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A Cohort Mortality Study of Chemical Laboratory Workers at Department of Energy Nuclear Plants

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Objective *This study evaluates the mortality experience of 6,157 chemical laboratory workers employed at United States Department of Energy facilities.*
Methods *All cause, all cancer and cause-specific standardized mortality ratios were calculated. Cox regression analyses were conducted to further evaluate the relation between chemical exposure and mortality risk due to selected cancers.*
Results *The mortality due to all causes combined and all cancers combined were below expectation for the cohort. There were no statistically significant elevations reported among males for any specific cancer or non-cancer outcome. There no statistically significant elevations among females for any specific non-cancer and most specific cancers; however, multiple myeloma deaths were significantly elevated (SMR = 3.56; 95% CI = 1.43–7.33; number of observed deaths, n = 7). Statistically significant elevations were seen among workers employed 20+ years for leukemia using both 2- and 5-year lag periods. Also, a statistically significant positive trend of elevated lung cancer mortality with increasing employment duration was seen using both 5- and 10-year lags. A similar trend was seen for smoking related cancers among men.*
Conclusion *While lymphatic and hematopoietic cancer mortality was below expectation, a significant elevation of multiple myeloma deaths among females and an elevation of leukemia among workers employed 20+ years (possibly due to radiation and benzene exposure) were observed. A NIOSH case–control study is underway to examine more closely the relation between multiple myeloma and a variety of chemical exposures among workers employed at the Oak Ridge K-25 facility.* Am. J. Ind. Med. 51:656–667, 2008. © *2008 Wiley-Liss, Inc.*

KEY WORDS: laboratory workers; multiple myeloma; cancer; mortality study; Department of Energy

INTRODUCTION

Laboratory workers are regularly exposed to many highly toxic chemical agents [Fawcett, 1972; Kauppinen et al., 2003] and as a result these workers have long been suspected of having an increased risk of developing cancer. Previous epidemiologic studies of laboratory workers consistently show low overall mortality, which is usually attributed to the healthy worker effect [Hunter et al., 1993; Cordier et al., 1995; Brown et al., 1996; Gustavsson et al., 1999]. However, some studies report increased mortality among laboratory workers from some site-specific cancers

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including leukemia [Olin, 1976; Olin and Ahlbom, 1980; Brown et al., 1996; Andersen et al., 1999] lymphatic and hematopoietic cancers among males [Harrington and Shannon, 1975; Maher and Defonso, 1986; Cordier et al., 1995] and urinary cancers [Dosemeci et al., 1992; Cordier et al., 1995; Wennborg et al., 1999]. Study results for cancers of the digestive system, brain, and bone are equivocal, with some reporting elevations [Daly et al., 1994; Cordier et al., 1995; Sorahan et al., 1998; Wennborg et al., 1999; Kauppinen et al., 2003] and others reporting no elevations [Dosemeci et al., 1992; Brown et al., 1996; Andersen et al., 1999]. Previous cohort studies have reported elevations in genito-urinary cancers (bladder, kidney, and prostate) among laboratory workers [Silverman et al., 1989, 1990; Dosemeci et al., 1992; Daly et al., 1994; Cordier et al., 1995; Wennborg et al., 1999].

There are several important limitations in previous research of chemical laboratory workers (CLWs). First, many of these studies include workers who have limited actual laboratory work experience. Second, many of the studies do not include detailed chemical exposure assessments, or even duration of employment in a laboratory as an exposure surrogate in their analyses. Third, many studies of United States chemical laboratory workers have been limited by the inclusion of very few, if any females [Hoar and Pell, 1981; Maher and Defonso, 1986; Dosemeci et al., 1992]. The current study evaluates the mortality experience of 6,157 male and female chemical laboratory workers employed from 1943 to 1998 at the Department of Energy (DOE) Oak Ridge, Tennessee facilities (K-25, X-10, and Y-12) and the Savannah River Plant in South Carolina. Chemicals generally encountered by these laboratory workers are the primary exposures of interest. This study improves upon previous CLW studies by restricting the study population to workers who actually worked in a laboratory, by including female workers, and by examining metrics related to chemical exposure in the analyses.

Outcomes of Interest

Cancer outcomes of a priori interest include lymphatic and hematopoietic cancers (i.e., lymphoma, leukemia, multiple myeloma), and cancers of the bladder, kidney, prostate, brain, bone, and digestive system. Because there was no individual smoking information available for the study subjects, standardized rate ratio (SRR) analyses were conducted for combined smoking-related cancers (trachea, bronchus, and lung, buccal cavity and pharynx, larynx, esophagus, pancreas, kidney and bladder) to evaluate potential confounding due to smoking. Causes of death strongly related to lifestyle (e.g., emphysema, ischemic heart disease, and alcoholism) were also examined to evaluate potential confounding.

Study Site Description

Three of the four study facilities are located in Oak Ridge, Tennessee. These include the Oak Ridge National Laboratory (ORNL), also known as X-10; the East Tennessee Technology Park (formerly known as K-25), and the Y-12 facility. Much of the early work at X-10 was devoted to the development and operation of a graphite-moderated plutonium production reactor. The facility contains many chemical laboratories that conduct basic and applied research in chemical separation techniques, radioisotope production, and reactor design. The K-25 site, constructed in 1943, enriched naturally occurring uranium to obtain higher quantities of the isotope ^{235}U in a process called gaseous diffusion. The chemical laboratories that supported the K-25 facility conducted barrier studies and research activities pertaining to uranium enrichment. The Y-12 site initially (1943–1947) enriched uranium for use in nuclear materials. After World War II, the mission changed to the research, fabrication, and assembly of nuclear materials, and nuclear recycling and recovery. Chemical laboratories supporting Y-12 activities conducted analyses of process materials, beryllium studies, metal composition studies, bioassays, and isotopic analyses.

