A Probabilistic Approach for the Assessment of Internal Dose to Chronic Lymphocytic Leukemia Precursor Cells

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Abstract. Under the U.S. Energy Employees Occupational Illness Compensation Program Act (EEOICPA), the National Institute for Occupational Safety and Health (NIOSH) is responsible for reconstructing radiation doses to certain workers who developed cancer, based on their exposures received while employed in nuclear weapons-related activities for the U.S. Department of Energy or its predecessor agencies. The reconstructed exposure to the organ or tissue that developed cancer is then used by the U.S. Department of Labor to determine whether the cancer was at least as likely as not caused by the worker's weapons-related exposure. While the organ for which a dose needs to be reconstructed is obvious for solid tumors, the relevant tissue for tumors of the hematopoietic and lymphatic system is more difficult to define. Under the original published regulations (U.S. 42 CFR Part 82), chronic lymphocytic leukemia (CLL), which is a form of lymphoma, was the only cancer not covered under the EEOICPA. Recently, however, NIOSH has amended the federal regulation to include CLL. To reconstruct doses for claimants with CLL, a method must be available to reconstruct doses to the relevant tissue(s) that contain the precursor cells for this disease. Recent studies of the etiology of CLL indicate that cells of origin for CLL appear to be mature B lymphocytes which could have been transformed into cancerous cells potentially anywhere within the lymphatic system. Since radiation damage to any precursor B lymphocytes may occur for cells distributed throughout the body, it was clear that a calculation of dose to a single, anatomical organ would not be appropriate. In light of this, an extensive literature review of the distribution of lymphocytes and precursor B lymphocytes in the body was conducted. This review identified quantitative estimates for B cell precursors in six discrete lymphoid organs/tissues, and in nine other lymphocyte-containing compartments. Uncertainty distributions have been developed for the number of precursor cells in each tissue. Using these data, a probabilistic model has been applied to estimate a weighted dose to these cells. This weighted dose can then be used with the existing Interactive Radio Epidemiology Program (IREP) to determine the probability that a worker's CLL was at least as likely as not caused by nuclear weapons-related exposure.

KEYWORDS: dose reconstruction, chronic lymphocytic leukemia, compensation

1. Introduction

The U.S. Energy Employees Occupational Illness Compensation Program Act of 2000 (EEOICPA) established a program for compensating workers for cancers incurred as a result of occupational exposure to ionizing radiation at over 300 U.S. Department of Energy (DOE) and contractor facilities [1]. Under the EEOICPA, the U.S. National Institute for Occupational Safety and Health (NIOSH) has been designated as the agency responsible for reconstructing the radiation doses received by these workers [2]. An overview of the components of the NIOSH compensation program has been published elsewhere [3].

The decision to award compensation is based on a determination of the likelihood that the cancer that developed was caused by the employee's radiation exposure in the workplace. For each case, the U.S. Department of Labor must make a determination that the cancer was at least as likely as not the cause of the cancer. In the implementing regulations by the U.S. Department of Health and Human Services, this has been defined to be a probability of causation (PC) of greater than or equal to fifty percent as calculated by the NIOSH Interactive RadioEpidemiological (NIOSH-IREP) program. A detailed description of the technical aspects of the NIOSH-IREP program has been published by Kocher et al. [4]. A real-time interactive version of the program, along with associated technical documentation, can be viewed on the NIOSH website at: http://www.cdc.gov/niosh/ocas/ocasirep.html.

Under the original published regulations (U.S. 42 CFR Part 82), chronic lymphocytic leukemia (CLL) was the only cancer not covered under the EEOICPA. Recently, however, NIOSH has amended the federal regulation to include CLL as a covered cancer [5]. Because of this, a method must be available to reconstruct doses to the relevant tissues (i.e., the target organ) that contain precursor cells for CLL.

For most cancers, the identification of the target organ or tissue is straightforward. For example, the risk of developing liver or thyroid cancer is estimated from the radiation dose to the entire liver or thyroid gland. For other cancer types (e.g., oral cavity, stomach, or colon), the dose of interest is that to the tissues within these organs that contain the cells which lead to cancer (e.g., to the lining of the stomach). For CLL, the situation is more complex. Contrary to the indication in its name, CLL is not a form of leukemia, but is actually considered a form of non-Hodgkin's lymphoma [6]. Current information indicates that the cells of origin of NHL are *mature* B lymphocytes, i.e., cells that could have been transformed to cancerous clones *outside* the bone marrow and, in the case of CLL, potentially anywhere within the circulatory or lymphatic systems because of normal lymphocyte movements and recirculation. Thus, the precursor for CLL is most probably a mature, antigen-experienced lymphocyte of currently uncertain lineage (among the known subsets of normal B cells) and of unknown location in lymphoid tissues when it was transformed to a CLL cell (by radiation or some other stimulus) [7]. Thus, the risk of developing CLL from radiation exposure cannot be estimated using a conventional single "target organ" approach.

