Notice of Proposed Rulemaking to Include Chronic Lymphocytic Leukemia as a Covered Cancer under EEOICPA

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Background

- CLL is the only cancer assigned a probability of causation of zero under 42 CFR Part 81
- Rationale behind this decision was:
  - Unavailability of existing epidemiological studies to demonstrate a link between radiation exposure and CLL
  - Infeasibility of developing a quantitative risk model
- At the time of publication of the rule in 2002, NIOSH was committed to revisiting this decision as new scientific information became available

Summary of NIOSH Activities

- **Public meeting convened by NIOSH Office of Energy Research Programs**
  - **Participants determined that current evidence is inconclusive**
- **NIOSH polled subject matter experts regarding radiogenicity of CLL**
  - **Majority of reviewers supported the position that CLL should be considered radiogenic for compensation program purposes**
- **NIOSH conducts research into appropriate risk model for CLL**

Summary of NIOSH Activities—cont.

- NIOSH polls subject matter experts on the etiology of CLL
- NIOSH researches dosimetric target organ for CLL and develops approach to dose reconstruction
- Risk model and dose reconstruction approach completed
- Notice of proposed rulemaking published in the Federal Register

CLL Risk Model

- Conducted a comprehensive review of published papers on the epidemiological, molecular and clinical bases of CLL
- Compiled sex and age-specific incidence rates from the databases of the National Cancer Institute and the International Agency for Research on Cancer
- Critically evaluated epidemiologic data related to the issue of latency

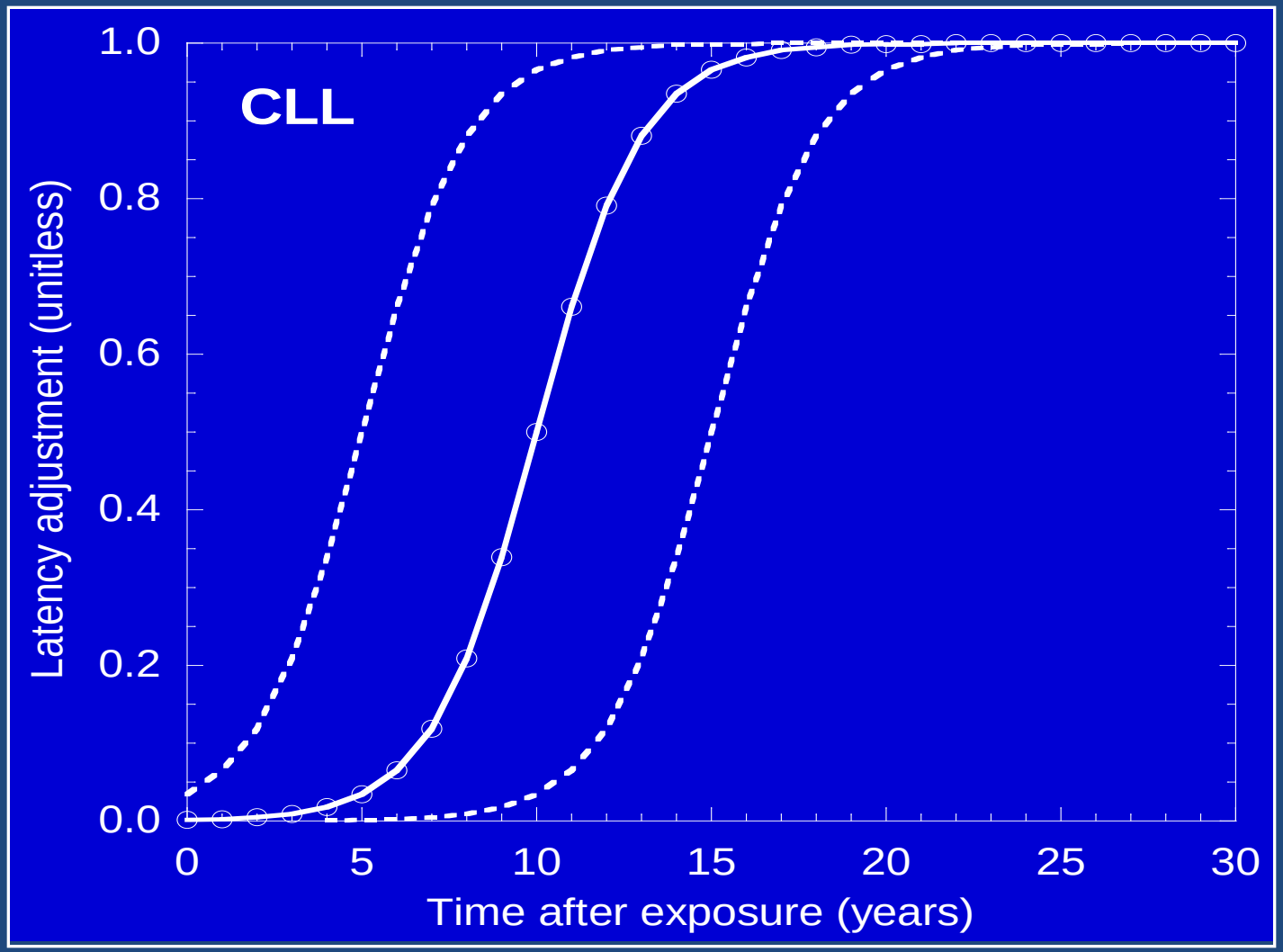
CLL Risk Model—cont.

