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

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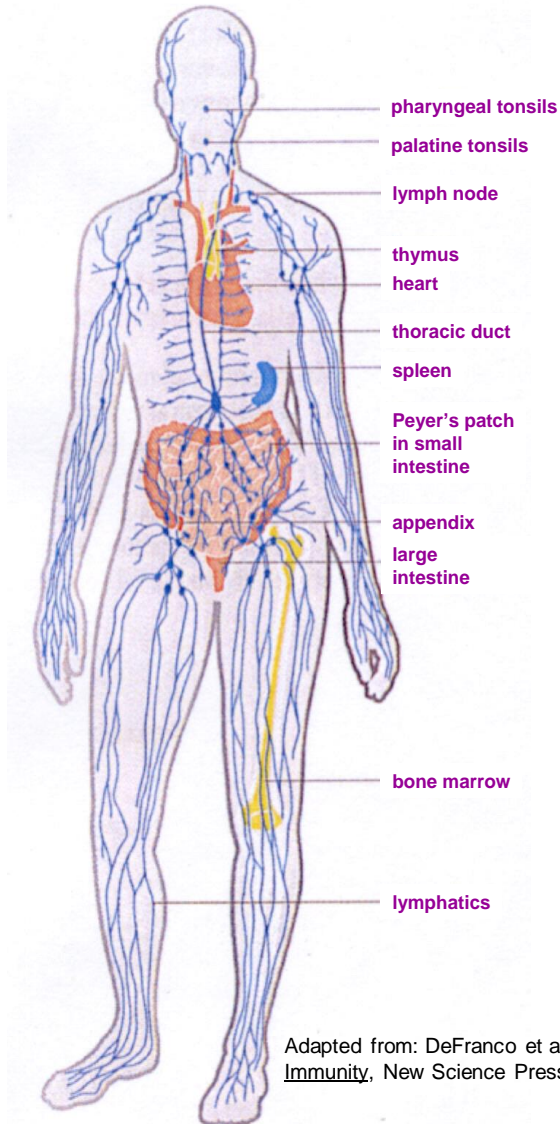[2]SENES Oak Ridge, Inc.

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Background

- **The U.S. National Institute for Occupational Safety and Health (NIOSH) reconstructs radiation doses for the U.S. Energy Employees Occupational Illness Compensation Program Act (EEOICPA)**

- **Doses are used by the U.S. Department of Labor to establish the probability of causation for a worker's cancer**

- **Original federal regulations governing the program excluded coverage for Chronic Lymphocytic Leukemia (CLL)**

- **Regulations have recently been amended to include CLL as a covered cancer**

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Background—cont.

- **Change in regulation required a dosimetric approach for target cells that result in CLL**

  - Not straightforward for the case of CLL
  - Is considered a form of non-Hodgkin's lymphoma
  - CLL precursor cells could reside in any lymphoid tissue of the body

- **Approach best suited for a probabilistic model**

  - Requires knowledge of the distribution, and associated uncertainty of CLL precursor cells in the lymphatic tissues of the body
  - Once distribution established can calculate weighted dose to the precursors

The Lymphoid Organs

pharyngeal tonsils
palatine tonsils
lymph node
thymus
heart
thoracic duct
spleen
Peyer's patch in small intestine
appendix
large intestine
bone marrow
lymphatics

Adapted from: DeFranco et al. (2007) Immunity, New Science Press Ltd.

Dose Reconstruction Methodology

- **CLL is a disease that originates from a population of mature (antigen stimulated) B lymphocytes**

- **Lymphocytes could undergo transformation to CLL clones anywhere in the hematopoietic or lymphatic system**

- **Dose reconstructions for non-homogeneous exposures (e.g., internal dose) must account for this**

- **NIOSH has developed a probabalistic approach based on the weighted average of the doses to the various irradiated sites**
  - **Specifically includes the uncertainty in the distributions of the target cells in the body**

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Establishing the Distribution of CLL Precursor Cells

