Report of

Public Meeting to Seek Input on Gaps in Chronic Lymphocytic Leukemia (CLL) Radiogenicity Research

Held July 21, 2004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

Report of
Public Meeting to Seek Input on Gaps in Chronic Lymphocytic Leukemia (CLL) Radiogenicity Research

Held July 21, 2004

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Acronyms and Abbreviations

ALC	absolute lymphocyte count
BCML	B-cell monoclonal lymphocytosis
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia
DDT	dichlorodiphenyltrichloroethane
DOE	U.S. Department of Energy
EEOICPA	Energy Employees Occupational Illness Compensation Program Act
ERR	excess relative risk
Hct	Hematocrit
HERB	Health-related Energy Research Branch
Hgb	Hemoglobin
IARC	International Agency for Research on Cancer
INEEL	Idaho National Engineering and Environmental Laboratory
LET	linear energy transfer
MBL	monoclonal B-cell lymphocytosis
MGUS	monoclonal gammopathy of unknown significance
MM	multiple myeloma
NCRP	National Council on Radiation Protection
NHL	non-Hodgkin's lymphoma
NIOSH	National Institute for Occupational Safety and Health
OERP	Occupational Energy Research Program
RBC	red blood cell count
RECA	Radiation Exposure Compensation Act
RR	relative risk
SMR	Standardized Mortality Ratio
Sv	Sievert
WBC	white blood cell count
WHO	World Health Organization

Background and Purpose

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world. While the etiology of CLL is largely unknown, it is currently the only cancer assigned a probability of causation by ionizing radiation of zero under the US Energy Employees Occupational Illness Compensation Program Act (EEOICPA). In support of this decision many epidemiologic studies have shown no evidence of an association between external ionizing radiation and CLL. However, uncertainties remain, and recently new evidence was presented that suggest that this decision should be revisited (Richardson et al. 2005).

While the decision to treat CLL as non-radiogenic was based on a review of medically and occupationally exposed Western populations, additional studies may be informative.
In the appropriations language for fiscal year 2004, the U.S. Congress directed the National Institute for Occupational Safety and Health (NIOSH) to conduct epidemiologic research and other activities to "establish the scientific link between radiation exposure and the occurrence of chronic lymphocytic leukemia." To this end, a focus on CLL radiogenicity was added to existing research conducted under the NIOSH Occupational Energy Research Program (OERP).

On July 21, 2004, NIOSH conducted a 3-hour public meeting to: 1) discuss available research strategies for investigating the potential relationship between the incidence of CLL and worker exposures to ionizing radiation and 2) identify gaps in current research. The meeting was announced in the Federal Register on June 10, 2004. This document summarizes the meeting proceedings and provides an updated report of related research activities.

Expert Panelists: Six experts in epidemiologic and molecular CLL research were invited to provide opinions. The table below lists names and information about the panelists.

Panelist	Affiliation	Title	Research Interests
Glyn Caldwell, MD	University of Kentucky, College of Public Health	Professor	Infectious disease, cancer, environmental and radiation epidemiology
David Hoel, PhD	Medical University of South Carolina	Professor	Cancer epidemiology and risk assessment
Geoffrey Howe, PhD	Columbia University Mailman School of Public Health	Professor	Radiation and cancer; nutrition and cancer; methodological issues in epidemiology
Martha Linet, MD, MPH	National Cancer Institute (NCI)	Chief, Radiation Epidemiology Branch, Division of Epidemiology and Genetics	Radiation epidemiology, risk factors for leukemia
Gerald Marti, MD, PhD	Food and Drug Administration (FDA)	Section Chief, Laboratory of Stem Cell Biology; Division of Cellular and Gene Therapy; Office of Therapeutics Research and Review	Cytogenetic markers for chronic lymphocytic leukemia, risk factors for leukemia and other B-cell diseases
Lew Pepper, MD, MPH	Boston University School of Public Health	Professor	Environmental health, occupational medicine

Twenty-five people attended the meeting, including the six panel members, NIOSH and other federal staff, and the public. The meeting began with introductions of the panelists and all attendees, followed by a brief overview of the CLL literature and a focused discussion of research gaps and methods.

The meeting was not transcribed. What follows is a compilation of notes recorded at the meeting. Some panelist provided detailed written responses during the review of the proceedings. These instances are indicated by an asterisk (*) following the panelist's name.

I. Overview of Chronic Lymphocytic Leukemia – Mary Schubauer-Berigan, PhD, NIOSH

The presentation slides used by Dr. Schubauer-Berigan are provided in Appendix A. The following is a summary of information presented to the panel during her presentation.

A. Subtypes/Diagnosis

Leukemia subtypes include lymphoid, myeloid (aka myelogenous and granulocytic), monocytic, and others (specified and unspecified).

Lymphoid leukemia has additional subtypes, including acute lymphocytic (excluding acute exacerbation of chronic), chronic lymphocytic, subacute lymphocytic, and others.

Chronic lymphocytic leukemia is divided into two subtypes: B-lymphocyte, which is approximately 95% of cases, and T-lymphocyte. B-lymphocyte CLL is characterized by the accumulation of B-cells through impeded apoptosis. While CLL is primarily identified by the expression of the CD-5 cell surface receptor, inhibition of the p53 tumor suppressor protein can also be an indicator. CLL may have an inherited component.

CLL is routinely diagnosed as an elevated lymphocyte count in the complete blood count. The use of automated instrumentation and diagnostic algorithm greatly increase the pre-clinical diagnosis of CLL. If infections and autoimmune complications are recognized, increased treatment is necessary. Half of early-stage CLL progresses to advanced stage and death.

B. Prevalence and Incidence of CLL

The adult lifetime probability of developing any leukemia (white male age 20–95+) is 1.51%. By subtype, the probability of developing CLL = 0.56%, chronic myelogenous leukemia (CML) = 0.20%, acute lymphocytic leukemia (ALL) = 0.06%, and acute myelogenous leukemia (AML) = 0.46%.

In 2001, the U.S. prevalence of CLL cases (0–11 years post-diagnosis) was 58,574 cases. CLL is most common among white males. The prevalence for myeloid and monocytic leukemia was 33,017.

There is no clear secular trend for the incidence of CLL. CLL is especially low among Asians and Native Americans. The probability of having CLL increases greatly with age.

C. Etiology of CLL

The current epidemiologic evidence does not conclusively show a relationship between exposure to ionizing radiation and the development of CLL in medically, occupationally, or environmentally exposed populations.

The existing evidence has several limitations. Exposures of Japanese A-bomb survivors and U.S. workers are not comparable. A-bomb survivors primarily received acute, external exposures to radiations of low linear energy transfer (low LET), while U.S. workers have chronic, low and high LET exposures. Death certificate-based studies are not the best approach for the study of CLL given that leukemia subtypes are often not specified and CLL is usually a chronic illness not leading to death. Studies with primarily internal, high LET exposures are inconclusive.

The importance of other etiologic factors is unclear. Recently, a review panel determined that exposure to Agent Orange defoliant has shown some evidence of linkage to risk factors for non-Hodgkin's lymphoma and B-CLL [Institute of Medicine (IOM) of the National Academies 2003].

D. Current NIOSH studies

NIOSH has three ongoing CLL research studies.

- A multi-site leukemia case-control study of 257 cases and 1027 controls. Approximately 40 of the cases are CLL. Cases are identified according to the underlying cause of death. Exposure measurements include bone-marrow doses for gamma, x-ray, neutron, and plutonium. Some limited exposure data are also available for chemical exposures such as benzene and carbon tetrachloride.

- A cohort mortality study of the Idaho National Engineering and Environmental Laboratory (INEEL) workforce. This study includes 63,561 workers and over 10,000 deaths. Of the 73 underlying and non-underlying leukemia deaths among radiation-monitored workers, 21 were due to CLL.

- An analysis of risk for CLL among nuclear workers. NIOSH has contracted with the International Agency for Research on Cancer (IARC) to conduct this analysis as an add-on to a large, 15-country, 400,000-person cohort study of nuclear workers conducted by IARC. The CLL analysis and report will be completed following the report of the full study.

In addition, NIOSH is evaluating the literature to determine if a meta-analysis of existing studies of radiation-exposed populations is feasible. The meta-analysis would use published studies and possibly unpublished data, if available from the investigators.

E. Possibilities for Future Research

Epidemiologic Studies: Some possible study designs that warrant feasibility assessment include:

- additional epidemiologic analyses of occupational or radiotherapy cohorts
- exploring the inclusion of CLL cases recorded as non-underlying cause of death
- incidence studies
- DOE-wide exposure-based cohort studies involving internal exposures, including plutonium and uranium, and neutron exposures, to address major gaps in the epidemiologic knowledge with respect to CLL's associations with high-LET forms of radiation

Other research needs include:

- basic radiobiological research on CLL
- biomarkers (or other pre-clinical disease markers for CLL)
- other non-radiological etiologic studies to better understand risk factors for CLL

II. Discussion

Following the presentation, panelists provided comments on several topics. Time was allotted for comments from the public after panel discussion was completed on each discussion topic.

A. Epidemiologic Studies

The panelists discussed several prominent studies of radiation exposure such as the Japanese Atomic Bomb Survivor Lifespan study, commonly used for radiation risk analysis. Some of the discussion stems from studies described in the Annotated Bibliography (Appendix B), which was provided to panelists prior to the meeting.

G. Howe:

An important concern related to the Japanese Atomic Bomb Survivor Lifespan study is that CLL is rare in Asian populations, and there is a lack of defined CLL diagnostic criteria to identify a true CLL case.

G. Caldwell:

Studies of CLL and radiation are predominantly negative. There is considerable interest in finding a link between CLL and radiation. There is a need to study all cohorts individually and analyze CLL separately. Researchers should not consider the "case closed" on whether CLL is caused by radiation. Also, more incidence studies are needed.

D. Hoel:

There are a number of limitations with existing epidemiologic studies:

- CLL diagnostic problems with death certificate information
- A-bomb cohort – not started until 5 years out
- Ankylosing spondylitis studies are not conclusive. "Pre-leukemics selectively eliminated."

The Savannah River Site Study showed an increase in CLL with radiation exposure (W. E. Fayerweather, R. M. Hall, and M. E. Karns. Epidemiologic study of a possible link between occupational radiation exposure and respiratory cancer, prostate cancer, and leukemia in Savannah River Plant employees. Draft Westinghouse Savannah River Company report. February 7, 1991.)

Tumor registry studies do not show increases in CLL.

There is also the issue of internal emitters. General studies have not found increases from α-emitters on bone surfaces.

More radiobiological evidence is needed to understand plausibility. Researchers should consider studying B-CLL, non-Hodgkin's lymphoma (NHL), and multiple myeloma (MM) together as a group

L. Pepper:

Most investigations start with the common assumption that CLL is not radiogenic. This assumption affects the published literature. Intriguing issues were raised in the NIOSH literature review: blood versus lymph tissue as point of origin, and distinguishing CLL from non-CLL.

There is a predominant paradigm that CLL is a disease of aging. Questions include: What are the key issues related to aging in producing CLL? The timing of exposure may be a factor; it has not been adequately addressed for CLL and should be further explored.

Genetic susceptibility has not been adequately studied for CLL or most other cancers.

M. Linet*:

Initial descriptions of leukemia mortality and incidence were restricted to all forms of leukemia combined. Because death certificates and early population-based cancer registries often did not designate leukemia subtype, evaluation and comparison of long-term trends in leukemia occurrence across populations is restricted to total leukemia prior to 1980, and to major leukemia subtypes subsequently. The landmark French-American-British (FAB) classification (first proposed in 1976 for the acute leukemias and for the chronic B- and T-cell lymphoid leukemias in 1989) achieved international consensus on morphologic criteria. Subsequent efforts to incorporate developmental and functional aspects of hematopoiesis according to lineage as well as key aspects of pathogenesis, and cytogenetic and immunophenotypic characteristics in the 1990s culminated in the World Health Organization (WHO) classification of neoplastic and related hematopoietic and lymphoid tissue diseases in 2001. The WHO classification was incorporated in the third revision of the International Classification for Diseases in Oncology.

For decades, there were differences between North American and European expert hematopathologists on whether CLL was considered as a separate entity or part of a spectrum of well-differentiated forms of non-Hodgkin's lymphoma. CLL was not included as part of non-Hodgkin's lymphoma in the Working Formulation classification developed primarily by North American expert hematopathologists, but CLL and well-differentiated NHL were considered as a combined grouping in the Kiel classification employed by European expert hematopathologists. With the advent of the WHO classification, CLL is classified with the lymphomas as one of the peripheral lymphoproliferative diseases. Morphologically, CLL appears as a homogeneous disease of small lymphocytes, but the increasingly wide application of flow cytometry and molecular analysis reveals that CLL is not homogeneous, but can be classified into two major subtypes based on the pattern of immunoglobulin gene mutations of pre- and post-germinal center CLL. Several cytogenetic abnormalities have been described in CLL cases, with the commonest including interstitial deletions of 13q and trisomy 12 (both of which are most likely involved in tumor progression). Complex chromosomal abnormalities may arise along with disease progression.

In the past, there has been some disagreement among expert hematopathologists and hematologists about the CLL diagnostic criteria and in some instances the disagreement has likely led to the under-diagnosis of CLL. In addition, approximately 25% of CLL cases are identified in individuals with no specific symptoms attributable to CLL, but who are seeking treatment for other diseases.

Compared with other leukemia subtypes, CLL demonstrates the greatest amount of familial aggregation, but occurrence of multiple cases of CLL or other

lymphoproliferative malignancies in close family members only occur in a small percent of CLL cases.

CLL has not been found to be increased in populations with exposure to low- or high-LET forms of ionizing radiation, but the critical studies have been conducted in populations with low incidence of CLL (e.g., Japanese atomic bomb survivors or other Asians) or in populations that are too small to provide stable estimates of increased or decreased risk.

Little evidence has supported a relationship between CLL and benzene exposure. A few studies have described excesses of lymphocytic leukemia or CLL among petroleum industry workers (see Appendix B, Part V., CLL and Solvent Exposure), but no excess was found in other studies or in a leukemia subtype-specific analysis of 208,000 workers with potential exposure to benzene (Wong and Raabe 1995). Excess risks of lymphocytic leukemia were observed in large cohorts of rubber manufacturing workers in the United Kingdom in reports published in the mid-1970s and early 1980s. These were followed by more detailed investigations that linked solvent exposures with increased risks of lymphocytic leukemia based on small numbers of cases. More recent studies in rubber workers in the United Kingdom showed no excess CLL or lymphocytic leukemia, but an IARC committee reported a small increase in a detailed review of 12 cohort studies in 1998 (Kogevinas et al. 1998). Findings of excess lymphatic leukemia and lymphoma in three small Swedish cohorts were replicated in some, but not most subsequent studies. Early studies reporting excesses of leukemia and lymphoma in small cohorts were followed by inconsistent results for workers exposed to monomeric styrene and butadiene. A retrospective study of 40,683 European workers employed in the reinforced plastics industry revealed no excesses overall nor evidence of increasing risk with longer duration of exposure, but mortality from leukemia and lymphoma rose twofold 20 years after first exposure (Kogevinas et al. 1993).

Some studies have implicated farming and related exposures with elevated risks for CLL. Specific agricultural exposures linked with excess risk of CLL, generally in small studies or via self- or proxy-report within interviews include DDT, animal breeding, and employment in flour mills.

Among the difficulties in many epidemiologic studies of CLL is the difficulty of determining whether or not CLL is increased in mortality studies because death certificates often lack specificity of subtype in listing leukemia as an underlying cause of death. Hence, mortality studies could fail to identify excess risks for CLL, even if there is a causal association. There are similar problems with meta-analysis, including the rarity of CLL and changes over time or differences across populations in the classifications used for leukemias and lymphomas. An additional problem is the difficulty of combining cohort occupational studies focusing on incidence of CLL if a substantial proportion of CLL cases are identified from death certificates with incomplete specification of subtypes of leukemia or lymphoma rather than when the workers are still alive.

G. Howe:

The problem of diagnostic uncertainty among CLL cases was encountered while conducting a study of 100,000 Chernobyl clean-up workers in Ukraine (Dyagil et al. 2002; Gluzman et al. 2005). The study used an internal panel with much diagnostic disagreement on whether cases were NHL or CLL.

G. Marti:

There have been recommendations made to conduct a study of B-cell monoclonal lymphocytosis in CLL, but there is much uncertainty in its feasibility. Flow cytometry has been used with very small numbers of cases. A colleague, Robert Vogt of the Centers for Disease Control and Prevention (CDC), became interested in reported excesses of CLLs at Superfund sites, as they were beginning to see CD5+ B-cells in nearby residents. However, only 11 cases were observed, of whom 10 were from Superfund sites. They calculated an incidence of 0.7% among the exposed residents, which was much higher than expected.

M. Linet:

Accurate case attainment from death certificates and other sources has been a problem because of incomplete specification of leukemias according to subtype, or differences among expert hematopathologists from different countries. North American expert hematopathologists tend to consider CLL as an entity distinct from the NHL, while European expert hematopathologists generally used classifications that combined CLL and well-differentiated forms of NHL.

To correct problems of under ascertainment of CLL even in studies focusing on cancer incidence, it would have been necessary to review medical records for cohort members diagnosed with NHL, even in North American studies, to identify CLL cases designated as well-differentiated NHL cases.

G. Howe:

CLL research may use occupational cohorts, which may be the most feasible, but they lack power due to low numbers of cases. A large number of studies lack power. For example, the multi-national study of nuclear radiation workers (Cardis et al. 1995) is the largest CLL study. There were a total of 27 CLL cases; 1 CLL case was reported in the >100 millisievert (mSv) category. An occupational cohort of >400,000 may be required to yield a significant result for CLL.

M. Linet:

According to the annotated bibliography prepared by NIOSH-HERB (see Appendix B), most radiation epidemiologic studies have excluded CLL or not even reported risks for CLL in epidemiologic studies because many investigators assumed that “CLL is not radiogenic.”

D. Hoel:

Prevalence in medical radiological technologists has also suggested that CLL is non-radiogenic.

L. Pepper:

This common assumption affects published literature and potentially creates a publication bias; i.e., if they do conduct dose-response analysis for CLL, it is not reported. Researchers need to develop an appropriate statistical model for radiation-induced CLL.

G. Howe:

In large occupational studies, it is difficult to indicate the role of low dose rates of radiation exposure. Researchers cannot afford to dismiss high-dose studies and should include high-dose and low-dose cohorts in the study populations for CLL research. Such populations include Chernobyl, A-bomb, DOE workers, radiotherapy patients, ankylosing spondylitis patients, and Mayak workers. Researchers could conduct dosage studies to get more thorough results on dose rate effects.

In general, for leukemia, dose rate has not been much of a factor. Is dose rate multiplicative or additive, and is this relation independent of the different radiation energy levels?

D. Hoel:

Researchers need radiobiological evidence to determine the effect of α-emitters on bone and stem cells.

G. Howe:

Bone seekers like plutonium deposit on the surface of bones, but the effects of radiation are unknown. What is the fate of the bone marrow? Is the dose reaching the bone marrow?

A meta-analysis could be useful, especially if a sufficient number of cases and study results are available. However, a meta-analysis does not prove association and may not be a useful tool to make inferences. For CLL research, a meta-analysis is not the most practical methodology due to the rarity of the disease and inadequate identification of true CLL cases. Instead of conducting a meta-analysis, re-analyzing the data is suggested, i.e., doing a pooled analysis. This would require researchers to obtain original data sets from previous studies and reanalyze the individual data sets. (Researchers usually need to look at whether among-cohort heterogeneity exists to explain results.) A pooled analysis would require greater amounts of detailed epidemiologic data, cooperation from outside researchers, and additional money and time. One such example is a pooled analysis for the miners/radon study (Darby et al. 1995). This type of study would lead to a more precise risk estimate and greater statistical power.

David Richardson (public comment):

Most of the discussion has been driven by epidemiology. Limitations of the available epidemiologic research include statistical power. Is meta-analysis possible given the large number of studies with a very small number of cases? Many studies have no cases. Therefore, how can we talk about dose-response? Findings from low-dose studies are an example: we should look at the total number of cases and their distribution by dose category. For example, in the IARC 1995 study only one case was observed with a dose > 100 mSv (Cardis et al. 1995).

In CLL research, the use of an inappropriate lag period could lead to exposure misclassification. Many studies use a 0–2 year lag assumption. This lag period is more appropriate for acute forms of leukemia, not chronic forms. CLL is a slow-progressing disease with a protracted latent period. For CLL research, it is necessary to increase lag assumptions to avoid exposure misclassification. Question: What are the effects of age-at-exposure and time since exposure?

Richard Miller (public comment):

After submitting a claim for CLL, workers are receiving a letter explaining that there is a 0% probability that CLL is attributed to work-related exposures. The Radiation Exposure Compensation Act (RECA) and Energy Employees Occupational Illness Compensation Program Act (EEOICPA) specifically exclude CLL. Is it appropriate to exclude CLL from compensation? This exclusion of CLL raises very direct, meaningful policy implications on the radiogenicity of CLL. Question: How long will it take to complete CLL research? Is it possible to come up with an interim excess relative risk per sievert (ERR/Sv) coefficient that could be used for worker compensation? How long will it take before CLL claims will be considered eligible for compensation? Congressional mandate is in the beginning phase of requiring the inclusion of CLL in worker compensation.

B. Molecular Studies

G. Caldwell:

We must understand relationships with CLL subsets and multiple myeloma and NHL. Molecular studies are very important, but not a major function of NIOSH.

D. Hoel:

More molecular etiologic work is needed.

G. Howe:

Studying CLL on molecular/etiologic levels is important, but there are some doubts as to how fruitful molecular research is for CLL. Questions: The molecular approach may be informative but what questions can it answer? Is it biologically plausible that there is an association with radiation exposures? How can the pre-clinical markers be used to evaluate association between dose and disease? What is the biological plausibility of radiation as the cause for the deletions that are observed? What kind of molecular or

cellular markers exist? How strong is the link between genetic susceptibility and the development of CLL?

Keeping biological specimens/samples in exposed populations is important. Most useful would be a marker of genetic susceptibility present in a reasonable proportion of the population. Examples: Ataxia-telangiectasia heterozygotes constitute 1% of population. Are they more susceptible? Caution should be observed when considering the ultimate utility of molecular approaches.

G. Marti:

Molecular research could potentially identify a marker for genetic susceptibility and approximate its proportion in the population. CLL molecular research could also assist in defining the relations between CLL subsets, MM and NHL using 4–6 color flow cytometry. Molecular detection for the 13q14 deletion would also be useful.

L. Pepper:

In response to R. Miller's comments on policy implications, these studies will have a long path to completion. What can be done in the interim? It would be most useful to identify a marker for genetic susceptibility for CLL that is present in a percentage of the population, especially because elevated prevalence of biological markers has been identified in populations living near hazardous waste. If a marker for genetic susceptibility is identified, researchers could explore the gene-environment relation in CLL.

There is some interest in looking at individual gene loci. This has been proven very helpful in understanding beryllium sensitization.

M. Linet:

There is a problem of substantial under-diagnosis of CLL: about 25% of CLL cases are identified during routine examinations.

An international consortium of investigators is looking at risk factors in "loaded" families (i.e., with a high prevalence of CLL).

NCI is studying leukemia incidence and mortality in a cohort of U.S. radiologic technologists. Leukemia incidence and mortality are also being studied in Chinese and Japanese cohorts of radiologic technologists. The British radiologist studies have 100 years of follow-up. From early in the 20th century through the 1940s, there were mortality studies of U.S. radiologists, but follow-up stopped a few decades ago. Can epidemiologic investigations of U.S. radiologists be resuscitated?

G. Marti:

Diagnosis is usually a trivial matter: a count of > 5000 lymphocytes per microliter that persists for >30 days. Historically, diagnosis has required a bone marrow aspirate, but flow cytometry has replaced this. In patients who present with CLL, the physician can

always track back the complete blood count to extrapolate back a number of years (one patient was found whose lymphocyte doubling began at age 4). Earliest known reported case of CLL was in a 12-year-old child. It is suggested that investigations of patients whose disease incidence went back a number of years be performed. What kinds of molecular or cellular markers exist?

Flow cytometry and cluster analysis of a small number of cells has significant power. Researchers can now do single-cell polymerase chain reaction and count the number of identically sequenced B-cells. "Presence of light chain restriction," e.g., BCML aka MBL (monoclonal B-cell lymphocytosis) may be important. A need exists to identify a cohort of people who could be studied. In the Rawstron cohort (Rawstron et al. 2003), approximately 1 out of 3 BCML cases progressed to CLL; 2 out of 3 BCML cases stabilized or decreased. In the Superfund population, 12 BCML positives were found. Nine out of 12 need additional follow-up, 5 are dead of CLL, 4 are alive, and 1 BCML status decreased after retirement.

Will there be a genetic marker? A possible marker is 13q14 deletion, which is found in 55% of CLL patients. This would help identify molecular and cellular markers that potentially exist.

Unknown Name (public comment):

Target organs, other than bone marrow (thymus gland, lymphatic system, circulating lymphocytes), should be considered for study.

D. Richardson (public comment):

What is the biologic plausibility of radiation as cause of the deletions that are observed?

Brant Ulsh (public comment):

Molecular approach is great way to go, but what kinds of questions can it answer? "Is it plausible that there's an association?" This may not be sufficient for risk modeling.

How can these pre-clinical markers be used to evaluate the association between dose and disease? Some of these markers are very stable. What is the correlation between BCML (MBL) and CLL?

G. Marti:

An investigator in Leeds, England (Rawstron) has a cohort with two of three individuals having stable or decreased MBL cells. The other one of three did progress to disease. A blood donor population would be good potential cohort.

C. Animal Studies

G. Caldwell:
Animal models may not be the most useful tools for CLL epidemiological studies. CLL is not observed often in large animals. There is not a readily apparent counterpart to CLL in animals.

D. Hoel:
Hematopoietic cancers in animals do not relate directly to CLL. Vogel and others were working with Argonne National Laboratory data looking at neutron and gamma exposure in Sprague-Dawley rats (Vogel and Jordan 1960). Also, others were looking at beta and alpha exposures in the lung to evaluate relative biological effectiveness (Lafuma et al. 1989). Still, this doesn't relate to leukemia. A review of the National Council on Radiation Protection (NCRP) report on similarities between men and animals is suggested. There is also a large leukemia project at the University of Colorado, and one being done at UC Berkeley. Obtaining information from a number of radiobiologists may prove useful in understanding the relevance of animal studies in CLL research.

G. Marti:
No animal studies show evidence of radiation causing hematopoietic disease; hematopoietic cancers in animals do not directly relate to CLL. German Shepherd dogs do show high background levels of CLL. Mice are an excellent model for effects of aging on producing a lymphoma. The New Zealand mouse is a good model of CLL (it is a model of lymphoma rather than CLL). There may be possibilities of studying cell lines from CLL. These are quite rare, but might be useful.

G. Howe:
Animal models are not extremely helpful here. Hematology needs to be comparable, but we are very far from being able to do this. Can animal studies be used to elucidate mechanisms? These are not of much short-term use.

Richard Miller (public comment):
A more diverse group of panelists would encompass different views.

