world standard population, as is required for use in PC calculations in IREP. World-standardized cancer rates for the combined population from Hiroshima and Nagasaki are used in NIOSH-IREP to model the transfer of risk from the LSS cohort to the U.S. population.

The data in Tables A.1, A.2, A.3, and in Fig. A.1 show that there are large differences in background incidence rates of CLL in the U.S. and Japan. Incidence rates are more than an order of magnitude lower in the Japanese than in the U.S. population. The rates for Asians and Pacific Islanders who reside in the U.S. are also lower than for other population subgroups and are similar to those of the Japanese population, suggesting that the influence of genetic background may be stronger than that of environment on the incidence of CLL in Asians (see Section 3.4 in the main text). This conclusion holds not only for incidence rates of CLL alone, but also for rates of CLL + SLL. (Dores et al. 2007).

The data in the tables represent snapshots in time of expected incidence rates. Incidence rates have been changing over time for a variety of reasons. For example, Dores et al. (2007) showed that incidence rates compiled by the Surveillance, Epidemiology, and End Results (SEER) Program in the U.S. are affected by delays in reporting of CLL (but not of SLL). The age-adjusted rates reported by Dores et al. (2007) based on records covering 1993−2004 and standardized to the U.S. population in the year 2000 (5.34 per 10^5 person-years for males and 2.70 per 10^5 person-years for females), which take this factor into account, are about 60% higher than the incidence rates shown in Table A.1. However, only a small portion of the 60% difference is due to the delay in reporting. The majority of this difference is due to the fact the age-adjusted rates reported by Dores et al. (2007) were obtained using the 2000 U.S. standard

population, while the age-adjusted rates included in this report were based on the world standard population.

Dores et al. (2007) showed that the incidence rate for SLL was about 1/3 that for CLL. They also reported what appeared to be differences in the gender and age-specific trends of SLL when compared to CLL. However, differences in methods of detection of CLL and SLL and lack of information from epidemiological studies prevented them from drawing firm conclusions about the meaning of their observations, i.e., without further investigation.

Table A.1. Incidence rates of CLL (ICD-9 204.1) in the United States based on SEER-13 data covering the 1992−2002 period.

	CLL incidence rates in the U.S.[a] [per 100,000 per year]	
Age group	Male	Females
newborn	0	0.033
01-04	0	0.0082
05-09	0	0
10-14	0	0
15-19	0	0
20-24	0.0068	0.014
25-29	0.012	0.013
30-34	0.12	0.040
35-39	0.43	0.14
40-44	1.0	0.4
45-49	2.4	1.2
50-54	4.9	2.2
55-59	9.0	4.0
60-64	13.5	6.6
65-69	20.3	10.2
70-74	27.6	13.3
75-79	32.6	17.5
80-84	39.4	21.2
85+	47.9	24.6
Age-adjusted[b]	3.3 (0.0375)[c]	1.6 (0.0239)[c]

[a] SEER (2005) - SEER database: Incidence - SEER 13 Registries Public-Use, Nov 2004 Sub (1992-2002).
[b] Adjusted to the world standard population.
[c] Standard error in the age-adjusted rate.

Table A.2. Incidence rates of CLL (ICD-9 204.1) in the Japanese population.

	CLL incidence rates[a] [per 100,000 per year]	
Age group	Male	Females
newborn	0	0
01-04	0	0
05-09	0	0
10-14	0	0
15-19	0	0.034
20-24	0	0.038
25-29	0.041	0
30-34	0.035	0
35-39	0.089	0
40-44	0.139	0
45-49	0.077	0.037
50-54	0.46	0
55-59	0.41	0.23
60-64	0.90	0.11
65-69	0.87	0.22
70-74	0.87	0.37
75-79	1.0	1.2
80-84	2.6	0.68
85+	0	0
Age-adjusted[b]	0.13 (0.016)[c]	0.037 (0.0078)[c]

[a] Rates represent the combined population of all cancer registries in Japan – IARC Publication No. 143 (Parkin et al. 1997).
[b] Adjusted to the world standard population.
[c] Standard error in the age-adjusted rate.

Table A.3. Incidence rates of CLL (ICD-9 204.1) in the Hiroshima and Nagasaki population.