The Savannah River site (SRS) located in Aiken, South Carolina, was constructed in 1951 to produce, purify, and process plutonium, tritium, and other radioisotopes. Chemical laboratories at the SRS conducted analyses in the area of radiochemical separation, nuclear fuels development, reactor design, waste characterization, and environmental technology.

METHODS

Cohort Definition

The study cohort consists of 6,157 CLWs employed for at least one day at SRS or the Oak Ridge sites (X-10, Y-12, and K-25 facilities) from January 1, 1943 to December 31, 1998. Job titles and departments associated with chemical laboratory operations and recorded in employee work history records were used to identify the chemical laboratory workers included in the study. Hard copy work history records were obtained from each site and the following dates were required for each worker included in the study: date of birth, hire date, termination date, and date of death if a worker was known to be deceased. Details of the procedures for identifying chemical laboratory workers and descriptions of potential chemical exposures have been reported elsewhere [Henn et al., 2007].

Vital Status Ascertainment

Follow-up for each worker began with either the start of facility operations (i.e., 1943 for Oak Ridge workers or

1952 for SRS workers) or the first date employed at a study facility, whichever was later, and ended on date of death or December 31, 1998, whichever was earlier. The primary data sources used to ascertain deaths were the National Death Index-Plus (NDI-Plus) and the Social Security Administration Death Master File (SSA-DMF). In addition, the SSA's ''presumed living'' file was used to confirm that workers not found to be deceased by NDI-Plus were alive as of December 31, 1998.

Underlying and contributing causes of death were obtained directly from NDI-Plus for workers deceased in 1979 or later. For those who died before 1979, death certificates were obtained from the states in which death occurred. The state of death was identified for the majority of deaths before 1979 using the SSA-DMF. When the date or state of death was not identified in the SSA-DMF, state electronic records were searched to identify decedents. Underlying and contributing causes of death prior to 1979 were coded by certified nosologists trained by the National Center for Health Statistics (NCHS) in the revision of the International Classification of Diseases in effect at the time of death.

Description of Exposures

Chemical Exposure Assessment

Job titles and department names in the work histories were used to identify individuals as CLWs and to determine their length of employment. Facility records were reviewed to identify typical laboratory analyses conducted and chemical compounds used in the laboratories at the study facilities (Table I).

Although all study subjects had employment histories that included some assigned duties in a chemical laboratory, many workers also had assignments outside the chemical

TABLE I. Analyses Conducted (Panel A) and Chemicals Handled (Panel B) by Chemical Laboratory Workers

Panel A: Typical Laboratory Analyses

- Uranium and Fluoride Studies:
  - Reduction & Oxidation Studies; Uranium Exchange Reactions; X-ray and Electron Diffraction; Fluorination Techniques; Uranium Recovery; Sampling and Control Analyses; Gravimetric and Volumetric Analyses
- Barrier Studies:
  - Surface Flow Studies; Diffusion Studies; Barrier Preparation
- Biochemistry:
  - Nucleic Acid Studies; Body Fluids Analyses
- Radiochemical Analyses:
  - Half Life Measurements; Activation Analysis; Decay Transitions; Nuclear Properties; Solvent Extraction; Isotope Separation
- Reactor Fuel Chemistry:
  - Corrosion Studies; Molten Salt Experiments; Reactor Fuel Processing; Fission Product Solubility
- Waste Treatment:
  - Radioactive Waste Characteristics
- Process Support:
  - Product Certification; Metal Composition
- Miscellaneous:
  - Compound Syntheses; Structure Determination Studies; Bioassay Analyses; Beryllium Studies

Panel B: Typical Chemicals

- Alcohols:
  - Ethanol; Methanol; Butanol; Phenol
- Acids:
  - Hydrochloric Acid; Nitric Acid; Sulfuric Acid; Hydrobromic Acid; Acetic Acid; Oxalic Acid; Phosphoric Acid
- Solvents:
  - Tributyl Phosphate; Carbon Tetrachloride; Trichlorethylene; Benzene; Methylene Chloride; Formaldehyde; Chloroform
- Radioisotopes:
  - Uranium; Plutonium; Thorium; Krypton; Cesium; Tritium; Americium
- Metal Alloys:
  - Zirconium; Nickel; Silver; Aluminum; Beryllium; Copper
- Miscellaneous:
  - Hydrogen Fluoride; Mercury; Sodium Hydroxide; Hydrazine; Asbestos

laboratory during their employment at these facilities. Therefore, based on job and department titles, the work history information for each worker was segregated into two categories for analyses: employment that occurred only in a chemical laboratory and employment that occurred outside the chemical laboratory in process areas supported by a chemical laboratory. Chemical laboratory job titles included lab technician, lab analyst, chemist, metallurgist, and biochemist; process area job titles included process engineer, instrument mechanic, electrician, and chemical operator. While process area workers likely received exposure to some of the chemical compounds found in the supporting laboratory, the potential exposure was much greater in process production areas, where larger volumes of chemicals compounds were present.

Given that monitoring data were sparse, employment duration was used in the primary analysis as a surrogate for cumulative chemical exposures. We conducted analyses to account for temporal and job-specific differences in exposures using cumulative exposure scores [i.e., Potential Exposure Index (PEI)] derived from employment duration, job titles, employment era, and available exposure monitoring data [Henn et al., 2007].

Radiation Exposure Assessment

CLWs were also potentially exposed to ionizing radiation while performing duties both in the laboratory and outside the laboratory in process areas. Radiation exposure information for each worker was abstracted from available site exposure records and NIOSH databases maintained from previous studies. External occupational radiation exposure was evaluated as equivalent dose in millisievert (mSv) to the whole-body. The dose for each worker was assessed through the study end date using available site records, and imputation methods were used when monitoring data were not available but exposure was expected. Annual exposure data (as reported by each facility) were coded into a relational database, with the exception of corrections to International System of Units (SI).

Available dosimetry records, medical records, and analytic files were also searched for information regarding previous exposures during employment outside of the primary study facilities. When a cumulative dose was reported for a range of exposure-years at other facilities, the dose was distributed among the years according to working-months derived from employment histories.

