Mortality Patterns Among Paducah Gaseous Diffusion Plant Workers

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Objective: To determine whether Paducah Gaseous Diffusion Plant workers had mortality patterns that differed from the general US population and to investigate whether mortality patterns were associated with job title or workplace exposures. **Methods:** A retrospective occupational cohort mortality study was conducted on 6759 workers. Standardized mortality ratio analyses compared the cohort with the referent US population. Internal comparisons producing standardized rate ratios were conducted by job title, metal exposure, and cumulative internal and external radiation exposures. **Results:** Overall mortality and cancer rates were lower than the referent population, reflecting a strong healthy worker effect. Individual not significant standardized mortality ratios and standardized rate ratios were noted for cancers of the lymphatic and hematopoietic tissue. **Conclusions:** Although relatively low exposures to radiation and metals did not produce statistically significant health effects, no significant elevations for lymphatic and hematopoietic cancers were consistent with previous studies of nuclear workers.

The Paducah Gaseous Diffusion Plant (PGDP) located in western Kentucky is currently the only operating uranium enrichment facility in the United States, and the only one whose worker cohort has not undergone a mortality study. This US Department of Energy (DOE) owned, contractor-operated uranium enrichment facility was commissioned in 1952 as part of a US government program to produce enriched uranium to fuel military reactors and produce nuclear weapons.[1,2]

The plant's mission changed in the 1960s from enriching uranium for nuclear weapons to enriching uranium for use in commercial nuclear reactors to generate electricity.[1–3] PGDP currently enriches uranium-235 (U-235) up to 5.5% using the gaseous diffusion process for use in domestic and foreign commercial power reactors.[2,3] In the gaseous diffusion process, the gas is forced through a series of porous membranes with microscopic openings. Because the U-235 is lighter, it moves through the barriers more easily. As the gas moves, the two isotopes are separated, increasing the U-235 concentration and decreasing the concentration of U-238. The enrichment process removes ~85% of the U-238 by separating gaseous uranium hexafluoride into two streams: One stream is increased, or enriched, in its percentage of U-235, and the other is reduced or depleted. The enriched uranium is then transported to nuclear power reactors to generate electricity. The depleted uranium is considered waste and is stored in cylinders on-site. Approximately 7000 individuals have worked at the plant since its inception.[1,3]

The 1990s witnessed a growing public awareness and concern about present and historical environmental, safety, and worker health issues from radiation and chemical exposures at the PGDP. Independent studies sponsored by the DOE fueled these concerns.[4,5] Comparisons of findings between uranium enrichment facilities are complicated because exposure processes and historical periods of operation have differed between facilities, and exposure and dosimetry methods have changed over time.[5] Mortality studies among workers exposed to ionizing radiation at other uranium enrichment facilities had yielded mixed results. For example, studies conducted at the Oak Ridge facility in Tennessee revealed elevated standardized mortality ratios (SMRs) for several outcomes. In the K-25 plant, white males who were hired between 1943 and 1972 had an SMR for leukemia of 1.63 for follow-up until 1984.[6] However, when the follow-up was extended to 1990, the SMR remained elevated but dropped to 1.35.[7] Another study conducted at the Y-12 plant found elevations in SMRs for lung cancer (1.17), lymphatic cancers (1.32), brain (1.13), and pancreatic cancers (1.36).[8] Yet another study at the K-25 plant found elevations in the overall SMR (SMR = 1.03, 95% confidence interval [95% CI] = 1.01 to 1.05) together with lung and bone cancer.[9] In contrast, a later study conducted at Portsmouth[10] revealed "all-cause" and "all-cancer" SMRs that were less than expected using US rates, demonstrating a strong healthy worker effect (HWE). The HWE is a phenomenon observed in occupational studies; workers usually exhibit lower overall death rates than the general population because ill and chronically disabled people are ordinarily not able to meet the demands of labor-intensive work.[11,12] The Portsmouth study did not reveal any statistically significant SMRs for any individual cancers, although excesses of stomach, female genital organs, bone, Hodgkin's, and lymph-reticulosarcoma cancers were noted. The largest occupational retrospective study to date for assessing low doses of ionizing radiation exposure and cancer mortality involved 407,391 nuclear workers in 15 countries. It revealed an excess relative risk for leukemia, excluding chronic lymphocytic leukemia (1.93 per Sv [95% CI = <0{estimate on boundary of parameter space} to 8.47]) but did not show an increased risk for other cancers.[13]

In response to concern about past and present radiation and chemical exposures, the National Institute for Occupational Safety and Health (NIOSH) funded a collaborative study by the Universities of Louisville, Kentucky, and Cincinnati to conduct an occupational cohort mortality study titled "Health effects of occupational exposures in PGDP workers." Of specific concern was exposure to uranium hexafluoride and the presence of transuranic

materials including neptunium and plutonium,[3–5] but the study also attempted to quantify exposure to ionizing radiation, chemicals, and toxic metals at the plant. Mortality patterns associated with job titles that have been grouped according to similarity of tasks and exposures, exposure to arsenic, beryllium, chromium, nickel, uranium, and cumulative internal and external radiation exposure within the plant are explored.