	CLL incidence rates[a] [per 100,000 per year]	
Age group	Male	Females
newborn	0	0
01-04	0	0
05-09	0	0
10-14	0	0
15-19	0	0
20-24	0	0.23
25-29	0	0
30-34	0	0
35-39	0.19	0
40-44	0.56	0
45-49	0.48	0
50-54	0.52	0
55-59	0.27	0
60-64	0.61	0
65-69	0.84	0
70-74	2.94	0.40
75-79	0.80	0.51
80-84	0	2.32
85+	5.11	0
Age-adjusted[b]	0.25 (0.055)[c]	0.043 (0.022)[c]

[a] Rates are for the combined population of Hiroshima and Nagasaki, Japan – IARC Publication No. 143 (Parkin et al. 1997).
[b] Adjusted to the world standard population.
[c] Standard error in the age-adjusted rate.

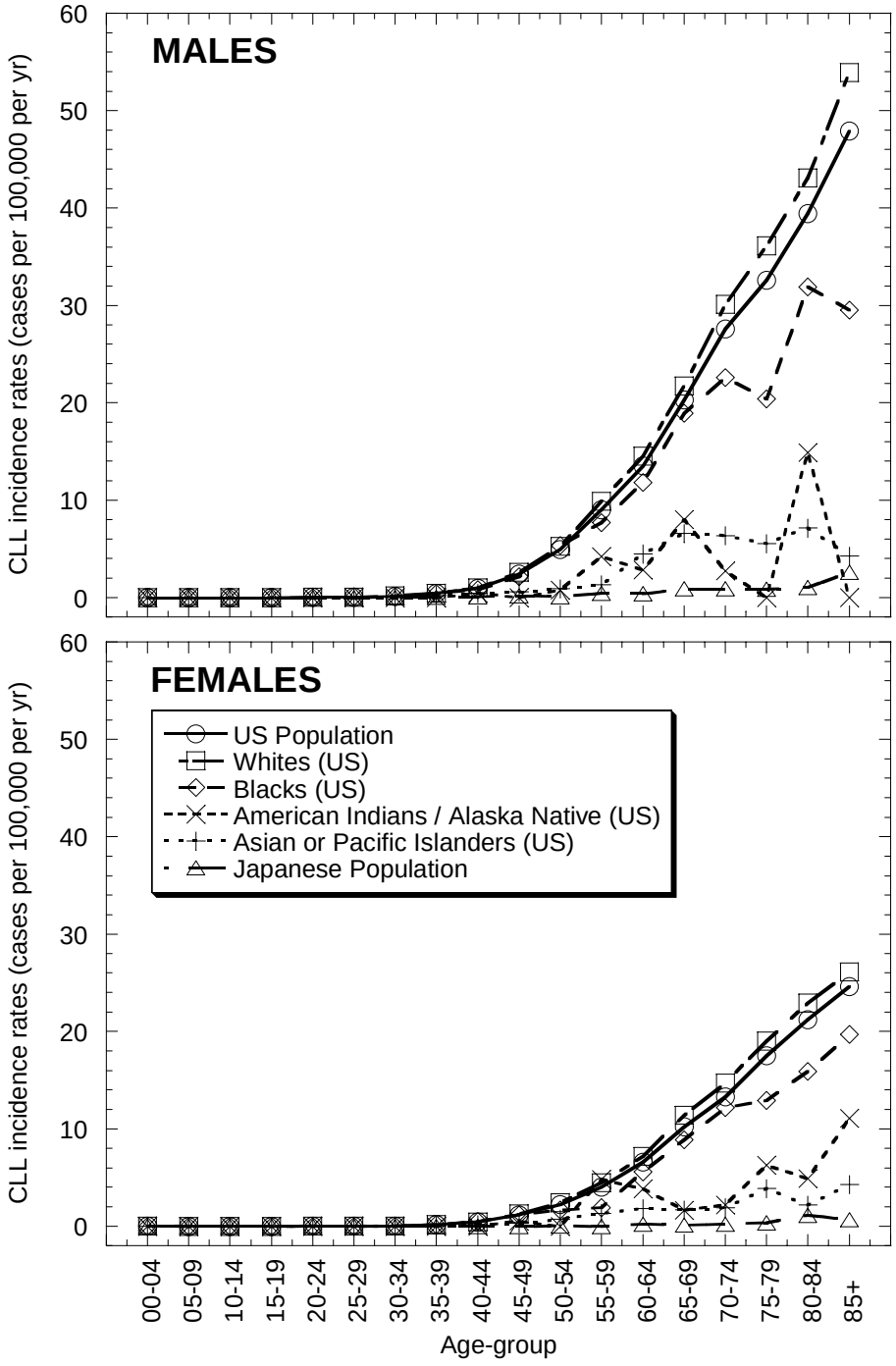

Figure A.1. Comparison of incidence rates of CLL in different groups in U.S. and Japanese populations. Incidence data for the US population is obtained from SEER (1992-2002 dataset). Incidence data for the Japanese population is obtained from IARC (Parkin et al. 1997).