In some instances, evidence of potential exposures found in historical records was not accompanied by quantitative exposure data. Estimates of recorded dose were needed when dosimetry records were not available. For example, many former X-10 workers were also employed at the Y-12 or K-25 facilities. However, personal monitoring was not available to all potentially exposed workers until 1961 at Y-12 and 1975 at K-25 [Watkins et al., 1993]. In these cases, separate methods were developed for dose estimation similar to those suggested by Watson et al. [1994] and Richardson et al. [1999] using employment and facility histories and the monitoring results of nearby workers and time periods.

Limited bioassay information was available and used to evaluate the potential of having internal radiation deposition. If dosimetry records indicated that a worker had a ''positive bioassay,'' it was assumed there was some internal deposition.

Standardized Mortality Ratio Analysis

The National Institute for Occupational Safety and Health (NIOSH) Personal Computer Life Table Analysis System (PC-LTAS, version 1.0d) was used to generate expected numbers for all deaths, all cancer deaths, and cause-specific deaths, by race and sex, within 5-year age and 5-year calendar time periods [NIOSH, 2001; Cassinelli et al., 1998]. Person-years and observed deaths were accumulated for each of these age and calendar time periods from the worker's follow-up begin date through the end of follow-up.

Expected numbers of deaths were based on U.S. population death rates specific for the race, gender, and 5-year age and calendar time periods. United States expected rates were based on deaths from 1940 forward except for non-Hodgkin's lymphoma and multiple myeloma, causes for which rates were available only from 1960 forward. For these outcomes, enumeration of observed deaths and person-years at risk began in 1960 or the first date employed at a study facility whichever came last. Because differences between mortality among members of the study population and that of the United States population could be in part the result of regional (non-occupational) differences, mortality for selected cancers was compared to Tennessee state rates, which were also available from 1960 forward.

Numbers of deaths observed for each cause were divided by the expected number of deaths to obtain cause-specific standardized mortality ratios (SMR). The precision of each estimated SMR was assessed assuming a Poisson distribution, with two-sided 95% confidence intervals.

Internal Analysis

Because SMRs are affected by the age structure of the study population, comparison of SMRs for different populations can be misleading. SRRs allow for comparison among populations by weighting observed stratum-specific rates according to a common (internal) standard [Rothman and Greenland, 1998]. SRR analyses were performed for the entire cohort to assess the associations between mortality outcomes and employment duration. Duration of employment categories of 0 to <5 years employed, 5 to <10 years employed, 10 to <20 years employed, and 20+ years

employed were used in the analyses. For dose–response analysis, a linear trend is calculated in a person-year-weighted regression of directly standardized rates [Rothman and Greenland, 1998]. Statistical significance of each trend was determined using a two-tailed *z*-test with an alpha of 0.05.

Modeling Analysis

Cox regression analyses were conducted to further evaluate the relation between occupational exposure and the risk of mortality due to selected cancers. Risk sets were defined from the entire cohort of CLWs for each case of interest. Each risk set also included all controls who were under observation and who lived to an age equal to or greater than the age of the case at death. Time is defined as the length of life (attained age) of the case; the cases and controls are matched on attained age because it is a strong predictor of cancer mortality and therefore an important potential confounder of the association of interest in the analyses. All occupational exposures of the controls are truncated at the age attained by the case minus any lag.

Conditional logistic regression was calculated using the SAS procedure PHREG. This procedure performs a regression analysis of survival data, the results of which are identical to those provided by the Cox proportional hazards model [SAS Inc, 1999]. The probability of death from lymphatic and hematopoietic cancers was modeled as a function of the following candidate variables: duration of employment (surrogate for chemical exposures—the primary exposure of interest), external ionizing radiation exposure, gender, and employment in a process area. A change of plus or minus 10% in the parameter estimate of the primary exposure variable was used as an indicator of confounding in determining the final model. Lag periods of 2 years for leukemia, 10 years for multiple myeloma, and 5, 10, and 20 years for lung cancer were evaluated. Because latency and risk factors may be different for chronic lymphatic leukemia (CLL) the leukemia analysis was performed both with and without CLL deaths.

RESULTS

Descriptive Statistics

The full cohort includes 6,157 workers, with 4,462 males and 1,695 females (Table II). There were 307 (5%) non-white workers, 5,733 (93%) white, and 117 (2%) of unknown race (presumed to be white). At the end of vital status follow-up, 4,764 workers (77%) were alive and 1,393 (23%) were deceased.

Standardized Mortality Ratio Results

All-cause mortality in the full cohort was much lower than would be expected from U.S. population rates (SMR = 0.62; 95% confidence interval [CI] = 0.58–0.65; number of deaths, n = 1,393). The mortality from all cancers in the full cohort was also much lower than expected from U.S. population rates (SMR = 0.66; 95% CI = 0.59–0.72, n = 406). There were no statistically significant elevations for any specific cancer or non-cancer cause of death (Table III). No thyroid cancer or Hodgkin's disease deaths were identified in the cohort.

There were fewer deaths than expected among males due to all cancers combined and no statistically significant elevations for any specific cancer or non-cancer site. There were also fewer deaths than expected among females due to

TABLE II. Cohort and Subcohort Demographics; DOE Chemical Laboratory Workers Study

	Full cohort	Workers employed in chemical lab only ("non-processing")	Workers employed in both chemical lab and process area ("processing")
No. of workers	6,157	3,382	2,775
Males	4,462	2,204	2,258
Females	1,695	1,178	517
Year of birth (mean)	1931	1932	1931
Year first employed (mean)	1958	1958	1957
Year last employed (mean)	1972	1967	1979
Years employed (mean)	14	8	21
Years employed (median)	8	2	22
Percent employed at least 5 years	56%	37%	85%
Years since last employed (mean)	22	27	15
Total person years at risk[a]	227,556	122,422	98,670

[a]Person-years (6,464) are categorized as unknown—chemical laboratory or process area.