Rather than using a single target organ approach to estimate the dose to the CLL precursor cells, it is necessary to calculate the dose to the CLL precursor cells based on their distribution in the body. To accomplish this, an extensive literature search was conducted to establish the known inventory and distribution of these precursor cells in the body. Once the distribution was established, this information was analyzed to derive compartment-specific weights based on relative sizes of B-lymphocyte pools to be used in estimating a weighted average radiation dose for assessment of the risk of developing radiogenic CLL.

2. Establishing the Distribution of CLL Precursor Cells in the Body

The estimated distribution of CLL precursor cells in the body was derived in a stepwise fashion using data available in the literature, including a review of the anatomy and physiology of the lymphatic system. The steps involved establishing:

1. The total number of lymphocytes of all types [B-, T-, and natural killer (NK) cells] in the human body;
2. The numbers of lymphocytes (all types combined) in a given organ, tissue, or other compartment in the body, both inside and outside the lymphatic system;
3. The fraction of the pool of lymphocytes in a given organ, tissue, or other compartment represented by B lymphocytes and;
4. The fraction represented by potential B-CLL precursors, data for which is found in widely scattered publications in the literature.

A variety of calculations and extrapolations, many requiring application of Monte Carlo methods to propagate existing uncertainties in data, were performed to assemble a meaningful set of information on inventories and distributions of B cells.

2.1 Synthesis of Information

As discussed above, a stepwise analysis was needed to arrive at a meaningful estimate of the distribution of CLL precursor cells in the body. Some judgment was required to generate compartment-specific inventories of B lymphocytes because there is not a one-to-one correspondence between compartments with lymphocyte inventory data and those with information on fractions of B lymphocytes (for example, information on intestinal and respiratory mucosa). In addition, in some

cases only a single published value was available for the lymphocyte inventory or B-lymphocyte fraction in a body compartment.

To account for the uncertainly in our knowledge of these distributions, probability distribution functions (PDFs) were assigned to the number of lymphocytes and to the fraction representing B cells for each organ of interest based on: 1) the ranges of values found in the literature; 2) the ranges of values based on professional judgment; or 3) results of specific calculations. The ranges of values that were used are thought to represent the potential extremes of the values (i.e., reasonable estimates of minima and maxima). Thus, in most cases these ranges were used to define the 1^{st} and 99^{th} percentiles of the assigned PDFs, which are intended to reflect uncertainty due to the current lack of knowledge about the true value.

The uncertainties in the published estimates of total lymphocyte pools in human body compartments appear to be on the order of a factor of 2 and, in some cases more [8,9]. In cases where only a single published value was available, an uncertainty range was assigned equal to +100%, −50% of that value. The uncertainties in the published estimates of the B-lymphocyte fractions in specific body compartments were on the order of ±50%. Thus, in those cases where only a single published value was available, an estimate of uncertainty equal to ±50% of that value was assigned.

Lognormal distributions were used to estimate uncertainties in the numbers of lymphocytes for most body compartments other than tonsils (for which a uniform distribution was used), spleen and liver (for which normal distributions were used), and blood and the lamina propria of the intestinal mucosa (for which Weibull distributions were used). These alternate distributions were chosen because they provided a better representation of the data. Normal distributions were used to quantify uncertainties in the fractions of total lymphocytes represented by B cells for most body compartments. Weibull distributions were used for lymph nodes and vermiform appendix; uniform distributions for thymus and skin; and a triangular distribution for spleen. The shape of the distribution was selected according to the nature and quality of the available data (e.g., a uniform distribution means that the true value is believed to be anywhere in the provided range with equal probability, while lognormal, normal, Weibull and triangular distributions assume that there is a better chance that the true value is around the provided central value, and that the provided central value and range can be fitted by a distribution with the selected shape.) Uniform, normal and triangular distributions were typically applied when the state of knowledge indicated small uncertainty. Log-transformed distributions reflect uncertainties that were expressed as a multiplier (e.g. a factor of 2) around a median.