III. Additional Written Comments Received Following the July 21, 2004 Meeting

G. Marti:

(1) Re-analysis (pooled analysis) or meta-analysis remain good ideas. (2) Careful review of CLL patient medical records and their radiation exposure is needed. Researchers need to evaluate the number of potential records available and consider other factors such as sex, age of onset, family history, and other exposures. Complete blood count (CBC) metrics [white blood cell count (WBC), hemoglobin (Hgb), hematocrit (Hct), red blood cell count (RBC), absolute lymphocyte count (ALC), and platelets] that were collected prior to diagnosis could be plotted as a function of time in order to identify the first indications of CLL. The diagnosis could be questioned and any cytotometry or cytogenetic information on the patient evaluated. (3) As pointed out earlier, the best surrogate tumor marker is the flow cytometric multicolor detection of MBL, which is the cellular analogue of a monoclonal gammopathy of unknown

significance (MGUS). Researchers need to know the prevalence of this finding in the radiation exposed group. I would envision the following groups: blood donors over the age of forty years as controls; other occupational exposures; and radiation exposed group. Of course first degree relatives of wild type and familial CLL are examples of extreme positive controls. Ideally one would like to define a cohort of radiation exposed individuals to follow.

D. Richardson:

Numerous radiation epidemiologic studies include limited numbers of CLL cases so they may be unsuitable for meta-analysis or for pooled studies. Even fewer cases would have exposure records that confirm exposures to 5 rem or greater. Lags of one or two decades need to be analyzed due to the natural history of CLL. One panelist stated the logical fallacy of drawing conclusions about the radiogenicity of CLL from multiple low power epidemiologic studies. Dr. Howe made persuasive arguments for pooled analysis over meta-analysis so that multiple temporal factors could be tested. A two stage approach is recommended. First, determine if radiation exposure influences CLL incidence. Second, estimate the magnitude of the association. The first line of investigation could include molecular studies as well as epidemiology.

G. Caldwell:

The following suggestions are offered as potential improvements to CLL research:

- Expand the investigation of CLL within the radiation occupational cohorts and include other exposures in the analysis such as chemicals and non-ionizing radiation.

- Incidence studies would be more informative as could be studies of medical personnel who administer radiation therapies.

- Synergistic interactions could be evaluated. Studies could be conducted among workers exposed to chemicals such as benzene, toluene, xylene, carbon disulfide, carbon tetrachloride, trichloroethylene, perchloroethylene, plasticizers, individual pesticides and individual herbicides. Such studies could be conducted among farmers, furniture manufacturers, and petroleum workers. Multiple chemical exposures in these populations could be considered. Evaluate CLL risks associated with radiomimetic drugs and other cancer chemotherapy agents.

- Evaluate genetic and immunological influences on CLL incidence by following families with multiple cases and include those with NHL. Attempt to merge genetic and molecular studies with epidemiology, particularly B-cell abnormalities.

- Develop additional studies on CLL and immunological factors. Merge flow cytometry with epidemiologic analysis, refine the definition of CLL, refine the diagnostic criteria for CLL, and evaluate the links among CLL, NHL and MM.

- Complete the update of existing cohorts to examine the radiogenicity of CLL and conduct meta-analysis where feasible. Lower priority options are to conduct incidence studies as well as relationships between cosmic radiation and secondary cancers among CLL patients.

G. Caldwell:

The National Cancer Institute's Surveillance, Epidemiology, and End Results Program have collected incidence data as well as exposure data since the early 1970's. NIOSH should determine the feasibility of using that large database to further its CLL research. NIOSH should investigate the applicability of the radiation exposure data and other occupational exposure data that may be available in the database. These data may be matched to the current case entries in the occupational studies already underway and supported by NIOSH.

NIOSH should consider a combined study of all "lymphocytic" malignancies. Such a study would counter problems stemming from misdiagnosis and promote the collection of a larger pool of cases. There is some uncertainty in whether a study of both molecular biology and epidemiology falls under NIOSH's mandate.

IV. Action Items and Update

Based upon the discussions at the July 2004 meeting, NIOSH took actions toward some epidemiologic studies or analyses that could be informative.

A. Epidemiologic Studies

Despite the limitations of epidemiologic research in this area, panel members had several suggestions for future studies or analyses. Below are some activities undertaken by NIOSH that can address the radiogenicity of CLL.

i. Meta-Analysis

It was suggested that a meta-analysis or a pooled analysis of previously published CLL studies might be useful in evaluating the radiogenicity of CLL. Since the July 21, 2004 meeting, NIOSH researchers have investigated the feasibility of conducting a meta-analysis and found that it was not feasible. This decision is based on the following observations:

- There is a large amount of heterogeneity in exposures among the studies: occupational exposure (chronic low dose), medical exposure (acute dose), A-bomb (acute high dose), and internal versus external radiation.
- Much heterogeneity exists in the radiation-exposed populations available for study: occupational cohorts (healthy worker effect), medical cohorts (possible increased susceptibility, failure to control for chemotherapy, short follow-up due to short survival), A- bomb (low background incidence of CLL).
- The lack of reporting on CLL explicitly (many studies exclude CLL *a priori*, or report on leukemia and leukemia-CLL) left few non-overlapping study populations; this, coupled with differences among reporting measures did not

allow for synthesis of results (ERR, SMR, RR, categorical observed/expected ratio with trend test).
- Requests for data sets from other medical studies were largely unsuccessful.

Instead, a systematic review on the radiogenicity of CLL is currently underway. The review will focus on the available epidemiologic literature regarding the radiogenicity of CLL, derived from studies of medically exposed cohorts, as well as occupationally exposed populations. Results from the systematic review are anticipated to be published in a peer-reviewed journal in early 2006.

ii. Pooled Analysis

The IARC study, a 15-country, 400,000-person study of mortality among nuclear workers, has been underway for several years. The overall study findings were reported in June 2005 (http://www.cdc.gov/niosh/pdfs/IARCabstract2.pdf). The June 2005 publication did not provide specifics on CLL but NIOSH has commissioned the IARC researchers to conduct such a pooled analysis including dose-response analysis on the individual and combined U.S. cohorts from Hanford, Idaho National Engineering and Environmental Laboratory, and Oak Ridge National Laboratory. Consistent with the research gaps identified in the public meeting, various lags up to 20 years are being used. Uncertainties in the dose estimates will also be included in the full statistical model. We expect the publication to be completed and released in early 2006.

iii. CLL Research Studies

- INEEL Study
  This study includes 63,561 workers, and over 10,000 deaths. Of the 73 underlying and non-underlying leukemia deaths among radiation-monitored workers, 21 were due to CLL. This study was completed in 2005 (http://www.cdc.gov/niosh/docs/2005-131/pdfs/2005-131.pdf). No association was found between external radiation and CLL risk when all underlying and non-underlying causes of death were considered.

- Portsmouth Naval Shipyard Study
  This leukemia case-control study of the Portsmouth Naval Shipyard workers, conducted by NIOSH, included 115 leukemia cases, of which 14 were CLLs. Only 3 of the CLL cases received radiation exposure; their collective dose was only 50 mSv. Analysis of leukemia and leukemia excluding CLL showed no change is the odds ratio per 10 Sv upon exclusion of the CLL cases (http://www.cdc.gov/niosh/docs/2005-104/pdfs/2005-104.pdf).

- Multisite Leukemia Case-Control Study
  This NIOSH case-control study has gathered leukemia cases from six cohorts comprised of approximately 95,000 workers. Five of these cohorts are from the Department of Energy (DOE) complex and one from a naval shipyard. A total of 257 leukemia cases have been identified, which includes 43 known CLL cases.

NIOSH has accelerated efforts pertaining to CLL analyses to expedite communication of CLL results. The study is nearing completion and the results are anticipated in early 2006.

iv. Other Studies

- NIOSH will continue to evaluate the relationship between ionizing radiation exposures and CLL in radiation-exposed cohorts that are studied in the future.

- Based on funding and current work projections, the epidemiologic data system for radiation-exposed cohorts at NIOSH is anticipated to be fully functional and populated in about 2 years. This system provides a centralized data bank of epidemiologic data pertaining to occupational cohorts studied by NIOSH and others. The system will increase the efficiency of examining causes of death such as CLL across the DOE cohorts.

B. Molecular Studies

The cellular and molecular changes associated with the onset of CLL are being intensively investigated by research organizations around the world. Recent discoveries indicate that even B-cell CLL is likely not a single disease. For example, multiple B-cell genetic markers help differentiate familial and aggressive subtypes of the disease in tissues collected from CLL patients. Strategies for the analysis of the relationship between ionizing radiation and the genetic markers associated with CLL could follow several lines of investigation. The relationships among CLL subsets, MM, and NHL will be better understood when the underlying genetics and cellular markers for these diseases have been identified. Molecular research could also identify possible sources of genetic susceptibility for CLL and estimate its prevalence in populations. The specific locations on the gene where ionizing radiation may alter the structure and change genetic expression might also be identified. Stored tissue samples from CLL patients could be used to follow the time course of mutations and cellular expressions.

Although the line of inquiry could ultimately be informative, the course of the research would likely require many years to develop, as several experts commented. On the other hand, the epidemiologic studies such as the NIOSH multi-site study and the IARC multi-national study were very close to completion and thus received the earmarked resources needed for completion. NIOSH will continue its focus on epidemiologic research but will also examine ways to promote the continuation of molecular studies.

C. Animal Studies

None of the panel members considered current animal models to be a promising approach for elucidating the relationship between radiation and CLL. However, it is recognized that the panel expertise was not primarily in animal research.

V. Summary of NIOSH Focus

The CLL public meeting was very useful in assisting NIOSH to identify avenues of research to examine CLL radiogenicity. NIOSH will continue its focus on completion of epidemiologic projects to assess CLL radiogenicity. In concordance with the panel, NIOSH will pursue pooled analyses, with examination of alternate lag assumptions, in both the IARC-commissioned CLL analyses and the multi-site leukemia case-control study. The findings of these research activities should be available soon and will provide more information on the radiogenicity of CLL.

VI. Appendices

A. Overview of Chronic Lymphocytic Leukemia (Microsoft® Office PowerPoint® presentation)
B. Annotated bibliography

VII. References

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Appendix A
Overview of Chronic Lymphocytic Leukemia
(Microsoft® Office PowerPoint® presentation)

Overview of Chronic Lymphocytic Leukemia

Current knowledge and NIOSH research activities

National Institute for Occupational Safety and Health
Division of Surveillance, Hazard Evaluations, and Field Studies
Health-Related Energy Research Branch

October 2005

Chronic lymphocytic leukemia*

- Diagnosis:
  - Automated instrumentation & diagnostic algorithm greatly increased pre-clinical diagnosis of CLL
  - Now routinely diagnosed as elevated lymphocyte count in CBC
- Prognosis:
  - "Watchful waiting" given way to increased treatment as infectious & autoimmune complications recognized
  - Current estimates: 50% of early-stage CLL will progress to advanced stage & death

*Shanafelt et al. Mayo Clin Proc 2004; 79:388-398

Leukemia subtypes (ICD-9)

- Lymphoid
  - Acute lymphocytic (204.0); excludes acute exacerbation of chronic)
  - Chronic lymphocytic (204.1)
  - Subacute lymphocytic (204.2)
  - Other (204.9)
- Myeloid [aka myelogenous, granulocytic] (205)
- Monocytic (206)
- Other specified (207)
- Unspecified (208)

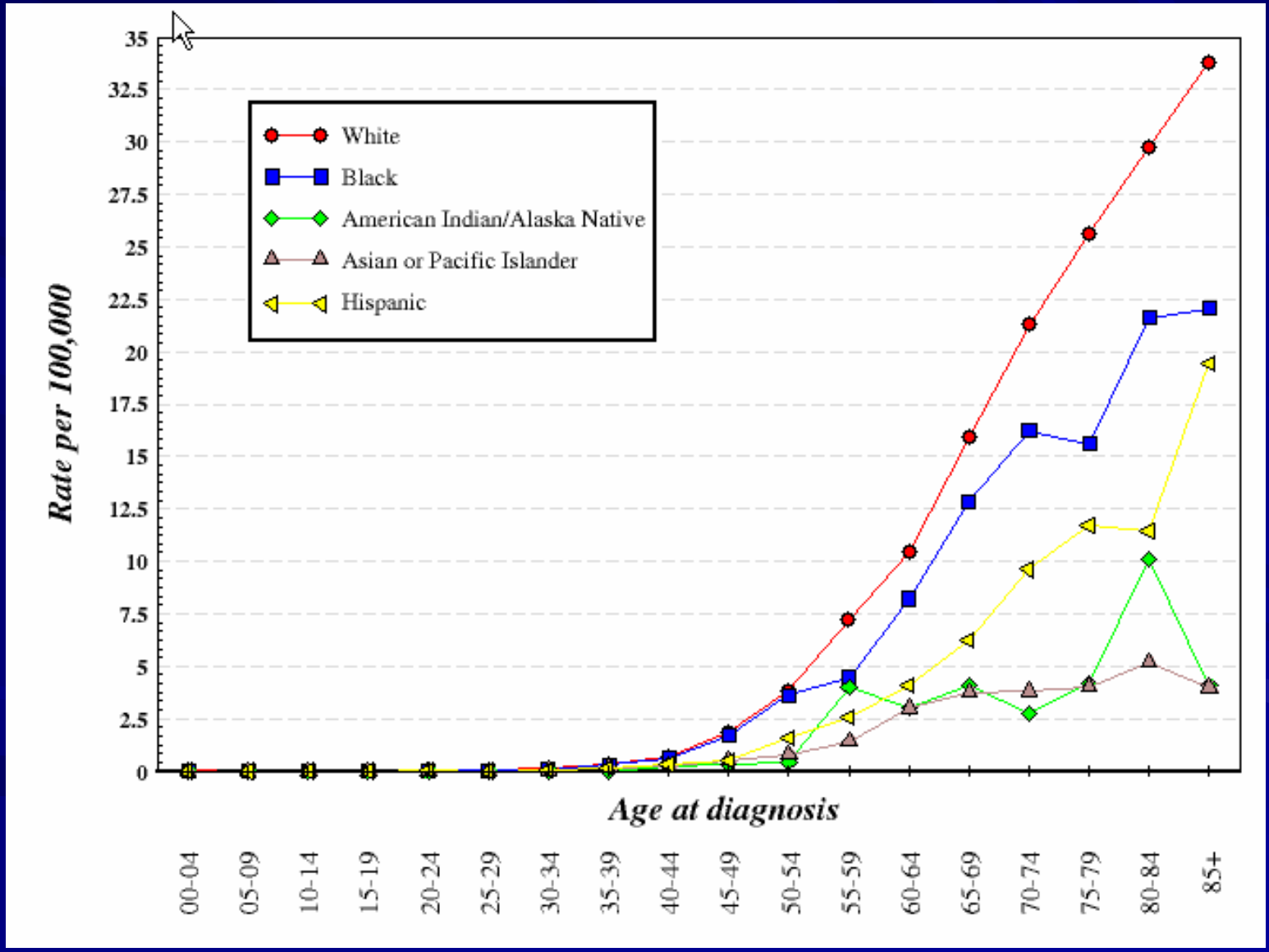
CLL subtypes

- B-lymphocyte CLL (approximately 95%)
  - Characterized by accumulation of B-cells through impeded apoptosis
  - Identified by expression of CD-5 cell surface receptor
  - p53 suppression also has been indicated;
  - susceptibility may have an inherited component
- T-lymphocyte CLL (5%)

Incidence & prevalence of CLL (SEER 2003)

- Prevalence:
  - In 2001, 58,574 cases in US (0-11 years post-diagnosis), compared to 33,017 for myeloid & monocytic
  - More common among whites, males
- Incidence:
  - No clear secular trends
  - Adult lifetime probability of developing any leukemia (WM age 20-95+) is 1.51%. By subtype:
    - CLL = 0.56%, ALL = 0.06%
    - CML= 0.20%, AML = 0.46%
  - Especially low among Asian- and Native-Americans
  - Increases greatly with age

Crude CLL incidence rates 1992-2001 (SEER 2003)



Etiology of CLL: epidemiologic evidence

- Ionizing radiation:
  - No medically-exposed, occupationally-exposed or environmentally-exposed populations have shown significantly increased risks of CLL
- Other exposures:
  - Some evidence of linkage to risk factors for non-Hodgkin's lymphoma; e.g., Agent Orange defoliant (IOM 2003, pp. 372-375)

Limitations of existing evidence

- Comparability of studied populations (e.g., Japanese A-bomb survivors) to U.S. workers
- Comparability of exposures (acute external low-LET) to U.S. workers
- Studies with primarily internal, high-LET exposure are inconclusive
- Limitations inherent in death certificate-based studies of CLL

Current NIOSH studies

- Multi-site Leukemia Case-Control Study (late 2005)
  - ~260 cases, >40 CLLs
  - Underlying cause of death only
  - Bone marrow doses for γ, x-ray, neutron & Pu
  - Adjustment for benzene & carbon tetrachloride
- Cohort mortality studies
  - Contract with IARC to estimate γ risk for CLL, including non-underlying causes (Nov. 2004)
  - INEEL cohort mortality study (21 cases; Sept 2004)

Current NIOSH studies, cont.

- Meta-analysis of existing radiation-exposed studies
  - Using published and unpublished data (depending on co-operation of other researchers)
  - Will conduct analysis separately for externally and internally-exposed populations

Possible future NIOSH studies

- Possible extramural research
- If merited, additional epidemiologic analysis of occupational or radiotherapy cohorts
- Inclusion of non-underlying cause of death or incidence studies
- DOE-wide exposure-based cohort studies
  - Internal exposures (e.g., Pu, U)
  - Neutron exposures

Other research needed

- Additional occupationally-exposed cohorts?
- Basic radiobiological research on CLL?
- Biomarkers (or other pre-clinical disease markers) for CLL?
- Other non-radiological etiologic studies?

Appendix B
Chronic Lymphocytic Leukemia
Annotated Bibliography
July 21, 2004

Preface

This annotated bibliography was compiled from the available scientific literature and presented at the Public Meeting to Seek Input on Gaps in Chronic Lymphocytic Leukemia (CLL) Radiogenicity Research held in Washington, DC on July 21, 2004. It is intended to inform interested parties on the types and breadth of research that has been conducted on the radiogenicity of CLL and some related issues. This bibliography should not be considered a complete review of all scientific research on these topics. Statements in this document should not be interpreted as official policy from the National Institute for Occupational Safety and Health and the Centers for Disease Control and Prevention.

Acronyms and Abbreviations

ABCC	Atomic Bomb Casualty Commission
ALL	acute lymphocytic leukemia
AML	acute myelogenous leukemia
AMPS	acute myeloproliferative syndrome
ANL/ANNL	acute non-lymphocytic leukemia
AT	ataxia telangiectasia
ATB	at the time of the (atomic) bomb
ATL	adult T-cell leukemia
ATM	ataxia telangiectasia mutated
BCML	B-cell monoclonal lymphocytosis
BCLL	B-cell chronic lymphocytic leukemia
BGD	benign gynecological disorders
BNHL	B-cell non-Hodgkin's lymphoma
BPLL	B-cell prolymphocytic leukemia
cCLLa	common chronic lymphocytic leukemia antigen
CGL	chronic granulocytic leukemia
cGy	centigray
CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia
DOE	Department of Energy
DS1986	dose system 1986
EAR	excess absolute risk
EBV	Epstein-Barr virus
EMF	electro-magnetic field
ERR	excess relative risk
EMC	essential mixed cryoglobulinemia
FAB	French-American-British (leukemia classification system)
Gy	gray (unit of radiation dose)
HARDTACK	nuclear test
HCL	hairy cell leukemia
HCV	hepatitis C virus
HLA	human leukocyte antigens
HTLV-1	human T-cell lymphotropic virus-1
HTLV-2	human T-cell lymphotropic virus-2
IARC	International Agency for Research on Cancer
ICD	International Classification of Disease
IL-4	interleukin-4
K25	DOE's Oak Ridge K25 facility
LET	low-energy transfer
LL	lymphocytic leukemia, lymphatic leukemia, lymphoblastic leukemia or lymphoid leukemia
LLNL	Lawrence Livermore National Laboratory
LOH	loss of heterozygosity
LPT	lymphocyte phenotype
LSS	Life Span Study
MGUS	monoclonal gammopathy of unknown significance

mGy	milligray
MHC	major histocompatibility complex
MM	multiple myeloma
mSv	millisievert
nCi	nanocurie
NHL	non-Hodgkin's lymphoma
NIOSH	National Institute for Occupational Safety and Health
NRPP	Nuclear Reactor Propulsion Program
O/E	ratio of observed to expected cases
ORNL	DOE's Oak Ridge National Laboratory (X-10)
OR	odds ratio
PCR	polymerase chain reaction
PHA	phytohemagglutinin
PL/PLL	prolymphocytic leukemia
PMR	proportionate mortality ratio
PNS	Portsmouth Naval Shipyard
PPBL	persistent polyclonal B-cell lymphocytosis
ppm	parts per million
PY	person years
PYR	person-years per rad
RA	rheumatoid arthritis
RB	retinoblastoma
RBE	relative biological effect
RES	reticulo-endothelial system
RR	relative risk
RT	radiation treatment or radiotherapy
SEER	Surveillance, Epidemiology, and End Results program
SES	socio-economic status
SIR	standardized incidence ratio
SL	small lymphocytic lymphoma
SMOKY	nuclear test in 1957 as part of operation PLUMBOB
SMR	standardized mortality ratio
SRR	standardized rate ratio
Sv	sievert
TBI	total body irradiation
TCLL	T-cell chronic lymphocytic leukemia
TPLL	T-cell prolymphocytic leukemia
UK	United Kingdom
UKAEA	United Kingdom Atomic Energy Authority
US	United States
USPHS	United States Public Health Service
μT	microtesla
WLM	working-level months
X-10	DOE's Oak Ridge X-10 facility
Y-12	DOE's Oak Ridge Y-10 facility

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I. Occupational Radiation Exposure

a. Ionizing Radiation

i. Nuclear Industry Workers

Muirhead CR, Goodill AA, Haylock RGE, et al. [1999]. Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers. J Radiol Prot *19*: 3-26.

This update of the cohort mortality study of the National Registry for Radiation Workers included 124,743 workers with follow-up through 1992. The unlagged standard mortality ratios (SMRs) for leukemia, leukemia excluding chronic lymphocytic leukemia (CLL), and non-Hodgkin's lymphoma (NHL) were 0.91 (95% CI=0.75-1.10), 0.94 (95% CI=0.75-1.15), and 1.00 (95% CI=0.81-1.21), respectively. Two year lags were employed for leukemia; the SMR for leukemia was 0.95 (95% CI=0.78-1.15) and the SMR for leukemia excluding CLL was 0.98 (95% CI=0.79-1.20). The SMR for NHL using a 10 year lag was 1.05 (95% CI=0.83-1.30). Internal analysis by dose level revealed borderline significant results for leukemia and leukemia excluding CLL, with p values of 0.18 and 0.061, respectively. There was no evidence of a positive trend for NHL (10 year lag). Estimated excess relative risks (ERR) per sievert (Sv) for leukemia, leukemia excluding CLL, and NHL were 1.20 (90% CI=-0.68-4.61), 2.55 (90% CI=-0.03-7.16), and 0.03 (90% CI=-1.33-3.06), respectively.

Dupree Ellis E, Watkins JP, Ingle JN, Phillips JA [1998]. External radiation exposure and mortality among a cohort of uranium processing workers: Final Report. Oak Ridge Associated Universities, Oak Ridge, TN. Unpublished. 26 pgs.

The mortality experience through 1993 of uranium processing workers employed at Mallinckrodt Chemical Works between 1942 and 1966 was evaluated in this study. Among this cohort of 2,514 workers, 13 cases of leukemia occurred, one of which was a CLL. This case of CLL was categorized in the 20-40 millisievert (mSv) cumulative external exposure group. Dose response analysis was performed, where the observed to expect (O/E) ratio was calculated for the following exposure categories, in mSv: 0-5, 5-10, 10-20, 20-40, 40-80, 80-160, and 160+. For leukemia, the ratios for the aforementioned categories were as follows: 3/4.05, 3/1.34, 1/2.79, 2/1.55, 0/0.71, 3/0.81, 0/0.75. For leukemia excluding CLL, the ratios were: 3/3.81, 3/1.25, 1/1.60, 1/1.39, 0/1.58, 3/0.70, 0/0.67. There was no evidence of a dose-response relation as the p values for the trend test were 0.74 and 0.79 for leukemia and leukemia excluding CLL, respectively.

Frome EL, Cragle DL, Watkins JP, et al [1997]. A mortality study of employees of the nuclear industry in Oak Ridge, Tennessee. Radiat Res 148: 64-80.

SMR analysis of this cohort of 106,020 Oak Ridge workers employed at least 30 days between 1943 and 1985 demonstrated a deficit of leukemia deaths compared to the United States (US) population, with the exception of non-white males, where the SMR was 1.11. No association was seen between leukemia deaths and radiation dose using a 2 year lag. No CLL specific results were presented. It was found that the leukemia mortality differed by Oak Ridge facility, "except for those born after 1930, leukemia mortality rates at X-10 were higher than those for US white males and higher than those for similar Y-12 and multiple-facility workers."

Fry SA, Dupree EA, Sipe DL, et al. [1996]. A study of the mortality and morbidity among persons occupationally exposed to ≥ 50 mSv in a year: Phase 1, mortality through 1984. Appl Occup Environ Hyg *11*:334-343, 1996.

A mortality analysis was conducted of white male workers, who were ever employed between 1943 and 1978 at Department of Energy (DOE) or US Navy's Nuclear Reactor Propulsion Program (NRPP) facilities, and who had at least one annual dose that exceeded 50 mSv. The SMR for leukemia, using the general US population as the comparison group, was below expectation, at 0.47 (95% CI=0.05-1.68). The categories including NHL demonstrated non-significant elevations; the SMR for lymphosarcoma was 2.26 (95% CI=0.72-5.27) and the SMR for other lymphatic cancers was 1.46 (95% CI=0.47-3.42).

Cardis E, Gilbert ES, Carpenter L, et al [1995]. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. Radiat Res *142*:117-132.

The International Agency for Research on Cancer (IARC) performed a multinational study of nuclear radiation workers, combining cohorts from the US, United Kingdom (UK) and Canada. The combined cohort included 95,673 workers contributing 2,124,526 person years at risk; the purpose of such a large study population was to increase power to detect differences in mortality and to increase the precision of risk estimates. There were 15,825 total deaths (16.5 % of the cohort), including 147 leukemia deaths, where 27 were from CLL. O/E deaths of CLL per dose category are as follows: 0-10 mSv: 12/13.7, 10-20 mSv: 4/4.0, 20-50 mSv: 6/4.4, 50-100 mSv: 4/2.2, 100-200 mSv: 1/1.5, 200-400 mSv: 0/0.9, 400+ mSv: 0/0.3, showing a non-significant negative trend of -0.74 (p=0.771). Using Poisson regression and controlling for age, sex, socio-economic status (SES), calendar time, and facility, the relative risk (RR) per Sv took the form $1+\beta z$, where z is the cumulative dose in Sv. A 2 year lag was employed for leukemia. For CLL, the ERR per Sv was estimated to be -0.95 (90% CI <0, 9.4). The RR of CLL comparing 100 mSv to 0 mSv was 0.91, indicating no increased risk of CLL as a result of radiation dose. Leukemia excluding CLL was significantly associated

with cumulative radiation, presenting a trend of 1.85 (p =0.046). Modeling demonstrated an RR of 1.22 comparing 100 mSv to 0 mSv. The authors note that as most of the workers in this cohort are still young, and only 16.5% have died, additional follow-up studies are needed to increase the precision in risk estimates.

Swift M [1995]. Cancer mortality and low doses of ionizing radiation. Lancet *345*:253.

In a comment to the Lancet regarding the IARC study, by Cardis et al. (1994), Swift points out that "leukemia is unique among radiogenic cancers in that the latency after exposure is typically 1-5 years. Almost all the excess risk of leukemia is dissipated within 5-10 years after that exposure. There is no reason to expect a cumulative effect on leukemia mortality from non-leukemogenic doses over several or many years. None was found."