APPENDIX B

ADDITIONAL INFORMATION BEARING ON ETIOLOGY OF CLL

Models for the progression of many solid cancers from pre-malignant tumors to full-blown malignancies have been established, but the precursor lesions for lymphomas, including low-grade forms such as CLL, have yet to be identified (Dewald et al. 2003; Braig et al. 2005). As assays have become more sensitive for detecting monoclonal B-CLL-like cells in peripheral blood, researchers have detected a monoclonal B-cell lymphocytosis (MBL) in about 3% of adults over 40 years of age with otherwise normal blood counts (<5000 lymphocytes mm^{-3}) (Rawstron et al. 2002), but a higher percentage has been reported in families with an increased incidence of CLL (Rawstron et al. 2007). Currently however, the significance of these findings with respect to the etiology of CLL in the general population is not fully clear, because only a small percentage of those with detected MBL show progression to CLL, requiring treatment, while in others the MBL may spontaneously disappear or simply remain stable (Marti et al. 2007; NCI 2009b).

Molecular and cellular changes associated with the onset of CLL are being intensively investigated by research organizations around the world. A diverse set of B-cell genetic and cell surface markers has been identified and used to differentiate the indolent and aggressive subtypes of the disease (Stevenson et al. 1998; Stilgenbauer et al. 2002; Crespo et al. 2003; Dewald et al. 2003; Chiorazzi 2005; Chiorazzi 2007; Rai 2007b). It has been suggested that even B-cell CLL may not be a single disease because the clinical and genetic information indicate that median survival time post-diagnosis can range from a few months to >20 years, depending on the genetic characteristics, mutation status of the V genes, and expression of surface proteins, such as CD38 and ZAP70. Such characteristics often appear to correlate with disease progression and survival time (e.g., Stilgenbauer et al. 2002; Crespo et al. 2003; Dewald et al. 2003; Chiorazzi 2005; NCI 2009b; Rai 2007b).

B lymphocytes mature in the bone marrow and in the process rearrange immunoglobulin variable (V) genes to create the code for an immunoglobulin molecule that serves as the B-cell

receptor for antigen. When an antigen of adequate affinity engages the receptor, the cell typically enters a germinal center in lymph-node follicles, where it rapidly divides and its V genes undergo somatic hypermutation (see Fig. 2 in Chiorazzi et al. 2005). The somatic hypermutation process requires antigen stimulation, B-cell activation, cooperation of T lymphocytes and other cells, and, typically, the germinal center reaction (Keating et al. 2003). However, the process can occur without the involvement of T cells and outside germinal centers, in the marginal zones around lymphoid follicles (see Fig. 2 in Chiorazzi et al. 2005).[14]

Both processes can lead to the development of plasma (antibody-secreting) cells or memory B cells.[15] The latter retain a "memory" of the specific antigen that can be used to mobilize the immune system faster if the body encounters the antigen later in life. Although memory cells without V gene mutations that derive from T-cell-independent stimulation are often referred to as "antigen-experienced" B cells, to distinguish them from memory cells with somatic mutations acquired inside germinal centers (Chiorazzi et al. 2003), both types of cells are obviously "antigen-experienced" and "antigen-stimulated" (Fig. 2 in Chiorazzi et al. 2005; Table 1; see more below).

Those B-CLL cells that *have* been mutated must have come from immunologically competent cells, but, using this parameter as the sole definition of immune competence, "unmutated" B-CLL cells could derive from immature, naïve incompetent cells (i.e., possibly residing in the bone marrow).