This report describes the analysis of mortality patterns for 92 causes of death including more than 40 cancers for the entire cohort using SMRs. In addition, mortality patterns for defined groups within the cohort are described using standardized rate ratios (SRRs). Although all outcomes were examined, a priori outcomes of interest were based on the literature. For radiation exposure, outcomes of interest include lymphatic and hematopoietic cancers, as well as lung, brain, bone, pancreatic, and stomach cancers. For exposure to metals, the a priori cancer of interest was lung cancer.

MATERIALS AND METHODS

Study Population

This retrospective occupational cohort mortality study consisted of eligible PGDP workers enumerated from employee personnel records. The Institutional Review Boards for the Protection of Human Subjects at the Universities of Louisville, Kentucky, and Cincinnati reviewed and approved the study. Because the study involved the collection of existing data, the risk to subjects was low, and consent was waived.

Demographic, work history, and vital status data were collected on 6820 workers. Inclusion criteria required workers to have been employed at the PGDP for at least 30 days from the start of plant operations in September 1952 through December 2003. Expected rates of death from the 1940 to 2002 US population were compared with actual deaths in the cohort study population for NIOSH's 92 death categories.

Vital Status

Vital status was determined as outlined by Checkoway et al[14] by linking cohort members' personal identifying information from employee records with data from the US Social Security Administration, the National Death Index (NDI), and individual state departments of health. All known deceased and any workers with unknown vital status were submitted to the NDI for cause of death information. Workers of unknown vital status were counted and considered alive with contributed person-years of observation up to the date of termination of employment.[14] For known deaths occurring before 1979, before the establishment of NDI, death certificates were requested from departments of health in the state; each individual worker was believed to have resided at the time of death. All data were subsequently de-identified and was only reported in aggregate form. The characteristics of the cohort are shown in Table 1.

Cause of Death

A total of 1674 deaths were identified out of 6820 workers in the cohort (24.6%). Because of incomplete history and outcome data, 61 workers were eliminated resulting in analyses on 6759 workers and 1638 deaths. Deaths were classified and coded to the international classification of diseases code that was in effect at the time of death (fifth through 10th revision) for the time period 1952–2003 for 92 causes of death including more than 40 cancers. A qualified nosologist coded deaths to the international classification of diseases code in effect at the time of death for all deaths that occurred before 1979 and for whom death certificates were obtained. Cause of death was obtained on 1638 deaths. Known deaths for which a death certificate could not be retrieved were counted in the other and unspecified causes of death category.

Grouped Job Titles

An original list of job titles consisting of 2727 unique entries was obtained and edited for duplications and misspellings. Information was provided by company representatives and long-term employees about job duties and work organization. The job titles were subsequently grouped according to similarity of task and exposure, resulting in a total of 44 grouped job titles.[15] The grouped job titles were then ranked in a qualitative and categorical manner based on the relative degree of exposure to various chemicals. Because many employees worked several jobs during their tenure at the plant, an analysis plan was devised that accounted for each grouped job title by developing a binary variable indicating whether the employee ever or never held a particular grouped job title. To ensure maximum power, analyses were limited to grouped job titles that had a minimum of 100 workers and 5% of the person-years for the whole cohort. This reduced the number of individual grouped job titles in the analysis from 44 to 11. An initial analysis of job category outcomes based on sex and race revealed that the sample size was limited for all categories except white males; therefore, all subsequent grouped job analyses included only white males.

Examination of the raw work history records indicated that employees who worked as a Chemical Operator frequently moved to Cascade or Maintenance. Chemical Operator consistently had the highest categorical rankings for five metals and trichloroethylene (TCE) of all the grouped job titles.[15,16] Two additional groups were created to better discriminate between workers who had and had not had exposures as a Chemical Operator. The additional groups were defined as ever worked Cascade not Chemical Operator and ever worked Maintenance not Chemical Operator. The addition of these groups brings the total job title categories analyzed to 13. The analyzed job titles are shown in Table 2 along with each job title's number of workers and person-years at risk (PYAR).

Analysis of Maintenance Groups

The 44 grouped job titles included 17 job titles that were considered "maintenance" positions. Depending on the category of maintenance, workers may have worked throughout the plant and may have been exposed to a variety of contaminants. Although not all 17 maintenance job titles met the criterion for analysis as a separate job title, further grouping of maintenance titles into high, medium, and low levels of exposure was undertaken to better understand mortality patterns for maintenance workers. Relative exposures for each grouped job title were estimated by building on the work of Hahn[15] and Moser.[16] Their studies assigned categorical exposure levels for the five metals and TCE that were widely used at the plant. Rankings of 0 to 5 were assigned based on long-term employee interview and plant records. Exposure levels frequently changed over time. To estimate all nonradiation hazards of interest, a qualitative exposure level was calculated by adding the levels of the five metals and TCE (additive exposure level; possible range 0 to 30). Where levels changed over time for a given exposure, the mean was used.