Cardis E, Gilbert ES, Carpenter L, et al. [1994]. Direct estimates of cancer mortality due to low doses of ionizing radiation: an international study. Lancet *344*:1039-1043.

A combined analysis of seven cohorts from 3 countries was performed to assess leukemia risk resulting from radiation. The ERR per Sv for leukemia excluding CLL was 2.2 (90% CI=0.1-5.7). No estimates were given for all leukemia or for CLL separately.

Carpenter L, Higgins C, Douglas A, et al [1994]. Combined analysis of mortality in three United Kingdom nuclear industry workforces, 1946-1988. Radiat Res 138: 224-238.

A combined cohort mortality study was carried out on workers from the United Kingdom Atomic Energy Authority (UKAEA), Sellafield, and British Nuclear Fuels. Over 75,000 workers (40,761 monitored for radiation) were followed through 1988. The SMR analysis for leukemia revealed no excess in leukemia deaths in either group of workers, compared to the population of England and Wales. The rate ratio comparing monitored workers to non-monitored workers for all leukemia was 1.03 (95% CI=0.67-1.59), the point estimate for the rate ratio increased with exclusion of CLL cases (RR=1.20, 95% CI=0.73-1.97). According to the stratified analysis by dose level, there was evidence of increasing leukemia deaths with increasing dose level. This relationship strengthened with the exclusion of CLL cases. The ERR per Sv for leukemia excluding CLL, using a 2 year lag, was estimated to be 4.18 (95% CI=0.4-13.4). The SMR for NHL among monitored workers was 1.10, whereas the SMR for NHL for non-monitored workers was 0.76. The rate ratio for NHL for monitored workers relative to non-monitored workers was 1.37 (95% CI=0.81-2.31).

Douglas AJ, Omar RZ, Smith PG [1994]. Cancer mortality and morbidity among workers at the Sellafield plant of British Nuclear Fuels. Brit J Cancer 70: 1232-1243.

This cohort study of 14,282 Sellafield workers employed 1947-1975 included follow-up through 1988. SMR analyses were performed using the general population of England and Wales as the comparison group. The SMRs for leukemia for radiation and non-radiation workers were 0.81 and 0.30 ($p<0.05$), respectively. Leukemia and leukemia excluding CLL (there was only 1 observed case of CLL) did demonstrate evidence of positive trend which was significant at the 1% level, even after a 2 year lag was employed. The ERR estimate, per Sv, for leukemia excluding CLL (2 year lag) was 13.92 (90% CI=1.94-70.52). The SMR for NHL among the radiation workers was 1.07, whereas the SMR among the non-radiation workers was 0.44. Stratified analysis by dose level did not reveal evidence of increasing NHL mortality with increasing dose.

Fraser P, Carpenter L, Maconochie N, et al. [1993]. Cancer mortality and morbidity in employees of the United Kingdom Atomic Energy Authority, 1946-1986. Brit J Cancer *67*:615-624.

This mortality study update included additional follow-up of 34,869 employees of the UKAEA cohort. The UKAEA cohort consists of workers from weapons facilities in Harwell, London, Culham, Dounreay and Winfrith, in the UK. The SMRs, adjusting for age, sex, calendar period, establishment and social class, were calculated based on death rates in England and Wales. The SMRs for leukemia among radiation workers and non-radiation workers were 1.10 (31 observed deaths) and 1.30 (29 observed deaths). The rate ratio comparing radiation workers to non-radiation workers with 0 lag was 0.97 (95% CI=0.53-1.78) for leukemia and 1.11 (95% CI=0.56-2.20) for leukemia excluding CLL, respectively. With a 2 year lag, the rate ratios were estimated at 1.09 (95% CI=0.59-2.01) for leukemia and 1.28 (95% CI=0.65-2.53) for leukemia excluding CLL. For NHL, the SMRs among radiation workers and non-radiation workers were 1.35 (7 observed deaths) and 0.75 (11 observed deaths), respectively. The rate ratio for NHL comparing radiation workers to non-radiation workers was 1.57 (95% CI=0.71-3.50) for a 0 lag and 1.74 (95% CI=0.80-3.79) for a 10 year lag. There was no evidence of a dose response relationship for radiation with leukemia or NHL. The ERR per Sv for leukemia, based on a 2 year lag, was -4.2 (95% CI=-5.7-2.6).

Gilbert ES, Omohundro E, Buchanan JA, Holter NA [1993]. Mortality of workers at the Hanford site: 1945-1986. Health Phys *64*:577-590.

This update of the Hanford cohort mortality study included 44,154 workers first employed at the site from 1944-1978 with follow-up through 1986. O/E estimates (expected deaths were calculated based on the experience of all workers in the study population, controlling for age, calendar year, gender, number of years monitored and SES), by dose category, did not indicate a radiation dose response

relationship with CLL. For the dose category 0-<10 mSv: O/E=6/5.6=1.07, 10-<50 mSv: O/E=1/2.1=0.48, 50-<100 mSv: O/E=2/0.6=3.33, no cases were observed in the highest two dose categories of 100-<200 mSv and over 200 mSv. The trend test statistic was -0.45 for a 2 year lag. For NHL the O/E ratios for the exposure levels defined above were 37/39.1, 17/13.7, 3/2.6, 1/1.8, and 1/1.8. The trend test statistic was -0.85 with a 10 year lag. Other analyses were performed to specifically examine leukemia risk, excluding CLL (2 year lag, ERR estimate=-1.1% (90% CI=<0-1.9%, 95% CI=<0-3.0%)).

Gilbert ES, Cragle DL, Wiggs LD [1993]. Updated analysis of combined mortality data for workers at the Hanford site, Oak Ridge National Laboratory, and Rocky Flats weapons plant. Radiat Res 136: 408-421.

An update of the 1989 cohort mortality study of Hanford, Oak Ridge National Laboratory (ORNL), and Rocky Flats workers, this study included additional years of follow-up. An internal stratified analysis by dose was conducted for specific cancers, adjusting for age, calendar year, sex, years monitored, and SES. For CLL the O/E ratios for the dose categories were: 8/9.1 (0-<10 mSv), 5/3.9 (10-<50 mSv), 2/1.0 (50-<100 mSv), 0/0.5 (100-<200 mSv), 0/0.3 (200-<400 mSv), and 0/0.1 (400+ mSv); the trend test statistic was negative and non-significant (-0.37). The ratios for leukemia excluding CLL, using the aforementioned dose categories, were 41/41.0, 20/17.6, 1/3.5, 3/2.5, 1/2.0, and 1/0.5; the test statistic for the trend test was non-significant at 0.47. The results for the NHL-specific analysis were as follows for the same dose categories: 44/47.4, 22/16.9, 3/3.3, 2/2.3, 1/1.7, and 0/0.4, with a non-significant test statistic of -0.90. The combined ERR estimate per Sv for leukemia excluding CLL was -1.0 (90%CI=<0-2.2). No ERR estimate was reported for CLL.

Gribbin MA, Weeks JL, Howe GR [1993]. Cancer mortality (1956-1985) among male employees of Atomic Energy of Canada limited with respect to occupational exposure to external low-linear-energy-transfer ionizing radiation. Radiat Res 133: 375-380.

Workers in the Canadian nuclear industry were studied to assess the relationship between external radiation and mortality. Of the 8,977 workers studied, 227 developed cancer. The SMR for NHL, based on Canadian national rates, was 0.84 (95% CI=0.34-1.73). The SMRs for leukemia and leukemia excluding CLL were 0.60 (95% CI=0.22-1.30) and 0.45 (95% CI=0.12-1.16), respectively. SMRs by dose category were calculated, as was a corresponding test of trend. The p value for the test of trend for all leukemia was 0.11. This analysis was based only 6 total cases of leukemia (2 CLL). Excluding the 2 cases of CLL, both of which were unexposed to radiation, strengthened the observed positive trend between leukemia and increasing dose (p=0.058). Using a linear excess risk model and a 2 year lag, the excess relative risk % per 10 mSv for leukemia and leukemia excluding CLL were 7 (95% CI=-0.54-47.4) and 19 (95% CI=0.14-113), respectively.

Kendall GM, Muirhead CR, MacGibbon BH, et al. [1992]. Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers. BMJ 304: 220-225.

The National Registry for Radiation Workers was established in 1976 for British workers. This analysis included approximately 95,000 workers with a collective dose of 3,200 man Sv, followed through 12/31/1988. Sixty-two percent of the cohort accumulated a lifetime dose of less than 10 mSv, whereas only 9% had a dose greater than 100 mSv (approximately 50% of the latter worked at Sellafield). SMR analyses, adjusting for age, calendar year, and sex, were performed where the external comparison group was the general population of England and Wales. The SMR for leukemia was 0.87 (no lag) and 0.91 (2 year lag). SMRs were also calculated for leukemia excluding CLL, these SMRs were 0.88 (no lag) and 0.93 (2 year lag). Internal analyses were also executed to examine whether increasing dose was related to cancer mortality. For all leukemia (59 cases), the O/E estimates for each dose category were as follows: <10 mSv: 0.95 (O=24), 10-<20mSv: 0.87 (O=6), 20-<50 mSv: 0.89 (O=8), 50-<100 mSv: 0.96 (O=6), 100-<200 mSv: 1.30 (O=7), 200-<400 mSv: 1.06 (O=4), 400+ mSv: 1.63 (O=4). The p value for the one-tailed trend test was 0.10 and the ERR per Sv was estimated as 2.286 (90% CI=-0.322, 8.367). All leukemia excluding CLL was also analyzed with the following O/E ratios for the same dose categories listed above: 0.93 (O=20), 0.75 (O=4), 1.07 (O=7), 0.66 (O=3), 1.21 (O=5), 1.37 (O=4), and 1.97 (O=4). The one-tailed test of trend was determined to be significant, with a p value of 0.03. The ERR per Sv was 4.277 (95% CI=0.396, 13.58). The authors note as a limitation that the study could not control for internal radiation or chemical exposure.

Wiggs LD, Cox-DeVore CA, Wilkinson GS, et al [1991]. Mortality among workers exposed to external ionizing radiation at a nuclear facility in Ohio. Journal of Occupational Medicine *33*:632-637.

A retrospective cohort study was conducted to evaluate the mortality experience of workers at the Mound nuclear weapons facility. In this cohort of 4,182 white males ever employed between 1947 and 1979, 593 deaths occurred, yielding an overall SMR below expectation (SMR=0.89, 95% CI=0.82-0.97). SMRs for cause specific cancers were not significantly elevated. Internal analysis was also performed in order to further assess the role of radiation and cancer. This analysis was restricted to the 3,229 members of the cohort who were monitored for external ionizing radiation (mean cumulative dose=29.7 mSv, median dose=5.8 mSv). The overall SMR for this population was 0.79 (95%CI=0.70-0.88), consistent with a strong healthy worker effect. An elevated SMR was observed for leukemia among these workers, though it was not significant as it was based on only 4 cases (SMR=1.24, 95% CI=0.34-3.16). Maximum likelihood estimates of the rate ratio were generated comparing those with ≥ 10 mSv to those with an exposure of less than 10 mSv. The rate ratio for lymphatic leukemia (LL), using a 10 year lag, was 7.04 (0.20-191.71). Standard rate ratio (SRR) analyses, breaking dose into 3 categories, were also performed. For LL, the SRR for the highest dose category (>50 mSv)

compared to the referent category (<10 mSv) was 31.65 (95% CI=1.98-506.35). The SRR analysis also indicated a significant positive trend; however, the analysis was based on only 2 LL cases. Of the 2 lymphatic cases, at least 1 was a CLL. This case occurred in the highest exposure category of >50 mSv.

Wilkinson GS, Dreyer NA [1991]. Leukemia among nuclear workers with protracted exposure to low-dose ionizing radiation. Epidemiology *2*:305-309.

A pooled analysis was performed to calculate an overall RR for leukemia for nuclear workers, using data from seven published studies. The pooled RR comparing workers exposed to >10 mSv to workers exposed to <10 mSv, with an external adjustment for age and calendar time, was determined to be 1.5. RRs for workers exposed to 10-50 mSv and >50 mSv, compared to workers exposed to <10 mSv, were 1.8 and 1.2, respectively. No results by leukemia subtype were given.

Wing S, Shy CM, Wood JL, et al. [1991]. Mortality among workers at Oak Ridge National Laboratory. JAMA *265*:1397-1402.

Workers employed at ORNL from 1943-1972 were followed until 1984 to assess mortality trends. Of the 8,318 white male workers considered in the analysis, 1,524 were identified as decreased prior to 1984. The SMR, comparing mortality among ORNL workers to that of the US white male population, was significantly elevated for leukemia (SMR=1.63, 95% CI=1.08-2.35). The SMR was also significantly elevated for the subcohort of workers monitored for internal radiation, at 2.23 (95% CI=1.27-3.62). Lymphosarcoma and reticulosarcoma SMRs were above 1 for all workers and for the internally monitored workers, however the SMRs were not statistically significant. The category "other lymphatic", including International Classification of Disease (ICD)-8 codes 202 and 203, demonstrated deficits in all workers and in all internally monitored workers; the SMRs were 0.41 (95% CI=0.13-0.95) and 0.19 (95% CI=0.00-1.06), respectively. Modeling of the leukemia deaths (excluding CLL), adjusting for age, cohort, and age by cohort, gave a % increase per 10 mSv of 6.88 for a 5 year lag and 9.15 for a 10 year lag. "The standard errors were larger than the parameter estimates and the chi square values indicate that the linear term for radiation dose did not contribute to the goodness of fit of the model. Analyses repeated with chronic lymphocytic deaths that were excluded from the leukemia category showed similar results."

National Academy of Sciences/National Research Council (NAS/NRC) [1990]. Health Effects of Low Levels of Ionizing Radiation (BEIR V). National Academy Press, Washington, DC.

The model proposed by the BEIR V committee to predict leukemia risk from radiation dose was derived from leukemia data excluding CLL. The BEIR V report cites three major studies of radiation and leukemia where no excess of CLL was

observed: Preston et al. (1987) which found no excess of CLL in the LSS cohort of atomic bomb survivors, Darby et al. (1987) where only 2 cases of CLL arose in a cohort of 14,106 patients treated with x-ray for ankylosing spondylitis (2.38 expected), and Boice et al. (1987 and 1988) where among 30,000 women treated with fractionated doses of radiation for cervical cancer, no excess of CLL occurred.

Gilbert ES, Peterson GR, Buchanan JA [1989]. Mortality of workers at the Hanford site: 1945-1981. Health Phys *56*:11-25.

Gilbert et al. performed an update of the mortality experience of the Hanford workers to include additional years of follow-up. Again, no increased risk was seen for leukemia. The ERR of leukemia was estimated to be -2 per million person-years per 10 mSv (95% limits=-2, 8). A lagged analysis (2 years and 10 years) was conducted on the monitored workers. Observed and expected deaths ("expected deaths may be interpreted as the number of cases expected in the category if exposure to radiation were unrelated to the cause of death and should not be confused with expected deaths calculated from US mortality rates") were calculated by level of exposure and a trend test was performed. For CLL, 8 deaths occurred between 1955 and 1981, all of which occurred in the lowest exposure category of 0-19 mSv; this was slightly higher than the expected number of 6.7.

Gilbert ES, Fry SA, Wiggs LD, et al [1989]. Analyses of combined mortality data on workers at the Hanford site, Oak Ridge National Laboratory, and Rocky Flats nuclear weapons plant. Radiat Res *120*:19-35.

A combined mortality study examined cancer deaths among white male workers who were monitored for external radiation at Hanford, ORNL, and Rocky Flats. Data analysis by cumulative dose, lagged 2 years, demonstrated no significant excess in deaths from CLL (0-10 mSv: O/E=6/5.3, 10-50 mSv: O/E=3/2, 50-100 mSv: O/E=0/0.5, 100-200 mSv: O/E=0/0.3, >200 mSv: O/E=0/0.3). The combined (all-site) trend test statistic (-0.76) for CLL was non-significant, based on 9 cases. A positive, though non-significant, trend was seen at ORNL only. Lymphoma also showed no evidence of a dose relation (trend test statistic=-0.17, based on 49 cases).

Beral V, Fraser P, Carpenter L, et al [1988]. Mortality of employees of the Atomic Weapons Establishment: 1951-1982. BMJ *297*:757-770.

This cohort mortality study involved 22,522 workers ever employed at the atomic weapons establishments of Aldermaston, Fort Halstead, Orfordness, Foulness, and Woolrich Common from 1951-1982. Follow-up was completed through 1983. Of the 3,115 deaths occurring in this cohort, 865 were due to cancer. Among the radiation monitored workers, leukemia and NHL deaths amounted to 4 and 3, respectively. Stratified analysis by dose level was conducted, adjusting for age, sex, calendar period and social class. The expected numbers were based on rates in

all subjects with a radiation record. For leukemia, all 4 cases among radiation workers occurred in the <10 mSv category, yielding an O/E of 1.21. None of the 5 CLL cases that arose in the cohort occurred in radiation workers. The rate ratio for employees with a radiation record compared with other employees was 0.42 (95% CI=0.15-7.47) for leukemia and 0.53 for leukemia excluding CLL (p>0.05). For NHL, the O/E ratio (10 year lag) was 0.75 for workers with a dose <10 mSv and 5.55 for workers with a dose of 10-19 mSv. The rate ratio for NHL comparing monitored workers to non-monitored workers was 0.53 (95% CI=0.10-5.03) with no lag and 0.90 (95% CI=0.16-12.43) with a 10 year lag.

Checkoway H, Pearce N, Crawford-Brown DJ, Cragle DL [1988]. Radiation doses and cause-specific mortality among workers at a nuclear materials fabrication plant. Am J Epidemiol *127*:255-266.

The study included 6,781 Y-12 white male workers ever employed during the period 1947-1979. The SMR for leukemia, with a referent population of US white males, was lower than expectation (SMR=0.50, 95% CI=0.14-1.28, 4 observed cases). Leukemia subtypes were not specified. SMRs for the categories containing cases of NHL were 0.62 (95% CI=0.13-1.81) for lymphosarcoma (ICD-8 200) and 1.86 (95% CI=0.85-3.53) for other lymphatic cancers (ICD-8 202, 203, and 208). Dose response analyses for alpha and gamma radiation were performed for lung cancer only.

Cragle DL, McLain RW, Qualters JR, et al. [1988]. Mortality among workers at a nuclear fuels production facility. Am J Ind Med *14*:379-401.

Duration of employment was used as a proxy for exposure in this cohort mortality study of workers employed at the Savannah River Plant. The study population was restricted to white males employed at least 90 days between 1952 and 1974, yielding a cohort of 9,860 individuals. The cohort was followed for vital status until the end of 1980. SMRs were calculated for subcohorts stratified by SES (hourly, salaried, or combined) and employment period (pre-1955, post 1955). The SMRs, based on US population rates, for leukemia for hourly and salaried workers were 1.63 and 1.05, respectively. The SMRs for hourly workers employed before 1955, by duration of employment, were as follows: 1.24 (<5 years), 2.75 (5-15 years), and 1.57 (>15 years). The finding of an SMR of 2.75 for the workers employed 5-15 years was significant at the 5% level. There were 4 cases of CLL among the 13 leukemias observed in hourly employees. (Note: the year of death, age of death, length of employment, cumulative dose, and ever exposure to internal radiation were presented in tabular format for each salaried leukemia case.)

Reynolds P, Austin DF [1985]. Cancer incidence among employees of the Lawrence Livermore National Laboratory, 1969-1980. Western J Med *142*:214-218.

Cancer incidence was studied among workers of the Lawrence Livermore National Laboratory (LLNL), a high-energy physics research center in Alameda County, California. The cohort was restricted to employees aged 20-69 years, who resided in the San Francisco metropolitan area. The Resource for Cancer Epidemiology database was used to identify incident cancer cases. Cases were excluded if their cancer diagnosis was not concurrent with active employment at LLNL. Three leukemias (none of which were CLL) and 6 NHLs were observed among the male workers, yielding SMRs of 0.90 and 1.08, respectively, where the comparison group was the San Francisco metropolitan general population.

Gilbert ES [1983]. An evaluation of several methods for assessing the effects of occupational exposure to radiation. Biometrics *39*:161-171.

Power curves were generated from data on 15,375 Hanford radiation-monitored workers to evaluate the ability of different analytical methods to detect significant differences for the outcome of leukemia. The results are summarized as follows; "it is found that the introduction of an external control can increase power, although not when an overall adjustment factor must be estimated from the data or when death rates for the study population are substantially lower that those for the control population. It is also found that little power is lost if exposures are grouped. Finally the power calculations indicate, as expected, that in the analyses of occupationally exposed populations, such as the Hanford workers, there is very little chance of detecting radiation effects at the levels of our current estimates. However, power is reasonably good for detecting effects that are 10 to 15 times larger."

Tolley HD, Marks S, Buchanan JA, Gilbert ES [1983] A further update of the analysis of mortality of workers in a nuclear facility. Radiat Res *95*:211-213.

Tolley et al. report on the mortality experience of 15, 992 white male Hanford workers first employed before 1965 with follow-up for vital status through 1978. Trend analysis showed no evidence of a relation between "other leukemia" (ICD 204, 206, 207) and increasing cumulative radiation dose. There were only 5 cases of "other leukemia"; none of these cases was exposed to a cumulative radiation dose >2 rem. The distribution of leukemia subtype within this category is not given.

Rinsky RA, Zumwalde RD, Waxweiler RJ, et al. [1981] Cancer mortality at a naval nuclear shipyard. Lancet *8214*:231-235.

Rinsky et al. conducted a cohort mortality study of workers at the Portsmouth Naval Shipyard (PNS) to confirm the finding of a 5-fold increase in proportionate

mortality from leukemia among radiation workers at PNS, reported by Najarian et al. in 1978. The study population of the current study included 24,545 workers employed between 1952 and 1977. The cohort was further divided into subcohorts according to radiation monitoring status, where subcohort I included all exposed radiation workers (monitored workers with measurable dose reading), subcohort II consisted of non-radiation workers (not monitored), and subcohort III included unexposed radiation workers (workers who were monitored but had a 0 dose). The SMR for the full cohort, as standardized by the US white male population, was 0.94 (95% CI=0.67-1.28) for leukemia, based on 39 cases. The SMRs for leukemia by subcohort were 0.84 (95% CI=0.34-1.74) for subcohort I, 1.06 (95% CI=0.72-1.51) for subcohort 2, and 0.43 (no CI given, only 1 death observed, 2.3 expected). Internal SMR analyses were also conducted using subcohort II to derive the number of deaths expected to occur in subcohort I (radiation exposed workers). The SMR for subcohort I was 0.70 (non-significant), based on 7 leukemia deaths, of which 2 were characterized as "lymphatic". Further analysis of subcohort I stratifying by dose category did not reveal a dose response trend. In summary, the authors found no excess of leukemia in radiation exposed workers at PNS, contradicting the results found by Najarian et al. The authors do acknowledge that the internal comparison group used in their analysis (subcohort II) "did not account for the possible selection of particularly healthy individuals for radiation work." No analysis of subcohort I was presented using subcohort III, a cohort of individuals qualified for radiation work, as the internal comparison group.

Gilbert ES, Marks S [1979]. An analysis of the mortality of workers in a nuclear facility. Radiat Res *79*:122-148.

Unlike the prior studies of the Hanford facility, this study utilized data on both deceased and living workers in order to determine whether excess mortality occurred in this population due to radiation exposure. Workers hired after 1965 were excluded, leaving 20,842 white male employees who were followed until 4/1/1974. At Hanford, radiation exposure was primarily for whole-body, penetrating gamma radiation. In terms of internal radiation, only 450 plutonium deposition cases were documented. Since only 3 died of cancer (brain, buccal and lung), such radiation exposure was not further considered. An SMR analysis was conducted, stratifying on duration of employment. The SMR for leukemia was not elevated in either employment group (<2 years SMR=0.56, ≥ 2 years SMR=0.46). The SMR for lymphosarcoma and reticulosarcoma (ICD-8 200) was below expectation in the short term worker category (SMR=0.71), whereas among the longer term workers the SMR was 1.05. Other neoplasms of the lymphatic and hematopoietic tissue (ICD-8 202, 203, 208, and 209) showed an SMR for short term workers of 0.78 and an SMR for longer term workers of 1.18. Restricting SMR analysis to deaths occurring during or after 1965, in order to examine rates by leukemia subtype, did not reveal a significant excess of leukemia deaths for any subtype. The SMRs for LL were 0.42 among the short term workers and 0.29 among the long term workers. Only multiple myeloma (MM) showed a greater number of deaths than was expected, with SMRs for short term and long term

workers of 1.60 and 1.32, respectively. Additional analyses by dose for the group employed greater than 2 years showed no evidence of a trend by level of exposure, except for MM. With a 10 year lag, the trend for MM remained positive, and the p value for the test of trend by dose for lymphosarcoma and reticulum cell sarcoma was 0.15. Again, there was no evidence for an increasing risk of leukemia with increasing exposure level. This study did not find an excess of deaths due to myeloid leukemia, which was associated with radiation in several other studies, but did find evidence of radiation-induced MM. The authors offer a possible explanation that "chronic exposure to radiation manifests itself differently from acute exposure." The authors also caution the reader that the results for MM were based on small numbers.

Hutchinson GB, MacMahon B, Jablon S, Land CE [1979]. Review of report by Mancuso, Stewart and Kneale of radiation exposure to Hanford workers. Health Phys *37*:207-220.

Hutchinson et al. performed new proportionate mortality ratio (PMR) analyses standardized by age and year, for the Mancuso data on 24,939 male Hanford facility workers employed between 1943 and 1971 and followed until 1972. PMRs were presented by dose interval, with a test of trend. For haemopoietic and lymphopoietic cancers (ICD 200-209), the PMRs were as follows: 0.01-0.24 rads O/E=1.02, 0.25-0.64 rads O/E=1.16, 0.65-1.04 rads O/E=0.52, 1.05-4.04 rads O/E=0.72, 4.05-10.04 rads O/E=0.80, 10.05+ rads O/E=2.0. For lymphomas, (same dose categories as above) the PMRs were 0.67, 1.32, 0.59, 1.41, 1.43, and NA (0 observed cases). Exposed LL cases existed in only the first two dose categories, with PMRs of 1.43 and 2, respectively. The cumulative dose of the 2 exposed LLs was 0.29 rads and the cumulative dose including the unexposed case of lymphatic leukemia was 0.19 rads. Myeloma, in contrast to the aforementioned cancers, did present evidence of a significant trend. Based on this new analysis, Hutchison et al. states "there is no evidence of radiation relationship for lymphatic and haemopoietic cancers other than myeloma."

Anderson TW [1978]. Radiation exposures of Hanford workers: a critique of the Mancuso, Stewart and Kneale report. Health Phys *35*:743-750.

Anderson criticizes the SMR results contained in Mancuso et al. (1977) tables 4 and 17, which are not age-adjusted. Furthermore, he notes these SMRs were calculated using observed deaths classified in ICD-8, but expected deaths classified in ICD-7. As there were differences in ICD-7 and 8 for reticulo-endothelial system (RES) cancers, he notes this may have affected RES SMR results. Anderson presents age-adjusted excess deaths and compares these to excess deaths derived by Mancuso. For LL, the excess number of deaths, with age adjustment, was -4.6, whereas the Mancuso unadjusted number of excess deaths was -6.4. Lymphoma excess deaths decreased following age adjustment, from 6.3 excess deaths to -0.8 excess deaths. RES deaths decreased as well, from -6.8 to -9.0, after adjustment for age.