However, surface membrane phenotypic studies and measurements of telomeric shortening indicate that antigen stimulation and response to it are *prerequisites* for the development of B-CLL, even in those cases that do not exhibit V_H gene mutations. B-CLL cells over-express activation markers and under-express markers down-regulated by cell activation. Leukemic cells *uniformly express* CD27, identifying them as B cells that were triggered and had entered the memory (or plasma) cell pool. Telomere shortening occurs with each round of cell division. Telomeres of B-CLL cells are much shorter than those in normal B-cells, and those in

[14] Marginal zone B cells are so named because they reside in the marginal zones of the spleen and other lymphoid organs/tissues and are thought by many investigators to develop in the marginal zone of the spleen (Brown 1992; Kraal 1992; Weller et al. 2004; Pillai et al. 2005). In humans, they circulate and are found in lymph nodes, mucosal-associated lymphoid tissue, Peyer's patches, and tonsils (Tierens et al. 1999; Pillai et al. 2005; Boyd 2007).

[15] Other potential CLL precursors are: mature B-cells residing in either the marginal zone or follicular mantle; the human equivalents of murine B-1 cells; V-preB^+L^+ cells; and transitional B cells that routinely exit the marrow and circulate to solid lymphoid tissues (Chiorazzi et al. 2005; Hervé et al. 2005; Chiorazzi 2007). The first three of these groupings include some types of memory cells.

"unmutated" B-cells are much shorter than those in cells bearing V_H gene mutations, suggesting that the "unmutated" leukemic cells have a much more extensive history of cell division than those in mutated cells (Keating et al. 2003; Rai 2007b). As noted above, rapid cell division takes place in the lymph-node follicle after antigen exposure.

Whether they are mutated or not, current information indicates that B-CLL cells have passed through developmental stages that are not associated with the bone marrow, raising serious questions about its current designation as the most appropriate target organ for induction of CLL by radiation exposure.

APPENDIX C

ASSESSMENT OF POTENTIAL LATENCY FOR INCIDENCE OF CLL, LYMPHOMAS, AND MULTIPLE MYELOMA

Our review of the epidemiological data indicated that the extended latency period (20+ years) for mortality from CLL suggested by Richardson et al. (2005) would not be applicable to a risk model for incidence of CLL (i.e., as in IREP). One reason is that the post-diagnosis survival time for CLL patients is highly uncertain, potentially ranging from a few months to a normal life expectancy (NCI 2009b). Another is that it is questionable whether existing epidemiological data on CLL induction by radiation are capable of providing useful information on an extended latency period (see Section 5.4 in main text). Four earlier studies in addition to that of Silver et al. (2007) *potentially* provide information on the latency period for radiogenic CLL:

- Mortality in women with benign gynecological disease (mean age 46.5 y) treated with radiotherapy (mean dose to bone marrow: 1.2 Gy) (Inskip et al. 1993) (Table C.1). Fourteeen CLL cases were coded to ICD-8 (code 204.1), but then were lumped with 3 lymphocytic leukemias, not otherwise specified (code 204.9).

- Mortality in ankylosing spondylitis patients (83.5% male) treated with radiotherapy (93.2% aged between 20−60 at first treatment; mean dose to bone marrow: 4.4 Gy) (Weiss et al. 1995) (Table C.2). CLL deaths prior to 1979 were coded to ICD-8. ICD-9 codes were grouped to correspond with subtypes coded under ICD-8 (204.1, 207.8).

- Incidence in cervical cancer patients (mean age 52 y) treated with radiotherapy (mean dose to bone marrow: 7.5 Gy) (Boice et al. 1985) (Table C.1). Mean age at leukemia diagnosis was in the range 60−64 y for acute lymphocytic leukemia and acute or chronic myeloid leukemia, but was 67 y for CLL (Boice et al. 1987). CLL = chronic and unspecified lymphatic leukemia (ICD-7 code 204.0); direct correspondences were made from ICD-8 to ICD-7 codes (Boice et al. 1985).

Table C.1. Risks for CLL plus unspecified lymphocytic leukemia by time since treatment in patients with cervical cancer (incidence) or benign gynecological disease (mortality) treated with radiotherapy

	Time since treatment (y)					Source
	0−9	10−19	20−29	≥30	All years	
Observed	9	6	3	0	18	Boice et al. (1985)
Expected	13.2	6.8	2.2	0.2	22.3	
SIR	0.7	0.9	1.4	0.0	0.8	
Observed	1	6	3	7	17	Inskip et al. (1993)
Expected	1.08	2.06	2.90	3.19	9.23	
SMR	0.9	2.9	1.0	2.2 (0.9−4.5)[a]	1.8 (1.0−2.9)[a]	

[a]95% C.I.