The additive exposure level was then used to condense the 17 Maintenance job title groups into the three categories: high-,

TABLE 1. Paducah Gaseous Diffusion Plant Cohort Description (1952–2003)

Demographic	No. Workers	Percent
White males	5,016	74
White females	1,069	16
Other races male	564	8
Other races female	171	3
Deaths	1,638	24

TABLE 2. Grouped Job Titles That Meet the Analysis Criteria of a Minimum of 100 Workers and 5% of the Total Cohort PYAR

Job Title	No. Workers	PYAR
Cascade	1,242	37,824.87
Cascade not Chemical Operator	581	13,791.25
Chemical Operator	1,242	58,178.49
Engineer	832	20,731.59
Laboratory	570	16,584.66
Maintenance	1,301	40,437.56
Maintenance not Chemical Operator	855	24,860.31
Maintenance/converter shop	347	11,655.23
Maintenance/custodial	512	12,560.33
Maintenance/electrician	433	12,866.33
Maintenance/roads and grounds	662	18,848.95
Office	1,441	41,924.91
Security	372	11,649.91
Total		215,114.77
5% cutoff		10,755.74

These values are for the full cohort (all race and gender categories). Workers are included in a job title category if they ever held that position; therefore, a worker may be included in two or more categories.

TABLE 3. Maintenance Categories and Additive Exposure Rankings

	No. Workers	PYAR	Additive Exposure Ranking
High maintenance			
Maintenance	1,301	40,437.56	22.5
Maintenance not Chemical Operator*	855	24,860.31	22.5
Medium maintenance		17,412.97	
Maintenance/fabrication	6	167.40	14.5
Maintenance/instrument mech.	321	10,507.69	13.5
Maintenance/lubrication	57	1,511.13	17.5
Maintenance/machining	220	8,269.91	16.0
Maintenance/sheet metal	32	1,088.30	15.0
Maintenance/welding	13	338.53	17.8
Low maintenance		38,300.58	
Maintenance/carpenter	32	904.51	10.8
Maintenance/converter shop	347	11,655.23	8.3
Maintenance/custodial	512	12,560.33	10.0
Maintenance/electrician	433	12,866.33	11.8
Maintenance/garage	35	1,046.08	9.0
Maintenance/painter	45	1,191.35	6.5
Maintenance/pump and seal	1	20.23	11.8
Maintenance/refrigeration	14	385.33	9.0
Maintenance/roads and grounds	662	18,848.95	10.0
Maintenance/truck driver	46	1,379.95	8.0

An overall qualitative exposure level was, for each job title, by adding the levels of the five metals and TCE (additive exposure level; possible range 0–30). Where levels changed over time for a given exposure, the mean was used. The additive exposure level was then used to condense the 17 maintenance job title categories into the three categories: high-, medium-, and low-exposure maintenance groups. These values are for the full cohort (all race and gender categories). Workers are included in a job title category if they ever held that position; therefore, a worker may be included in two or more categories.

*This is a subset of the maintenance grouped job title.

medium-, and low-exposure maintenance groups. The high-exposure maintenance group consisted of one grouped job title, Maintenance. Subsequently, both Maintenance and the category to discriminate from the effects of work as a Chemical Operator, Maintenance not Chemical Operator, were considered separately for the high-exposure category. Table 3 displays the maintenance categories and the additive exposure rankings for each grouped maintenance job title.

Neurodegenerative Disease Analysis

In addition to the standard referent data set of 92 causes of death, NIOSH's Life Table Analysis Software (LTAS) includes a neurodegenerative disease death rate file that analyzes specific causes of death under the category "other motor neuron disease." This broad category includes the outcomes of Alzheimer's disease, Parkinson's disease, and amyotrophic Lateral Sclerosis. Initial analyses indicated an elevation in "other motor neuron disease"; therefore, the neurodegenerative disease rate file was used to examine specific outcomes in this category.

Metals Analyses

Categorical exposure levels to the metals arsenic, beryllium, chromium, nickel, and uranium were described for each job title in the work of Hahn.[15] Because some ranks were represented by sparse person-years, this analysis divided the ranks of 0 to 5 into low-, medium-, and high-exposure categories. Ranks 0 and 1 were assigned to the low-exposure category, 2 and 3 to medium exposure, and ranks 4 and 5 to the high-exposure category. An individual was considered in the medium or high exposure category beginning at the time that he began working in a job title with a rank corresponding to that category. Although an employee could move from a lower rank to a higher rank during their tenure, moving to a lower-ranked position did not result in a lower exposure category. For each metal, an internal comparison with the low-exposure category as the referent was conducted resulting in an SRR for medium and high exposure to the metal. Because of limited sample sizes for other demographic categories, analyses were conducted for white males only.

Internal and External Radiation Analyses

A surrogate measure, in microgram years, of total cumulative internal radiation exposure was derived from urine data to represent the cumulative dose of internally deposited radionuclides. Total cumulative external radiation exposure was taken from badge data and expressed in millirems. The distribution of total person-years assigned to all workers was broken down to four equal categories according to how much person-time was spent in each of the four-ordered cumulative dose categories. The second, third, and fourth quartiles were compared with the first quartile of exposure to generate SRRs for white males.