Mancuso TF, Stewart A, Kneale G [1977]. Radiation exposures of Hanford workers dying from cancers and other causes. Health Phys 33: 369-385.

The 3,250 pre1973 deaths occurring in white, male, Hanford workers were investigated in this study to examine the relation between radiation and cancer. In a case-control analysis, the mean radiation dose among cancer deaths (cases) was compared to the mean radiation dose among non-cancer cases (controls). The mean cumulative radiation dose for workers dying of cancer was 138 centirads (13.8 milligray (mGy)), whereas the mean cumulative radiation dose for workers dying of non-cancers was 99 centirads. The researchers also compared mean cumulative radiation dose by cancer type to the mean cumulative dose of all the deceased workers (107 centirads). Mean dose greater than 107 centirads was seen among those dying from myeloma (775 centirads), myeloid leukemia (122 centirads) and lymphomas (119 centirads). LL deaths and other RES neoplasms had cumulative mean doses less than 107 centirads, with doses of 19 and 12 centirads, respectively. The O/E ratio for LL, as derived from death rates among white males in the year 1960, was 0.32 based on 3 cases. This ratio is not age-adjusted. No further analyses of LL were performed; rather "all RES" analyses were conducted. Comparing deaths in the Hanford cohort to the expected number of deaths based death rates from the US white male population in 1960, an SMR of 1.58 was observed for RES. Comparisons of mean cumulative dose among RES deaths compared to non-cancer deaths, stratified by pre-death interval, though not age-adjusted, showed significantly higher mean cumulative doses from 0-18 years before death. No difference in dose, by pre-death interval, was found among the non-cancer group. The authors also performed calculations to estimate the doubling dose, or the dose needed to double the normal risk of dying from any form of cancer, for cancer and RES. These doubling doses were determined to be 12.2 and 2.5 rads, respectively, which the researchers note are lower than estimates based on atomic bomb data. Another analysis was performed by age to identify any significant difference in cumulative mean dose among RES cancers compared to non-cancers, by age group. Ages 55-71 among the RES group had a higher cumulative mean dose than non-cancers.

ii. Radiologic Technologists and Radiologists

Doody MM, Mandel JS, Lubin JH, Boice Jr JD [1998]. Mortality among United States radiologic technologists, 1926-1990. Cancer Cause Control *9*:67-75.

Radiologic workers certified for at least 2 years by the American Registry of Radiologic Technologists during 1926-1982 were followed until 1990 to assess excess mortality in this population. Unlike other studies to date, the majority of the cohort consisted of women (73%). The SMRs for leukemia and lymphosarcoma, based on age, sex, and calendar year adjusted US mortality rates, were 0.93 (95% CI=0.76-1.13) and 1.03 (95% CI=0.72-1.38), respectively. No significant trend was observed for leukemia by increasing number of years certified nor by calendar

year of certification. Of the 103 leukemia deaths observed in this cohort, 18 were due to CLL. Age, gender and calendar year adjusted RRs were calculated where the referent group was defined as radiologic technologists certified after 1940 for less than 10 years. For radiologic technologists certified after 1940, the RRs for the years certified categories of <10, 10-<20, 20-<30 and 30+ were as follows: 1.0 (referent) 0.5, 1.5, and 1.0. For workers certified before 1940, the RRs for the aforementioned categories were 5.0, NA, 2.5, and 3.0, respectively. No significant increase of CLL was found. The authors comment that the similar pattern observed for leukemia excluding CLL and CLL, "is noteworthy since CLL has never been linked to radiation in any study."

Yoshinaga S, Aoyama T, Yoshimoto Y, Sugahara T [1998]. Cancer mortality among radiological technologists in Japan: updated analysis of follow-up data from 1969-1993. Journal of Epidemiology *9*:61-72.

A study of 12,195 male Japanese radiological technologists born before 1951 was carried out to determine whether an increase of cancer deaths occurred in this population compared to the general Japanese population. The analysis also considered 2 subcohorts, workers born before 1934 (cohort 1) and workers born in 1934 or after (cohort 2), in order to account for the institution of the Radiation Hazard Prevention Act of 1958. It was thought that cohort 1 may have experienced greater exposure to radiation than cohort 2. Of the 20 leukemia deaths observed in the entire cohort, 14 occurred in cohort 1 (including 1 CLL death), and 6 leukemia deaths occurred in cohort 2. The SMRs for leukemia and lymphoma in the full cohort were 1.31 (95% CI=0.80-2.02) and 1.24 (95% CI=0.72-1.99), respectively. The SMRs for leukemia and lymphoma for cohort 1 were 1.55 (95% CI=0.85-2.60) and 1.48 (95% CI=0.83-2.44), respectively. For cohort 2 the SMR for leukemia was 0.95 (95% CI=0.35-2.08) and the SMR for lymphoma was 0.56 (95% CI=0.08-2.04). The SMRs for leukemia achieved significance when a comparison population of Japanese professional and technical workers was used to derive the expected number of leukemia deaths (age and calendar year adjusted). The SMR for cohort 1 was 1.82 (95% CI=1.00-3.06).

Wang J, Inskip PD, Boice JD, et al. [1990]. Cancer incidence among medical diagnostic x-ray workers in China, 1950-1985. Int J Cancer *45*:889-895.

To assess the relationship between diagnostic x-ray exposure and cancer risk, 27,011 x-ray workers in China were compared to 25,782 physicians without work-related x-ray exposure. The RR for lymphatic leukemia was found to be 4.3, which was significant at the 5% level (one-sided). This RR was based on 8 cases of LL, only 1 of which was of the CLL subtype. The study also found, for all leukemia, a difference in the RR for males and females; the RR for males was 3.0, whereas the RR for females was 1.1.

Smith PG, Doll R [1981]. Mortality from cancer and all causes among British radiologists. Brit J Radiol *54*:187-194.

Radiologists ever belonging to a British radiological society from 1897 to 1954 were studied to determine if excess cancer deaths occurred in this group compared to men of the same social class (social class 1) residing in England and Wales. Follow-up for mortality was completed though January 1, 1977. Within this cohort of 1,338 men, 8 leukemia deaths were identified, 3 of which were of the CLL subtype. SMR analysis (age and calendar year adjusted) was performed, stratifying by date of entry in the cohort (before or after 1921). Since radiation regulations were not imposed prior to1921, it was suspected that the group entering the cohort before 1921 had a greater exposure to radiation. The SMR for all leukemia for the pre1921 cohort, based on 4 cases, was 6.15 (one-sided $p<0.01$); one of these leukemia cases was a CLL (0.2 expected CLL cases). Where the date of entry in the cohort was after 1920, 4 additional leukemias were observed, 2 of which were of the CLL subtype (0.7 expected CLL cases). The O/E for CLL for the full cohort was 3.45 (3 observed CLL cases), which was almost significant at the 5% level ($p=0.06$).

Matanoski GM, Seltser R, Sartwell PE, et al [1975]. The current mortality rates of radiologists and other physician specialists: specific causes of death. Am J Epidemiol *101*:199-210.

Mortality patterns of members of the Radiological Society of North America during 1920-1969 were examined in this study. The SMRs for leukemia, stratified by date of entry into the society, were as follows: 1920-1929 (all ages) 3.01 ($p<0.05$), 1930-1939 (through age 74) 4.06 ($p<0.05$) and 1940-1949 (up to age 64) 0.58 ($p<0.05$). Expected values were derived from 1960 US white male mortality rates. The SMRs for the radiologists were higher than the SMRs observed for physicians of other specialties.

iii. Nuclear Test Workers

Dalager NA, Kang HK, Mahan CM [2000]. Cancer mortality among the highest exposed US atmospheric nuclear test participants. JOEM *42*:798-805.

This study assessed the effect of radiation exposure from nuclear fallout by comparing the mortality experience of 1,010 nuclear test participants exposed to $\geq$ 5 rem, to the mortality experience of the HARDTACK cohort, a group of nuclear test participants exposed to $\leq$ 0.25 rem. Cox regression yielded a leukemia RR, adjusted for age, rank at participation, and length of follow-up, of 1.51 (95% CI=0.23-9.69).

Bross ID, Bross NS [1987]. Do atomic veterans have excess cancer? New results correcting for the healthy soldier bias. Am J Epidemiol *126*:1042-1050.

A study in 1985 by Robinette et al. confirmed the finding of increased leukemia in the SMOKY cohort of nuclear test participants reported by Caldwell et al. (1980). Robinette et al. (1985) concluded, in their examination of 5 nuclear test series, that there was "no consistent or significant evidence for an increase in leukemia or other malignant disease in nuclear test participants." Bross and Bross (1987) critiqued the findings of Robinette, since their SMRs, calculated based on rates in U.S. white males, did not account for the "healthy soldier effect." Bross et al., reanalyzed the Robinette data, dividing the reported leukemia SMRs by a chosen "referent" SMR (cardiovascular disease among the lowest dose category) in order to alleviate the "healthy soldier effect". This methodology, coupled with the exclusion of the lymphatic cancer (4 cases of 24), led Bross and Bross to believe there was evidence of an excess of radiogenic cancers among these nuclear participants. No CLL results are reported.

Raman S, Dulberg CS, Spasoff RA, Scott T [1987]. Mortality among Canadian military personnel exposed to low-dose radiation. Candian Medical Association Journal *136*:1051-1056.

A study was executed to assess the relationship between radiation and cancer among Canadian military personnel exposed to nuclear tests. The mortality experience of 954 nuclear test participants was compared to the mortality experience of an unexposed cohort of military personnel. The referent population was compiled by selecting 2 unexposed, age-matched military controls per each exposed individual. One case of leukemia arose among the exposed group and 5 cases of leukemia arose among the controls (leukemia subtype not specified). The RR for leukemia was 0.40. A leukemia SMR was also calculated based on death rates for Canadian males. The SMR was below expectation at 0.68.

Caldwell GG, Kelley DB, Heath CW. [1980]. Leukemia among participants in military maneuvers at a nuclear bomb test site. JAMA *244*:1575-1578.

Nine of 3,224 men who participated in the SMOKY nuclear bomb test in Nevada held on August 8, 1957 have developed leukemia (4 acute myelogenous leukemia (AML), 3 chronic myelogenous leukemia (CML), 1 hairy cell leukemia (HCL), and 1 acute lymphocytic leukemia (ALL)). This was a significant excess of leukemia, as only 3.5 cases were expected to occur. No cases of CLL have yet been observed among these test participants; however, follow-up of the cohort has only reached 76% completion.

iv. Radionuclides, including Plutonium Exposure

Omar RZ, Barber JA, Smith PG [1999]. Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. Brit J Cancer *79*:1288-1301.

The 14,319 Sellafield workers ever employed between 1947 and 1976, and with known date of birth, were followed until 1993 to assess patterns of mortality in relation to internal (plutonium) and external radiation exposure. The SMRs for leukemia, comparing mortality rates among the Sellafield workers to mortality rates among the general population of England and Wales, were 0.71 for plutonium workers, 0.88 for other radiation workers, and 0.49 ($p<0.05$) for non-radiation workers. The SMRs for NHL were found to be 1.47 among the plutonium workers, 0.98 among other radiation workers, and 0.33 ($p<0.05$) among non-radiation workers. Rate ratios were derived from maximum likelihood estimates; the rate ratio for leukemia for plutonium workers compared to other radiation workers was 0.79 and the rate ratio for radiation workers compared to non-radiation workers was 1.27. The rate ratio for NHL for plutonium workers compared to other radiation workers was 1.39 and the rate ratio for NHL comparing radiation workers to non-radiation workers was 2.83. No confidence limits were given around these estimates. Trend analysis was conducted to determine if increasing radiation dose led to increased mortality. Unlagged analysis of leukemia by external dose did demonstrate a significant trend, as did leukemia excluding CLL. The observed positive trend between leukemia excluding CLL and radiation dose was still significant after a 2 year lag. There was no evidence of trend for leukemia or NHL by plutonium dose.

Carpenter LM, Higgins CD, Douglas AJ, et al [1998]. Cancer mortality in relation to monitoring for radionuclide exposure in three UK nuclear industry workforces. Brit J Cancer *78*:1224-1232.

The 40,761 employees who were monitored for external radiation were analyzed in terms of internal exposure to tritium, plutonium, or other radionuclides. For leukemia the SMRs for each group were below expectation, except for the group of workers not monitored for internal radiation, where the SMR was 1.17. Non-significant rate ratios below 1 were observed upon comparing the different groups of internally monitored workers to workers not monitored for internal dose. A trend analysis by cumulative dose was performed for workers ever monitored for internal radiation, as well as for workers never monitored for internal radiation. For leukemia excluding CLL the strength of association of the positive trend differed little between the two groups. Analysis of NHL revealed elevated SMRs for each internal exposure group. The rate ratios for NHL comparing workers monitored for internal radiation to workers not monitored for internal radiation were 1.90 (95% CI=0.74-4.30) for tritium, 1.48 (95% CI=0.76-2.83) for plutonium, and 0.90 (95% CI=0.43-1.81) for other radionuclides.

Voelz GL, Lawrence JNP, Johnson ER [1997]. Fifty years of plutonium exposure to the Manhattan project plutonium workers: an update. Health Phys *73*:611-619.

Twenty-six white male workers exposed to plutonium through work on the Manhattan Project have been evaluated periodically over the past 50 years to identify any health consequences resulting from their radiation exposure. As of 1994, 7 deaths have occurred among these workers; 18 deaths were expected to occur based on US rates. There have been no leukemia diagnoses in these workers.

Wiggs LD, Johnson ER, Cox-DeVore CA, Voelz GL [1994]. Mortality through 1990 among white male workers at the Los Alamos National Laboratory: considering exposures to plutonium and external ionizing radiation. Health Phys *67*:577-588.

Examination of the mortality of a cohort of 15,727 white male workers ever employed at Los Alamos National Laboratory from 1943-1977, and followed for vital status until 1990, revealed SMRs for leukemia, lymphosarcoma, and other lymphatic malignancies of 1.01, 0.94, and 0.77, respectively. The results of the dose response analysis for LL (4 cases, all CLL) were as follows: 0-9 mSv: RR=1.0 (3 cases), 100+ mSv: RR=4.00 (1 case); the trend statistic was 1.33. No cases were observed in the dose categories of 10-49.9 mSv and 50-99.9 mSv. This trend became significant (test statistic=1.73) when the dose response analysis was limited to non-plutonium workers, as none of the CLL cases were plutonium workers.

Wiggs LD, Cox-DeVore CA, Voelz GL [1991]. Mortality among workers monitored for ^{210}Po exposure: 1944-1972. Health Phys *61*:71-76.

The mortality experience of 2,181 workers monitored for polonium-210 at the Mound facility from 1944-1972 was evaluated in this study. Two cases of CLL were observed in this cohort, one of the cases had a polonium-210 dose < 10 mSv, whereas the other cases had an exposure >1000 mSv. Employing a 2 year lag, the RR for CLL comparing the risk in the highest exposure category (>1000 mSv) to the risk in the referent category (<10 mSv) was 2.55. This RR rose slightly to 2.58 using a 10 year lag.

Wilkinson GS, Tietjen GL, Wiggs LD, et al. [1987]. Mortality among plutonium and other radiation workers at a plutonium weapons facility. Am J Epidemiol *125*:231-250.

Plutonium workers at Rocky Flats were studied with respect to their mortality experience. Among the 5,413 white male workers employed at least 2 years, only 4 leukemia deaths occurred. The SMR for leukemia, where expected deaths were derived from US rates, was 0.75 (90% CI=0.26-1.71). Analysis was completed comparing risk of lymphopoietic cancer among those exposed to ≥ 2 nanocurie

(nCi) to those exposed to <2 nCi for various lag periods. Leukemia was not considered alone in the RR analysis for plutonium. For a lag period of 2 years, the RR for all lymphopoietic cancer (ICD 200-209) was 7.69 (90% CI=0.99-72.93). The 4 cases of plutonium exposed workers were due to reticulum cell sarcoma, NHL, MM, and myeloid leukemia. With a 5 year lag the RR increased to 9.86 (90% CI=1.26-94.03); a non-significant RR of 5.22 was observed when a lag of 10 years was employed. Analysis by external radiation exposure revealed no increase in risk of lymphopoietic cancer comparing those exposed to ≥1 rem to those exposed to <1 rem (RR=0.84, 90% CI=0.12-3.95). The RR for leukemia in the analysis of external radiation was 1.01 (90% CI=0.80-9.12)

Voelz GL, Hempelmann LH, Lawrence JNP, Moss WD [1979]. A 32-year medical follow-up of Manhattan Project plutonium workers. Health Phys *37*:445-485.

Twenty-six male workers exposed to high levels of plutonium were selected for medical follow-up. The workers had exposure to inhaled plutonium during 1944-1945, during their work for the Manhattan Project. For the follow-up period of 1975-1978, there were no cancer cases other than skin cancer. Medical surveillance revealed normal hematology.

v. Uranium

Ritz, B [1999]. Radiation exposure and cancer mortality in uranium processing workers. Epidemiology *10*:531-538.

A mortality study was conducted of 4,014 white male uranium workers employed during 1951-1989 at the Fernald plant in Ohio. The SMR for leukemia was 1.16 (95% CI=0.62-1.98), which included 1 case of CLL out of 38 total leukemia and aleukemia cases. Further analyses excluded CLL.

Roscoe RJ [1997]. An update of mortality from all causes among white uranium miners from the Colorado Plateau study group. Am J Ind Med *31*:211-222.

The study population of this cohort mortality study was derived from white male uranium miners who mined the Colorado Plateau for at least one month prior to 1964 and who also participated in the United States Public Health Service (USPHS) health surveys. The resultant 3,238 workers were followed until 1990 for vital status. It has been previously demonstrated that decay products of uranium are related to lung cancer, and associations between leukemia and NHL with radon have also been suggested. In this study, the SMR for leukemia and aleukemia (unlagged) was elevated, though not significantly (SMR=1.6, 95% CI=0.8-2.7). The SMR for NHL was below expectation at 0.8 (95% CI=0.3-1.7). SRR analysis revealed no evidence of trend with increasing exposure to radon progeny for neither leukemia nor NHL. Leukemia subtype was not specified.

Cragle DL, Watkins JP, Ingle JN, Robertson-Demers K, Tankersley WG, West CM [1995]. Mortality among a cohort of white male workers at a uranium processing plant: Fernald feed materials production center, 1951-1989. Oak Ridge, TN: Center for Epidemiologic Research, Oak Ridge Institute for Science and Education. Unpublished. 29 pg.

Cragle et al. studied 4,014 white male workers employed at the Fernald plant from 1951-1981. Workers were followed for vital status until 1989. Leukemia deaths were not in significant excess (SMR for salaried workers=1.59, 95% CI=0.51-3.71; SMR for hourly workers=1.07, 95% CI=0.48-2.11). There was no evidence of increasing risk for leukemia excluding CLL (test of trend statistic =0.04) or for CLL (test of trend statistic=0.02) with increasing cumulative internal radiation exposure. There were only two CLL deaths observed in this cohort; the two cases were assigned to the 20-40 mGy and the 40-80 mGy categories, respectively.

Darby SC, Whitley E, Howe GR, et al. [1995]. Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. J Natl Cancer I *87*:378-384.

Combination of data from 11 studies allowed for the examination of cancer mortality among 64,209 uranium miners. The O/E ratios for leukemia, leukemia excluding CLL, and NHL were as follows: 1.16, 1.11, and 0.80. O/Es were also calculated stratifying on time since first employment. Among workers whose time since first employment was less than 10 years, the O/E for leukemia was significantly elevated (1.93, 95% CI=1.19-2.95, based on 21 cases). The O/E for leukemia excluding CLL was increased, though not significantly (1.28, 95% CI=0.51-2.64, based on 7 cases). The SMR for NHL was below expectation at 0.81 (95% CI=0.30-1.77). For workers whose time since first employment was greater than 10 years, the O/E ratios for leukemia, leukemia excluding CLL, and NHL were 0.99, 1.08 and 0.79, respectively; these estimates were not significant at the 5% level. Analysis by cumulative radon exposure demonstrated no evident trend for increasing leukemia risk with increasing radon dose. For leukemia there were 14 cases (16.3 expected) in the lowest exposure category of <50 working-level months (WLM), 3 cases (2.4 expected) in the 50-<100 WLM category and 5 cases (2.8 expected) in the 100-<500 WLM category. There were no cases observed in the remaining 3 exposure categories (500-<1000 WLM, 1000-<1500 WLM, and 1500+ WLM). The distribution of cases of leukemia excluding CLL, by dose, was as follows: 5 cases (6.3 expected) in the lowest exposure group, and 2 cases (0.4 expected) in the 50-<100 WLM group.

Roscoe RJ, Deddens JA, Salvan A, Schnorr TM [1995]. Mortality among Navajo uranium miners. Am J Public Health *85*:535-540.

A retrospective cohort study of 757 Navajo uranium miners was undertaken to assess mortality in this cohort compared to non-whites in New Mexico and

Arizona. Eligibility criteria included mining the Colorado Plateau for at least one month prior to 1964 and participation in the USPHS health surveys. No excess of leukemia was observed in the study cohort, as there were no observed cases (SMR=0.0, 95% CI=0-2.8). The SMR for NHL was also below expectation (SMR=0.6, 95% CI=0.01-3.3).

Polednak AP, Frome EL [1981]. Mortality among men employed between 1943 and 1947 at a uranium-processing plant. JOM *23*:169-178.

In a cohort mortality study examining the relationship between uranium exposure and cancer, workers employed at the Oak RidgeY-12 facility from 1943-1947 were followed for vital status until 1974. SMRs for specific causes of death were calculated for these workers, where expected numbers were derived from age and calendar period adjusted death rates among US white males. With the exception of respiratory cancer, the cause-specific SMRs were all below expectation, indicating a healthy worker effect. The SMR for leukemia was 0.92, based on 40 cases (data on subtype not provided). SMRs for lymphosarcoma and other lymphatic malignancies were 0.67 and 0.57, respectively. Internal analysis was also performed, classifying workers by department: alpha and beta chemistry, all alpha and beta departments, electrical workers, and all other. The alpha and beta chemistry, all alpha beta departments, and electrical worker groups were thought to have exposure to uranium dust, whereas the "all other" group was considered unexposed. "SMRs" were calculated for each exposure group, where the expected numbers were derived from mortality rates in the "all other" category. The SMRs for leukemia by department subgroup were all below expectation.

vi. Cosmic Radiation

Gundestrup M, Storm HH [1999]. Radiation-induced acute myeloid leukaemia and other cancers in commercial jet cockpit crew: a population-based cohort study. Lancet *354*:2029-2031.

Risk of cancer from exposure to cosmic radiation among airline crews was investigated in this study. Cosmic radiation consists of neutron and gamma radiation; the dose received by flight crews is estimated to be 3-6 mSv/year. The dose of cosmic radiation received is dependent on flight hours, flight altitude and latitude, and solar activity. 3,877 individuals with Danish cock-pit crew licenses were identified for follow-up. The standardized incidence ratio (SIR) for CLL, using Denmark incidence rates, was 1.3 (95% CI=0-7.2) for jet crews, based on 1 case. There were no cases of CLL among non-jet crews. SIRs by flight hours showed that the CLL case occurred in the highest exposure category of $\geq$ 5,000 flight hours (SIR=1.3). Small numbers of cases limited the ability to detect any significant effect of cosmic radiation.

Band PR, Le ND, Fang R, et al. [1996]. Cohort study of Air Canada pilots: mortality, cancer incidence, and leukemia risk. Am J Epidemiol *143*:137-143.

In this cohort study, 2,740 Air Canada pilots, employed at least 1 year after 1950, were followed until 1992. SMRs and SIRs were calculated for leukemia, using mortality and incidence rates of the Canadian male population to obtain expected numbers. The SMR for all leukemia was below expectation (0.86, 3 cases), whereas the SMR for myeloid leukemia was higher than expected, at 1.32 (2 cases), though not significantly. SIRs for leukemia were elevated: the SIR for all leukemia was 1.65 (90% CI=0.86-2.88, 9 cases), the SIR for leukemia excluding CLL was 1.88 (90% CI=0.80-3.53, 7 cases), the SIR for CLL was 1.15 (90% CI=0.20-3.61, 2 cases), and the SIR for myeloid leukemia was 2.93 (90% CI=1.37-5.50, 7 cases).

b. Non-Ionizing Radiation

i. EMF

Floderus B, Persson T, Stenlund C, et al. [1993]. Occupational exposure to electromagnetic fields in relation to leukemia and brain tumors: a case-control study in Sweden. Cancer Cause Control 4: 465-476.

A case-control study design was used to evaluate the relationship between occupational exposure to electro-magnetic fields (EMF) and the outcomes of leukemia and brain cancer. Eligible cases and controls were chosen from the study base of all men who were ages 20-64, employed, and living in mid-Sweden, in the year 1980. From this cohort, cases of leukemia and brain cancer occurring between 1983 and 1987 were eligible for inclusion in the study. 850 such cases (250 leukemias, 112 CLL) were identified (using the Cancer Registry) and 2 controls per case were selected matching on age. A questionnaire to obtain data on work history, area of residence, smoking status, and exposure to benzene, ionizing radiation, and solvents, was administered to the study subjects. The workplace of the task held the longest during the 10 years prior to diagnosis of the case (primary exposure) was identified from the questionnaire, enabling the researchers directly measure the EMF of the identified workplaces with a dosimeter. EMF exposure was divided into quartiles in the analysis. The CLL risk increased with increasing EMF exposure upon comparing the referent quartile (Q1) to the exposed quartiles, though no test of trend was reported (Q2/Q1 odds ratio (OR)=1.1(95% CI=0.5-2.3), Q3/Q1 OR=2.2 (95% CI=1.1-4.3), Q4/Q1 OR=3.0 (95% CI=1.6-5.8), 90th percentile (P90) OR=3.7 (95 %CI=1.8-7.7)). By stratifying singly by the potential confounders, the authors concluded that "the results were not changed when controlling for the confounding factors considered."

Gilman PA, Ames RG, McCawley MA [1985[. Leukemia risk among US white male coal miners. J Occup Med *27*:669-671.

A case-control study was undertaken to assess the relationship between occupational EMF exposure and leukemia. Coal miners were studied, as this group works around high voltage power distribution lines, step-down transformers and converters, and electronic trolleys. Study subjects were identified from four National Institute for Occupational Safety and Health (NIOSH) cohorts of coal miners, where all subjects were deceased. Forty cases of leukemia were identified from this cohort; 4 controls (coal miners dying from a cause other than cancer or accident) were selected for each case, matching on birth year and age at death. A dichotomous exposure scheme was used, where greater than or equal to 25 years employment as a coal miner was considered exposed and less than 25 years employment as a coal miner was considered unexposed. A significant increase in leukemia risk was observed for all leukemia (OR=2.53). The OR for CLL was 6.33 ($p<0.05$) comparing long term coal mining workers to those with <25 years employment. Analysis by smoking status and analysis by pneumoconiosis revealed no significant difference in exposure between cases and controls, thus the authors concluded "the increased risk observed for 'all leukemia' cannot be related to cigarette smoking (OR=1.02 not significant) or to coal workers' pneumoconiosis (OR=0.15, not significant)." The researchers do acknowledge that exposure to chemicals, like benzene, could account for the observed increase in leukemia.

II. Environmental Radiation Exposure

a. Atomic Bomb Survivors

Little MP, Weiss HA, Boice Jr JD, et al. [1999]. Risks of leukemia in Japanese atomic bomb survivors, in women treated for cervical cancer, and in patients treated for ankylosing spondylitis. Radiat Res *152*:280-292.