Monte Carlo methods have been used to propagate the uncertainties in the numbers of lymphocytes and in the fractions of B lymphocytes in individual body compartments. That is, the number of B lymphocytes in a given organ was obtained by multiplying the PDF for the number of lymphocytes in that compartment by the PDF for the fraction of the pool of lymphocytes represented by B cells (expressed as percentages in our tabulated information). Resulting ranges of values for the number of B lymphocytes in individual body compartments are 95% credibility (rather than confidence) intervals obtained using Latin Hypercube sampling (LHS) and a sample size of 2000. These ranges are termed credibility intervals because they rely on judgment-based ranges for the number of lymphocytes in that compartment or for the fraction of the pool of lymphocytes in the compartment represented by B cells.

The percentages of the total number of B lymphocytes in the body located in specific compartments were also estimated. These values were obtained from the Monte Carlo uncertainty propagation algorithm as follows. In the first Monte Carlo iteration, one value of the number of lymphocytes in each compartment and one value of the fraction represented by B lymphocytes were sampled from the input distributions for all compartments of interest. The number of lymphocytes and the fraction of B lymphocytes were multiplied to obtain one estimate of the number of B lymphocytes for each compartment of interest. An estimate of the percentage of the total B lymphocytes in the body present in any given organ was obtained by dividing the number of B lymphocytes in the compartment of interest by the total number of B lymphocytes (obtained as a sum of the number of B lymphocytes across all compartments for that iteration). The operation was repeated for each of the 2000 Latin Hypercube samples.

A similar operation was performed to obtain estimates of the percentages of potential CLL precursors in the body present in a specific compartment. That is, the number of lymphocytes in a compartment was combined with the fraction of the pool of lymphocytes represented by B cells and with an uncertain fraction of B cells that could be CLL precursors in that same compartment.

2.2 Inventory of Lymphocytes in Body Compartments

Estimated inventories of lymphocytes of all types (B, T, and NK cells) in individual body compartment are given in Table 1. These inventories were based mainly on human data, with limited animal data, being used to cover gaps in human data [8, 9, 10, 11, 12, 13, 14].

The synthesis of current published information on lymphocyte inventories provided in Table 1 includes estimates of the numbers of lymphocytes in lymph nodes *in toto*, spleen, Peyer's patches, thymus, bone marrow, tonsils, peripheral blood, intestinal mucosa (lamina propria), respiratory mucosa (lung parenchyma), and "Others" (lymph, skin, liver, vermiform appendix, interstitial fluids of the body cavity, cerebrospinal fluid, and residual soft tissue). The residual soft tissue pool is intended to represent muscle and other not-listed soft tissue organs, mucosa of the urogenital tract, greater omentum, and some of the "Others" constituents listed individually: lymph and body cavity fluids.

Table 1. Estimated distribution of lymphocytes in the human body

Compartments of the human lymphatic system			**Number of lymphocytes** [$\times 10^9$]
Discrete lymphoid organs/tissues			
	Lymph nodes		190 (95−380)
	Spleen		75 (70; 80)
	Peyer's patches		10 (6−20)
	Thymus		50 (25−100)
	Red bone marrow		50 (25−100)
	Tonsils		0.8 (0.2−2)
	Subtotal for discrete organs/tissues		**380 (290−540)**
Other lymphocyte-containing organs, tissues, or compartments			
	Blood		**10 (5−25)**
	Intestinal mucosa (lamina propria)		**90 (30−180)**
	Respiratory tract mucosa		
		Alveolar space	Not available
		Epithelium	Not available
		Interstitium	Not available
		Lung parenchyma	4−10
	Subtotal for Respiratory Mucosa		**30 (15−60)**
	Others		
		Lymph	0.4 (0.2−0.8)
		Skin	13 (6.5−26)
		Liver	6 (2; 10)
		Vermiform appendix	0.2 (0.1−0.4)
		Interstitial fluids of body cavity	Not available
		Cerebrospinal fluid	0.0006
		Residual soft tissue	20 (10−40)
	Subtotal for Others		**40 (22−72)**
Grand total			**570 (440−740)**

2.3 Distribution of B Cell Lymphocytes in the Body

Information on fractions of pools of lymphocytes in different compartments of the human body that are B cells was summarized by Westerman and Pabst [12], and was based solely on human data (Table 2). Numerous other studies and publications reporting fractions of lymphocytes that are B cells have been obtained and reviewed; the data collected from those studies has also been included, where applicable, and was used to define the uncertainty ranges.