Statistical Analysis

The overall mortality patterns of the PGDP cohort were examined by using LTAS to compare occupational cohort mortality with the US population from 1940 to 2002 for 92 causes of death including more than 40 cancers.[17] For data beyond 2002, LTAS estimated rates with data from 2000 to 2002.[18] Data analysis focused on SMRs for the entire period of the cohort (1952–2003), producing summary estimates of relative risks over the entire cohort experience. Expected deaths were calculated by multiplying the PYAR in the cohort by the rates in the US referent population. LTAS analysis was used to compare the "cause specific" observed

number of deaths with the expected number of deaths (SMRs) in each of the 92 causes of death supplied by LTAS. The study also examined the cohort by race, sex, 5-year age category, and 5-year calendar period.

Statistical significance testing was performed by comparing observed with expected numbers of deaths, under the assumption that the observed deaths were Poisson variates (random variables with a Poisson distribution) and the expected deaths were estimated without error. 95% CIs were calculated when the number of observed deaths was ≤10 and significant results flagged as $P <$ 0.05 or $P < 0.01$. All reported CIs are the 95% CI. For greater numbers of observed deaths, LTAS uses an approximation suggested by Breslow and Day.[19]

SRRs, a direct standardization method in LTAS,[19] were used to compare individual grouped job titles with the rest of the cohort, high and medium metal exposures to low metal exposures, and second, third, and fourth quartiles of cumulative internal and external radiation exposure with the first quartile of exposure. This internal comparison controls for external factors that may affect outcomes in particular the HWE and regional influences (such as local smoking rates or dietary differences). Job title, metals exposure, and cumulative internal and external radiation were analyzed for white males and, unless otherwise noted, included all ages and calendar periods.

RESULTS

Overall Findings

Table 1 provides the demographic and duration of employment characteristics of the cohort. The majority of the cohort was composed of white males (74%). Among the 6820 workers employed at PGDP between 1952 and 2003, 24.6% (1674) were deceased. Incomplete history or outcome data resulted in the elimination of 61 workers (<1%), and 2.2% (36) of deaths had an unknown underlying cause of death. Of the 1674 deaths, complete person, history, and outcome data were available for 1638. Therefore, the cohort analysis was performed on 6759 workers and 1638 deaths. Looking at duration of employment, the largest group of workers, 33% (2235), was employed at the plant for a period of 1 to 5 years.

The all-cause mortality and all-cancer mortality experience of the PGDP cohort was significantly lower than that of the US referent population. The all-cause SMR (SMR = 0.73; 95% CI = 0.69 to 0.76) was based on 1638 observed deaths versus 2253 expected (Table 3). The all-cancer SMR (SMR = 0.78; 95% CI = 0.71 to 0.85) was based on 461 observed cases versus 592 expected. Deaths related to "other causes," which include all deaths that do not have a known cause of death, were also significantly reduced indicating higher rates of death classification than the US referent (SMR = 0.42; 95% CI = 0.27 to 0.61).

The a priori cancers of interest (hematopoietic, lung, bone, kidney, and stomach cancers) did not show any statistically significant increased mortality rates (Table 4). However, individual nonsignificant excess mortality rates (SMR >1) were noted for cancers of the lymphatic and hematopoietic tissue (SMR = 1.19; 95% CI = 0.85 to 1.61). These included non-Hodgkin's lymphoma (SMR = 1.43; 95% CI = 0.98 to 2.01), leukemia (SMR = 1.11; 95% CI = 0.71 to 1.65), and multiple myeloma (SMR = 1.02; 95% CI = 0.49 to 1.87). Pancreatic cancer was nonsignificantly elevated (SMR = 1.10; 0.75 to 1.56). Lung cancer had significantly lower mortality rates (SMR = 0.72; 95% CI = 0.58 to 0.89).

Outcomes from the analyses of race, sex, 5-year age category, and 5-year calendar period were similar to the overall cohort experience (data not shown). All-cause SMRs were significantly lower than the US referent for all race and gender categories. The

TABLE 4. SMRs for Selective Causes of Death Among 6,820 Workers at the Paducah Gaseous Diffusion Plant 1952–2003

Category Cause	Observed Deaths	Expected Deaths	SMR	95% Confidence Limits Lower	95% Confidence Limits Upper
All deaths	1,638	2,253.50	0.73*	0.69	0.76
All cancers	461	592.35	0.78*	0.71	0.85
Other causes[a]	27	64.74	0.42*	0.27	0.61
Cancers of the lymphatic and hematopoietic tissue					
All	68	57.20	1.19	0.92	1.51
Non-Hodgkin's lymphoma	32	22.43	1.43	0.98	2.01
Hodgkin's disease	2	3.32	0.60	0.07	2.18
Leukemia and aleukemia	24	21.61	1.11	0.71	1.65
Multiple myeloma	10	9.83	1.02	0.49	1.87
Cancers of the bone and connective tissue, brain, lung, pancreatic, and unspecified sites					
Bone	1	1.40	0.72	0.02	3.99
Connective tissue	2	3.32	0.60	0.07	2.18
Brain	16	15.94	1.00	0.57	1.63
Kidney	14	14.39	0.97	0.53	1.63
Lung	146	201.55	0.72*	0.58	0.89
Pancreas	32	29.05	1.10	0.75	1.56
Other	37	40.88	0.91	0.64	1.25
Stomach	11	17.47	0.63	0.31	1.13

*Two-sided $P < 0.01$.
[a]Other causes include all deaths that do not have a known cause of death and all deaths related to other causes not included in NIOSH's death categories and corresponding International Classification of Diseases codes.