Table C.2. Risks for mortality from CLL plus unspecified lymphocytic leukemia by time since treatment in ankylosing spondylitis patients treated with radiotherapy

	Time since treatment (y)					Source
	0−4	5−14	15−24	≥25	All years	
Observed	0	1	0	6	7	Weiss et al. (1995)
SMR	0.0	1.8	0.0	2.0 (0.7−4.3)[a]	1.4 (0.6−2.8)[a]	
Adjusted SMR	0.0	2.8	0.0	1.6	Not given	

[a]95% C.I.

- Incidence in patients (79% female; mean age 47 y) exposed to I-131 for diagnostic or therapeutic (hyperthyroidism or thyroid cancer) procedures (Hall et al. 1992) (Tables C.3 and C.4). The mean doses to bone marrow varied by exposure group as follows: diagnostic (mean 0.19 mGy), treatment for hyperthyroidism (48 mGy), and treatment for thyroid cancer

Table C.3. Incidence of CLL[a] plus unspecified lymphocytic leukemia by time since treatment in patients exposed to I-131 in diagnostic or therapeutic procedures

	Time since treatment (y)				Source
	2−9	10−19	≥20	All years	Hall et al. (1992)
Observed	13	30	22	65	
SIR[b]	0.71 (0.38−1.21)	1.22 (0.83−1.75)	1.26 (0.79−1.90)	1.08 (0.84−1.38)	

[a]Hall et al. (1992) do not specify which cancer classification was used in diagnosing CLL; however, because of the time frame in which the analyses were conducted, "CLL" may include unspecified lymphocytic leukemia (see text).

[b]95% C.I. given in parentheses.

Table C.4. Incidence of CLL[a] in relation to dose to bone marrow in patients exposed to I-131 in diagnostic or therapeutic procedures

	Dose to bone marrow (and mean dose) (mGy)					Source
	0.00−0.01 (0.009)	0.02−0.10 (0.058)	0.11−10 (3.5)	11−100 (39)	>100 (221)	Hall et al. (1992)
Observed	2	17	30	9	7[b]	
SIR[c]	0.53 (0.06−1.90)	1.15 (0.67−1.83)	1.22 (0.82−1.74)	0.62 (0.28−1.17)	3.17 (1.27−6.53)	
RR[c]	1.00[d]	2.22 (0.52−9.63)	2.54 (0.61−10.6)	1.17 (0.25−5.41)	6.49 (1.34−31.3)	

[a]Hall et al. (1992) do not specify which cancer classification was used in diagnosing CLL; however, because of the time frame in which the analyses were conducted, "CLL" may include unspecified lymphocytic leukemia (see text).

[b]4 of the 7 "CLL" cases occurred in patients treated for thyroid cancers (4 in 802 patients) vs 3 cancers in 46,186 patients exposed to I-131 in diagnoses or treatment for hyperthyroidism.

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

[d]Low-dose group was used as comparison group in estimating relative risk.

(250 mGy). As might be expected, the highest incidence rate for "CLL" was in the latter group (see footnote b to Table C.4). No CLL classification scheme was referenced.

Beyond the obvious concerns about potential for misdiagnoses and classification of CLL, all of the studies are potentially limited by the (1) confounding effects of prior disease on CLL incidence, (2) uncertainties in diagnosis and classification of CLL, (3) limited statistical power, particularly in the last case, because of the low doses involved, and (4) meaningfulness of bone

marrow doses for lymphoma induction. However, the epidemiological studies of *mortality* cited by Richardson et al. (2005) as providing the best evidence for an extended latency period [studies of patients treated for benign gynecological disorders (Inskip et al. 1993) or ankylosing spondylitis (Weiss et al. 1995)] have another major drawback for our purposes (i.e., beyond the fact that the numbers of "CLL" cases in the exposed groups are small and thus none of the results indicate an excess risk significantly different from zero) (Tables C.1 and C.2). Namely, the clinical and genetic information on CLL indicate that median survival time post-diagnosis can range anywhere from a few months to >20 years, depending on the genetic characteristics of the malignant cells involved , but with an estimated median survival time of ~10 y (e.g., Stilgenbauer et al. 2002; Crespo et al. 2003; Dewald et al. 2003).

As Richardson et al. (2005) acknowledge, patients with CLL can live many years without developing significant symptoms, and often die with the disease, but from causes other than CLL (e.g., Kyasa et al. 2004). Thus, although the two epidemiological studies cited could contain evidence of an extended latency with respect to mortality (assuming that CLL *was* the predominant cause of mortality), the results would still have to be adjusted for estimated survival post-diagnosis to be useful for estimating a latency period for CLL *incidence*.