In a pooled analysis of three cohorts (283,139 individuals) including atomic bomb survivors, women treated for cervical cancer, and patients treated for ankylosing spondylitis, 383 leukemias were observed. Models were fit separately and combined by leukemia subtype (AML, ALL, and CML). "The most parsimonious dose-response model fitted to the three datasets had a purely quadratic term combined with an exponential cell sterilization term, together with adjustments to the RR for time after exposure and attained age." CLL was excluded from the analysis as there was no excess risk from this leukemia subtype in the atomic bomb studies, nor in the studies of medical exposures; the RR for CLL comparing irradiated patients to non-irradiated patients was 1.03 (90% CI=0.3-3.9) in the cervical cancer study and 1.44 (95% CI=0.62-2.79) in the ankylosing spondylitis study. The authors comment that "the absence of risk of CLL suggests a marked heterogeneity in the radiation risk for various subtypes of leukemia, which is further reinforced by the finding of significant heterogeneity in the optimal model parameters in our analysis of three main radiogenic subtypes (AML, ALL, CML)."

Hoel DG, Li P [1998]. Threshold models in radiation carcinogenesis. Health Phys 75: 241-250.

The authors fitted the total leukemia model devised by Preston et al. (linear quadratic in form) to the A-Bomb Life Span Study (LSS) data to determine whether the model was effective in predicting leukemia risk at low doses of radiation. The researchers found that the model over-predicted leukemia incidence in the lowest dose group; the predicted values were 30-60% greater than the observed values. This suggests that the dose-response may not be linear at low doses. Upon adding a term to the model to account for a threshold effect, it was found that this model provided a better fit to the data. The authors report that the estimated threshold values for leukemia appear to be in the range of 0.05-0.10 Sv.

Little MP, Muirhead CR [1998]. Curvature in the cancer mortality dose response in Japanese atomic bomb survivors: absence of evidence of threshold. Int J Radiat Biol *74*:471-480.

The authors fitted the atomic bomb survivor LSS data to various models to determine the best fitting model to describe leukemia incidence. The linear-threshold model, (where dose response is assumed to be linear above the threshold) estimates a threshold value of 0.16, which was found to be significantly different from zero (value for no-threshold effect). But upon adding a quadratic term to the linear-threshold model, the threshold estimate was found to be non-significant, whereas the quadratic term improved model fit. Therefore the authors concluded that "the most parsimonious description of the leukemia dose response is provided by a linear-quadratic function of dose."

Akiyama M [1995]. Late effects of radiation on the human immune system: an overview of immune response among the atomic-bomb survivors. Int J Radiat Biol *68*:497-508.

An update is provided on the late effects of radiation on the immune systems of atomic bomb survivors. T-cell abnormalities were noted among survivors exposed to 1 gray (Gy) and greater. Such abnormalities included a decreased proportion of CD3+ T-cells in the periphery and an increased number of CD4- CD8- (double negative) αβ+ T-cells (observation period 1987-91). A defective T-cell response to mitogens and alloantigens was noted in the observation period of 1974-85. B-cell abnormalities were also present in atomic bomb survivors, including increased numbers in the periphery (1987-91), increased serum immunoglobulin (Ig) A in females (1987-89) and increased IgM and rheumatoid factor in both males and females, and an increased level of anti-Epstein Barr virus (EBV) antibody (1987-90).

Preston DL, Kusumi S, Tomonaga M, et al. [1994]. Cancer incidence in atomic bomb survivors part III: leukemia, lymphoma and multiple myeloma, 1950-1987. Radiat Res *137*:S68-S97.

Of 339 leukemias occurring in the LSS cohort of atomic bomb survivors, 261 cases were eligible for analysis. Nonresident cases, second primary cases, and cases with diagnosis dates outside the follow-up period (diagnosis <1950 or >1987) were excluded from analysis. Analysis was further restricted to cohort members with a Dose System 1986 (DS1986) dose estimates between 0-4 Gy; thereby excluding 24 cases with unknown dose and 6 cases with dose >4 Gy. There were 17 leukemias in Hiroshima residents characterized as "other", 15 were included in the analysis (4 CLL, 7 acute leukemia unspecified, 2 HCL, and 2 myelodysplastic syndrome). "As a result of the Leukemia Registry-FAB [French-American-British] reclassification, most of the cases previously classified as CLL or 'lymphosarcoma leukemia', including many of the cases in the earlier report by Finch and Hoshino, are now classified as ATL [adult T-cell leukemia]." For the "other" leukemia grouping, the authors report a significant linear dose response for the Hiroshima data ($p<0.004$). The risk for "other" leukemia was consistent across age at exposure and time since exposure categories. Only 0.03 excess "other" leukemia cases occurred among those exposed to less than 0.01 Gy; however 5.54 excess cases were observed among those exposed to 0.01-4 Gy. Also, there were significant risk differences by sex for "other" leukemia; females had an excess absolute risk (EAR) of 0.44 per 10^4 person-year (PY) Sv (95% CI=0.14-0.92), whereas males showed a negative EAR estimate (upper 95% bound=0.20). For NHL, the EARs for men and women were 0.56 (95% CI=0.08-1.39) and 0.00 (upper 95% bound=0.28) cases per 10^4 PY Sv, respectively.

Kato H [1988]. Radiation-induced cancer and its modifying factor among A-bomb survivors. Unusual Occurrences as Clues to Cancer Etiology. R.W. Miller et al, Japan Sci Soc Press, Tokyo/Taylor & Francis, LTD., pp 117-124.

This study described temporal patterns in relation to leukemia risk. An increase in leukemia risk emerged in both Hiroshima and Nagasaki about 3 years after the bombs were dropped, where the peak incidence occurred in 1951-1952. Incidence of leukemia has since declined, however an elevation of leukemia in Hiroshima was found to be present in the most recent atomic bomb study update (1981-1985). The author observed that the "younger the age ATB [at the time of the bomb], the greater the risk of leukemia during the early period, and the more rapid the decline thereafter. Moreover, the length of the latency period seems to decrease with dose." The article also evaluated the appropriateness of the absolute risk model versus the relative risk model in predicting leukemia risk. In an absolute risk model the excess deaths are assumed to be constant by age at death. The relative risk model assumes that the relative risk is constant by age at death throughout life, but that the excess deaths increase with age at death in proportion to age-specific mortality rates of the control population. By examining relative risk by ATB cohort and age at death, it was found that the relative risk remained essentially constant. By computing excess deaths by age ATB and age at death, it was found the excess deaths were not constant across age at

death categories, rather in each age ATB cohort excess deaths increased with age at death. This analysis suggests that the relative risk model is more appropriate in predicting leukemia risk in the atomic bomb survivors than is the absolute risk model.

Tanaka K, Kamada N [1985]. Leukemogenesis and chromosome aberrations: de novo leukemia in humans with special reference to atomic bomb survivors. Acta Haematol Jpn *48*:1830-1842.

Chromosome aberrations were found in 10-30% of bone marrow and peripheral lymphocytes of apparently healthy atomic bomb survivors who were within 1 kilometer of the hypocenter of the bombing. In these heavily exposed survivors, a non-random distribution of chromosome breakage was observed. There were 50 bands that demonstrated a significant increase in breakage frequency, including 11q22, 11q23, 13q14, and 14q32.

Ichimaru M, Ishimaru T, Belsky JL [1978]. Incidence of leukemia in atomic bomb survivors belonging to a fixed cohort in Hiroshima and Nagasaki, 1950-1971. Radiat Res *19*:262-282.

This study examined the 136 cases of leukemia occurring between 1950 and 1971 in the leukemia registry cohort of 109,000 atomic bomb survivors. This report demonstrated that the "leukemogenic effect of atomic radiation, which has been declining since the peak was reached in 1951-1952, was still evident in the period 1965-1971, especially among Hiroshima survivors." Only 1 case of CLL was reported in the Leukemia Registry; the age ATB was 37 and the age of onset of CLL was 58. The individual was a Nagasaki survivor with a reported dose of "0" for both gamma and neutron exposure.

Ishimaru T, Otake M, Ichimaru M [1978]. Incidence of leukemia among atomic bomb survivors in relation to neutron and gamma dose, Hiroshima and Nagasaki, 1950-1971. Radiation Effects Research Foundation Technical Report 14-77.

Models describing the dose curve of the effects of radiation on leukemia were evaluated using data from the atomic bomb Leukemia Registry, from 1950-1971. The first model considered a linear dose response for both gamma and neutron radiation, whereas the second model had a linear term for neutron exposure and a squared term for gamma exposure. Risk estimates by kerma dose from model 1 and model 2 for all leukemia for gamma radiation were calculated to be 1.08 cases per million person-years per rad (PYR) and 0.00364 cases per million PYR^2. For neutron related leukemia risk, the estimates from models 1 and 2 were 6.13 and 7.37 cases per million PYR, respectively. The authors concluded that "data on leukemia in Hiroshima and Nagasaki for the period 1950-1971 do not point clearly to a dose response model which is linear or one which is quadratic with respect to gamma radiation." The data did suggest a difference in chronic granulocytic leukemia (CGL) risk with respect to type of radiation exposure; "the incidence of CGL appears to depend principally upon the neutron dose."

Finch SC, Hoshino T, Itoga T, et al. [1969]. Chronic lymphocytic leukemia in Hiroshima and Nagasaki, Japan. Blood *33*:79-86.

In Japan, CLL comprises 2-3% of all leukemia, whereas it the US this figure is about 30%. The authors estimated the incidence rate of CLL in Japan to be 0.8 per million per year. In the US the incidence rate is 20-fold higher, with an estimated rate of 15 per million per year. Six CLL cases were identified in Nagasaki residents from 1946-1965, yielding a Nagasaki-specific incidence rate of 0.88 per million per year. Five of these residents were within the city limits ATB, but all were more than 3,000 meters from the hypocenter (estimated dose <1 rad). The mean year of diagnosis of these 5 cases was 1961 (range=1959-1965), with an average age of onset of 56 years (range=51-61). Where the surrounding areas of Nagasaki were included, 6 more cases of CLL were identified in 1946-1965 (no incidence rate given). In Hiroshima there were no cases of CLL reported among residents during 1946-1965; however when surrounding areas were included, 2 cases of CLL were found. The authors state that "reports from the ABCC [Atomic Bomb Casualty Commission] have failed to demonstrate an excessive leukemia incidence beyond 1,600 meters from the hypocenter. If exposure to ionizing radiation had been an important factor, one would have expected chronic lymphocytic leukemia to have developed more frequently in the proximally exposed populations of both cities. This has not been observed." The study thus concluded that there is no evidence to suggest that the bombings increased risk of development of CLL in Hiroshima and Nagasaki.

b. Nuclear Test Fallout

Boice JD, Lubin JH [1997]. Occupational and environmental radiation and cancer. Cancer Cause Control *8*:309-322.

In this review the authors discuss research which has explored the relationship between exposure to nuclear fallout and risk of cancer. The authors describe the 1990 study by Stevens et al.: "a more recent case-control study of 1,000 individuals who died of leukemia in southwest Utah …found a weak, but non-significant, association between estimated bone marrow dose and all leukemia…While acute leukemia following childhood exposure was increased, similar levels of risk for chronic lymphocytic leukemia (CLL), a tumor not shown to be elevated after irradiation, tempers the causal interpretation."

Stevens W, Thomas DC, Lyon JL, et al. [1990]. Leukemia in Utah and radioactive fallout from the Nevada Test Site. JAMA *264*:585-591.

Dose from nuclear fallout from the Nevada test site was estimated to assess leukemia risk in this population-based case-control study. Eligibility criteria included residing in Utah at time of death (with death between 1/1/1952 and 1/31/1981), birth before 11/1/1958, and membership in the Church of Jesus Christ of Latter-day Saints during 1950-58 (these records were used to determine

residence prior to fallout exposure). Cases had to have mention of leukemia somewhere on their death certificate, except for CLL, where CLL had to be cited as the underlying cause of death. 1,177 leukemia cases and 5,330 controls were identified and assigned dose categories of low (0-2.9 mGy), intermediate (3-5.9 mGy), and high (6-30.0 mGy). Analysis was performed by leukemia subtype. The OR for CLL for the intermediate and high groups, using the low category as the referent group, were 1.06 (95% CI=0.76-1.50) and 1.70 (95% CI=0.61-4.73), respectively. The trend test for CLL was not significant (p>0.10). Analyses for ALL and for leukemia excluding CLL showed increased RRs over dose groups, where the tests of trend were significant at the 10% level (ALL p=0.068, leukemia excluding CLL p=0.084).

III. Radiotherapy and Risk of CLL as a Secondary Cancer

dos Santo Silva I, Malveiro F, Jones ME, Swerdlow AJ [2003]. Mortality after radiological investigation with radioactive Thorotrast: a follow-up study of up to fifty years in Portugal. Radiat Res *159*:521-534.

Portuguese patients who were administered Thorotrast during 1928-1959 and a comparison group of patients who received non-radioactive contrast agents were followed until 1996. An effort was made to frequency-match the control group to the Thorotrast group on sex, age, calendar period and underlying condition for treatment. The author's note this effort was not fully achieved as Thorotrast was the most common radiographic contrast agent administered before 1940. Of the 1,096 patients who were administered Thorotrast systemically, 6 developed leukemia. One case of leukemia occurred among the 1,014 controls. As there were no cases of the CLL subtype, analysis was specific for leukemia excluding CLL. The SMR for leukemia excluding CLL for those systematically exposed was 8.17 (p<0.001), whereas the SMR for leukemia excluding CLL for the control group was 0.80. The RR for leukemia excluding CLL, comparing the Thorotrast exposed group to the unexposed group, was significant at 10.2, though the confidence interval was wide (95% CI=1.24-471). For hematologic disorders other than leukemia, the SMR for the Thorotrast group was 10.3 (95% CI=3.80-22.5), based on 4 cases of NHL, 1 case of Hodgkin's disease and 1 case of MM. No cases of other hematologic disorders were observed in the comparison group.

Fowble B, Hanlon A, Freedman G, et al. [2001]. Second cancers after conservative surgery and radiation for stages I-II breast cancer: identifying a subset of women at increased risk. Int J Radiation Oncology Biol Phys *51*:679-290.

The study included 1,253 breast cancer patients who were treated with conservative surgery and radiation between 1978 and 1994 at the Fox Chase Cancer Center or the University of Pennsylvania. 167 patients developed a second cancer. A total of 3 leukemias were observed in the cohort, yielding a 10 year cumulative incidence for leukemia of 0.2%. Two of the 3 leukemias were of the CLL subtype. One of these CLLs received adjuvant therapy with tamoxifen in addition to their surgery and radiation treatment. Four cases of NHL arose in the cohort (cumulative incidence not given).

Neugut AI, Ahsan H, Robinson E, et al. [1997]. Bladder carcinoma and other second malignancies after radiotherapy for prostate carcinoma. Cancer *79*:1600-1604.

This retrospective cohort study investigated the relationship between radiation treatment (RT) for prostate cancer and the development of a second primary cancer. A cohort of 141,761 prostate cancer patients was identified from the Surveillance, Epidemiology, and End Results program (SEER) data. 34,889 of the patients in this cohort received RT. As RT for prostate cancer is focused in the pelvic area, second cancers considered in the analysis included bladder, rectal and acute non-lymphocytic leukemia (ANL). CLL, which has not been demonstrated to be associated with radiation exposure, was analyzed as a negative control. SIRs were calculated to estimate relative risk. "The ratio of the observed to the expected number of cases gives an estimate of the relative risk for developing a second primary cancer for patients with primary prostate carcinoma compared with people without a prior primary tumor." Bladder cancer was significantly elevated for the RT group diagnosed more than 8 years following RT (RR=1.5, 95% CI=1.1-2.0), but not for the non-RT group (RR=1.0, 95% CI=0.7-1.2) The authors also reported a non-significant increased risk of CLL more than 8 years after RT for prostate cancer (RR=1.3, 95% CI=0.5-2.9, 6 observed cases).

Chao CKS, Lai PP, Michalski JM, et al. [1995]. Secondary malignancy among seminoma patients treated with adjuvant radiation therapy. Int J Radiation Oncology Biol Phys *33*:831-835.

This study examined 128 patients with seminoma of the testis, who had undergone RT, to determine if the development of secondary cancer was increased in this study group compared to the general population. The median age of the study population was 37 years with a median follow-up time of 11.7 years. Expected numbers of secondary cancers were estimated from the SEER data based on the Connecticut tumor registry. Nine cases of secondary cancer arose in the study population, yielding an elevated, but non-significant, SIR of 2.09 (95% CI=0.39-3.35). A significantly increased SIR was observed when stratifying by latency period, where the 11-15 year latency group showed an SIR of 4.54 (95% CI=1.22-11.63). Of the 9 secondary cancers, one was a case of CLL. The CLL case was 50 years old at the age of diagnosis for seminoma and developed CLL 2 years after RT. As there were so few cases of secondary cancer, the effect of RT on CLL could not be isolated. Furthermore, the authors acknowledge that it cannot be determined whether the increase in secondary cancers was a result of RT or rather a result of a biological disposition to developing secondary cancers.

Holowaty EJ, Darlington GA, Gajalakshmi CK, et al. [1995]. Leukemia after irradiation for endometrial cancer in Ontario. Cancer *76*:644-649.

A nested case-control study investigated the relationship between RT and leukemia risk among endometrial cancer patients. 13,843 women who were diagnosed with endometrial cancer during 1964-1987, and who had survived at least one year following diagnosis, were identified via the Ontario Cancer Registry. Leukemia was subsequently diagnosed

among 47 of these women (15 CLL, 20 acute non-lymphocytic leukemias (ANLL), 2 ALL, and 10 CML). Controls were matched to cases on age and calendar year of endometrial cancer diagnosis (4 controls per case for ANLL, ALL, and CML; 2 controls per case for CLL). In this study, CLL was "retained for the purpose of detecting a significant ascertainment bias." The authors report that the "association between radiotherapy and CLL approached unity" (data not shown).

Curtis RE, Boice Jr JD, Stovall M, et al. [1994]. Relationship of leukemia risk to radiation dose following cancer of the uterine corpus. J Natl Cancer I *86*:1315-1324.

A case-control study was performed to evaluate the relationship between RT and the development of leukemia. 218 cases of leukemia (57 CLL) were observed in a cohort of 110,000 women with cancer of the uterine corpus. The mean age of the cohort was 62 years, enabling the researches to study older populations. A 1:4 case to control ratio was employed in this study to maximize power, yielding 775 controls matched on age at diagnosis and race. Among the CLL cases, 35 of 54 received RT for cancer of the uterine corpus, whereas 84 of 127 matched controls received RT for cancer of the uterine corpus (matched RR=0.90, 95% CI=0.4-1.9). Subsequent analyses excluded CLL; no results were presented for CLL by dose category. A significant risk was observed for leukemia excluding CLL (RR=1.92, 95% CI=1.3-2.9). Regarding a dose response relationship between radiation and leukemia (excluding CLL), the authors concluded that "overall the pattern of risk in relation to dose was erratic and was most consistent with a constant increased risk across the entire dose range." The authors also explored linear models and linear-exponential models for dose; both models yielded almost identical results. Risk did not appear to drop off at high doses, as the exponential "cell-killing" term did not contribute meaningfully to the model. Upon examination of age at exposure, the RRs for leukemia excluding CLL were found to be relatively constant across age groups.

Griem ML, Kleinerman RA, Boice Jr JD, et al. [1994]. Cancer following radiotherapy for peptic ulcer. J Natl Cancer I *86*:842-849.

Patients treated for peptic ulcer at the University of Chicago during 1937-1965 were identified and categorized by RT status. 1,831 of the patients received RT, whereas 1,778 did not. The RR for leukemia and aleukemia (ICD-8 204-207), adjusting for sex, age, smoking, calendar year and time since entry in the cohort, was 3.28 (95% CI=1.0-10.6). For NHL, the RR comparing the RT exposed group to the non-RT group was 1.88 (95% CI=0.07-5.0). RT was found to increase the risk of all cancers by 50%. The RR (1.53) remained constant when stratifying by time since irradiation, suggesting that "radiation damage persists for many years." The authors did note that the "patients treated with radiotherapy appeared to be less fit than those treated by other means, and they were less likely to be candidates for surgery", which may have contributed to the observed relationship between RT and cancer.

Andersson M, Carstensen B, Visfeld J, et al. [1993]. Leukemia and other related hematological disorders among Danish patients exposed to thorotrast. Radiat Res *134*:224-233.

Of 1,003 Danish patients who were treated with thorotrast during 1935-1947 and followed until 1992, 37 developed leukemia. There were 2 cases of CLL where the age at injection of thorotrast was 42 and 48, respectively. The age at diagnosis of both cases was over 70 years, and the diagnosis of the cases occurred 22 and 34 years after injection (mean dose=1.68 Gy). CLL was excluded from all analysis.

Inskip PD, Kleinerman RA, Stovall M, et al. [1993]. Leukemia, lymphoma and multiple myeloma after pelvic radiotherapy for benign disease. Radiat Res *135*:108-124.

A multi-center retrospective cohort study was undertaken in New England to assess the relationship between RT and cancers of the blood or lymph. 12, 955 women treated for benign gynecological disorders (BGD) between 1925 and 1965 were eligible for inclusion in the study. Of these subjects, 9,770 received RT, whereas 3,185 did not. CLL and lymphocytic leukemia (LL) were grouped together in the SMR analyses. Mortality due to CLL and LL for RT BGD patients was found to be significantly higher than that of the US population (SMR=1.8); a similar SMR (1.6), though non-significant, was also observed among the non-RT BGD patients. An internal comparison of patients receiving RT compared to those not receiving RT showed a non-significant RR of 1.1 for CLL and LL (90% CI=0.5-3.0). The RR for NHL (0.90, 90% CI=0.6-1.6) also did not show any significant effects of radiation. Further SMR analyses for CLL and LL by latency were performed, demonstrating SMRs that "fluctuated erratically over time after treatment for BGD." The SMRs for both the RT group and the non-RT group showed excesses of CLL and LL deaths compared to the US population (time since treatment 0-5 years: RT SMR=2.3, non-RT SMR=5.2; 5-10 years: RT SMR=0 (no cases), non-RT SMR=0 (no cases); 10-20 years: RT SMR=2.9, non-RT SMR=3.2; 20-30 years: RT SMR=1.0, non-RT SMR=0 (no cases); >30 years: RT SMR=2.2, non-RT SMR=1.5). RRs comparing the RT group to the non-RT group by time since first treatment were not provided. Additional analyses revealed "no evidence of a monotonic trend in the SMR with mean marrow dose for any of the lymphoreticular cancers" and that "all of the excess mortality due to CLL and LL among radium-treated patients occurred among women whose mean marrow dose exceeded 50 cGy [centigray], but the association between SMR and dose ≥ 0 was not significant ($p>0.09$)." The authors observed little evidence of an association between CLL, Hodgkin's disease, NHL, or MM and RT; however, the researchers' findings did support an association between RT and acute myelocytic or monocytic leukemia.

Hellbardt A, Mirimanoff RE, Obradovic M, et al. [1990]. The risk of second cancer (SC) in patients treated for testicular seminoma. Int J Oncology Biol Phys *18*:1327-1331.

A study of patients treated at the Geneva University Cantonal Hospital during 1951-1986 for testicular seminoma was conducted to assess the relationship between RT and second cancer. The study cohort included 116 patients treated with RT for testicular seminoma, of which 11 developed a second cancer. None of the second cancers had prior chemotherapy

treatment. The distribution of the second cancers was as follows: 8 solid tumors, 2 NHL and 2 leukemias (1 CLL, 1 AML). The O/E for leukemia, where the expected numbers were derived from the leukemia incidence of a similar age group of Danish males, was 13.37 (p=0.006). However, when the leukemias were considered separately, the associations were not significant (data not shown). The NHL cases were not found to be in excess.

Inskip PD, Monson RR, Wagoner JK, et al. [1990]. Leukemia following radiotherapy for uterine bleeding. Radiat Res *122*:107-119.

The association of RT and cancer was examined in this study of women treated with RT for BGD. Eligible cases (4,483) included women diagnosed with BGD from 1925-1965 in selected hospitals in Massachusetts and Rhode Island. Follow-up was through 1/1/1985, except for 515 women whose records were destroyed in a flood and did not allow additional tracing after 1967. The overall mortality rate for the BGD cohort did not differ from that of the general population (SMR=1.0, 95% CI=1.0-1.1); however the SMR for cancer was significantly increased (SMR=1.3, 95% CI=1.2-1.4). The BGD group experienced a 2-fold excess of leukemia deaths compared to the general female population. The SMR for CLL and LL was also found to be significantly elevated in this study (SMR=2.1, 95% CI=1.96-8.14). This SMR was based on 9 cases (6 CLL, 3 LL) all of whom received an estimated dose greater than 50 cGy. CLL and LL could not be separated in the analyses as individual rates were not available. The authors speculate that women with BGD were under closer medical surveillance than the US population, and that "CLL, as an indolent malignancy, was detected more frequently." The authors state that "in view of the low case fatality rate and the fact that it is predominantly a disease of old age, there is clearly room for differential misclassification error to have occurred."

Curtis RE, Boice JD, Stovall M, et al. [1989]. Leukemia risk following radiotherapy for breast cancer. J Clin Oncol *7*:21-29.

A nested case-control study was undertaken to examine risk of leukemia following RT for breast cancer. From a cohort of 22,753 women diagnosed with breast cancer between 1935 and 1972 in Connecticut, 48 leukemias were identified via the Connecticut Tumor Registry. Ten of these leukemias were of the CLL subtype. Controls were matched to leukemia cases 2:1 on age and calendar year of diagnosis of breast cancer. The matched RR describing the association between RT and development of CLL was elevated, though not significantly (RR=1.84, 90% CI=0.5, 6.7). For leukemia excluding CLL, the RR approached unity at 1.02 (95% CI=0.5-2.1). The authors limited further analyses by dose and time since diagnosis to leukemia excluding CLL.

Boice Jr JD, Engholm G, Kleinerman RA, et al. [1988]. Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res *116*:3-55.

From a multinational cohort of 150,000 cervical cancer patients, 4,188 second cancers arose. A matched case-control study was undertaken to evaluate the risk of second cancer following RT, where 6,880 controls were selected. The matched RR for CLL was 1.03

(90% CI=0.3-3.9), whereas the matched RR for leukemia excluding CLL was significantly elevated (RR=2.02, 90% CI=1.0-4.2). In this study, the risk of developing NHL among those receiving RT was 2.5 times that of those not receiving RT (90% CI=0.8-7.6). Risk estimates by dose were calculated for 1 year survivors of cervical cancer. For CLL and leukemia excluding CLL the excess absolute risks were 0.00 (90% CI=0.00-0.17) and 0.10 (90% CI=0.00-0.31), respectively. The authors acknowledge that the small number of unexposed cases, due to receipt of RT by the majority of the cervical cancer patients, was a statistical limitation of the study.

Boice Jr JD, Blettner M, Kleinerman RA, et al. [1987]. Radiation dose and leukemia risk in patients treated for cancer of the cervix. J Natl Cancer I *79*:1295-1311.

A case-control study was performed to assess the risk of leukemia following RT among patients treated for cervical cancer. The study utilized data from 17 cancer registries and 16 oncologic clinics from Canada, Europe, and the US to identify cases and select controls. 195 cases of leukemia were identified, including 52 CLL. Controls were matched 4:1 to cases on cervical cancer diagnosis age and year. The matched RR for CLL comparing the frequency of RT among cases and controls was 1.03 (90% CI=0.3-3.9). Further analyses excluded CLL.

Holm LE, Wiklund KE, Lundell GE, et al. [1989]. Cancer risk in population examined with diagnostic doses of ^{131}I. J Natl Cancer I *81*:302-306.