5-year age categories all-cause SMRs were significantly lower than the US referent up to the 70- to 74-year age category. Age categories from 75 to 89 and above had all-cause mortality rates approximately equal to the US referent. No deaths were observed for several 5-year age category and calendar periods for groups other than white males, limiting the robustness of this analysis for white females and males and females of other races. For white males, all categories had observed deaths, although the youngest age categories (15 to 19 and 20 to 24) had few observed deaths (one and three, respectively), and the first calendar period, 1950–1954, representing the first 2.5 years of plant operations had only three observed deaths. For the remaining 5-year age categories, observed deaths ranged from 11 to 241, and observed deaths for the remaining 5-year calendar periods ranged from 16 to 290.

Non-Cancer Mortality

Most mortality rates for non-cancer causes of death were also lower in the cohort than the general US population (data not shown). For example, the SMR for heart disease was 0.75 (95% CI = 0.67 to 0.83). Nonsignificantly elevated SMRs were noted for "other nervous system diseases" (SMR = 1.30; 95% CI = 0.96 to 1.72) and "other mental disorders" (SMR = 1.11; 95% CI = 0.62 to 1.83). The neurodegenerative disease rate file was used to

examine specific outcomes in the category "other nervous system diseases." The SMR for Alzheimer's disease was significantly elevated (SMR = 2.16; 95% CI = 1.38 to 3.21). Further analysis for this outcome by 5-year age category showed a significant elevation for Alzheimer's deaths for the 70 to 74 years age category (SMR = 3.30; 95% CI = 1.21 to 7.18) and near significance for the 75 to 79 and 80 to 84 age categories (SMR = 2.35; 95% CI = 0.94 to 4.84 and SMR = 2.42; 95% CI = 0.97 to 4.99, respectively). Statistically significant excesses in mortality from suicide deaths were observed when stratified by year and age. An SMR of 2.21 (95% CI = 1.01 to 4.19) for years 1970–1974 and an SMR of 8.13 (95% CI = 1.69 to 23.75) for years 1975–1979 in the 40 to 44 age group was found. Further analysis of suicide deaths in the cohort is explored in a separate analysis (Figgs LW, personal communication).

Analysis by Job Title

SMRs were used for a preliminary look at grouped job titles. Among the a priori cancers of interest, non-Hodgkin's lymphoma was significantly elevated for the category Security (SMR = 3.39; 95% CI = 1.10 to 7.91) and nonsignificantly elevated for Cascade, Chemical Operator, Maintenance, Maintenance/converter, Maintenance/custodial, Maintenance/roads and grounds, and Office. No significant elevations for kidney cancer were found for Chemical Operator (SMR = 1.61; 95% CI = 0.69 to 3.17) and Maintenance (SMR = 2.13; 95% CI = 0.78 to 4.63). Chemical Operator also had an elevation in brain cancer (SMR = 1.52; 95% CI = 0.66 to 3.00). For most grouped job titles, significantly lower rates of death were found for most cancers and for heart disease. A significant elevation was found for colon cancer for the category Office (SMR = 2.73; 95% CI = 1.18 to 7.91).

The primary focus of our analyses was internal comparisons using SRRs. Table 5 provides the SRRs for select job titles and causes of death (also see Table, Supplemental Digital Content 1, http://links.lww.com/JOM/A34, which provides SRRs for all analyzed job titles and additional causes of death). Job titles with elevated SRRs for all causes include Maintenance/converter shop (SRR = 1.35; 95% CI = 0.83 to 2.17) and Maintenance/roads and grounds (SRR = 1.25; 95% CI = 0.96 to 1.63). All-cause mortality was significantly higher for security compared with all other white males in the cohort (SRR = 1.34; 95% CI = 1.06 to 1.71). No significant elevations in leukemia were found for the job titles Cascade (SRR = 1.16; 95% CI = 0.42 to 3.20), Chemical Operator (SRR = 1.49; 95% CI = 0.62 to 3.58), and Security (SRR = 1.90; 95% CI = 0.56 to 6.47). In addition, security had a no significant elevation in non-Hodgkin's lymphoma (SRR = 2.44; 95% CI = 0.91 to 6.55). Significantly elevated SRRs for specific causes of death included colon cancer for the category office (SRR = 4.91; 95% CI = 2.08 to 11.63), diseases of the heart for maintenance/roads and grounds (SRR = 1.70; 95% CI = 1.13 to 2.55), and Security (SRR = 1.78; 95% CI = 1.17 to 2.71), lung cancer for Maintenance/converter shop (SRR = 1.99; 95% CI = 1.19 to 3.35), and Maintenance/custodial (SRR = 2.56; 95% CI = 1.09 to 5.98).