The evidence for an extended latent period is weak in the results from the study by Inskip et al. (1993), where 41% of the cases of mortality attributed to "CLL" were observed in the first 20 years, even if it is assumed that the grouped lymphocytic malignancies analyzed in the study were dominated by CLL (Table C.1). Although the trend appears to be stronger in the data from the study by Weiss et al. (1995), where 86% of the deaths occurred after 25 or more years had elapsed (Table C.2), the case for a significant effect is weakened by the very small numbers involved (7 total cases).

If a median survival time post-diagnosis of 10 y is subtracted from the results for latency with respect to mortality in these two studies (i.e., a time since treatment of 20−29 y becomes 10−19 y), an estimate for the mean latency period appears to fall in the range ~10−20 y (Table C.5). Even if the median survival time was skewed to a much lower value (say, 2 y), on the assumption that the "CLL" cases in these two studies were all more aggressive and thus led to earlier mortality than expected or that median survival time during the periods that the studies were conducted was much lower than reported, the results, when combined with the "CLL"

Table C.5. Adjusted numbers of CLL cases in patients treated with radiotherapy as a function of treatment condition and time since treatment

Reason for radiotherapy	Time since treatment (y)		
	0−9	10−19	≥20
Cervical cancer	9	6	3
Benign gynecological disease	7[a]	3[a]	7[a]
Ankylosing spondylitis	1[a]	2[b]	4[b]
Thyroid diseases	13	30	22
Total including thyroid diseases	30	41	36
Total excluding thyroid diseases	17	11	14

[a]Adjusted by moving original time since treatment range forward by one decade to reflect estimated time of incidence.

[b]Moving original time since treatment range forward by one decade to estimate time of incidence results in 6 cases observed at ≥15 y. These were apportioned between the decade 10−19 y and all decades >20 y, as shown.

incidence data from the studies by Boice et al. (1985) and Hall et al. (1992), still lead to the same conclusion: a mean latency ~10−20 y (see Tables C.1 and C.2).

The results on *incidence* of "CLL" from the studies by Boice et al. (1985) of second cancers in cervical cancer patients and by Hall et al. (1992) of patients exposed to I-131 in diagnostic or therapeutic procedures both suggest that peak incidence occurs before 20 y has elapsed. Eighty-three percent of "CLL" cases in cervical cancer patients and 66% of cases in patients exposed to I-131 were recorded within 20 years of treatment (Tables C.1 and C.3). Both of these studies have their drawbacks (effects of previous cancer in both, and relatively high doses in the first study, and very low doses and lower statistical power in the second case). On the other hand, the study by Hall et al. (1992) showed the greatest effect at the highest doses (Table C.4), albeit with large uncertainties and with perhaps the greatest potential for confounding (i.e., by thyroid cancer) .

Taken as a whole, the limited data on the latency period for CLL induction by radiation exposure do not support the contention that the latency period is in excess of 20 years, but

instead indicate that the uncertainty associated with defining a latency period is quite large, even when the data for thyroid diseases are excluded (i.e., because radiation doses to this cohort were so low). However, even using our admittedly crude approach, it appears possible to make a reasonable case for a peak latency occurring prior to 20 y (28 total cases over 0−19 y vs 14 occurring at or beyond 20 y), *if* the assumption is made that the lymphocytic malignancies identified in the other three studies were predominantly made up of CLL alone (ICD-9 code 204.1).

A question that immediately arises, however, is whether the latency period for the grouping of lymphoma and multiple myeloma [which include NHL, Hodgkin's disease (lymphoma), and multiple myeloma; ICD-9 codes 200−203)] selected as a surrogate for CLL is similar to that of CLL. If it is not, it is conceivable that the risk coefficients in the IREP risk model (which was based on data on cancer incidence in individuals with a much wider age range than those treated with radiotherapy) could be affected.

Data bearing on latency of the cancer types in the lymphoma and multiple myeloma grouping was available from three of the four epidemiological studies discussed above (Tables C.6 and C.7). The data for *incidence* of NHL and multiple myeloma as a function of time since treatment do not indicate a prolonged latency period; 92% and 80% of cases, respectively, were diagnosed in the first 19 y post-treatment (Table C.6). The mortality data are somewhat divergent (Tables C.6 and C.7). While both studies of mortality suggest the possibility of an extended latency period for multiple myeloma, one (Weiss et al. 1994) indicates that the peak latency for both NHL and Hodgkin's lymphoma occurs before 25 y has elapsed, the other (Inskip et al. 1993) shows no clear pattern for Hodgkin's lymphoma (50% of cases diagnosed before and after 20 years have elapsed, respectively), and the data for NHL in Table C.6 are not comparable to the data in Table C.7 because information on latency for 10 cases of NHL with ICD-8 code 202 were not included in the former.