35,074 people treated with radioactive iodine in Sweden, between 1951 and 1969, were followed though 1984 to assess whether radioactive iodine treatment induced cancer. The Swedish Cancer Registry was used to determine incidences of cancer following ^{131}I treatment, excluding cancers developing less than 5 years after the treatment. The overall SIR of 1.01 (95% CI=0.98-1.04) indicated that the incidence of cancer among the study cohort was not significantly different than expected based on US cancer incidence rates. Leukemia incidence, however, was elevated. Separating CLL from non-CLL revealed significant elevations for both leukemia groups with SIRs of 1.30 (36 cases) and 1.38 (83 cases), respectively. Further SIR analyses by number of years of follow-up demonstrated a significant risk for leukemia only in the group followed 15-19 years (SIR=1.60, 95% CI=1.12-2.22). With respect to this result the authors state that, "radiogenic leukemia…would be expected to be highest within 5-9 years and then decrease; this pattern is not consistent with our finding the highest risk 15-19 years after exposure". Results by years of follow-up were not presented for CLL and non-CLL leukemia subgroups. The researchers speculate that closer medical surveillance of the study population may account for the observed findings and that "without the ^{131}I examination, the indolent tumors detected would not otherwise have led to clinically apparent disease."

Boice JD, Day NE, Anderson A, et al. [1985]. Second cancers following radiation treatment for cervical cancer: an international collaboration among cancer registries. J Natl Cancer I *74*:955-975.

A study of second cancers following treatment of cervical cancer was performed using data from 15 cancer registries in 8 countries. From the cohort of 182, 040 cervical cancer patients, 22 were subsequently diagnosed with CLL. The O/E ratios for CLL, where the expected numbers were based on rates from the general population, were 0.70 (16 cases) for patients receiving RT and 2.00 (6 cases) for those not receiving RT. Restricting the data to follow-up greater than 10 years gave an O/E for CLL among those receiving RT of 0.90, based on 9 observed cases. No cases of CLL were seen among the non-RT group followed for greater than 10 years, though 1.2 cases were expected based on the age and calendar period specific rates for the general female population. An excess of NHL was seen among the cervical cancer patients followed for more than 10 years who received RT (O/E=1.3), but a deficit was observed for the women not treated with RT (O/E=0.3). Neither CLL nor NHL demonstrated a significant trend when analyzed by time since first RT treatment (CLL: p=0.141, NHL: p=0.416).

Harvey EB, Brinton LA [1985]. Second cancer following cancer of the breast in Connecticut, 1935-1982. Natl Cancer Inst Monogr *68*:99-112.

Examination of 41,109 women diagnosed with breast cancer in Connecticut between 1935 and 1982 revealed that 3,984 of the women had been diagnosed with a subsequent cancer. The authors report that the risk for CLL, among women with breast cancer, was below expectation, with an RR of 0.5 (95% CI=0.2-1.0). The RR for NHL was also below the null value (RR=0.90). The RRs restricted to patients receiving RT were 1.2 and 1.7 for CLL and NHL, respectively. The RRs were lower among women not receiving RT (CLL: RR=0.4, NHL: RR=0.7).

IV. Diagnostic X-Rays and Risk of CLL

Boice JD, Morin MM, Glass AG, et al. [1991]. Diagnostic x-ray procedures and risk of leukemia, lymphoma and multiple myeloma. JAMA *265*:1290-1294.

A case-control study of members of two health plans was conducted to assess the relationship between RT and leukemia, lymphoma, and MM. Diagnoses were available between 1959 and 1979 for the Portland, Oregon health plan and between 1956 and 1982 for the northern California plan. Eligibility was restricted to subjects who had not received RT or chemotherapy for a prior malignancy. A 2:1 and 1:1 control to case match was performed for Portland members and California members, respectively, where subjects were matched on sex, age, plan, years in plan, and year membership began. Dose was estimated upon examination of each subject's x-rays and an exposure score was assigned from 0-4. The RRs for CLL comparing ever exposed to never exposed, for various lags, were 0.66 (95% CI=0.4-1.2, 3 month lag), 0.56 (95% CI=0.56, 2 year lag), 0.67 (95% CI=0.4-1.3, 4 year lag) and 0.51 (95% CI=0.30-0.90, 5 year lag). The authors speculate this protective effect could be due to chance or ascertainment bias. The study did find that

NHL cases were more frequently exposed to x-rays than controls (RR=1.32, 3 month lag); however, the association disappeared after a 2 year lag was employed (RR=0.99). The study demonstrated some evidence that risk of MM increased concordant with diagnostic x-ray exposure level, as significant trends at the 10% level were seen irrespective of lag.

Darby SC, Doll R, Gill SK, Smith PG [1987]. Long term mortality after a single treatment course with x-rays in patients treated for ankylosing spondylitis. Brit J Cancer *55*:179-190.

Of 14,106 patients treated with x-ray for ankylosing spondylitis in Great Britain and Northern Ireland between 1935 and 1954, 39 cases of leukemia were observed. The O/E based on age, sex, and calendar year specific mortality rates in England and Wales was 3.17 for leukemia ($p<0.001$). A significant increased risk persisted 15 years after treatment (RR=1.87). No trend by age at exposure was observed in the leukemia data. Analysis of leukemia by subtype yielded an O/E ratio for CLL of 1.09 in the $\geq$ 15 years since exposure stratum, based on 2 cases. The CLL cases occurred 26 and 31 years after exposure, respectively, and both cases were treated between the ages of 25-34. The author acknowledges that these results are constrained because 1/3 of the leukemia deaths were not specified by subtype, including 6 cases of unspecified lymphatic.

Gibson R, Graham S, Lilienfeld A, et al. [1972]. Irradiation in the epidemiology of leukemia among adults. J Natl Cancer Inst *48*:301-311.

A case-control study was undertaken to examine the relationship between diagnostic x-ray exposure and leukemia risk. The study consisted of 1,414 cases identified in the areas of upstate New York, Baltimore, and Minneapolis and 1,370 population controls from these areas. The age-adjusted RR demonstrated that male CLL cases (n=304) were more frequently exposed to diagnostic x-rays to the trunk than were controls (all RRs were below 1 for x-rays to all sites). When male exposure status was defined as 11+ x-rays to the trunk the RR was 1.03 (p=0.89), and when exposure status was defined as 16+ x-rays to the trunk the RR was 1.25 (p=0.56). A significant difference was observed between male cases and controls when exposure was defined as 21+ x-rays to the trunk. The RR was found to be 2.03 (p=0.02). Female CLL cases (n=170) had similar exposure to x-rays as did the controls. The only excess was for self-respondents with 21+ x-rays for all sites combined (RR=1.02, p=0.57). No categorical trend analysis was performed to determine whether increasing number of x-rays corresponded to increasing leukemia risk.

V. CLL and Solvent Exposure

Adengoke OJ, Blair A, Shu XO, et al. [2003]. Occupational history and exposure and the risk of adult leukemia in Shanghai. AEP *13*:485-494.

A case-control study of leukemias reported to the Shanghai Cancer Registry from 6/1/1987-8/31/1989 was performed to identify risk factors for leukemia. There were 21 cases of CLL, 81 ALL, 236 AML, and 79 CML. A questionnaire was distributed to the cases (or next of kin) and the 502 controls selected from the general population, to obtain

information on demographics, occupation, lifestyle factors, family history, education, and exposure to chemicals, radiation, and diagnostic x-rays. Results were presented by subtype of leukemia with the exception of CLL.

Glass DC, Gray CN, Jolley DJ, et al. [2003]. Leukemia risk associated with low-level benzene exposure. Epidemiology *14*:569-577.

This study utilized a nested case-control design to examine the relationship between benzene exposure and lympho-hematopoietic cancer in a cohort of Australian male petroleum workers. From the conditional logistic regression analysis, the ORs for CLL were increased among the exposure groups compared to the referent category, though not significantly (referent ≤ 4 cumulative lifetime parts per million (ppm) years OR=1, 4-8 ppm years OR=2.76 (95% CI=0.42-18.1), >8 ppm years OR=4.52 (95% CI=0.89-22.9)). This analysis was based on only 11 cases of CLL, thereby limiting the ability to detect a significant effect.

Huebner WW, Schnatter AR, Nicolich MJ et al. [1997]. Mortality experience of a young petrochemical industry cohort: 1979-1992 follow-up study of US-based employees. JOEM *39*:970-982.

A retrospective cohort study of 81,746 former and current petrochemical workers was performed to determine whether these workers had increased mortality rates compared to the general US population. The cohort was relatively young, as only approximately 4% of the cohort had died. Cause-specific SMRs were calculated, stratified by race and sex, for the entire cohort and by job subtype. Overall, the cohort exhibited SMRs below expectation, indicative of a strong healthy worker effect. However, a non-significant elevation in mortality was seen for CLL across the entire cohort, where the SMR was 1.60 (95% CI=0.85-2.73, 13 deaths). Of the 13 cases of CLL, 11 of these workers began employment between 1934 and 1955, worked at least 30 years, had greater than 35 years latency, and died between the ages of 56-76. The stratum specific SMR for CLL among white males employed prior to 1960 was 1.81 (95% CI=0.90-3.24). Nine of these 11 workers had "some plant, field or laboratory experience, at least early in their careers. However, no patterns or consistencies were seen with regard to jobs, units, or specific chemical exposures."

Ireland B, Collins JJ, Buckley CF, Riordan SG [1997]. Cancer mortality among workers with benzene exposure. Epidemiology *8*:318-320.

4,172 male hourly workers beginning employment between 1940 and 1977 at the Monsanto Company plant in Sauget, Illinois were followed though 1991 to assess mortality associated with benzene exposure. The O/E ratios for CLL, based on Illinois rates, were presented for production workers by benzene exposure categories. Among those without benzene exposure, the O/E was 1.00 (95% CI=0.0-5.5), based on only one case. The <12 ppm-months category showed as O/E of 5.9 (95% CI=0.1-32.6), again based on 1 case. There were no cases in the 12-72 ppm-months category, consistent with an expected number of 0.15 cases. In the highest exposure group, ≥ 72 ppm-months, 1

CLL case was observed, yielding an O/E of 6.7 (95% CI=0.2-37.7). No deaths of NHL were seen among the exposed workers.

Nordlinder R, Jarvholm B [1997]. Environmental exposure to gasoline and leukemia in children and young adults—an ecology study. Int Arch Occup Environ Health *70*:57-60.

Benzene exposure from gasoline and car exhaust has been implicated as a risk factor for childhood leukemia. This study categorized 277 areas in Sweden into 4 groups according to car density, which served as a surrogate for childhood benzene exposure. Incidence rates for leukemias during the study period of 1975-1985 were collected via the National Swedish Cancer Register for children and young adults aged 0-24 years. As only 3 cases of CLL were reported in this age group in the 10 years time, this leukemia was not analyzed. The study did have adequate numbers, however, to separately analyze NHL, ALL, AML, and CML. The only significant finding of the study occurred upon comparing AML incidence in the highest car density category to the lowest car density category (RR=1.62, p=0.05). The authors acknowledge that as an ecological study there was a lack of control for confounding; the observed relationship may have been due to another factor that is associated with both AML and living in areas of high car density.

Savitz DA, Andrews KW [1997]. Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. Am J Ind Med *31*:287-295.

In a review of benzene and lymphatic and hematopoietic cancer, Savitz et al. cites studies that investigated the relationship between benzene and CLL. Linet et al. (1987a) reported an RR for CLL of 0.9 (95% CI=0.5-1.5) and 1.5 (95% CI=0.9-2.5), using two versions of a job exposure matrix to estimate benzene exposure. An RR of 1.1 (95% CI=0.6-2.0) was observed by Malone et al. (1989) for risk of CLL following benzene exposure.

Landrigan PJ [1996]. Benzene and blood: one hundred years of evidence. Am J Ind Med *29*:225-226.

This editorial speaks to the effects of benzene in relation to blood disorders. The author cites the findings of Yin et al. (1996), where a significant excess of leukemia was found among benzene exposed workers. Yin observed elevations for CML, AML, and LL; though AML was the only significant association at the 5% level. The author also emphasizes that the observed dose-response relationship, where increasing benzene levels lead to decreasing absolute lymphocyte levels, adds to the biologic plausibility of an association between benzene and leukemia.

Paxton MB [1996]. Leukemia risk associated with benzene exposure in the Pliofilm cohort. Environ Health Persp *104 (Suppl 6)*:1431-1436.

A mortality update through 1987 of the Pliofilm cohort revealed 22 leukemia cases among the benzene-exposed population of non-salaried Goodyear rubber workers. No CLL cases were reported.

Yin SN, Hayes RB, Linet MS et al. [1996]. A cohort study of cancer among benzene-exposed workers in China: overall results. Am J Ind Med *29*:227-235.

In a cohort study involving 74,828 benzene-exposed factory workers (as determined by job title and department) and 35, 805 unexposed workers, a significant elevation in leukemia mortality was observed among the exposed population (RR=2.3, 95% CI=1.1-5.0). By subtype, AML mortality occurred significantly more frequently among the benzene exposed (RR=3.1, 95% CI=1.2-10.7). The RRs for CML and LL were also elevated, though not significantly. All lymphatic leukemia among the exposed were due to AML; there were no cases of CLL among the exposed. The investigators do note, however, that CLL is rare in Asian populations.

Austin H, Delzell E, Cole P [1988]. Benzene and leukemia: a review of the literature and a risk assessment. Am J Epidemiol *127*:419-439.

This review article cites CLL specific results from several benzene studies. Girard et al. (1970), in a hospital based case-control study, found an RR for benzene and toluene exposure of 4.1 (95% CI=1.4-12.0) for CLL. Linos et al. (1980) assessed the risk of leukemia following benzene exposure via a case-control study; the RR for leukemia was 3.3 (95% CI=0.6-28.0), where 3 of the 4 exposed cases were CLLs. In a cohort mortality study, Decoufle et al. (1983) observed 3 leukemia deaths among chemical workers (1 CLL); only 0.44 deaths were expected (SMR=682, 95% CI=141-1992). An RR of 2.5 for LL risk was reported by Checkoway et al. (1984) among benzene exposed workers.

Wilcosky TC, Checkoway H, Marchall EG, et al. [1984]. Cancer mortality and solvent exposures in the rubber industry. Am Ind Hyg Assoc J *45*:809-811.

A study of the carcinogenic effects of solvent exposure was performed on a cohort of 6,678 male rubber workers, followed for vital status until 1974. Solvent exposure among those members of the cohort dying of stomach cancer, respiratory cancer, prostate cancer, lymphosarcoma, and leukemia was compared to a 20% age-stratified random sample of the cohort. Exposure to a solvent was defined as working in an area where the solvent was authorized for use. Ten cases of LL and 9 cases of lymphosarcoma occurred in this cohort of rubber workers. The proportion of CLL cases in the LL category was not provided. The OR comparing the carbon tetrachloride exposure of cases to controls was 15.3 ($p<0.001$) and 4.2 ($p<0.05$) for LL and lymphosarcoma, respectively. Significantly elevated ORs at the 1% level were observed for exposure to carbon disulfide; the OR for LL was 8.9 and the OR for lymphosarcoma was 5.6. Both LL and lymphosarcoma exhibited an OR of 4.0 for hexane exposure, significant at the 5% level. Ethyl acetate (OR=5.3) and acetone exposure (OR=6.8) occurred significantly more frequently among the LL cases than the controls. There was evidence of increased risk of lymphosarcoma following xylene exposure (OR=3.7, $p<0.05$). The authors note that the results of this study may "reflect a single causative agent that is correlated with several of the solvents" since "different solvents were used simultaneously in a given process area".

VI. CLL and Farming

Lee E, Burnett CA, Lalich N, et al. [2002]. Proportionate mortality of crop and livestock farmers in the United States, 1984-1993. Am J Ind Med *42*:410-420.

This study investigated the mortality trends of crop farmers and livestock farmers, with cause-specific PMRs calculated for each group of farmers. CLL was significantly elevated in both groups; the PMRs for white, male crop farmers and white, male livestock farmers were 1.14 (95% CI= 1.04-1.25) and 1.28 (95% CI= 1.06-1.53), respectively. These results suggest that both types of farmers, crop and livestock, undergo a common exposure to carcinogens, such as pesticides or chemicals, leading to their increased risk for CLL. The authors also report a significant increase of LL and MM among both farming groups. Only the livestock workers had a significant excess of deaths due to NHL, ALL, and myeloid leukemia.

Gonzalez CA, Agudo A [1999]. Occupational cancer in Spain. Environ Health Persp *107*:273-277.

In a review of occupational cancer in Spain the author cites the 1991 study by Lopez-Abente where a statistically significant increase of stomach cancer, brain cancer, CLL, MM and NHL was observed among the agricultural occupations. The case-control study utilized death certificates from the region of Castilla-Leon.

Brandt L [1985]. Environmental factors and leukaemia. Med Oncol & Tumor Pharmacother *2*:7-10.

In this review of the literature regarding environmental exposures and leukemia, the author considers farming as an environmental exposure for CLL. Brandt cites Milham (1971), who reported CLL as a common death among farmers, and Donham et al. (1980), who suggested that bovine leukosis may be transmitted to humans. The relationship between bovine leukosis and leukemia was examined in a study by Kvarnfors et al. (1975); leukemia was not found to be increased in an area where bovine leukosis was prevalent.

Thomas TL, Krekel S, Heid M [1985]. Proportionate mortality among male corn wet-milling workers. Int J Epidemiol *14*:432-437.

Corn wet-milling workers are exposed to a variety of potentially hazardous agents including: grain dusts, pesticides and fumigants, acids, solvents, sulphur dioxide, and other chemicals involved in the production of oil, starch, syrup, and animal feed. Proportionate mortality analysis was conducted on 748 male corn wet-milling workers who died between January 1947 and June 1981. Significant excesses of proportionate deaths were observed among whites for the outcomes of leukemia and other lymphoma, with PMRs of 2.21 and 3.10, respectively. Calculation of PMRs by work type demonstrated that 4 of the 8 leukemia deaths occurred in white maintenance workers. The PMR for leukemia (1 case of lymphatic) among the maintenance workers was 3.08.

VII. Other Risk Factors for CLL

Adami J, Gridely G, Nyrén O, et al. [1999]. Sunlight and non-Hodgkin's lymphoma: a population-based cohort study in Sweden. Int J Cancer *80*:641-645.

The study was undertaken to evaluate the relationship between ultra-violet light exposure and NHL and CLL cancer incidence. The eligible study population included all Swedish residents who were gainfully employed according to either the 1960 or 1970 census, resulting in 4,171,175 study subjects followed from 1/1/1971 until cancer diagnosis, death, or the end of study date, 12/31/1989. Cancer incidence data were obtained by record linkage to the Swedish Cancer Registry. Sunlight exposure was measured by place of residence according to the census data, where residence was grouped into one of 4 latitude categories. The census also provided occupational data, allowing the researchers to analyze occupational exposure to sunlight and occupational exposure to pesticides and chemicals. Poisson regression was used to model the effects of the exposure variables (latitude and occupation) controlling for potential confounding by age, residence in a large city or not, SES, number of hours worked per week, and exposure to pesticides/solvents. The final model, adjusted for age, showed a significant increase in NHL among the 2 southernmost regions compared to the referent upper north category. The risk ratios for CLL, however, did not demonstrate any relationship with latitude, as the rates for the 3 southernmost latitude exposure groups were not significantly different than that of the northernmost latitude group; furthermore, all point estimates for the RRs were less than 1 in comparison to the referent latitude category.

Miligi L, Seniori Constantini A, Crosignani P, et al. [1999]. Occupational, environmental, and life-style factors associated with the risk of hematolymphopoietic malignancies in women. Am J Ind Med *36*:60-69.

This case-control study attempted to identify risk factors for hematolymphopoietic cancers among women living in Italy, where NHL and CLL were considered together in the analysis. Twelve areas were selected for study: 2 industrialized areas, 6 agricultural areas and 4 mixed areas. From these areas, 1,183 female cases of hematolymphopoietic cancers (reflecting a 9.4% nonresponse rate), were included in the study, as were 828 female controls (reflecting a 19.8% nonresponse rate). A 1:1 case to control ratio was used for the 611 combined NHL and CLL cases, with a greater case to control ratio employed for the other cancer types. The authors singly considered various risk factors, including occupation, hair dye use, education level, and smoking status, in logistic regression analyses adjusting for age. Borderline significant elevations in NHL/CLL were observed among smokers (OR=1.2, 95% CI=1.0-1.5) and teachers (OR=1.7, 95% CI=1.0-2.7). Non-significant elevations of NHL/CLL were found among medical, dental and veterinary workers (OR=1.4), clerical workers (OR=1.1), textile workers (OR=1.1), rubber and plastic workers (OR=1.5), production workers not elsewhere classified (OR=2.4), bleachers, dyers and textile product finishers (OR=2.1) and housewives (OR=1.2).

Adami H, Tsaih S, Lambe M, et al. [1997]. Pregnancy and risk of non-Hodgkin's lymphoma: a prospective study. Int J Cancer *70*:155-158.

As the etiology of NHL and CLL is likely related to immune function, and since pregnancy affects the immune system, the relationship between pregnancy and risk of NHL and CLL was investigated in this study. Incidence data from the Swedish Cancer Registry was linked with exposure data from the Swedish Fertility Register. 1,546 cases of NHL and 198 cases of CLL were identified among women aged 15 and older born during the period 1925-1972. Using 5 age-matched controls per case, conditional logistic regression was performed adjusting for age at first birth. The ORs for NHL and CLL comparing ever parous women to never parous women were 0.96 (95% CI=0.82-1.12) and 0.92 (95% CI=0.60-1.40), respectively. Examination of the relationship between NHL and CLL with number of births revealed non-significant negative trends. For CLL, the ORs for 3, 4 and 5 births were 0.76 (95% CI=0.44-1.30), 0.76 (95% CI=0.37-1.55) and 0.62 (95% CI=0.22-1.75) respectively, yielding a test of trend p value of 0.18. These results suggest that pregnancy may be protective against development of NHL and CLL.

Verkasalo PK [1996]. Magnetic fields and leukemia—risk for adults living close to power lines. Scand J Work Environ Health *22 (Suppl 2)*:1-56.

Eligibility criteria for this study of magnetic fields and leukemia included residing in Finland within 500 meters of 110, 220, and 400 kilovolt overhead power lines with a magnetic field $\geq$ 0.01 μT during 1970-1989, and age >20 years. 383,700 people were included in the cohort study. The SIR for CLL was 1.03 (95% CI=0.80-1.29). No other leukemia subtype showed an elevation of disease incidence compared to the general Finish population. A nested case-control study was also performed, where 10 controls were matched on age and sex to each of the 196 leukemia cases. Again, only CLL demonstrated evidence of increased risk due to exposure to magnetic field, though the risk estimates were based on small numbers. When stratifying on time since first exposure, a significant increase in CLL risk was observed for those exposed to $\geq$ 0.40 μT, at least 10 years prior to diagnosis of CLL (RR=4.62, 95% CI=1.41-15.1). Also, among subjects who were exposed to $\geq$ 0.10 μT, those exposed for a duration of at least 12 years had an almost 5-fold increase in risk compared to those exposed less than 12 years (RR=4.86, 95% CI=1.54-15.4). As noted by the authors, these results suggest that a latency period greater than 10 years should be considered for future studies of CLL.

Markovic-Denic LJ, Jankovic S, Marinkovic J, et al. [1995]. Brick mortar exposure and chronic lymphocytic leukemia. Neoplasma *42*:79-81.

A case-control study consisting of 130 CLL cases and 130 controls, matched on hospital, sex, age, residence area and type, and income was performed. The risk factors examined were occupation category, work in hazardous industry (category appears not to include radiation work), family history of leukemia and other malignancies, tonsillectomy, and exposure to pesticides, manure, organic solvents, dyes, oil, acids, brick mortar, hair dye, farming, and electromagnetic radiation. Data on exposure were obtained through interview of cases and controls. Conditional logistic regression analysis revealed 5

significant risk factors at the 10% level for CLL: family history of leukemia (OR=2.40, 95% CI=1.10-5.23), hair dye use (OR=1.97, 95% CI=1.08-3.59), brick mortar exposure (OR=1.79, 95% CI=0.96-3.26), work in hazardous industry (OR=1.55, 95% CI=1.01-2.39), and exposure to electromagnetic radiation (OR=1.25, 95% CI=0.97-1.63).

Linet MS, Cartwright RA [1988]. Chronic lymphocytic leukemia: epidemiology and etiologic findings. Nouv Rev Hematol *30*:353-357.

The results of 2 case-control studies are presented in this report: a study in Baltimore, Maryland and a sister study in Yorkshire, England. In Baltimore, 342 cases of CLL were diagnosed between 1975 and 1982. Hospital controls (non-cancer patients) were selected using a 1:1 match on age, sex, race, and year of diagnosis. The Yorkshire study included 330 CLL cases diagnosed from 1979-1984, where controls were matched (1:1.7) on the same criteria as listed above. A questionnaire was given over the phone to cases (or next of kin) and controls inquiring about SES, family history, mediation use, lifetime occupational history, occupational and environmental exposures, and use of cigarettes and alcohol. The authors report an increased OR for leukemia and lymphoma among close relatives of CLL patients compared to controls (Baltimore: OR for siblings=2.2 (95% CI=0.9-5.1), OR for parents=7.5 (95% CI=2.1-26.2); Yorkshire: OR for any blood relative=1.8 (95% CI=0.9-3.3)). For the Baltimore study, no association was observed between prior history of subacute or chronic bacterial infection and CLL. In the Yorkshire study, however, the odds of a having a prior diagnosis of scarlet fever were found to be 3.2 (95% CI=1.2-8.3) times higher among cases than controls. The OR comparing CLL cases to matched controls also revealed significant differences in prior exposure to chronic ear infections (OR=1.9) and bronchitis (OR=2.2). Furthermore, the Yorkshire study demonstrated that the cases more frequently reported migraine, hypertension, myocardial infarction, skin cancer, RT for skin cancer and history of prior malignancy than did controls. The Baltimore study showed that cases reported allergy-related disorders more than did controls. Both studies demonstrated that cases were less likely to have an appendectomy. The authors conclude that their results are consistent with a genetic predisposition to CLL, "although it is probable that environmental determinants are important in the etiology, given the substantial sporadic occurrence of CLL within families. Several of the findings also provide support for an association of CLL with preceding immune perturbation." The researchers do not report their findings regarding the relationship between occupational exposure and CLL.

VIII. CLL and Risk of Second Primary Malignancies

Potti A, Kishor Ganti A, Koch M, et al. [2001]. Identification of HER-2/neu overexpression and the clinical course of lung carcinoma in non-smokers with chronic lymphocytic leukemia. Lung Cancer *34*:227-232.

Previous studies have demonstrated that CLL patients have an increased risk for developing second primary cancers. Travis et al. (1992) reported the RR for lung cancer among CLL patients to be 1.90. The purpose of this study was to evaluate the role of HER-2/neu in the development of lung cancer in CLL patients. HER-2/neu codes for a

receptor tyrosine kinase which can act in several signal transduction pathways; furthermore, overexpression of HER-2/neu has been observed in several types of cancers. To eliminate smoking as a confounder, the study was restricted to nonsmokers who were diagnosed with lung cancer at least 6 months after being diagnosed with CLL. Of 417 patients with CLL, 14 patients met the study criteria. In 9 of the 14 cases (64%), HER-2/neu overexpression was observed. Nine of 10 patients with advanced stage lung cancer showed overexpression of HER-2/neu; whereas in the 4 patients with localized malignancies, HER-2/neu expression was not seen. The authors suggest that overexpression of HER-2/neu "may play a role in the development of secondary malignancies, that appear to be more advanced at the time of diagnosis; probably secondary to accelerated tumor growth." The study also suggests that HER-2/neu may be associated with a worse than expected prognosis in patients. In light of these findings, increased surveillance for lung cancer among CLL patients is recommended by the authors.