For the maintenance exposure groups, the SMRs for all causes were significantly lower than the US referent for all three levels of exposure reflecting the HWE that characterizes the entire cohort. Mortality from all cancers was also lower than the US referent for all three maintenance groupings, although a statistically significant deficit was only observed in the high-exposure category. An SRR analysis was not conducted on the maintenance groupings.

The NIOSH neurodegenerative disease rate file was used to examine specific mortality outcomes in the category "other nervous system diseases" for grouped job titles. An examination using SMRs found a significant elevation in this broad category for Chemical Operator (SMR = 1.65; 95% CI = 1.01 to 2.50) and not significant elevations for the job titles Engineer, Laboratory, and

TABLE 5. SRRs for Selective Outcomes and Job Titles for White Males

Category Cause	Job Title	Observed Deaths	SRR	95% Confidence Limits Lower	Upper
All deaths	Cascade	282	0.97	0.85	1.12
	Chemical Operator	532	1.01	0.88	1.14
	Maintenance	306	0.94	0.83	1.08
	Office	94	1.03	0.82	1.29
	Security	136	1.34	1.06	1.71
All cancers	Cascade	70	0.83	0.63	1.09
	Chemical Operator	143	0.96	0.74	1.23
	Maintenance	75	0.94	0.61	1.02
	Office	35	1.34	0.92	1.96
	Security	31	1.01	0.67	1.51
Cancers of the lymphatic and hematopoietic tissue					
All	Cascade	12	0.92	0.48	1.77
	Chemical Operator	26	1.18	0.69	2.02
	Maintenance	10	0.65	0.33	1.30
	Office	6	1.31	0.52	3.29
	Security	8	1.74	0.82	3.71
Non-Hodgkin's	Cascade	5	0.82	0.30	2.23
	Chemical Operator	9	0.82	0.35	1.92
	Maintenance	5	0.71	0.26	1.90
	Office	3	1.98	0.58	6.69
	Security	5	2.44	0.91	6.55
Leukemia	Cascade	5	1.16	0.42	3.20
	Chemical Operator	11	1.49	0.62	3.58
	Maintenance	3	0.58	0.17	2.00
	Office	2	0.54	0.13	2.33
	Security	3	1.90	0.56	6.47
Cancers of the brain, lung, and pancreas					
Brain	Cascade	3	0.79	0.22	2.85
	Chemical Operator	8	2.29	0.78	6.71
	Maintenance	3	0.74	0.21	2.66
	Office	1	0.34	0.04	2.62
	Security	2	3.78	0.78	18.29
Lung	Cascade	23	0.72	0.48	1.77
	Chemical Operator	46	0.89	0.54	1.45
	Maintenance	21	0.71	0.44	1.14
	Office	7	0.99	0.45	2.18
	Security	10	0.80	0.41	1.55
Pancreas	Cascade	0	0.94	0.36	2.47
	Chemical Operator	6	0.92	0.39	2.17
	Maintenance	7	1.01	0.43	2.41
	Office	3	1.57	0.42	5.84
	Security	1	0.36	0.05	2.64

Office (data not shown). The internal comparison found significant elevations in Alzheimer's deaths for the job title Engineer (SRR = 2.81; 95% CI = 1.01 to 7.86). No significant elevations were found for Maintenance (SRR = 1.56; 95% CI = 0.68 to 3.58), Maintenance not Chemical Operator (SRR = 2.22; 95% CI = 0.76 to

6.50), and Office (SRR = 1.63; 95% CI = 0.36 to 7.39). The job category Laboratory had a near significant elevation for the outcome amyotrophic lateral sclerosis (SRR = 5.30; 95% CI = 0.95 to 29.65).

Analysis of Metal Exposures

Those with medium and high exposures to metals had few differences in outcomes compared to those with low exposures (see Table, Supplemental Digital Content 2, http://links.lww.com/JOM/A35, which provides SRRs for medium and high exposures to metals). Those with medium exposure to nickel had a significant elevation in lung cancer (SRR = 1.74; 95% CI = 1.06 to 2.85), although those with high exposure had an SRR below 1.00 for that outcome. Medium exposure to uranium resulted in a near significant elevation for all causes (SRR = 1.17; 95% CI = 0.99 to 1.38), whereas high exposure to uranium had an all-cause SRR of 1.00 (95% CI = 0.88 to 1.14).

Internal and External Radiation Analyses

Table 6 shows an SRR analysis of internal and external radiation exposures for cancers of interest. The second and third quartiles of internal radiation exposures were significantly elevated relative to the first quartile for non-Hodgkin's lymphoma (SRR =

9.95; 95% CI = 1.22 to 81.26 and SRR = 8.85; 95% CI = 1.11 to 70.88, respectively). The fourth quartile was nonsignificantly elevated (SRR = 5.74; 95% CI = 0.72 to 45.48).