TABLE III. Standardized Mortality Ratios (SMRs) for the Total Cohort, 1940–1999 rates

Cause of death	Observed	SMR[a]	95% confidence interval
All cause	1,393	0.62**	0.58–0.65
All cancer	406	0.66**	0.59–0.72
MN digestive organs	101	0.70**	0.57–0.85
Intestine	49	0.92	0.68–1.21
Pancreas	21	0.70	0.44–1.08
Liver and gallbaldder	7	0.66	0.26–1.35
MN buccal cavity and pharynx	21	0.52	0.21–1.06
MN respiratory	114	0.53**	0.43–0.63
Trachea, bronchus, and lung	111	0.54**	0.44–0.64
MN breast	21	0.77	0.47–1.17
MN urinary organs	23	0.84	0.53–1.27
Kidney	14	0.97	0.53–1.62
Bladder	9	0.70	0.32–1.34
Prostate	20	0.54**	0.33–0.83
MN Skin	6	0.82	0.39–1.51
MN brain and nervous system	17	0.99	0.57–1.58
MN connective tissue	6	1.78	0.65–3.87
MN bone	1	0.67	0.02–3.72
MN lymphatic and hematopoietic	54	0.94	0.70–1.22
Non-Hodgkins lymphoma[b]	21	0.97	0.60–1.48
Leukemia	17	0.78	0.45–1.25
Multiple myeloma[b]	15	1.55	0.86–2.55
Diseases of the heart	447	0.58**	0.52–0.63
Ischemic heart disease	335	0.57**	0.51–0.63
Other diseases of the circulatory system	116	0.66**	0.55–0.79
Cerebrovascular disease	76	0.67**	0.53–0.84
Diseases of blood & blood forming org	3	0.40	0.08–1.17
diseases of the respiratory system	96	0.57**	0.46–0.69
Emphysema	11	0.49*	0.25–0.88
Pneumoconioses and other resp	47	0.54*	0.40–0.72
Diseases of the nervous system	34	0.99	0.69–1.39
Diseases of the digestive system	34	0.33**	0.23–0.46
Other mental disorders	14	1.20	0.66–2.02
Alcoholism	2	0.22*	0.03–0.80
Accidents	70	0.57**	0.45–0.73
Transportation accidents	47	0.70*	0.52–0.93
Violence	45	0.70*	0.51–0.94
Suicide	41	0.90	0.64–1.22
Symptoms and Ill-defined conditions	32	1.41	0.97–2.00
Other causes	60	1.17	0.89–1.50

MN, maligancy.
[a]Standardized mortality ratio as compared to U.S. death rates.
[b]Standardized mortality ratio based on U.S. death rates beginning in 1960.
*$P < 0.05$.
**$P < 0.01$.

all cancers combined, and no statistically significant elevations for any specific non-cancer and most specific cancer sites; however, a significant elevation in multiple myeloma deaths was observed (SMR = 3.56; 95% CI = 1.43–7.33; n = 7). There is a slight but non-statistically significant elevation in multiple myeloma deaths among males (SMR = 1.03; 95% CI = 0.45–2.04; n = 8).

Of note, multiple myeloma deaths among females in the study are also significantly elevated using Tennessee state rates (SMR = 3.49; 95% CI = 1.40–7.19; number of observed deaths, n = 7) and the expected number of multiple myeloma deaths among females is approximately 16% higher in Tennessee than in the U.S. population. Also, the multiple myeloma mortality rates among white women in the three-county region surrounding Knoxville that includes Anderson County, where the Oak Ridge facilities are located, are approximately 7% higher than those for the state of Tennessee [National Cancer Institute, 1999].

Standardized Rate Ratios (SRRs) by Employment Duration for the Full Cohort

To explore elevations for specific causes of deaths by duration of employment, SRRs were calculated categorizing employment duration (defined as employment in a laboratory or plant area where chemical exposure was likely) using categories of 5 to <10 years employed, 10 to <20 years employed and 20 or more years employed. These categories were compared to the baseline group of 0 to <5 years employed.

There is a significant positive trend with increasing employment duration for lung cancer using both 5- and 10-year lag periods. There is a significant positive trend for both lymphatic and hematopoietic cancers and leukemia using a 2-year lag period. Significant elevations are seen in the 20+ years category for leukemia using both a 2-year lag (SRR = 9.51; 95% CI = 1.67–54.17, n = 11), and a 5-year lag (SRR = 11.44; 95% CI = 1.88–69.54, n = 11; Table IV).

SRR analyses of all a priori cancers were conducted using both duration of employment and PEI score (results not shown). Although PEI was expected to be an improved exposure surrogate, SRR trend results obtained using PEI were similar (i.e., generally consistent in direction) to those using employment duration. Moreover, trend statistical significance did not differ meaningfully in comparisons made between surrogates. This was expected given the two metrics are highly correlated (r = 0.62; $P = 0.0001$). Because adequate job descriptions were available for work performed in the laboratories and not for work performed in process areas, PEIs were limited to workers with job assignments principally in the laboratory. Therefore, only SRR results using duration of employment are reported.