Nanjangud GJ, Saikia TK, Chopra H, et al. [1996]. Development of PH positive chronic myeloid leukemia in a patient with chronic lymphocytic leukemia treated with total body irradiation: a rare association. Leukemia Lymphoma *22*:355-359.

In this case report, a patient diagnosed with CLL in 1984 received total body irradiation (TBI) as treatment. He later developed CML about 73 months after the first course of TBI treatment, while the morphologic evidence of CLL disappeared. The authors recommend careful follow up of patients receiving TBI, or avoidance of TBI in favor of newer treatments that may become available in the future.

Schmidt HH, Sill H, Beham-Schmid C, et al. [1995]. Hodgkin's disease developing after spontaneous remission of chronic lymphocytic leukemia. Ann Hematol *71*:247-252.

The authors present a case of a woman diagnosed with CLL in 1967. In 1984, treatment was required due to disease progression; hence, a single course of chemotherapy was administered. The following year, spontaneous remission of the CLL was observed until 1993. Spontaneous remission is a rare event, occurring in about 1% of cases. Chemotherapy, radiation, and viral infections have been reported to precede spontaneous remission. The authors argue that the chemotherapy dose was "not sufficient to produce such a complete and long-lasting normalization of the WBC." This case is also unique in that the patient went on to develop Hodgkin's disease in 1993. The researchers performed a literature review of all documented cases of spontaneous remission of CLL and found that about 40% of spontaneous remission cases developed secondary neoplasms with follow-up of greater than 2 years; the authors did not speculate about the of role radiation treatment in the development of these cancers. Also of note in this CLL case is the finding of an inversion of chromosome 9 upon karyotyping. It is unclear whether this abnormality was related to the pathogenesis of CLL in this patient.

Travis LB, Curtis RE, Hankey BF, et al. [1992]. Second cancers in patients with chronic lymphocytic leukemia. J Natl Cancer I *84*:1422-1427.

An investigation into the relationship between CLL and development of secondary cancer was carried out using the SEER cancer registry. The registry was used to identify all cases of CLL diagnosed during 1973-1988. Additionally, the registry provided data on demographics, vital status, tumor histology, type of initial treatment, and occurrence of second cancers. Of the 9,456 CLL cases identified, 840 (9%) went on to develop a second cancer. The number of observed cases (840) was significantly greater than the number of cases expected to occur in the general population (658), yielding a O/E ratio of 1.28 (95% CI=1.19-1.37). Among men, but not women, an excess of brain cancer was observed (O/E=2.84, 95% CI=1.46-4.96); 7 of the 13 observed brain cancers were reported in Iowa. Lung cancer (O/E=1.90, 95% CI=1.65-2.17), intraocular melanoma (O/E=3.97, 95% CI=1.07-10.16), malignant melanoma (O/E=2.79, 95% CI=1.85-4.03) and Hodgkin's disease (O/E=7.69, 95% CI=4.09-13.14) were significantly elevated in the CLL cohort compared to the general population. There appeared to be a reduction in risk for breast cancer and cancer of the uterine cervix and corpus which the authors note has also been reported for women with NHL. The excesses of secondary lung cancer and cutaneous melanoma seen in this study have also been reported in NHL patients. Unlike what has been observed with past NHL reports, where "sharp increases in risk over time suggested a treatment-related effect", the elevations of secondary cancer among the CLL patients remained relatively constant across follow-up periods and treatment groups.

Greene MH, Wilson J [1985]. Second cancer following lymphatic and hematopoietic cancers in Connecticut, 1935-1982. National Cancer Institute Monographs *68*:191-217.

The risk of developing a second cancer following cancer of the lymphatic and hematopoietic system was evaluated, using data from Connecticut Tumor Registry for the years 1935-1982. 1,875 CLL patients were identified. The mean age of disease diagnosis was 67 and 17.5% of CLL patients received RT. 165 of these CLL patients developed a second cancer (RR=1.3, 95% CI=1.1-1.5). There were 6,734 NHL patients diagnosed during the interval studied; the average age of diagnosis among these patients was 58 and 51% received RT for NHL. A second cancer was diagnosed in 319 of the NHL patients (RR=1.24, 95% CI=1.11-1.39). The "pattern of increased risk for malignant melanoma, soft tissue carcinoma, and lung cancer that was seen in this series [of NHL patients] resembles that reported among patients with CLL, a neoplasm closely related to NHL." This pattern was first reported for CLL in data from the National Cancer End Results Program, by Green et al. (1978), where "the pattern of excesses of malignant melanoma, soft tissue sarcomas, and lung cancers…suggested a role for leukemia-related immunosuppression rather than leukemia therapy in the genesis of these subsequent cancers."

O'Donnell JF, Brereton HD, Greco FA, et al. [1979]. Acute nonlymphocytic leukemia and acute myeloproliferative syndrome following radiation therapy for non-Hodgkin's lymphoma and chronic lymphocytic leukemia: clinical studies. Cancer *44*:1930-1938.

At the National Cancer Institute, 113 patients with advanced NHL and 75 patients with CLL were treated with RT from 1965-1975. Among this cohort, 7 patients developed ANLL secondarily, and 1 developed acute myeloproliferative syndrome (AMPS). Only one of the CLL cases developed a second leukemia. The authors state that, "the hallmark of our eight patients who developed ANLL or AMPS was repeated courses of radiation, and each received multiple techniques. No leukemia has been seen to date in patients who received a single induction course of radiation."

Whang-Peng J, Knutsen T, O'Donnell JF, Brereton HD [1979]. Acute non-lymphocytic leukemia and acute myeloproliferative syndrome following radiation therapy for non-Hodgkin's lymphoma and chronic lymphocytic leukemia: cytogenetic studies. Cancer *44*:1592-1600.

One case of secondary ANLL was identified among 76 cases of CLL patients treated with RT at the National Cancer Institute's Clinical Center, as reported by O'Donnell et al. (1979). Cytogenetic analysis of this patient, an 82 year old woman, revealed the presence of multiple chromosome abnormalities. Seven cases of ANLL secondary to NHL were also examined for chromosome abnormalities. The CLL patient demonstrated a more complex pattern of chromosomal aberrations than did the NHL patients; furthermore, the authors state that "she exhibited…the most extensive and complex chromosome involvement…that has been observed in our laboratory to date."

Greene MH, Hoover RN, Fraumeni JF [1978]. Subsequent cancer in patients with chronic lymphocytic leukemia—a possible immunologic mechanism. J Natl Cancer I *61*:337-340.

According to data from the National Cancer Institute's End Results Program, 4,869 cases of CLL were diagnosed between 1935 and 1971. 234 of these CLL cases developed a second primary cancer, representing a 10% excess of cancer (RR=1.1, 95% CI=1.0-1.3). This excess was mainly due to malignant melanoma, soft tissue sarcoma, and lung cancer. The elevation in these cancers was apparently independent of sex, treatment group, and follow-up period.

Rosner F, Grunwald H [1975]. Hodgkin's disease and acute leukemia. Am J Med *58*:339-353.

This article includes a review of 37 cases of co-disease with CLL and Hodgkin's disease. In 29 of the 37 patients, the CLL diagnosis preceded the Hodgkin's disease diagnosis. In 19 of these patients the diagnosis of Hodgkin's disease was made at autopsy. The period between diagnosis of CLL and the subsequent diagnosis of Hodgkin's disease was less than 1 year in 9 patients.

IX. Descriptive Epidemiology and Literature Reviews of CLL

Call TG, Phyliky RL, Noel P, et al. [1994]. Incidence of chronic lymphocytic leukemia in Olmsted County, Minnesota, 1935 through 1989, with emphasis on changes in initial stage at diagnosis. Mayo Clin Proc *69*:323-328.

Patterns of incidence and stage of diagnosis were assessed over the time frame of 1935-1989 in Olmsted County, Minnesota. 148 cases of CLL were diagnosed in Olmsted residents during this period. Examination of these cases revealed that the incidence rate of CLL has increased over the 55 year study period among persons older than age 50. The rates of CLL for those younger than age 50, however, remained essentially constant. The researchers found that the sex ratio (male: female) for CLL decreased with advancing age (<50 years of age 2.3:1, 50-74 years of age 1.8:1, and >75 years of age 1.1:1). In addition, an increase in the proportion of cases diagnosed as stage Rai stage 0 (lymphocytosis only), the stage of CLL associated with the least risk, was observed in this cohort; however, survival time of the patients was lower than that reported in other studies. The authors offer a possible explanation for this phenomenon, that CLL may be "diagnosed incidentally in an increasing number of older patients seeking medical care for other chronic disease." They further speculate that the observed trend of increasing CLL in this study may not reflect an actual increase in the incidence of the disease, but rather increased detection of CLL due to improved diagnostic tools and increased diagnosis of asymptomatic cases.

Erlanson M, Osterman B, Jonsson H, et al. [1994]. Chronic lymphocytic leukemia: a retrospective study of 122 cases. Eur J Haematol *52*:108-114.

A retrospective study of 122 cases of CLL from the three northernmost counties of Sweden, diagnosed between 1978 and 1982 and followed until 1989, was performed to examine trends in survival. The researchers found that most of the cases of CLL were diagnosed incidentally; that is, CLL was detected during a check-up for another condition. At the time of diagnosis, only 55 of the 122 patients consulted their doctor because of symptoms related to CLL. Crude survival analysis demonstrated no difference in survival according to stage of disease; however, when cause-specific survival analysis was performed, with CLL as underlying cause of death, stage of disease was a slight indicator of prognosis (median survival time stage A=102 months, B=80 months and C=63 months). In an exercise of Cox regression model building, age, sex and stage were significant predictors for prognosis. The authors conclude that the crude survival results seen by disease stage reflect the fact that many of the CLL patients died from diseases other than CLL.

Storm HH, Clemmensen IH [1993]. Lymphatic and hematopoietic tissues. APMIS *33*:183-213.

Incidence and survival patterns of cancers of the lymphatic and hematopoietic tissues, diagnosed between 1943 and 1987, were reported in this Danish study. During 1983-1987,

NHL accounted for 2% of malignant neoplasms. The incidence of NHL increased during the period of 1983-1987; the rates for men and women were 7.6 and 5.5 per 100,000, respectively. Mortality remained stable at 4 and 2 deaths per 100,000 for men and women, respectively. A 14-16% increase in relative 5-year survival between the 1970s and 1987 was observed, reflecting the implementation of chemotherapy for treatment of NHL. CLL represented 1.3% of all cancers among men and 0.7% of cancers among women during the period 1983-1987. Incidence of CLL remained stable at <4 cases per 100,000 for males and 2 per 100,000 for females. Total leukemia mortality was essentially constant over this period. Of the 4,521 CLL cases diagnosed between 1943 and 1987, fewer than 10% were younger than 50 years of age. The majority of cases (over 50%) were older than 70 years. Steady increases in survival rates for CLL were seen in the periods 1953-1957 and 1983-1987.

Finch SC, Linet MS [1992]. Chronic leukemias. Bailliere's Clinical Hematology 5:27-56.

Potential problems in CLL diagnosis were described in this review. Among B-cell CLL (B-CLL) cases, over 25% may be asymptomatic or indolent for years; thus underdiagnosis of CLL may be substantial. In addition to underdiagnosis, diagnosis may be complicated by occurrences of Richter's syndrome (where B-CLL transforms terminally into NHL) or by instances where transformed lymphomas present as leukemias. In rare instances, MM has transformed into CLL. Furthermore, cases which are actually CLL may be ascribed to "infectious, autoimmune, benign hematological, or drug-induced disorders, or other hematopoietic malignancies." Lack of specification of leukemia subtype on death certificates is also problematic.

Also discussed in this review was the incidence of CLL by race, geographic area, and sex. CLL has been shown to exhibit the greatest variability among populations compared to other leukemia subtypes. In the US, the age-adjusted incidence rate of CLL is highest among whites, followed by blacks, then Hispanics and lastly Asians; there is a difference 8-9-fold in rates between whites and Asians. In most western populations, CLL comprises 30% of all leukemias, whereas in Asian populations CLL is responsible for only 3-5% of leukemia. CLL is seen more frequently in males that females; the sex ratio is estimated to be approximately1.5-2.5. The author also noted an unexplained peculiarity in the incidence of CLL over the past century; in the 1940s and 1950s mortality rates increased across several countries for males over the age of 45 and females over the age of 60.

Etiology was reviewed by the authors, who noted that familial leukemia is seen more frequently among CLL than the other subtypes. Chromosome aberrations were also discussed; it was stated that 50% of B-CLL cases have been demonstrated to have an abnormality in chromosome 12 or 14. The authors concluded that the fact that "over half of the CLL patients have no abnormality of chromosome 12 suggests that a specific CLL gene is unlikely."

Another interesting issue raised by the authors is association of CLL with several autoimmune disorders. "It has been hypothesized that some of the apparent associations of autoimmune disorders with CLL may reflect underlying perturbations of immune

mechanisms common to both disorders. The association with rheumatoid arthritis [RA] may be real, since CLL patients with this autoimmune disorder have been found to have the unusual subtype T-γ lymphocyte leukemia."

X. General Etiology of CLL

Marti GE, Carter P, Abbasi F, et al. [2003]. B-cell monoclonal lymphocytosis and B-cell abnormalities in the setting of familial B-cell chronic lymphocytic leukemia. Cytometry *52(B)*:1-12.

This study proposes that B-cell monoclonal lymphocytosis (BCML) is a precursor state for the development B-CLL, much like the relationship identified between monoclonal gammopathy of unknown significance (MGUS) and MM. Nine pedigrees were examined in this study of familial B-CLL, consisting of 19 individuals affected with B-CLL and 33 unaffected individuals. Flow cytometry and polymerase chain reaction (PCR) analysis were used to determine BCML status in the unaffected individuals, where BCML was defined as "a pattern of abnormalities suggestive of, but not fulfilling, the minimal criteria for the diagnosis of B-CLL." Of the 33 screened individuals, 6 (18%) were determined to have BCML. Compared to the population prevalence estimate of 0.7% for BCML, reported by Marti et al. (1995), the finding of 18% was highly significant ($p=5.7x10^{-9}$).

Lynch HT, Weisenburger DD, Quinn-Laquer B, et al. [2002]. Hereditary chronic lymphocytic leukemia: an extended family study and literature review. Am J Med Genet *115*:113-117.

This paper describes a CLL family where the father and all his children (4 sons, 2 of whom are identical twins) are affected with the disease. "This finding of male-to-male transmission excludes sex-linked inheritance and is consistent with an autosomal dominant mode of genetic transmission of susceptibility to CLL. The occurrence of CLL in identical twins in the sibship adds to the likelihood of a primary hereditary etiology. These results are also in agreement with a strong nongenetic familial factor, such as a common environmental exposure, but interviews with family members have not found any plausible environmental factors beyond growing up on a farm." Cytogenetic analysis was also performed, revealing an acquired (buccal cells were normal) monosomy of 13q14 in all 4 brothers to varying degrees. The authors note this finding suggests a genetic etiology that predisposes to loss of 13q14, which they propose would facilitate the expression of an oncogene on the homologous chromosome and result in CLL, or, alternatively, "it is also possible that the hereditary factor is a deleterious mutation on 13q14, for example, in a tumor suppressor gene, that is unmasked by the acquired deletion of the normal allele on 13q14."

Mueller LP, Machulla HKG [2002]. Increased frequency of homozygosity for HLA class II loci in female patients with chronic lymphocytic leukemia. Leukemia Lymphoma *43*:1013-1019.

CLL is characterized by a clonal proliferation of mature-appearing lymphocytes, where 95% of all cases are of B-cell origin. Since B-cell proliferation normally occurs in the adaptive immune response and can be initiated by major histocompatibility complex (MHC)-restricted T-cell activation, the frequency of human leukocyte antigens (HLA) was examined among CLL patients. This study is the first to investigate the distribution of HLAs with respect to gender and age of disease onset. To examine gender differences, the frequencies of HLA-A, -B, -Cw, -DRB 1/3/4/5, -DQB1, and -DPB1 loci were analyzed among male and female German CLL cases and compared to the frequencies of the alleles among the control group, which was derived from healthy Caucasian blood donors. An increased frequency of homozygosity was observed for the DRB and DQB1 loci among female patients compared to male patients; increased frequency of homozygosity was also observed upon comparing female patients to gender matched controls. These findings are consistent with the HLA-DR/DQ region within the MHC containing a recessive, gender-specific susceptibility factor. With regard to age of onset, the authors found an increased frequency of HLA-Cw*06 among the early onset patients (<61 years of age) compared to controls and compared to the late onset patients (≥ 61 years of age), though these differences were not significant after applying a correction factor for multiple comparisons. Finally, the study supported the previously reported finding of an increased frequency of HLA-DRB4*103 among CLL patients regardless of gender and .age.

Stankovic T, Stewart GS, Fegan C, et al. [2002]. Ataxia telangiectasia mutated-deficient B-cell chronic lymphocytic leukemia occurs in pregerminal center cells and results in defective damage response and unrepaired chromosome damage. Blood *99*:300-309.

It has been previously established that 1) B-cell CLL can be described by the stage of B-cell differentiation in which the cells are transformed—in either pregerminal or post germinal centers and 2) ataxia telangiectasia mutated (ATM) gene mutations can occur in B-CLL, leading to a defect in the p53 pathway and affecting cell cycle regulation and apoptosis. This study examined 50 B-CLL tumors in an attempt to ascertain the role of ATM mutations in the pathogenesis of B-CLL. Of the 50 tumors screened for ATM and TP53 status, 16 were found to have ATM mutations, 6 had TP53 mutations, and 28 expressed wild type ATM and TP53. ATM and TP53 mutations were found to be mutually exclusive. To determine pregerminal or post germinal center of origin of the 50 B-CLLs, the V gene family sequences from the tumor cells were compared with germline sequences. Less than 2% sequence homology was indicative of an absence of somatic variable region hypermutation, proving a pregerminal center origin. All 16 ATM mutant B-CLL tumors were of a pregerminal center origin, as were 5/6 of the TP53 mutant B-CLLs. All 28 wildtype ATM and TP53 tumors were of post germinal center origin, as the sequence comparisons showed the presence of somatic mutation in the VH region. The study also demonstrated that the ATM mutant tumors displayed a deficient p53 response following irradiation, followed by a lack of upregulation of TRAIL-2 (a downstream

target that links irradiation induced p53 response with apoptosis) and finally an inability to repair induced chromosome breaks. The authors hypothesize that "loss of ATM function during B-cell ontogeny drives B-CLL tumorigenesis in pregerminal B-cells by a dual defect in p53 response and repair of chromosome breaks."

Gharagozloo S, Khoshnoodi J, Shokri F [2001]. Hepatitis C virus infection in patients with essential mixed cryoglobulinemia, multiple myeloma and chronic lymphocytic leukemia. Pathology Oncology Research *7*:135-139.

It has been previously demonstrated that hepatitis C virus (HCV) can infect human lymphocytes, suggesting that HCV may play a role in the development of some lymphoproliferative disorders. In support of this theory, recent studies have shown HCV to be associated with essential mixed cryoglobulinemia (EMC), NHL, low grade mucosal associated lymphoid tissue lymphoma, and ALL. This study examined the prevalence of HCV in Iranian patients with EMC, MM, and CLL compared to a control group of patients with chronic RA. RA patients were selected as controls in an attempt to account for hospital-associated risk factors for blood-borne disease. The results of the study confirm the association between EMC and HCV. Furthermore, the study showed an increased prevalence of HCV in the MM patients (11%, $p<0.06$) compared to the RA controls where 0 of 30 patients were HCV positive. The finding of 11% prevalence was also considerably higher, though not significantly, than the prevalence of HCV among the normal Iranian population, which is estimated to be 0.3%. For CLL, of the 23 patients screened for HCV, 1 was found to be HCV positive (4.3%), a non-significant result.

Machulla HKG, Muller LP, Schaaf A, et al. [2001]. Association of chronic lymphocytic leukemia with specific alleles of the HLA-DR4:DR53:DQ8 haplotype in German patients. Int J Cancer *92*:203-207.

Considering B-cell proliferation normally occurs in response to MHC-restricted T-cell activation, the involvement of HLAs in the pathogenesis of CLL warranted investigation. This study examined the frequency of HLA alleles in 101 Caucasian CLL patients compared to 157 healthy Caucasian controls. An increased frequency of the single alleles of HLA-DRB1*0401 (RR=2.13, $p<0.035$), HLA-DRB4*0103 (RR=2.74, $p<0.0025$), HLA-DQB1*0302 (RR=2.03, $p<0.035$), and HLA-DPB1*0301 (RR=2.15, $p<0.04$) was observed; however, the statistical significance of these findings was lost after adjustment for multiple comparisons. An increased frequency of homozygosity of the HLA-DQB1 in CLL patients (RR=2.62, $p<0.025$, prior to correction factor) was observed which could be explained by a recessive susceptibility factor within or near the HLA-DR:DQ MHC region, according to the authors. The results of the haplotype analysis suggested to the researchers an association between CLL and the HLA-DR4:DR53:DQ8 haplotype. This association has been also been observed in insulin-dependent diabetes mellitus and RA, which is consistent with a common etiology among these diseases.

Pekarsky Y, Hallas C, Croce CM [2001]. Molecular basis of mature T-cell leukemia. JAMA *286*:2308-2314.

T-cell chronic lymphocytic leukemia (T-CLL) and T-cell prolymphocytic leukemia (T-PLL) both result from clonal proliferation of post-thymic immunocompetent lymphoid cells. It has not been resolved whether the two leukemias are in fact separate entities. Compared to T-PLL, T-CLL shows smaller, more mature lymphocytes, similar to B-CLL. Both T-CLL and T-PLL frequently demonstrate chromosome rearrangement of 14q32.1 at the TCL1 locus, leading to activation of the TCL1 gene. TCL1 is expressed in T-cells at an early stage, whereas mature T-cells do not normally express the gene. Several studies have reported activation of TCL1 in nearly 100% of sampled cases of T-CLL/T-PLL. This article proposes that Tcl1 (the protein product of the TCL1 gene) interacts with Akt to increase Akt kinase activity, which subsequently activates a prosurvival pathway. Akt is the human homolog of *v-akt,* a gene from the murine retrovirus AKT8 which causes T-cell lymphoma in mice.

Reimer P, Weibinger F, Tony HP, et al. [2000]. Persistent polyclonal B-cell lymphocytosis—an important differential diagnosis of B-cell chronic lymphocytic leukemia. Ann Hematol *79*:327-331.

Often patients with persistent polyclonal B-cell lymphocytosis (PPBL), an apparently benign disorder, are misdiagnosed with CLL. PPBL is characterized by high lymphocyte counts, binucleated B-cells, HLA-DR7 expression, and polyclonal increase of serum IgM. Evidence exists that a genetic disposition factors into the development of PPBL, as the vast majority of the cases are women and the cases are more frequently of the HLA-DR7 phenotype. Since most of the documented PPBL cases have been smokers, it is likely smoking may also contribute to the onset of this disorder. This study looked at interleukin-4 (IL-4) response, as measured by CD23 and HLA-DR expression, as a means to distinguish PPBL cells from normal B-cells and from B-CLL cells. The investigators found that PPBL cells showed no IL-4 response whereas normal peripheral B-cells and B-CLL cells responded to IL-4 stimulation. These results indicate that PPBL cells undergo different activation and differentiation than normal B-cells and B-CLL cells.

Bullrich F, Rasio D, Kitada S, et al. [1999]. ATM mutations in B-cell chronic lymphocytic leukemia. Cancer Res *59*:24-27.

Ataxia-telangiectasia (AT) is an autosomal recessive disorder arising from mutations in the ATM gene on the long arm of chromosome 11, at 11q22-23. AT has been implicated in the development of T-PLL/T-CLL. This research involved sequencing DNA from 5 patients with loss of heterozygosity (LOH) at 11q22-23 and lack of ATM expression, and 1 patient with undetermined LOH status, in order to identify mutations in the ATM gene. Four missense mutations were found among these patients. Two of the patients carried the mutation in their germline, "suggesting that ATM heterozygotes may be predisposed to B-CLL." The authors speculate the carrier rate (heterozygosity) to at least be 5.9%, as 2 heterozygotes were found among the 4 samples of germ-line DNA tested (the germ-line DNA was examined for only 4 out of 34 sporadic B-CLL cases with LOH and ATM

mutations). A rate of 0.2-1% of AT heterozygotes among Caucasians has been reported previously (Easton et al. 1994, FitzGerald et al. 1997); the current finding of 5.9% is significantly different than the estimate of 1%, with a one-sided p=0.045.

Caligaris-Cappio F, Hamblin TJ [1999]. B-cell chronic lymphocytic leukemia: a bird of a different feather. J Clin Oncol *17*:399-408.

The authors characterize the "distinctiveness" of B-CLL: 1) it is the only blood malignancy whose frequency was not increased among atomic bomb survivors 2) the etiology suggests a genetic element 3) the disease is typified by defects in induction of apoptosis 4) CLL patients are prone to autoimmune phenomena. The authors describe the immunophenotype of B-CLL as similar to that of lymphocytes of the mantle zone. B-CLL cells express the majority of the same membrane antigens as do normal mature B-cells; however B-CLL cells also express CD5 as well as very faint amounts of monoclonal surface immunoglobulins (sIgs). The sIgs frequently exhibit polyreactive autoantibody activity, and the low levels of sIgM characteristic of CLL are also seen in normal B lymphocytes that have been anergized by self-antigen (Ag). Taken together, this information suggests that "B-CLL is a malignancy of a mantle zone-based subpopulation of anergic self-reactive CD5+ B-cells that are devoted to the production of polyreactive autoAbs [autoantibodies]." The authors also speculate that "extended cell survival is further shielded by a kinetic refractoriness likely promoted by abnormalities of the B-cell receptor complex and favored by some cytokines that highlight a reciprocal dialog between malignant B and T-cells."

Bauer SR [1997]. B-cell differentiation and risks for neoplastic transformation. In: Marti GE, Vogt RF, Zenger VE editors. Proceedings of a USPHS workshop on laboratory approaches to determining the role of environmental exposures as risk factors for B-cell chronic lymphocytic leukemia and other B-cell proliferative disorders. Atlanta, GA p 51-60.

B-cell differentiation and the risks of neoplastic transformation are discussed by Bauer:

> "The B-cell's inherent capacity to rearrange and mutate its immunoglobulin genes is critical for generation of specific antibody-mediated immunity. However, this capacity also introduces risk since the process of immunoglobulin rearrangement or mutation can go awry, resulting in unintentional rearrangement or mutation of genes involved in control of cell growth. In addition to this high mutation risk, B-cells have an innate capability to undergo high rates of proliferation at various stages of differentiation or in response to antigen. Thus mutations which accumulate can be unintentionally selected when an altered B-cell is undergoing the high natural proliferation in response to antigen or during a normal phase of differentiation. This selection then sets the stage for further accumulation of mutation and consequent B-cell neoplasia."

Faguet GB [1997]. The common chronic lymphocytic leukemia antigen (cCLLa). In: Marti GE, Vogt RF, Zenger VE editors. Proceedings of the USPHS workshop on laboratory approaches to determining the role of environmental exposures as risk factors for B-cell chronic lymphocytic leukemia and other B-cell lymphproliferative disorders. Atlanta, GA, pp 103-105.