DISCUSSION

This analysis is consistent with the published literature.[6,7,12,13] As expected, a strong HWE was observed in this cohort. PGDP workers experienced lower mortality rates from all deaths (SMR = 0.73) and all cancers (SMR = 0.77) compared with the US referent population. Previous studies had suggested that long-term follow-up might reduce the HWE.[11] Another related phenomenon, however, observed more recently in long-term occupational mortality studies is the "healthy worker survivor effect,"[20] which tends to diminish exposure-related risk estimates in long-term workers because workers who remain employed tend to be healthier than those who terminate.

The analyses by race, sex, 5-year age category, and 5-year calendar period are also consistent with the overall cohort experience. For white males, the results suggest a strong HWE for all calendar periods and ages up to 75 years.

Despite limitations, SMRs are a critical first step in occupational analyses. It is important to note that results that lack signif-

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TABLE 6. SRRs for Cumulative Radiation Exposure for White Males

Outcome	1 0–20 μg yr (SRR = 1) n	2 21–50 μg yr SRR (95% CI)	n	3 51–125 μg yr SRR (95% CI)	n	4 >125 μg yr SRR (95% CI)	n
Internal radiation quartile							
All causes	208	1.02 (0.84–1.22)	286	1.06 (0.89–1.26)	411	0.70 (0.57–0.85)	475
All cancers	73	0.86 (0.62–1.19)	82	0.77 (0.56–1.05)	103	0.61 (0.40–0.94)	129
Lung cancer	21	0.91 (0.51–1.62)	27	0.95 (0.56–1.63)	41	0.51 (0.30–0.88)	40
Brain cancer	3	0.66 (0.10–4.16)	2	1.07 (0.24–4.80)	5	0.45 (0.10–2.15)	4
Bone cancer	0	NR	0	NR	1	NR	0
Kidney cancer	0	NR	3	NR	3	NR	7
Pancreatic cancer	5	1.42 (0.43–4.67)	8	0.49 (0.12–1.94)	4	0.97 (0.31–2.98)	13
Lymphatic and hematopoietic	6	1.79 (0.66–4.88)	13	1.48 (0.55–4.02)	13	1.35 (0.53–3.41)	25
Non-Hodgkin's	1	9.95 (1.22–81.26)	7	8.85 (1.11–70.83)	8	5.74 (0.72–45.48)	10
Hodgkin's	1	0.67 (0.04–10.73)	1	NR	0	NR	0
Leukemia	4	0.73 (0.18–3.01)	4	0.49 (0.11–2.26)	3	0.77 (0.24–2.50)	10
Multiple myeloma	0	NR	1	NR	2	NR	5

Outcome	1 0–100 mrem (SRR = 1) n	2 101–500 mrem SRR (95% CI)	n	3 501–1,000 mrem SRR (95% CI)	n	4 >1,000 mrem SRR (95% CI)	n
External radiation quartile							
All causes	236	0.86 (0.62–1.19)	289	0.77 (0.56–1.05)	261	0.61 (0.40–0.94)	594
All cancers	67	1.08 (0.90–1.29)	82	0.91 (0.76–1.10)	76	0.70 (0.60–0.82)	162
Lung cancer	24	1.04 (0.60–1.80)	29	0.77 (0.42–1.40)	22	0.61 (0.37–1.00)	54
Brain cancer	2	2.44 (0.46–12.86)	5	0.59 (0.05–6.58)	1	1.05 (0.21–5.26)	6
Bone cancer	0	NR	0	NR	1	NR	0
Kidney cancer	0	NR	3	NR	1	NR	9
Pancreatic cancer	3	1.66 (0.39–7.02)	6	1.72 (0.42–7.05)	6	1.48 (0.42–5.20)	15
Lymphatic and hematopoietic	11	1.14 (0.50–2.59)	13	0.67 (0.25–1.75)	7	0.70 (0.34–1.45)	26
Non-Hodgkin's	5	1.20 (0.36–4.01)	6	0.91 (0.24–3.48)	4	0.76 (0.26–2.25)	11
Hodgkin's	2	NR	0	NR	0	NR	0
Leukemia	3	2.19 (0.52–9.14)	1	0.36 (0.04–3.55)	1	1.14 (0.31–4.27)	11
Multiple myeloma	1	0.79 (0.05–12.70)	2	1.70 (0.15–18.76)	2	0.88 (0.10–7.88)	4

NR—statistic not reported because of one comparison group having 0 deaths; n, observed deaths.

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icance do not provide evidence against a true relationship.[21] Despite the overall health of the PGDP cohort, lymphatic and hematopoietic cancers reflected a nonsignificantly elevated SMR of 1.19 based on 68 observed deaths. Non-Hodgkin's lymphoma, leukemia, and multiple myeloma SMRs were elevated. Non-Hodgkin's lymphoma showed the most prominent excess (SMR = 1.43; 32 observed deaths).

The internal comparison using SRRs controls for the HWE and regional influences (such as local smoking rates or dietary differences) and therefore may address some of the SMR limitations. The internal comparison showed that the job titles Maintenance/converter shop, Maintenance/roads and grounds, Office, and Security had higher, but not significant, non-Hodgkin's lymphoma deaths compared with the rest of the cohort. These job titles were not known to have regular radiation exposure. Before 1955, however, security did patrol all buildings and may have had poorly characterized exposures.[16] After 1955, patrols were limited to the periphery. Examination of the work history of the five Security employees who died from non-Hodgkin's lymphoma showed that all five held the position before 1955 when Security patrolled all buildings.