TABLE IV. Standardized Rate Ratios (SRRs) for the Total Cohort, by Duration of Employment Intervals, 1940–1999 Rates—(Selected Lags)

	Duration of employment			
Cause of death	**0–5 years (Obs) SMR**	**5–10 years (Obs), SRR (95% CI)**	**10–20 years (Obs), SRR (95% CI)**	**20+ years (Obs), SRR (95% CI)**
MN lymphatic and hematopoietic				
2-year lag†	(20) 0.82	(3) 0.68 (0.19–2.42)	(10) 1.54 (0.68–3.45)	(21) 1.88 (0.90–3.95)
5-year lag	(21) 0.87	(4) 0.60 (0.18–1.97)	(9) 1.22 (0.51–2.91)	(20) 1.93 (0.85–4.37)
Leukemia				
2-year lag‡	(2) 0.22*	(1) 2.68 (0.23–31.10)	(3) 2.54 (0.37–17.33)	(11) 9.51* (1.67–54.17)
5-year lag	(2) 0.22*	(1) 2.70 (0.23–31.33)	(3) 2.29 (0.35–15.05)	(11) 11.44** (1.88–69.54)
MN lung				
5-year lag‡	(36) 0.44**	(8) 0.97 (0.41–2.32)	(19) 1.30 (0.70–2.42)	(48) 1.33 (0.84–2.09)
10-year lag‡	(37) 0.45**	(9) 1.00 (0.43–2.32)	(20) 1.24 (0.67–2.27)	(45) 1.29 (0.81–2.04)
20-year lag	(40) 0.47**	(11) 0.83 (0.41–1.70)	(31) 1.22 (0.72–2.05)	(24) 1.12 (0.59–2.10)

SRRs for multiple myeloma were not included due to a lack of sufficient deaths in several categories.
Obs, observed number of deaths.
*$P < 0.05$.
**$P < 0.01$.
†Significant positive trend; $P < 0.05$.
‡Significant positive trend; $P < 0.01$.

Analysis of Smoking Related Cancers

There were fewer than expected combined smoking-related cancer deaths (i.e., trachea bronchus and lung, buccal cavity and pharynx, larynx, esophagus, pancreas, kidney, and bladder) in the full cohort (SMR = 0.61; 95% CI = 0.52–0.71) deficits were observed in both the processing and non-processing subcohorts. A significant negative trend for smoking cancer deaths with increasing employment duration is seen for females in the full cohort and the non-processing subcohort. There were non-significant positive trends with increasing employment duration seen for males in the full cohort and each of the subcohorts.

Regression Analyses

Leukemia Deaths

The log-linear regression model using a 2-year lag period shows a borderline statistically significant positive relation between leukemia mortality (n = 17) and total duration of employment in jobs where chemical exposure was likely (Odds Ratio [OR] = 1.05 at 1 year; 95% CI = 1.00–1.10), adjusting for external ionizing radiation exposure, gender, and employment in a process area. There was a slight non-statistically significant positive exposure response relation between leukemia mortality and external ionizing radiation. However, the primary exposure variable (employment duration in jobs and areas where chemical exposure was likely) and radiation exposure are correlated (r = 0.33; $P = 0.0001$), and it is therefore difficult to accurately determine the risk from each variable separately. There was a non-statistically significant increased risk of leukemia mortality among female workers and a borderline statistically significant positive relation among workers who were employed in process areas (Table V). When the four identified chronic CLLs are excluded from the analysis, the relation between leukemia mortality (n = 13) and duration of employment in jobs where chemical exposure is likely is elevated but no longer statistically significant (OR = 1.04 at 1 year; 95% CI = 0.99–1.09).

A regression analysis including only multiple myeloma deaths (n = 15) using a 10-year lag period shows a non-statistically significant positive relation between multiple myeloma mortality and duration of employment in jobs where chemical exposure is likely (OR = 1.04 at 1 year; 95% CI = 0.98–1.10), adjusting for external ionizing radiation exposure, gender, and employment in a process area. Female workers show an elevated risk of multiple myeloma mortality, as do workers employed only in chemical laboratories (Table V).

Lung Cancer Deaths

Using a 10-year lag period, a regression analysis of lung cancer deaths shows a slightly elevated positive relation between lung cancer mortality and duration of employment in jobs where chemical exposure is likely (OR = 1.01 at 1 year; 95% CI = 0.99–1.03), adjusting for gender, employment in a process area, and potential exposure to internal ionizing radiation. External ionizing radiation was dropped from the model because its exclusion caused less than a

TABLE V. Log-Linear Regression Analyses: Leukemia, Multiple Myeloma, and Lung Cancer

Variable	Odds ratio	95% confidence limits
Leukemia with CLL deaths excluded—2-year lag		
Employment duration (for each additional year of exposure)	1.04	0.99 1.09
External radiation dose (for each additional 10 mSv of exposure)	1.02	0.99 1.06
Gender (male = 0 and female = 1)	1.99	0.52 7.63
Employed in both a chemical laboratory and process area (yes = 1 and no = 0)	4.78	0.97 23.6
Multiple myeloma—males and females combined—10-year lag		
Employment duration (for each additional year of exposure)	1.04	0.98 1.10
External radiation dose (for each additional 10 mSv of exposure)	0.30	0.09 1.03
Gender (male = 0 and female = 1)	2.10	0.72 6.10
Employed in both a chemical laboratory and process area (yes = 1 and no = 0)	0.81	0.24 2.70
Lung cancer—10-year lag		
Employment duration (for each additional year of exposure)	1.01	0.99 1.03
Gender (male = 0 and female = 1)	0.79	0.47 1.32
Monitored for potential internal ionizing radiation exposure (no = 1 and yes = 0)	1.28	0.82 2.00
Employed in both a chemical laboratory and process area (yes = 1 and no = 0)	1.80	1.18 2.76

10% change in the primary exposure variable. Female workers show a lower risk of lung cancer mortality than male workers, while workers not monitored for internal ionizing radiation exposure show a higher risk of mortality than their monitored counterparts. Workers employed in process areas in addition to laboratories show a significant elevation in mortality, adjusting for the other covariates in the model (Table V).

DISCUSSION

Mortality among the 6,157 workers included in this study is well below expectation for deaths due to all causes combined and all cancers combined, and no statistically significant elevations for any specific non-cancer or cancer site were found among the full cohort of workers. Further, there were no statistically significant elevations reported among males for any specific cancer site and there were fewer than expected deaths among females for most specific cancer sites.

As is the case in this study, the observed number of deaths in occupational cohorts often falls short of expected numbers that are calculated from national rates. This is likely due the healthy worker selection effect [Monson, 1986], a bias that occurs because potential employees who are ill at the time of application to the worksite are excluded from employment, leaving relatively healthy workers to be hired. A strong healthy worker selection effect is the likely explanation for the overall low mortality among the workers in this study.