- **Distribution derived in a stepwise fashion by establishing:**
  - The total number of lymphocytes of all types in the body (B, T, and NK cells);
  - The number of these cells in each compartment of the body;
  - The fraction in each compartment represented by B lymphocytes; and
  - The fraction of B lymphocytes that are potential B-CLL precursors
- **Relied on published literature values**
  - Required application of extrapolations, including Monte Carlo methods to evaluate uncertainties in the data
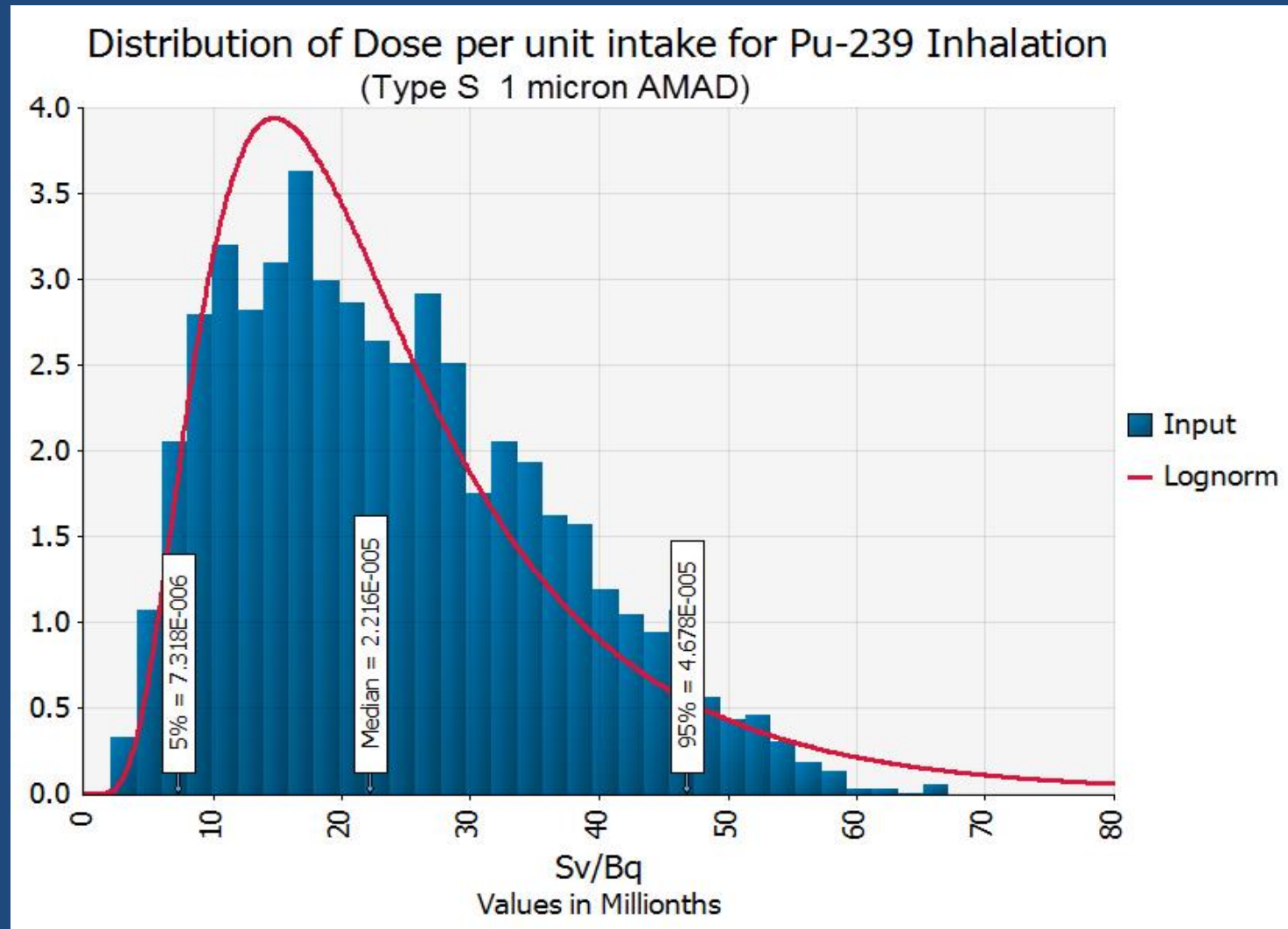
Distribution of Lymphocytes in the Body

Compartments of the human lymphatic system	% of total B-CLL precursors in human body Mean Value (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)

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Example Dose Calculation

Weighted dose components

Compartment	Fraction of all pre-CLL cells in this tissue [%]	Additional Fractions	Pu-239 Inh. doses per unit intake [Sv/Bq]	Pu-239 Inh. per unit intake [Sv/Bq]
Lymph Nodes	27.1			
Extrathoracic		0.06	7.50E-05	1.22E-06
Thoracic		0.08	8.20E-04	1.78E-05
Remainder		0.86	2.90E-07	6.76E-08
Spleen	23.0		2.90E-07	6.67E-08
Peyer's Patches	3.7		2.90E-07	1.07E-08
Thymus	0.24		2.90E-07	6.96E-10
Red bone marrow	18.5		8.50E-06	1.57E-06
Tonsils	0.45		4.20E-05	1.89E-07
Blood	2.3		2.90E-07	6.67E-09
Intestinal mucosa	19.4			
small intestinal wall		0.8	2.90E-07	4.50E-08
upper intestinal wall		0.1	3.00E-07	5.82E-09
lower large intestinal wall		0.1	3.10E-07	6.01E-09
Respiratory mucosa	3.4			
extrathoracic airways		0.001	4.20E-05	1.43E-09
lung		0.999	7.90E-05	2.68E-06
Skin	0.064		2.90E-07	1.86E-10
Liver	0.50		3.60E-05	1.80E-07
Vermiform appendix	0.036		3.10E-07	1.12E-10
Residual soft tissue	1.3			
adrenals, breast, esophagus, muscle, pancreas, thyroid, uterus, "remainder"		0.98	2.90E-07	3.69E-09
bladder wall		0.002	2.90E-07	7.54E-12
kidneys		0.009	7.30E-07	8.54E-11
ovaries		0.0003	2.20E-06	8.58E-12
stomach wall		0.005	2.90E-07	1.89E-11
testes		0.001	2.30E-06	2.99E-11

Example Calculation

Distribution of Dose per unit intake for Pu-239 Inhalation
(Type S 1 micron AMAD)

5% = 7.318E-006
Median = 2.216E-005
95% = 4.678E-005

Input
Lognorm

Sv/Bq
Values in Millionths

Summary

- **Dose reconstruction for some cancers of the lymphoid system requires consideration of the location of the precursor cells**

- **For CLL, the relevant dose is to antigen stimulated B lymphocytes**

- **Based on published values in the literature, the distribution of CLL precursor cells can be estimated**

- **Using Monte Carlo techniques, the distribution of doses to the target cells can be determined**

- **The distribution can be incorporated into a probability of causation calculation**

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Additional Information

Information on NIOSH's dose reconstruction and the Ineractive RadioEpidemiology Program (IREP) program can be found at:

http://www.cdc.gov/niosh/ocas

Disclaimer

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