In examining the SRRs for lymphatic and hematopoietic cancers, Chemical Operators had higher death rates than the cohort for leukemia and multiple myeloma but not non-Hodgkin's lymphoma, and the job titles Cascade and Security had nonsignificant elevations in leukemia deaths. For the Cascade category, however, when workers who had also been Chemical Operators were removed, no leukemia deaths were reported, suggesting that the elevation was associated with the job title Chemical Operator.

These findings support trends for hematopoietic cancer risk found in similar cohorts.[6,8] Hematopoietic cancers are of major interest because of the recognized association with radiation exposure. It is well documented that high-dose radiation exposure has resulted in immunosuppressive and carcinogenic effects in organs where radionuclides concentrate, specifically for most forms of leukemia.[22,23] Previous DOE studies have also revealed increased SMRs for hematopoietic cancers with low-dose radiation exposure, although not always statistically significant. For example, early studies at the Oak Ridge facility and the Mallincrodt Chemical Works revealed statistically higher SMRs for hematopoietic cancers,[8] but this trend was not reflected in later studies.[24] The Portsmouth study revealed nonsignificant excesses of hematopoietic cancers and Hodgkin's disease,[10] and the 15 country study revealed an elevated relative risk for lymphocytic leukemia.[13] Non-Hodgkin's lymphoma and leukemia showed consistently increased SMRs, an observation supported by this study. The PGDP cohort had low-dose radiation exposures comparable with workers in these studies, with ~75% of workers with <100 mrem cumulative external radiation exposure. The results of this study strengthen the association found in these studies between low-dose radiation exposure and hematopoietic cancers.

The internal comparison showed a significant elevation in colon cancer for the grouped job title Office (SRR = 4.91; 95% CI = 2.08 to 11.63). This job category also showed not significant elevations in pancreatic cancer, non-Hodgkin's lymphoma, Alzheimer's disease, and diabetes. Employees with this job title did clerical jobs, but their offices were located in production buildings, and they may have had transitory exposure to some chemicals.[16] Office workers typically performed more sedentary tasks and may not exhibit the HWE to the same degree as employees who execute more physical tasks.

Selective job titles underwent further analysis with the neurodegenerative disease rate file. Elevations in the "other nervous system diseases" outcome were found to be because of increases in deaths from Alzheimer's disease. As is typical for this disease, deaths from this outcome primarily occurred in individuals above the age of 70 and many in their 80s. Reductions in deaths from heart disease and cancers may account for the increase in Alzheimer's deaths.

A limitation of the internal analysis of metals was that few measurements of exposure were found for the early years of work for the cohort. Therefore, categorical values were assigned to each grouped job title, which can introduce misclassification, with bias toward the null hypothesis. In addition, job titles that had higher exposures for one metal tended to have high exposures to all metals, making it difficult to determine an association between a particular metal and an elevated outcome. The a priori outcome of interest with metals exposure was lung cancer. Medium exposure to nickel resulted in a significantly elevated SRR for this outcome, whereas nonsignificant elevations were found with medium exposures to uranium and beryllium. With the internal comparison of job titles, significantly elevated SRRs for lung cancer were found for the job titles Maintenance/converter shop and Maintenance/custodial. Maintenance/converter shop had slightly elevated exposures to nickel and uranium. Maintenance/custodial had slightly elevated exposures to beryllium and nickel and higher exposures to uranium. The job title with the highest exposure to these metals, Chemical Operator, did not have an elevation in lung cancer. Interpretation of these results is limited by overlap in metals exposure and the lack of smoking data.

No patterns from cumulative internal or external radiation exposure were apparent. Exposure to radiation at the plant observed a log-normal distribution, with the majority of employees accumulating little exposure. The categories for radiation exposure were quartiles based on PYAR. This strategy resulted in low exposures in the lower quartiles, which may have masked evidence of a dose-response relationship. A further analysis is underway employing modeling techniques to further explore radiation exposure-disease relationships (Hornung RW, personal communication).

Limitations to this analysis included lack of smoking data. Based on previous studies similar in scope, it was anticipated that smoking rates would not be significantly different between exposed and unexposed workers and thus would not adversely impact this analysis.[25,26] We did not carry out an analysis of solid cancers not associated with smoking, to minimize potential confounding from smoking, because of low numbers of these outcomes.

In conclusion, this study describes a cohort mortality analysis for a large gaseous diffusion plant. Despite significant reductions in SMRs for all causes and all cancers, elevations in lymphatic and hematopoietic cancers were found for the cohort. The internal comparison showed certain job titles with higher exposures had nonsignificant elevations of hematopoietic cancers. These findings confirm the relationship found in previous studies between slight elevations in risk of hematopoietic cancers and low levels of radiation exposure.[6,7,13]

ACKNOWLEDGMENTS

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