As has been reported in previous studies of laboratory workers, lung cancer deaths in the cohort were below expectation compared to the U.S. population [Carpenter et al., 1991; Belli et al., 1992; Rachet et al., 2000]; however, the SRR analysis utilizing an internal referent group shows a statistically significant positive trend with increasing employment duration, also a finding consistent with previous studies [Wennborg et al., 1999; van Barneveld et al., 2004]. Regression analysis of the 111 lung cancer cases and their controls shows a borderline statistically significant increased risk of mortality with increasing employment duration. It is possible that smoking was responsible in part for the increased risk in respiratory cancers. SRR analyses of smoking-related cancers shows an increased mortality risk with increasing employment duration among males in the full cohort and each of the subcohorts; however, the trends are not statistically significant. Of the 111 cases, 58 (52%) did receive potential internal ionizing radiation exposure, but regression analysis found no elevation in mortality risk due to the potential internal exposure.

It is also possible that chemical exposures that occurred during the workers' laboratory employment contributed to the increase in respiratory cancer. These workers were employed primarily as chemists, lab analysts, and lab technicians in biological and analytical chemistry laboratories, where it is possible that they were exposed to chemicals linked to lung cancer such as nickel [Boffetta et al., 1995] and beryllium [Steenland and Ward, 1991].

Consistent with previous studies of chemical laboratory workers [Hoar and Pell, 1981; Maher and Defonso, 1986; Dosemeci et al., 1992; Hunter et al., 1993; Brown et al., 1996] there are non-statistically significant elevations for cancer of the connective tissue, and mental disorders, primarily senile dementia (11 of 14 deaths due to mental disorders). There is

also a non-significant elevation of brain cancer deaths among females, a finding that is consistent with other studies of laboratory workers [Olin and Ahlbom, 1980; Belli et al., 1992; Hunter et al., 1993; Cordier et al., 1995]. The women who died of brain cancer were employed primarily in production assay laboratories at the K-25 facility during the very early years of plant operations when exposures to solvents, metals, and acids were likely. This elevation is also seen using Tennessee state rates.

Multiple myeloma deaths were significantly elevated among females a finding consistent with some previous studies [Cordier et al., 1995; Brown et al., 1996; Gustavsson et al., 1999]. The multiple myeloma cases were all employed during the early years of the Oak Ridge operations when the potential for chemical exposures was likely greater; all began work before 1955 and the average year first employed was 1947. Lab Analyst and Lab Technician accounted for the majority (74%) of the jobs held by the seven women compared with 43% among all females. While performing these jobs primarily in production and analytical and assay laboratories, it is possible that these women had exposures to a variety of compounds that have been linked to multiple myeloma such as nickel [Egedahl et al., 1993], benzene [Rinsky et al., 1987], low-molecular-weight solvents [Bethwaite et al., 1990], and acids [Morris et al., 1986]. Further, Wing et al. [2000], in a study of multiple myeloma among Department of Energy workers, reported positive associations between chemical exposures such as aromatic hydrocarbons and multiple myeloma death. While it is not possible to say with certainty why there is a difference in multiple myeloma rates for males and females in this study population a possible explanation could be that men more often worked as lab managers, supervisors, engineers, and chemists in research and development, technical evaluation, and production inspection laboratories where exposures were likely lower.

It is possible that the significantly elevated multiple myeloma mortality among women in this study is due in part to undefined circumstances (e.g., environmental, hereditable, or lifestyle conditions) related to Tennessee residence rather than exposures encountered while employed in the laboratory facilities. This is because employment duration is relatively short for the seven female multiple myeloma deaths and because it is likely that the majority of the seven females continued to live in the Oak Ridge vicinity or elsewhere in Tennessee (where rates are higher) after terminating employment; death certificates document that all but one of the women died in Tennessee. However, because the multiple myeloma risk among these women is still elevated compared to local rates further investigation of the occupational exposures at the Oak Ridge facilities is suggested.

Regression analysis of leukemia deaths excluding CLL shows a borderline positive exposure response relation between leukemia mortality and employment duration adjusting for external cumulative radiation exposure, gender, and employment in a process area. The 13 affected workers were employed for an average of 24 years during the early years of operation, primarily at the Oak Ridge X-10 facility. They were most often employed in analytical chemistry and biology laboratories as chemists and lab technicians. All were monitored for external ionizing radiation, with a median cumulative median exposure of 23 mSv, which is higher than the median cumulative exposure for the whole cohort (3 mSv). In addition to external ionizing radiation exposure, these workers possibly received exposures to chemical leukemogens such as benzene and carbon tetrachloride. Employment duration (which is the surrogate variable for cumulative chemical exposure in the full cohort) is correlated with the radiation exposure variable ($r = 0.33$; $P = 0.0001$), making it impossible to determine the role of each one independently.

LIMITATIONS

Workers in the study were exposed to many different chemicals by various routes of exposure while employed in both laboratories and process areas. Since individual chemical exposures were not directly assessed, inferences for specific chemical exposure–response relations are not possible. Because chemical exposure estimates were not available for jobs outside the laboratory it was necessary to use duration of employment as a surrogate for cumulative exposure estimates. Also, the work duration and external ionizing radiation exposure variables were highly correlated, making it impossible to determine if the elevated leukemia risk seen in the study is due to chemical or radiation exposure.

Because study participation and chemical exposures were both based on employment history, temporal and spatial differences in employment practices may exist that cannot be adequately accounted for in the current study design. Thus, these differences may affect study results. For example a total of 950 workers in the cohort (15%) were employed less than 1 year, of which 217 are deceased. The majority (86%) of these deceased short-term workers were employed at one of the Oak Ridge facilities during the early years of operation (median year first employed = 1945 and median year last employed = 1946).