Even with these limitations, when the mortality data are adjusted by subtracting the estimated time from diagnosis to mortality following treatment (as was done for CLL) to estimate the incidence patterns as a function of time and then are pooled with the incidence data (Table C.8), the results for both multiple myeloma and NHL are similar to those for CLL (particularly for the case where the data for thyroid diseases were excluded; see Table C.5). The results for Hodgkin's lymphoma suggest a mean latency on the order of 10 y or less (Table C.8).

Table C.6. Numbers of cases of non-Hodgkin's lymphoma, Hodgkin's lymphoma, and multiple myeloma by time since treatment in patients with cervical cancer (incidence) or benign gynecological disease (mortality) treated with radiotherapy

Cancer site (ICD-8 code)	Time since treatment (y) 0−9	10−19	20−29	≥30	All years	Source
Non-Hodgkin's lymphoma (200, 202)	34	26	5	0	65	Cervical cancer study (Boice et al. 1985)
Multiple myeloma (203)	13	15	5	2	35	
Non-Hodgkin's lymphoma (200 only)	0	3	11	10	24	Benign gynecological disease study (Inskip et al. 1993)
Hodgkin's lymphoma (201)	2	3	2	3	10	
Multiple myeloma (203)	1	1	8	4	14	

Table C.7. Numbers of deaths from non-Hodgkin's lymphoma, Hodgkin's lymphoma, and multiple myeloma by time since treatment in ankylosing spondylitis patients treated with radiotherapy

Cancer site (ICD-9 code)	Time since treatment (y) 5−24[a]	≥25	All years	Source
Non-Hodgkin's lymphoma (200, 202, exc. 202.4)	23	14	37	Weiss et al. (1994)
Hodgkin's lymphoma (201)	11	2	13	
Multiple myeloma (203, exc. 203.1, 238.6)	8	14	22	

[a]Five-year latency period was assumed.

Since Hodgkin's lymphoma contributed only 10 cases and NHL and multiple myeloma contributed 76 and 31, respectively, of the 117 cases in the combined set of data used to parameterize the Lymphoma and multiple myeloma model in IREP (our surrogate for CLL), the potential for confounding because of potential differences in latency when compared to CLL may not be a serious issue. However, the midpoint of the latency function used with the

Table C.8. Adjusted numbers of NHL, Hodgkin's lymphoma, and multiple myeloma cases in patients treated with radiotherapy as a function of treatment condition and time since treatment

Cancer site	Reason for radiotherapy	Time since treatment (y)			
		0−9	10−19	20−29	≥30
Non-Hodgkin's lymphoma					
	Cervical cancer	34	26	5	0
	Benign gynecological disease[a]	1[b]	7[b]	8[b]	8[b]
	Ankylosing spondylitis[a]	10[c]	13[c]	7[c]	7[c]
Hodgkin's lymphoma					
	Benign gynecological disease	5	2	1[d]	2[d]
	Ankylosing spondylitis[a]	7[e]	4[e]	1[e]	1[e]
Multiple myeloma					
	Cervical cancer	13	15	5	2
	Benign gynecological disease[a]	1[f]	2[f]	7[f]	4[f]
	Ankylosing spondylitis[a]	2[g]	6[g]	5[g]	9[g]
Non-Hodgkin's lymphoma					
	All conditions	44	46	20	15
Hodgkin's lymphoma					
	All conditions[h]	12	6	2	3
Multiple myeloma					
	All conditions	16	23	17	15

[a]Mortality studies.

[b]Moving original time-since-treatment range forward by 5 y to estimate time of incidence results in 3 cases observed at 5−14 y, 11 cases observed at 15−24 y, and 10 cases observed at ≥25 y. These were apportioned between the decades 0−9 y, 10−19 y, 20−29 y and all decades ≥30 y, as shown.

[c]Moving original time since treatment range forward by one decade to estimate time of incidence results in 23 cases observed at 0−19 y and 14 at ≥20 y. These were apportioned between the decades 0−9 y, 10−19 y, 20−29 y, and all decades ≥30 y, as shown.