Common chronic lymphocytic leukemia antigen (cCLLa), a 69 kilodalton surface glycoprotein, is expressed in B-CLL, prolymphocytic leukemia (PLL), and HCL. The expression is universal: the antigen is expressed in all clonal cells in all patients with these diseases. Furthermore, the antigen is not expressed by normal B or T-cells and rarely detected in diseases other than B-CLL, PLL, and HCL, demonstrating its value for diagnosis. The antigen also has implications for treatment, as monoclonal anti-cCLLa antibodies have been found to have clonal-specific cytoxicity.

Maiese RL, Braylan RC [1997]. Detection of low levels of B-cell lymphoproliferative disorders. In: Marti GE, Vogt RF, Zenger VE editors. Proceedings of the USPHS workshop on laboratory approaches to determining the role of environmental exposures as risk factors for B-cell chronic lymphocytic leukemia and other B-cell lymphoproliferative disorders. Atlanta, GA, pp 61-68.

This report discusses the utility of flow cytometry in detection of B-cell monoclonality. Normally B-cells in the tissue or the periphery are polyclonal; that is, they consist of a mixture of cells expressing kappa or lambda surface immunoglobulin light chains, where the κ/λ ratio is about 1.5:1. B-cell lymphomas and B-CLL are clonal in origin, expressing only one light chain. When examining normal tissue or blood via flow cytometry, a bimodal peak is observed when staining for κ or λ surface immunoglobulin. In B-cell lymphoma or B-CLL, however, only one peak is observed, demonstrating the mutually exclusive expression of a single light chain.

Marti GE, Muller J, Stetler-Stevenson M, Caporaso N [1997]. B-cell monoclonal lymphocytosis in three individuals living near a hazardous waste site. In: Marti GE, Vogt RF, Zenger VE editors. Proceedings of the USPHS workshop on laboratory approaches to determining the role of environmental exposures as risk factors for B-cell chronic lymphocytic leukemia and other B-cell lymphoproliferative disorders. Atlanta, GA, pp 37-50.

Eleven individuals were found, during the course of ten studies, to have a B-CLL like phenotype. Additional laboratory testing was completed on three of the 11 individuals to confirm monoclonality, since B-CLL and B-cell NHL (B-NHL) arise from malignant expansion of monoclonal B-cells. BCML was detected in all three. In light of these results, the authors stress the need to determine the incidence of BCML with or without CD5 expression in the normal adult population. The authors also speculate about the possible course of this disease: 1) BCML is transient and will disappear 2) BCML is stable or 3) BCML will progress to lymphoproliferative disease. If the latter is true, BCML could serve as a predictor for B-CLL.

Sarasua SM, Vogt RF, Middleton DC, et al. [1997]. 'CLL-like' B-cell phenotypes detected in superfund studies: epidemiologic methods and findings. In: Marti GE, Vogt RF, Zenger VE editors. Proceedings of the USPHS workshop on laboratory approaches to determining the role of environmental exposures as risk factors for B-cell chronic lymphocytic leukemia and other B-cell lymphoproliferative disorders. Atlanta, GA, pp 7-18.

Since 1991, ATSDR has carried out studies to assess the health consequences related to living near hazardous waste sites. In the course of completing 10 studies where immune testing was performed (5,868 participants combined), the researchers found that 11 individuals exhibited a "B-CLL like" phenotype characterized by a high proportion of B-cells relative to all lymphocytes, reduced staining of CD20 and/or CD45, and presence of CD5 on the surface of mature B-cells. All 11 individuals with the B-CLL like phenotype were over 45 years of age, yielding an overall prevalence of B-CLL like phenotype in those over age 40 (1,499 subjects) of 0.7%. The prevalence of the B-CLL like phenotype was greater, though not significantly, among those living closer to hazardous waste sites compared to those living farther (>5 miles) from hazardous waste sites (prevalence ratio=1.8, 95% CI=0.5-6.9). Further investigation into these cases revealed that 1 person had been previously diagnosed with CLL. As the estimated incidence of CLL among those age 50 and over is 5 per 100,000, less than 1 case of CLL would be expected, thus the 1 case of CLL fits with the known data. However, the finding of 11 B-CLL like cases was not anticipated; the researchers believe this "could indicate an emerging epidemic of B-CLL or simply a slow and uncertain progression from laboratory abnormalities to clinical disease."

Vogt, RF, Meredith NK, Powell J, et al. [1997]. Laboratory results in eleven individuals with B-CLL like phenotypes detected in environmental health studies. In: Marti GE, Vogt RF, Zenger VE editors. Proceedings of the USPHS workshop on laboratory approaches to determining the role of environmental exposures as risk factors for B-cell chronic lymphocytic leukemia and other B-cell lymphoproliferative disorders. Atlanta, GA, pp 19-35.

Flow cytometry is useful in characterizing the expression of receptor proteins on the surface of a lymphocyte, a process known as lymphocyte phenotyping. In an ATSDR study series (10 studies) examining the effects of living near hazardous waste sites, a "B-CLL like" phenotype was observed in 11 of 5,868 combined study participants. The lymphocyte phenotype (LPT) was marked by a high proportion of B-cells relative to total lymphocytes, with expression of CD5 on the B-cell along with reduced expression of CD45 and/or CD20. Such a profile is abnormal, as CD5 is usually highly expressed only by T-cells. Also, lymphocytes usually stain more brightly than other leukocytes for CD45; however, some of the CLL-like profiles showed reduced staining of this marker (such reduced staining is typical of certain types of B-CLL.) Furthermore, CD20 is normally expressed at high levels on mature peripheral B-cells, which make up about 25% of peripheral blood lymphocytes in adults. B-cells, on the other hand, account for the majority of peripheral lymphocytes in B-CLL patients and stain only slightly for CD20.

Montserrat E, Bosch F, Rozman C. [1997]. B-cell chronic lymphocytic leukemia: recent progress in biology, diagnosis, and therapy. Ann Oncol *8 (Suppl 1):*S93-S101.

Criteria for establishing a diagnosis of CLL are: 1) absolute lymphocytosis in peripheral blood: $>5x10^9$ (National Cancer Institute/Working Group) or $>10x10^9$ (International Workshop on CLL) 2) lymphocytes are mostly small and mature in appearance 3) expression of the characteristic phenotype (SmIg+/-, CD5+, CD19+, CD20+, CD23+, FMC7-/+, CD22-/+) and 4) bone marrow infiltration (>30% of lymphocytes in bone marrow aspirate, or consistent pattern in bone marrow biopsy). Three morphologic subtypes of CLL exist (FAB group): 1) typical or classic CLL (<10% atypical lymphocytes) 2) mixed CLL/ prolymphocytic leukemia (PL) (11-54% prolymphocytes in blood) and 3) atypical CLL (variable proportion of atypical lymphocytes in blood with <10% prolymphocytes). An association between trisomy12 and the atypical phenotype has been reported, as has an association between deletions in chromosome 6 and prolymphocytes in the blood. This review article also highlights that "chromosome abnormalities prevail in the advanced phases of the disease and in most cases are acquired events" and that karyotypic evolution, often related to disease progression, is found in 14-40% of CLL cases.

Montserrat E, Rozman C [1995]. Chronic lymphocytic leukemia: present status. Ann Oncol *6*:219-235.

A review of the current information on CLL, the article discusses the epidemiology and the biology of CLL. Discussed in the review is the variability of CLL among populations: CLL occurs less frequently in Asian populations and accounts for only 3-5% of all leukemia in Asians. The review references Nishiyama et al.1969 who found that the incidence of CLL is low even in Asians who have emigrated to the US. In terms of the biology of CLL, this article clarifies that "although earlier studies indicated that B-CLL lymphocytes were arrested at an early stage of development, studies with anti-idiotypic reagents and mitogenic stimulation have shown that the CLL B-lymphocyte can differentiate." Also emphasized in this review is the fact that most cases of CLL are diagnosed in an asymptomatic state, "at the Postgraduate School of Hematology in Barcelona, the proportion of patients diagnosed in an early stage has increased from 40% in the early 1970s to about 70%."

Gale RP, Caligaris-Cappio F, Dighiero G, et al. [1994]. Recent progress in chronic lymphocytic leukemia. Leukemia *8*:1610-1614.

The authors report on the sixth International Workshop on Chronic Lymphocytic Leukemia held in 1993; oncogenes were discussed in detail at the meeting. It is unclear which oncogenes are the cause or consequence of CLL. Abnormalities have been noted with retinoblastoma (RB) and P53 (15% of cases), BCL1, BCL2 and BCL3 (5% of cases), and other oncogenes (1% of cases). "Most abnormalities, such as MYC [a known oncogene] are likely to be a consequence. Others such as P53 and RAS, are likely to be late steps in leukemia development. However, data from other cancers, especially lymphomas, suggest that one or more oncogene abnormalities may cause CLL. The most

likely candidate is a gene linked to RB on chromosome 13." Another issue raised in the meeting was that of G_0 arrest. "CLL is often regarded as an accumulative disease: the clonal excess of B-cells is thought to result from extended B-cell survival rather than increased proliferation. Consequently, it is important to understand why CLL B-cells accumulate in G_0." Possible mechanisms responsible for the G_0 arrest include the following: abnormal phenotype, defective mitogen responsiveness, defective cytokine production or response, and impaired apoptosis. The authors state that "in CLL, BCL2 over-expression inhibits apoptosis resulting in the accumulation of B-cells in G_0".

Radovanovic Z, Markovic-Denic LJ, Jankovic S [1994]. Cancer mortality of family members of patients with chronic lymphocytic leukemia. Eur J Epidemiol *10*:211-213.

This matched case-control study compared cancer mortality among family members of CLL cases with cancer mortality among family members of controls. 119 new CLL cases were identified from 4 hospitals in Serbia in 1989. The cases were approached and administered the study questionnaire before their CLL diagnosis was revealed to them. Controls were matched to cases on sex, age, and place of residence and were administered the same form, which requested a listing of all 1^{st} ,2^{nd} ,3^{rd} and 4^{th} degree blood relatives, along with their age at the time of the questionnaire or age at death and cause of death. Matched ORs were calculated; the OR for leukemia was 5.50 (95% CI=1.44-20.97). SMR analyses were also performed. The SMR for leukemia among the 1^{st} and 2^{nd} family members of CLL cases was 2.04 (95% CI=0.99-3.09); no leukemia cases were observed among the 1^{st} and 2^{nd} degree family members of the controls.

Okazaki M, Luo Y, Han T, et al. [1993]. Three new monoclonal antibodies that define a unique antigen associated with prolymphocytic leukemia/ non-Hodgkin's lymphoma and are effectively internalized after binding to cell surface antigen. Blood *81*:84-94.

Monoclonal antibodies SN8, SN8a and SN8b, were generated via immunization of mice with PLL antigen. The SN8 series appears to bind a novel epitope on gp40/49. These monoclonal antibodies may serve as an important diagnostic tool, as they were able to distinguish between different types of leukemias and lymphomas. SN8 reacted with all 8 of the B-cell PLL (B-PLL) samples and 9/12 of the B-NHL samples; however, it did not react well with samples of B-CLL**,** HCL, or non-T/non-B ALL. The SN8 antibodies may also have implications for use as a mechanism to deliver cytotoxic agents to tumor targets, due to their tumor specificity. Finally, further studies of these antibodies may reveal information regarding the pathogenesis of B-PLL and B-NHL.

Murmane JP, Kapp LN [1993]. A critical look at the association of human genetic syndromes with sensitivity to ionizing radiation. Semin Cancer Biol *4*:93-104.

Factors that may influence the response to radiation were reviewed. Such factors include: variability within genes which may affect amount of cell damage, ability to respond to and repair cell damage, tolerance to DNA mutations, ability to eliminate free radicals, presence of mutations affecting cell structure and cell cycle regulation, and heterozygosity

for mutations in tumor suppressor genes. Various disorders, such as RB and Wilm's tumor, have been examined to determine if these diseases increase sensitivity to radiation. AT is thus far the only syndrome that has demonstrated sufficient evidence of clastogenicity (chromosome breakage) and cytotoxicity induced by ionizing radiation. Clinical characteristics of AT are radiosensitivity, immunodeficiency, ataxia (neurological problems), and telangiectasia (dilated blood vessels). AT patients are also predisposed to develop cancer; cancer occurs in 25-38% of patients. It has been postulated that the radiosensitivity observed in AT patients may arise from a defect in DNA repair or a defect in DNA recombination. Regarding AT heterozygotes, the general consensus is that these individuals show a slight increase in radiosensitivity.

Nilsson K [1992]. Human B-lymphoid cell lines. Human Cell *5*:25-41.

Several tumor cell lines have been developed to study B-cell tumors in the laboratory. Cell lines exist for most of the B-cell leukemias, B-lymphomas and myeloma; unfortunately no authentic cell line exists for CLL and PLL. Immortalization of B-CLL cells using infection with EBV has been attempted with limited success; only a few lines were able to be produced in this manner. These lines differ from *in vivo* CLL tumors due to the presence of EBV. "The reason why B-CLL cells are refractory to immortalization by EBV is not known but is not due to any of the following: an absence of EBV receptor expression, a defect in EBV-receptor binding, EBV uptake, or the expression of CD23 and EBNA. Walls et al. found that B-CLL cells became arrested in the GI/S phase of the cell cycle and did not express the transformation-associated LMP antigen or circularize EBV DNA, features suggesting that they were different from normal B-cells in their interaction with EBV. "

Rosenblatt KA, Koepsell TD, Daling JR, et al. [1991]. Antigenic stimulation and the occurrence of chronic lymphocytic leukemia. Am J Epidemiol *134*:22-28.

Between 1977 and 1981, 430 incident cases of CLL were identified in Seattle, Salt Lake City, Atlanta, and Detroit. A case-control study design was used to test the hypothesis that chronic antigenic stimulation is related to CLL. Population-based controls were selected from the same area of residence as the cases. ORs were calculated for 18 indices of chronic antigenic stimulation, adjusting for age, race, sex, study area, and education level. Cases more frequently reported syphilis exposure than did controls (OR=5.0, 95% CI=2.0-12.9). The authors speculated this association might be due to arsenic treatment, as arsenic treatment has been associated with other diseases of the blood forming organs. To further analyze the possible effect of arsenic exposure, stratification by year of the syphilis infection (pre or post 1943) was performed, since arsenic treatment was abandoned in 1943. This analysis revealed an OR of 9.6 for the pre-1943 period (95% CI=2.1-43.4) and 3.1 for the post 1943 period (95% CI=0.9-10.8). The authors also noted that immune suppression has been identified as a possible mechanism in CLL development, and that syphilis may cause immune suppression. In addition to syphilis, significant associations with tuberculosis (OR=1.9, 95% CI=1.0-3.7) and urinary tract infections (OR=1.4, 95% CI=1.1-1.9) were observed. Viral fever blisters also demonstrated a significantly elevated OR of 1.3 (95% CI=1.0-1.6). The authors concluded that "the findings of this study

provide little evidence of any general increase in risk for CLL associated with chronic antigenic stimulation…Furthermore, no apparent relation was found between the number of bacterial or viral conditions the subject reported having had and the development of CLL."

Butturini A, Gale RP [1990]. Oncogenes and leukemia. Leukemia *4*:138-160.

The relationship between oncogenes and leukemia development was addressed in this article. However, the role of oncogenes in terms of CLL was not discussed as "in most cases of acute lymphoblastic leukemia and chronic lymphocytic leukemia, oncogene abnormalities are uncommon." Relevant background information on oncogenes was provided in this paper; including differentiation of oncogenes by classes: growth factors, growth factor receptors, signal transducers, nuclear, and recessive oncogenes. Recessive oncogenes differ from the other types "in that it is their absence rather than abnormal expression that is correlated with tumorigenicity."

Morrison WH, Hoppe RT, Weiss LM, et al. [1989]. Small lymphocytic leukemia. J Clin Oncol *7*:598-606.

Small lymphocytic lymphoma (SL), a disease similar in morphology to CLL, makes up 4% of all malignant lymphomas. "It is often stated that SL is the solid tumor counterpart of CLL and that with time, SL patients usually progress to CLL." From 1963-1983, 54 patients diagnosed with SL were treated at the Stanford University Medical Center. Similar to the rate of 15% CLL progression as previously observed by Pangalis et al. (1977), ten of the Stanford patients (19%) went on to develop CLL. Patients with higher initial lymphocyte counts were significantly more likely to develop CLL than those with lower counts. The authors postulate the SL may be a precursor state for CLL.

Gale RP [1988]. Current issues in chronic lymphocytic leukemia. Nouv Rev Fr Hematol *30*:263-265.

The author contemplates the answers to three issues in CLL etiology. The first issue is whether CLL is a leukemia or a preleukemia. For example, CML is a preleukemia characterized by normally regulated growth and differentiation, but T-cells are in excess. CML almost always leads to an acute phase, AML, which is considered a leukemia due to the fact that growth is not regulated and differentiation is abnormal. It has been established that CLL arises from a clonal proliferation; however, whether the growth is normally regulated is unknown. It is also unknown whether the CD5 positive B-cell, characteristic of B-CLL, is a distinct subset or if it is also present as a rare, immature population of B-cells. "In the former instance CLL need not be interpreted as exhibiting a block in differentiation whereas the latter instance implies blocked differentiation. Presently most data support the second hypothesis." Hypothetically, if CLL were a preleukemia, the author offers plausible reasons why so few patients experience leukemia, namely that a) the transforming step is rare or b) the transforming step is not rare but the latency period is long. Another issue the author raises is where the CLL transformation occurs, "most data suggest that in B-CLL the leukemia clone is restricted to B-cells; T-

cells and myeloid cells are seemingly not involved." The final point Gale reflects on concerns whether immunodeficiency is secondary to CLL. Gale has "postulated that the initial lesion in CLL might be a non-malignant T-cell abnormality. This could lead to polyclonal expansion of the CD5 subset of B-cells and eventually lead to expansion or transformation of one clone. This would account for the T and B-cell abnormalities characteristic of B-CLL as well as explain the high incidence of polyclonal autoimmune antibodies."

Kipps TJ, Tomhave E, Chen PP, Carson DA [1988]. Autoantibody-associated κ light chain variable region gene expressed in chronic lymphocytic leukemia with little or no somatic mutation. J Exp Med *167*:840-852.

In a previous study the authors found that 5 of 20 κ light chain expressing CLLs reacted with a murine monoclonal antiidiotypic antibody, 17.109, which is specific for a cross-reactive idiotype associated with rheumatoid factor and other IgM autoantibodies. Stable idiotype expression was indicated from results of flow cytometric analysis, where the expression of 17.109 was directly proportional to the level of surface immunoglobulin κ chain. To further assess this relationship, sequence analysis on the genes encoding the immunoglobulin κ chain was done on 2 unrelated individuals whose cells were previously shown to react to 17.109. The analysis showed no evidence of sequence heterogeneity in the CLL clones. Also, the sequences expressed by the malignant T-cells of both patients were homologous to their germline Vκ. According to the authors these results suggest: "(a) that the malignant CD5+ B-lymphocytes in CLL use the same Vκ gene that has been highly associated with IgM autoantibodies and (b) that the expression of V genes is stable in CLL, in contrast to other B-cell malignancies examined to date." The investigators hypothesize that several CLL cases "represent malignancies of autoreactive CD5 B-cells that use a restricted set of conserved V genes" which may have implications for immunotherapy with antiidiotypic antibodies.

Butturini A, Gale RP [1988]. Oncogenes in chronic lymphocytic leukemia. Leukemia Res *12*:89-92.

Proto-oncogenes are a family of genes present in all eukaryotic cells, which are generally regarded as regulators of cell growth and development. Viral homologs of proto-oncogenes act in the pathogenesis of retroviruses, where the oncogene may contain deletions or insertions compared to the normal cellular homolog. Alternatively, retroviruses may not contain oncogenes in their genome, but rather act as a promoter or enhancer of the cellular proto-oncogenes. Retroviruses do not appear to be responsible for leukemia in humans, with the exception of the association of human T-cell lymphotrophic virus-1 (HTLV-1) with ATL and the association of human T-cell lymphotropic virus-2 (HTLV-2) with atypical hairy cell leukemia (neither virus is known to carry a viral oncogene with a normal cellular homolog). To examine the role of oncogenes in CLL pathogenesis, potential oncogenes were identified via the NIH/3T3 transformation assay and from chromosome mapping of cytogenic abnormalities. Using the NIH/3T3 method, Ki-ras has been implicated as an oncogene. Trisomy 12 is the most common chromosomal abnormality observed in CLL patients, occurring in 50% of cases. Trisomy 12 individuals

have a third copy of chromosome 12, and thus an extra copy of the Ki-ras gene. Other cytogenic abnormalities are seen in CLL patients, however they are rare. Such abnormalities and their envisaged oncogenes include t (11; 14) translocation leading the rearrangement of bcl-1, and 14q11-q32 abnormalities leading to rearrangement of tcl-1. The authors ponder the reasons why oncogenes are seen less commonly in CLL than in other leukemias. "One explanation is that relatively few cases have been studied. If trisomy 12 and therefore an additional copy of Ki-ras are important, then almost 50% of patients can be envisaged as having oncogene abnormalities. Another possibility is that oncogenes play a lesser role or no role in CLL. This could reflect the concept that CLL is a disorder of accumulation rather than proliferation."

Schrek R, Best WR, Stefani S [1988]. Relationship between in vitro and in vivo radiosensitivity of lymphocytes in chronic lymphocytic leukemia. Acta Haemat *80*:129-133.

About 25% of all CLL patients are resistant to chemotherapy, 50% of those with advanced stages of CLL are nonresponsive to chemotherapy. This aim of this research was to develop a method to detect CLL patients likely to be nonresponsive to chemotherapy. Schrek et al. found previously that "in vitro radioresistant lymphocytes from CLL patients at the time of diagnosis was associated with the resistance of patients to both radiotherapy and chemotherapy." This research demonstrated a correlation between in vitro radiosensitivity of the lymphocytes of patients with CLL and in vivo response to RT. The authors conclude that testing cells in vitro may predict nonresponsiveness to RT, which in turn may indicate resistance to chemotherapy.

Linet MS [1984]. Chronic lymphocytic leukemia and multiple myeloma in husband and wife. Am J Med Sci *288*:21-24.

This case of CLL in a husband and MM in a wife affords the researcher the opportunity to examine common environmental exposures as cause for the cancers. After interviewing the wife, four potential exposures were noted: 1) the wife painted the house interior once a year and used paint remover every few years to remove paint layers 2) the wife sprayed insecticide once a week to control cockroaches 3) the husband worked as an embalmer and the wife washed the work uniform a few times a week 4) the couple lived adjacent to a plant involved in the manufacturing of diesel engine parts. The most suspicious exposure, according to the author, is the weekly insecticide spraying. Benzene, which is found in some pesticides, has been implicated in the development of both CLL and MM.

Hull MT, Griep JA [1980]. Mixed leukemia, lymphatic and myelomonocytic. Am J Clin Pathol *74*:473-475.

A case of mixed lymphatic and myelomonocytic leukemia was reported in a 76 year old man. Only 21 such cases have been documented since the first known occurrence in 1906. The authors summarize that "mixed leukemia is a rare phenomenon that occurs mainly in elderly patients who have CLL in whom terminal blastic leukemia of either monocytic or

myelocytic type develops. Many of these patients had prior exposure to either ionizing radiation or alkylating agents during the course of their chronic lymphocytic leukemias."

Rozynkowa D, Rupniewska Z, Stepien J [1976]. T lymphocytes in chronic lymphocytic leukemia. Annals Med Sect Pol Acad Sci *21*:121-138.

This article concludes that "1. The lymphocytes in the peripheral blood in CLL are characterized by a late occurrence of the peak of blastic transformation under the influence of PHA [phytohemagglutinin]. They consist of a fraction of late-reacting cells to PHA and blasts arising by secondary proliferation of early-reacting cells. Lymphocytes of the late-reacting fraction occur also in the lymphocyte cultures of healthy subjects. 2. ….this fraction may be classified as normal thymus dependent lymphocytes. 3. The admixture of late-reacting lymphocytes to PHA which are incapable of producing E rosettes suggests participation in this fraction of yet another subpopulation. 4. Approximate estimation of the magnitude of early and late-reacting fraction to PHA permits the conclusion that the pool of normal T lymphocytes in the circulating blood is not diminished in the early years of untreated chronic lymphocytic leukemia."

Gunz FW, Gunz JP, Veale AMO, et al. [1975]. Familial leukemia: a study of 909 families. Scand J Haematol *15*:117-131.

Leukemia patients in the Sydney, Australia area were identified and a survey of leukemia in family members was completed via a questionnaire/interview. The occurrence of leukemia in 909 families was studied and compared to expected rates based on the New South Wales population. Of the 909 (200 CLL) patients, 72 had relatives with leukemia. For the CLL subtype, 16 of the patients had relatives with leukemia of which 7 were first degree relatives (43.7%). Among the 7 CGL patients with relatives with leukemia, only 1 was a first degree relative. Additionally, only one instance of concordance between subtypes of leukemia was observed among the CGL families, whereas with CLL 6 of the families exhibited concordance. The authors suggest that "familial leukemia was of greater importance in CLL than CGL." Overall, the O/E ratios for leukemia for first degree relatives and for other relatives were 2.43 and 2.15, respectively. This analysis was not performed by leukemia subtype.

XI. General Radiation/Radiobiological Effectiveness Factor

Darby SC, Inskip PD [1995]. Ionizing radiation: future etiologic research and preventive strategies. Environ Health Persp 103 Supp *8*:245-249.

Radiobiological effectiveness factor (RBE) is discussed in this review of ionizing radiation. Animal data have shown that cancer risk from penetrating low low-energy transfer (LET) radiation is lower for prolonged exposure than for acute exposure of equivalent dose. Thus when extrapolating risk from protracted exposures using data from acute exposures, the risk estimates have often been divided by a dose-rate effectiveness factor. A RBE factor between 2 and 10 has been suggested from available animal data. The authors note that preliminary data do not support dose-rate factors as large as 10.

"Estimates of the excess relative risk per Sv for all cancers combined are very similar for nuclear workers and atomic bomb survivors, while leukemia risk estimates differ by a factor of about three to four."

Voelz GL [1991]. Health considerations for workers exposed to plutonium. Occup Med *6*:681-694.

This article reviewed the basis for the argument that plutonium may be related to lymphopoietic diseases. "About 3-7% of Pu deposited in human bone is located in the bone marrow, which raises a question about the risk of inducing leukemia or myeloproliferative disorders. These diseases are not a significant finding in the dog studies; however high doses of Pu result in considerable damage to hematopoiesis and bone marrow function in mouse experiments."

Freeman SE, Ormiston-Smith HM [1994]. The biological hazard of plutonium. Medicine and War *10*:106-126.

In this review of the hazards of plutonium, the author cites the Kadhim et al. (1994) study of chromosome instability after plutonium irradiation. The chromosome abnormalities seen by Kadhim et al. "suggested that exposed (and surviving) stem cells transmit to their daughter cells some chromosomal instability that may result in some visible cytogenetic aberration many cell cycles later. They suggest that it is possible that the instability could, on occasions, disrupt a region of the genome involved in leukemic transformation." This review also mentions that "estimates of leukemia risk are based on epidemiological data for LET radiations, taking into account the enhanced effectiveness of high LET radiations such as alpha particles. It is suggested, however, that there may be unique, initial radiogenic damage induced only by high LET radiations. If this should be so then the RBE of alpha particles compared with low LET radiations would not be between 3 and 50, as is currently believed, but could approach infinity. Such a suggestion would complicate epidemiological studies, where a correlation between dose and effect is sought, since a low dose of alpha irradiation might be leukemogenic if a single track through a target T-cell were to be effective. It is likely, however, that the initial radiogenic damage would need some form of 'promotion', so that the damaged cells would have an advantage over undamaged cells."

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