Table 2. Estimated percentages of lymphocytes in human body compartments that are B lymphocytes

Compartments of the human lymphatic system		% B lymphocytes (range)
Discrete lymphoid organs/tissues		
Lymph nodes		20 (15−30)
Spleen		50 (20−60)
Peyer's patches		40 (25−55)
Thymus		0.55 (0.1−1)
Red bone marrow		50 (20−80)
Tonsils		50 (25−75)
Other lymphocyte-containing organs, tissues, or compartments		
Blood		25 (10−40)
Intestinal mucosa		
	Lamina propria	30 (15−45)
	Epithelium	1 (0.5−1.5)
Respiratory tract mucosa		
	Alveolar space	3 (1−5)
	Epithelium	<1
	Interstitium	Not available
	Lung parenchyma	15 (5−25)
	Lymph-afferent	5 (2.5−7.5)
	Lymph-efferent	10 (5−15)
	Skin	<1 (0.1−1)
	Liver	10 (5−15)
	Vermiform appendix	20 (15−30)
	Peritoneal fluid	5 (2.5−7.5)
	Cerebrospinal fluid	5 (2.5−7.5)
	Greater omentum	70 (35−100)
	Residual soft tissue	7.5 (5−10)

Our estimates of the inventories of B lymphocytes in compartments of the adult human body, expressed as percentages of the total number, are provided in Table 3. The organs or tissues with the largest inventories of B lymphocytes are the lymph nodes *in toto*, spleen, red bone marrow, and the intestinal mucosa. Although the lymphocyte pool in the thymus is comparable to that in red bone marrow, less than 1% are B lymphocytes. Similarly, the skin contains a significant number of lymphocytes (~10×10^9) but nearly all of them are T (or NK) cells [15]. Next in importance are the Peyer's patches, respiratory mucosa, peripheral blood, and residual soft tissue. Inventories of B cells in these sites are about an order of magnitude less than in the first four sites listed. Other sites have inventories that are two or more orders of magnitude less than the latter.

Table 3. Estimated distribution of B lymphocytes in compartments of the human body

Compartments of the human lymphatic system	% of total B lymphocytes in human body (95% C.I.)
Discrete lymphoid organs/tissues	
Lymph nodes	28 (15−45)
Spleen	23 (13−33)
Peyer's patches	3.1 (1.5−6.2)
Thymus	0.19 (0.04−0.50)
Red bone marrow	17 (8.0−32)
Tonsils	0.37 (0.08−0.87)
Other lymphocyte-containing organs, tissues, or compartments	
Blood	1.8 (0.64−4.5)
Intestinal mucosa	
Lamina propria	
Epithelium	
Subtotal: Intestinal Mucosa	19 (7.5−35)
Respiratory tract mucosa	
Alveolar space and epithelium	
Interstitium	
Lung parenchyma	
Subtotal: Respiratory Mucosa	2.9 (1.1−6.5)
Others	
Lymph	Included in residual
Skin	0.05 (0.01−0.12)
Liver	0.41 (0.16−0.81)
Vermiform appendix	0.03 (0.02−0.04)
Peritoneal fluid	
Cerebrospinal fluid	Included in residual
Greater omentum	
Residual soft tissue	1.0 (0.72−1.4)

2.4 Distribution of CLL Precursor Cells in the Body

At this time, several subsets of B cells are considered as possible candidates that could lead to the development of CLL. The inventories of potential CLL precursors could range from 0.5% (for circulating V-preB^{+}L^{+} B cells) to 30% (for memory cells or marginal zone B cells) of the inventories of B lymphocytes in individual body compartments. Given the wide range involved and the fact that expert opinion suggests that antigen-experienced/memory-like cells—and conceivably marginal zone B cells [15]—are the most likely candidates for the CLL precursor (15,16), a log-triangular distribution was used to represent the uncertainty in the percentage of CLL precursors in the inventory of B lymphocytes in any given compartment. That is, the calculations included in this report are based on a percentage of CLL precursors described as a log-triangular distribution with a minimum of 0.5%, and a mode and maximum of 30% of the inventories of B lymphocytes in any given compartment.