- Used existing multiple myeloma and lymphoma model as a starting point
  - CLL is classified as a form of non-Hodgkin's lymphoma
- Draft model set the latency period as 15 ± 5 years
- As with other models risk is low at short latency periods and increases as a function of time

CLL Risk Model—cont.

- Draft model reviewed by four subject matter experts
- Comments were reviewed and adjustments made as appropriate
- Resulted in one major modification to the risk model
  - Revised model contains a shortened latency period of 10 ± 5 years

Latency Adjustment



Quantitative Evaluation of the Model

- Final model was quantitatively evaluated by calculating the probability of causation (PC) for certain exposure scenarios
  - Calculated for males between 20 and 40 years of age
  - Acutely exposed to 1 Sievert of high-energy gamma radiation
- Although analysis restricted to males, results should be similar for females
  - Same risk coefficient is used for both
- PC results greater than 50% for some cases

Results of Quantitative Evaluation

Age at exposure (y)	PC (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

Dose Reconstruction Methodology

- CLL is a disease that originates from a population of mature 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 proposes to use a probabalistic approach based on the weighted average of the doses to the various irradiated sites

Distribution of Lymphocytes in the Body

Compartments of the human lymphatic system	% of total B-CLL precursors in human body (95% C.I.)
Lymph nodes	27 (2.7−65)
Spleen	23 (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 (1.5−52)
Tonsils (extrathoracic airways)	0.45 (0.018−1.9)
Blood (spleen)	2.3 (0.12−8.7)
Intestinal Mucosa	19 (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)

Example Dose Calculation

Compartment	Fraction of all pre-CLL cells in this tissue [%]	Additional Fractions	Sr-90 ingestion doses per unit intake [Sv/Bq]	Weighted dose components: Sr-90 ingestion per unit intake [Sv/Bq]
Lymph Nodes	27			
Extrathoracic		0.06	6.6E-10	1.1E-11
Thoracic		0.08	6.6E-10	1.4E-11
Remainder		0.86	6.6E-10	1.5E-10
Spleen	27		6.6E-10	1.8E-10
Peyer's Patches	2.8		8.0E-10	2.3E-11
Thymus	0.19		6.6E-10	1.3E-12
Red bone marrow	17.7		1.8E-07	3.2E-08
Tonsils	0.28		6.6E-10	1.9E-12
Blood	1.77		6.6E-10	1.2E-11
Intestinal mucosa	19.2			
small intestinal wall		0.8	8.0E-10	1.2E-10
upper intestinal wall		0.1	1.3E-09	2.5E-11
lower large intestinal wall		0.1	1.8E-09	3.5E-11
Respiratory mucosa	2.93			
extrathoracic airways		0.001	6.6E-10	1.9E-14
lung		0.999	6.6E-10	1.9E-11
Skin	0.051		6.6E-10	3.3E-13
Liver	0.425		6.6E-10	2.8E-12
Vermiform appendix	0.028		1.8E-09	5.1E-13
Residual soft tissue	1.06			
adrenals, breast, esophagus, muscle, pancreas, thyroid, uterus, "remainder"		0.98	6.6E-10	6.9E-12
bladder wall		0.002	1.5E-09	3.2E-14
kidneys		0.009	6.6E-10	6.3E-14
ovaries		0.0003	6.6E-10	2.1E-15
stomach wall		0.005	9.0E-10	4.8E-14
testes		0.001	6.6E-10	7.0E-15
Total Dose				3.2E-08

Summary

- Proposed rule would rescind the designation of CLL as non-radiogenic
- New risk model would be added to allow for calculation of PC for CLL
- Dose reconstruction methodology would use a probabalistic approach to calculate the weighted average dose to the population of mature lymphocytes in the body

Additional Information

- Information used in NIOSH's decision process is located in Regulatory docket #209 at:

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

- Includes NPRM, subject matter reviews, responses to reviews, proposed risk model, and dose reconstruction approach
- Public comment period closes June 20, 2011