Removing the deceased individuals with less than one year of employment from the cohort had negligible impact on the SMR for males and females combined. For example, for all cause mortality, excluding workers employed less than 1 year resulted in an SMR of 0.52 (95% CI = 0.49–0.55; n = 1,176), while including workers employed less than one year give an SMR of 0.62 (95% CI = 0.58–0.65; n = 1,393). For lung cancer, the risk estimate excluding those workers gives an SMR of 0.48 (95% CI = 0.39–0.59; n = 100) vs. an SMR of 0.54 (95%

CI = 0.33–0.83; n = 111) including them; for multiple myeloma an SMR of 1.24 (95% CI = 0.64–2.16; n = 12) is given versus an SMR of 1.55 (95% CI = 0.86–2.55; n = 15). For leukemia, all 17 cases worked more than 1 year.

However, among the female multiple myeloma cases, two of the seven cases (29%) were employed for 1 year or less. When we restricted the study population to those employed at least 1 year, the SMR remained elevated but was no longer statistically significant (SMR = 2.54; 95% CI = 0.82–5.92; n = 5). In the regression analysis of the restricted population, the risk estimate for females decreased slightly but remained elevated with an OR of 2.03 (95% CI = 0.58–7.17). Of note, in a case–control study of multiple myeloma among DOE workers Wing et al. [2000] found that 25% of the cases and 26% of the controls had employment of less than 1 year. Also, 61% of the cases and 49% of the controls were hired prior to 1948.

Subjective determinations, based on reviews of job and departmental description of activities, supplemented by discussions with DOE personnel, were used to identify the chemical laboratory jobs and departments, resulting in potential misclassification. Further, because sufficient chemical monitoring data were not available, it was not possible to quantify and analyze the likely variations in the intensity of chemical exposures due to differences in job and department titles. Variations in chemical exposure intensity within jobs and departments are likely and due in part to factors such as differences in work tasks, facility practices, and the use of personal protective equipment [Henn et al., 2007]. Primarily, duration of employment was used as a surrogate for cumulative exposure in this study. It is based on assumptions that exposures did not vary with time or across jobs. The PEI scores incorporated some overall trends in exposure magnitude related to time and jobs yet, in the end, the interpretation of trends for a priori health outcomes did not materially differ from results based on duration of employment. Also, information necessary to identify and quantify chemical exposures resulting from previous and subsequent employment was not available for analysis.

There were 326 (5%) of the study subjects who were assumed alive at the end of the study due to incomplete vital status information. The majority of these workers were female (71%), and worked only in a laboratory (78%), never in a process area. Because those individuals lost to follow up are assumed alive at the end of the study, the risk estimates may be biased toward the null.

Ascertainment of cause of death due to non-cancers seems to have been less specific in the study cohort than in the general U.S. population, as reflected by excesses in the LTAS categories ''symptoms and ill defined conditions'' and ''other causes.'' Most of the deaths in these categories were due to unspecified non-cancers or unknown causes. If the primary sites of these causes of death were known, SMRs for the corresponding outcomes would be higher. Also, given the multiple outcomes examined, significant positive associations could have occurred by chance [Shields, 2006]. In particular, positive associations lacking exposure response are less likely to be causal in nature and require further corroboration.

In evaluating these findings it is important to consider that there are small numbers of deaths for each of the significantly elevated cancers among the female workers. Detailed smoking information for all members of the study cohort was not available, limiting the clarity of the analyses of mortality risk for some cancers. Also, because the workers included in the study are overwhelmingly white, definitive analysis of the mortality risk for non-whites is extremely limited.

CONCLUSIONS

The workers included in this study were employed in chemical laboratories within the DOE complex. The mortality due to all causes combined and all cancers combined were both well below expectation for all workers which could be due in part or completely to a strong healthy worker effect.

Although there was no elevation in overall leukemia mortality there are statistically significant increases among workers employed for 20+ years using both 2- and 5-year lag periods. Also, regression analysis of the leukemia cases shows a borderline statistically significant positive relation between leukemia mortality and total duration of employment in jobs where chemical exposure was likely.

While the overall SMR for lymphatic and hematopoietic cancers was below expectation, multiple myeloma deaths were significantly elevated among females. These findings are consistent with some other studies reporting elevations of multiple myeloma among female laboratory workers [Cordier et al., 1995; Brown et al., 1996; Gustavsson et al., 1999]. Multiple myeloma deaths were also significantly elevated using Tennessee state rates for comparison. However, when the study cohort is restricted to workers employed for at least 1 year, multiple myeloma deaths among females remained elevated but no longer statistically significant. A NIOSH case–control study is currently underway is designed to examine more closely the relation between multiple myeloma and a variety of chemical exposures among workers who were employed at the Oak Ridge K-25 facility. This additional study should facilitate greater understanding of the excess multiple myeloma mortality observed in this study.

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REFERENCES

Andersen A, Barlow L, Engeland A, Kjaerheim K, Lynge E, Pukkala E. 1999. Work-related cancer in the Nordic countries. Scand J Work Environ Health 25(Suppl 2):1–116.

Belli S, Comba P, De Santis M, Grignoli M, Sasco AJ. 1992. Mortality study of workers employed by the Italian National Institute of Health, 1960-1989. Scand J Work Environ Health 18:64–67.

Bethwaite PB, Pearce N, Fraser J. 1990. Cancer risks in painters: Study based on the New Zealand Cancer Registry. Br J Ind Med 47:742–746.

Boffetta P, Kogevinas M, Simonato L, Wilbourn J, Saracci R. 1995. Current Perspectives on occupational cancer risks. Int J Occup Environ Health 1:315–325.

Brown TP, Paulson J, Pannett B, Coupland C, Coggon D, Chilvers CE, Sasco AJ. 1996. Mortality pattern among biological research laboratory workers. Br J Cancer 73:1152–1155.

Carpenter L, Beral V, Roman E, Swerdlow AJ, Davies G. 1991. Cancer in laboratory workers. Lancet 338:1080–1081.