[d]Moving original time since treatment range forward by one decade to estimate time of incidence results in 3 cases observed at ≥20 y. These were apportioned between the decade 20−29 y and all decades >30 y, as shown.

[e]Moving original time since treatment range forward by one decade to estimate time of incidence results in 11 cases observed at 0−14 y and 2 at ≥15 y. These were apportioned between the decades 0−9 y, 10−19 y, and all decades ≥20 y, as shown.

Table C.8 (continued)

[f]Moving original time since treatment range forward by 3 y to estimate time of incidence results in 1 case observed at 0−6 y, 1 case observed at 7−16 y, 8 cases observed at 17−26 y, and 4 cases observed at ≥27 y. These were apportioned between the decades 0−9 y, 10−19 y, 20−29 y, and all decades ≥30 y, as shown.

[g]Moving original time since treatment range forward by 3 y to estimate time of incidence results in 8 cases observed at 2−21 y and 14 at ≥22 y. These were apportioned between the decades 0−9 y, 10−19 y, 20−29 y, and all decades ≥30 y, as shown.

[h]Data not available for benign gynecological disease study.

lymphoma and multiple myeloma model in IREP is the same as that for solid tumors, and thus some modification appears to be justified for its use with a CLL model.

Another set of data that might provide information bearing on the issue of latency (or age dependencies on risks) is that for the Japanese atomic-bomb survivors (Table C.9). For individuals exposed at ages ≥40 (and at doses ≥0.01 Gy), the time-dependent incidence of NHL combined with Hodgkin's lymphoma as is reasonably similar to that for CLL in radiotherapy patients (Table C.5), who were of similar ages when exposed. However, the data for individuals exposed at younger ages and data for incidence of multiple myeloma for all ages at exposure indicate that most cases were diagnosed more than 25 y after the bombings. These observations could indicate a longer latency for lymphoma in individuals exposed at younger ages or at all ages at exposure for those diagnosed with multiple myeloma. However, because the patterns for individuals exposed at doses ≥0.01 Gy and at doses <0.01 Gy are so similar, these data probably result from the increase in incidence of CLL with increasing age (see Appendix A), and could be interpreted to mean that radiation exposure had little influence on development of their lymphomas. This is an issue that could be reexamined at some point, perhaps in conjunction with the reanalysis of the LSS data when the DS02-based dose-response information becomes available.

The only published atomic-bomb survivor data that include CLL are compromised because CLL is combined with HCL, acute leukemias of unspecified type, and cases of myelodysplastic syndrome (Table C.10). The small numbers involved also limit interpretation of the data, but, in general, the time-dependent incidence of these "other" leukemias is very similar to that for NHL and Hodgkin's lymphoma in Table C.9.

Table C.9. Number of lymphoma and multiple myeloma cases in Japanese atomic bomb survivors as a function of time since the bombings[a]

Cancer site	Age at exposure (y)	Exposure (Gy)	Time since bombings (y) 5−7	8−12	13−24	25−32
NHL and Hodgkin's lymphoma	0−19	≥0.01	0	3	2	12
		<0.01	0	0	9	11
	20−39	≥0.01	0	1	10	25
		<0.01	3	2	10	25
	≥40	≥0.01	0	5	17	11
		<0.01	1	6	17	1
Multiple myeloma	0−19	≥0.01	0	0	2	3
		<0.01	0	0	0	2
	20−39	≥0.01	0	1	2	6
		<0.01	0	0	1	9
	≥40	≥0.01	0	0	5	11
		<0.01	0	0	1	15

[a]Source: Table III in Preston et al. (1994).

C.10. Number of "other leukemia" cases in Japanese atomic bomb survivors from Hiroshima as a function of time since the bombings[a]

		Time since bombings (y)	
Age at exposure (y)	Exposure (Gy)	5−20	21−32
0−19	≥0.01	1	1
	<0.01	1	0
20−39	≥0.01	0	4
	<0.01	2	2
≥40	≥0.01	1	1
	<0.01	2	0

[a]Source: Table XI in Preston et al. (1994). "Other leukemia" cases include: 4 cases of CLL, 2 of HCL, 7 of acute leukemias of unspecified type, and 2 of myelodysplastic syndrome. They are based only on Hiroshima data because cases from Nagasaki were predominantly adult T-cell leukemia, for which no association with radiation exposure was found.