The application of this log-normal distribution relies on the assumption that the reported values for these types of B lymphocytes can be applied to *all* body compartments, even though quantitative data are available only for a limited number of compartments and the distribution of some types is clearly restricted. This approach was used because there was insufficient quantitative information to conduct a formal exercise to assign ranks and weights to the inventories and distributions of the types of B cells identified as the best candidates for potential CLL precursors, e.g., to establish a hierarchy of possibilities, as suggested by one of NIOSH's subject expert reviewers [15]. No information currently

exists on the magnitude of the individual weights that should be applied to inventories and distributions for potential precursors and the rankings suggested by different authors are often contradictory.

Using the log-triangular distribution discussed above, estimates were made of the percentages of total B-lymphocytes represented by potential precursors for CLL using the methods described above. As expected, the resulting estimates, provided in Table 4, have nearly the same central values as those for percentages of B lymphocytes in body compartments from which they were derived (Table 3), but with much wider credibility intervals, representing the additional uncertainty associated with our current lack of knowledge about the nature and distribution of potential CLL precursors.

One could argue that the distributions in Table 4 are a reasonable representation of the uncertainty in the fractional distributions of B-lymphocyte precursors for CLL, because they include both the uncertainties in the fraction of the B lymphocytes that could be CLL precursors and the uncertainties in the compartmental inventories of B lymphocytes as given in Table 3.

Table 4. Estimated percentage distribution of B-CLL precursors in compartments of the human body

Compartments of the human lymphatic system	**% of total B-CLL precursors in the human body**	
	Mean	(95% C.I.)
Lymph nodes	27.1	(2.7−65)
Spleen	23.0	(2.1−59)
Peyer's patches (small intestinal wall)	3.7	(0.24−14)
Thymus	0.24	(0.010−1.1)
Red bone marrow	18.5	(1.5−52)
Tonsils (extrathoracic airways)	0.45	(0.018−1.9)
Blood (spleen)	2.3	(0.12−8.7)
Intestinal Mucosa	19.4	(1.5−56)
Respiratory Mucosa	3.4	(0.20−13)
Skin	0.064	(0.002−0.27)
Liver	0.50	(0.028−1.9)
Vermiform appendix (lower large intestinal wall)	0.036	(0.002−0.14)
Residual soft tissue	1.3	(0.079−4.8)
TOTAL	**100.0**	

3.0 Application to Internal Radiation Dosimetry for CLL

To calculate the inventory-weighted dose to CLL precursors, estimates of radiation doses received by each lymphocyte-containing body compartment are multiplied by the estimated fraction of the total body inventory of potential precursors for CLL in that compartment. An total dose estimate covering all body compartments is obtained by summing the adjusted doses for all compartments. For internal exposures, this approach is specific for each radionuclide (and solubility class), and route of entry. This approach assumes that a single distribution for the fraction of B lymphocytes that are potential precursors for CLL can be applied to the B-lymphocyte inventories in all body compartments, even though quantitative data are available only for a limited number of compartments and some potential precursors are known to have restricted distributions.

A test case using this approach has been evaluated that estimates an average weighted dose resulting from inhalation of an insoluble form of plutonium-239. The lymphocyte-containing compartment receiving the highest dose from inhaled insoluble Pu-239 is the collection of thoracic lymph nodes. To perform the calculations, estimates of doses were obtained for each body compartment for unit intakes of plutonium-239 from the ICRP [17]. Plutonium is a reasonable choice because: 1) it is one of the radionuclides encountered in NIOSH's dose reconstruction program, and, 2) it has a long physical and biological half-life that accumulates preferentially in some body compartments, leading to non-uniform dose distributions. Because there is not a complete one-to-one correspondence between body compartments for which radiation doses are estimated and those for which there are estimates of inventories of CLL precursors, some interpolation was necessary. The information used in the calculation of radiation doses to CLL precursor cells is provided in Table 5.