Cassinelli R, Koch KJ, Steenland K, Spaeth S, Laber P. 1998. User documentation PC LTAS. Washington, DC: United States Department of Health and Human Services. Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

Cordier S, Mousel ML, Le Goaster C, Gachelin G, Le Moual N, Mandereau L, Carrat F, Michaud G, Hemon D. 1995. Cancer risk among workers in biomedical research. Scand J Work Environ Health 21:450–459.

Daly L, Herity B, Bourke GJ. 1994. An investigation of brain tumours and other malignancies in an agricultural research institute. Occup Environ Med 51:295–298.

Dosemeci M, Alavanja M, Vetter R, Eaton B, Blair A. 1992. Mortality among laboratory workers employed at the U.S. Department of Agriculture. Epidemiology 3:258–262.

Egedahl RD, Carpenter M, Homik R. 1993. An update of an epidemiology study at a hydrometallurgical nickel refinery in Fort Saskatchewan, Alberta. Health Rep 5:291–302.

Fawcett HH. 1972. Exposures of personnel to laboratory hazards. Am Ind Hyg Assoc J 33:559–567.

Gustavsson P, Reuterwall C, Sadigh J, Soderholm M. 1999. Mortality and cancer incidence among laboratory technicians in medical research and routine laboratories (Sweden). Cancer Causes Control 10:59–64.

Harrington JM, Shannon HS. 1975. Mortality study of pathologists and medical laboratory technicians. Br Med J 4:329–332.

Henn SA, Utterback DF, Waters KM, Markey AM, Tankersley WG. 2007. Task- and time-dependent weighting factors in a retrospective exposure assessment of chemical laboratory workers. J Occup Environ Hyg 4:71–79.

Hoar SK, Pell S. 1981. A retrospective cohort study of disability among chemists. J Occup Med 23:495–501.

Hunter WJ, Henman BA, Bartlett DM, Le Geyt IP. 1993. Mortality of professional chemists in England and Wales, 1965–1989. Am J Ind Med 23:615–627.

Kauppinen T, Pukkala E, Saalo A, Sasco AJ. 2003. Exposure to chemical carcinogens and risk of cancer among Finnish laboratory workers. Am J Ind Med 44:343–350.

Maher KV, Defonso LR. 1986. A historical cohort study of mortality among chemical researchers. Arch Environ Health 41:109–116.

Monson RR. 1986. Observations on the healthy worker effect. J Occup Med 28:425–433.

Morris PD, Koepsell TD, Daling JR, Taylor JW, Lyon JL, Swanson GM, Child M, Weiss NS. 1986. Toxic substance exposure and multiple myeloma: A case-control study. J Natl Cancer Inst 76:987–994.

National Cancer Institute (NCI). 1999. Atlas of Cancer Mortality in the United States, 1950–1994. Washington DC: National Cancer Institute, National Institutes of Health.

NIOSH. 2001. PC-Life Table Analysis System (Version 1.0d). Cincinnati, Ohio, United States Department of Health and Human Services, Center for Disease Control and Prevention; National Institute for Occupational Safety and Health. http://dshefs.niosh.cdc.gov/ltas/LT96Mast.html.

Olin GR, Ahlbom A. 1980. The cancer mortality among Swedish chemists graduated during three decades. A comparison with the general population and with a cohort of architects. Environ Res 22:154–161.

Olin R. 1976. Leukaemia and Hodgkin's disease among Swedish chemistry graduates. Lancet 2:916.

Rachet B, Partanen T, Kauppinen T, Sasco AJ. 2000. Cancer risk in laboratory workers: An emphasis on biological research. Am J Ind Med 38:651–665.

Richardson D, Wing S, Watson J, Wolf S. 1999. Missing annual external radiation dosimetry data among Hanford workers. J Expo Anal Environ Epidemiol 9:575–585.

Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. 1987. Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 316:1044–1050.

Rothman KJ, Greenland S. 1998. Modern epidemiology. Philadelphia: Lippincott-Raven.

SAS Inc, 1999. SAS/STAT User's Guide, Version 8. Cary, NC: SAS Institute Inc.

Shields PG. 2006. Understanding population and individual risk assessment: The case of polychlorinated biphenyls. Cancer Epidemiol Biomarkers Prev 15:830–839.

Silverman DT, Levin LI, Hoover RN. 1990. Occupational risks of bladder cancer among white women in the United States. Am J Epidemiol 132:453–461.

Silverman DT, Levin LI, Hoover RN, Hartge P. 1989. Occupational risks of bladder cancer in the United States: I. White men. J Natl Cancer Inst 81:1472–1480.

Sorahan T, Hamilton L, Wallace DM, Bathers S, Gardiner K, Harrington JM. 1998. Occupational urothelial tumours: A regional case-control study. Br J Urol 82:25–32.

Steenland K, Ward E. 1991. Lung cancer incidence among patients with beryllium disease: A cohort mortality study. J Natl Cancer Inst 83: 1380–1385.

van Barneveld TA, Sasco AJ, van Leeuwen FE. 2004. A cohort study of cancer mortality among Biology Research Laboratory workers in The Netherlands. Cancer Causes Control 15:55–66.

Watkins JP, Reagan JL, Cragle DL, Frome EL, West CM, Crawford-Brown D, Tankersley WG. 1993. Collection, validation, and description

of data for the Oak Ridge nuclear facilities mortality study. Oak Ridge, TN, ORISE 93/J-4: Oak Ridge Institute for Science and Education.

Watson JE, Jr., Wood JL, Tankersley WG, West CM. 1994. Estimation of radiation doses for workers without monitoring data for retrospective epidemiologic studies. Health Phys 67:402–405.

Wennborg H, Yuen J, Axelsson G, Ahlbom A, Gustavsson P, Sasco AJ. 1999. Mortality and cancer incidence in biomedical laboratory personnel in Sweden. Am J Ind Med 35:382–389.

Wing S, Richardson D, Wolf S, Mihlan G, Crawford-Brown D, Wood J. 2000. A case control study of multiple myeloma at four nuclear facilities. Ann Epidemiol 10:144–153.