Table 5. Information used in the calculation of radiation doses to CLL precursors based on unit intakes of inhaled insoluble plutonium-239

Compartments of the human lymphatic system (radiation doses assigned)	**% of total B-CLL precursors in the body (95% C.I.)**	**Dose to per unit intake Pu-239 (Sv/Bq)**
Lymph nodes	27.1 (2.7−65)	
Extrathoracic; fraction of nodes = 0.05−0.07		7.50E-05
Thoracic; fraction of nodes = 0.07−0.09		**8.20E-04**
Remainder; fraction of nodes = 0.84−0.88 (majority of residual soft tissues; see below)		2.90E-07
Spleen	23.0 (2.1−59)	2.90E-07
Peyer's patches (small intestinal wall)	3.7 (0.24−14)	2.90E-07
Thymus	0.24 (0.010−1.1)	2.90E-07
Red bone marrow	18.5 (1.5−52)	8.50E-06
Tonsils (extrathoracic airways)	0.45 (0.018−1.9)	4.20E-05
Blood (spleen)	2.3 (0.12−8.7)	2.90E-07
Intestinal Mucosa	19.4 (1.5−56)	
(small intestinal wall; fraction of mucosa = 0.8)		2.90E-07
(upper large intestinal wall; fraction of mucosa = 0.1)		3.00E-07
(lower large intestinal wall; fraction of mucosa = 0.1)		3.10E-07
Respiratory Mucosa	3.4 (0.20−13)	
(extrathoracic airways; fraction of mucosa <0.001)		4.20E-05
(lung; fraction of mucosa >0.999)		7.90E-05
Skin	0.064 (0.002−0.27)	2.90E-07
Liver	0.50 (0.028−1.9)	3.60E-05
Vermiform appendix (lower large intestinal wall)	0.036 (0.002−0.14)	3.10E-07
Residual soft tissue	1.3 (0.079−4.8)	
(adrenals, breast, esophagus, muscle, pancreas, thyroid, uterus, prostate; fraction of residual by mass = 0.98)		2.90E-07
(bladder wall; fraction of residual = 0.002)		2.90E-07
(kidneys; fraction of residual = 0.009)		7.30E-07
(ovaries; fraction of residual = 0.0003)		2.20E-06
(stomach wall; fraction of residual = 0.005)		2.90E-07
(testes; fraction of residual = 0.001)		2.30E-06

Multiplying each fractional compartmental distribution of B-lymphocyte precursors for CLL (with uncertainties) by the unit dose to that compartment and, where necessary, the fractional weights for

assigning the doses to sub-compartments just described, using Monte Carlo methods, and summing the results provides an integrated weighted estimate of unit dose for purposes of estimating the probability of causation of CLL from radiation exposure. This multiplication was repeated 2000 times for each Monte Carlo sample. Probability distributions for the inventory-weighted average doses obtained for the cases of Pu-239 inhalation are provided in Table 6.

Table 6. Estimated radiation doses relevant to risk assessment for chronic lymphocytic leukemia in adult workers, from unit intakes of inhaled insoluble plutonium-239

	Pu-239 50-y committed dose (Sv/Bq)					
	Percentiles of dose distribution estimated by Monte Carlo methods					
	2.5	5.0	50	Mean	95	97.5
CLL-precursor inventory-weighted average dose distribution	6.0E-06	7.5E-06	2.2E-05	2.4E-05	4.7E-05	5.1E-05

The Monte Carlo generated distribution of inventory-weighted average doses in Table 6 range from 6.0E-06 to 5.1E-05 over the 95% credibility interval. This distribution describes the uncertainty in the inventory-weighted average dose, and can be used to define a credibility range expected to contain the true but unknown dose. This probability distribution can be used as an input in any probabilistic risk assessment for CLL in adults exposed to radiation, reflecting the uncertainty in the distribution of CLL precursors in the body. Although this example calculated the committed dose to the various CLL precursor containing organs, the input to the NIOSH Interactive RadoEpidmiology Program requires the input of annual dose from the date of first exposure at a covered facility to the date of diagnosis. At the current time, models are being developed to perform these inventory-weighted dose calculations on an annual basis. Although somewhat more mathematically complex than using committed doses, the same principles discussed in this paper are applicable for calculations involving annual doses.

4.0 Summary and Conclusions

Current information indicates that CLL is produced by transformation of mature, antigen-experienced B lymphocytes, possibly memory cells, potentially anywhere in the body. This situation complicates an assessment of the risk of developing CLL of radiogenic origin because definition of an appropriate target organ or tissue is problematic because radiation doses from internally deposited radionuclides and also from some types of external exposures can be very different at different locations within the body. Thus, B cells at different sites could receive markedly different doses.

Because the state of knowledge of the distribution of various types of B cells in the body is incomplete, resolution of this problem is best addressed using a probabilistic solution. Namely, to be meaningful for assessment of the risk of developing radiogenic CLL, the radiation dose should be a weighted average based on both the dose to a given site and the probability that a B lymphocyte (more properly a B-cell precursor for CLL) will occupy that site.

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