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Lung Cancer Mortality among Uranium Gaseous Diffusion Plant Workers: A Cohort Study 1952–2004

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Abstract

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Background: 9%–15% of all lung cancers are attributable to occupational exposures. Reports are disparate regarding elevated lung cancer mortality risk among workers employed at uranium gaseous diffusion plants.

Objective: To investigate whether external radiation exposure is associated with lung cancer mortality risk among uranium gaseous diffusion workers.

Methods: A cohort of 6820 nuclear industry workers employed from 1952 to 2003 at the Paducah uranium gaseous diffusion plant (PGDP) was assembled. A job-specific exposure matrix (JEM) was used to determine likely toxic metal exposure categories. In addition, radiation film badge dosimeters were used to monitor cumulative external ionizing radiation exposure. International Classification for Disease (ICD) codes 9 and 10 were used to identify 147 lung cancer deaths. Logistic and proportional hazards regression were used to estimate lung cancer mortality risk.

Results: Lung cancer mortality risk was elevated among workers who experienced external radiation >3.5 mrem and employment duration >12 years.

Conclusion: Employees of uranium gaseous diffusion plants carry a higher risk of lung cancer mortality; the mortality is associated with increased radiation exposure and duration of employment.

Keywords: Lung neoplasms; Mortality; Radiation; Occupational exposure; Occupational diseases; Uranium compounds

Introduction

Worldwide, cancer has become the second leading cause of death.¹ The US National Cancer Institute estimated that approximately 12 million Americans with a cancer history were alive in 2008, 1.6 million diagnosed cancers and nearly 577 190 cancer deaths in the US in 2012.² Environmental risk factors are believed responsible

for two out of every three cancers and occupational exposures may account for 40 000 incident cases and 20 000 deaths each year.³ In the 20th century's last decade lung cancer became the most common cancer associated with occupational hazards.⁴ Metal exposures are a common workplace concern,^{5–8} especially among nuclear industry workers.

The difficulty with identifying associations between work-related exposures and

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cancer mortality among nuclear industry workers is based on the type of cancer, the exposure assessment, and the toxic properties of confounding hazards, especially radiation. For example, exposures may be unique to a specific workplace in character, duration, and/or intensity. In other instances, the mechanisms believed to be responsible for hazard-related neoplasia are incomplete and suggest multiple pathways.^{5,9-12}

Assessing a hazard's toxic properties, the duration of worker exposure, the intensity of that exposure, and other confounding factors may explain how past occupational cohort investigations discordantly report associations between some toxic metal exposures and lung cancer.^{8,11,13-17} For example, in 2004 Sorahan concluded that nickel exposure was not associated with increased lung cancer mortality.¹⁴ Concurrently, Sorahan and Esman reported that cadmium exposures do not support a carcinogenesis hypothesis¹⁵ despite earlier reports.¹⁸ A year later, Sorahan and Williams reported that nickel exposure could not be ruled out as a risk factor for increased lung cancer mortality.¹⁶ In 2009, Levy, *et al*, in an effort to assess lung cancer standardized mortality ratios (SMRs) among beryllium workers, observed little to support an association between lung cancer and beryllium exposure, after adjusting for tobacco smoking.¹¹ More recently, Brusk-Hohlfeld cited 87 references in a literature review and concluded that there was sufficient epidemiological evidence supporting a link between carcinogenesis and exposure to arsenic, beryllium, cadmium, chromium and nickel.⁷ In a separate review citing 160 references, Wild, *et al*, noted that some metals (arsenic, beryllium, cadmium, chromium and nickel) were “accepted” carcinogens based primarily on International Agency for Research on Cancer (IARC) assessments published prior to

2000.⁸

Recent nuclear industry cohort studies have featured cancer outcomes associated with radiation or metal exposure.^{19,20} Godbold and Tompkins reported that the expected number of deaths derived from the US population of white males exceeded the number of all cancers observed as well as lung cancers among 814 nickel-exposed “barrier workers” employed at the Oak Ridge gaseous diffusion plant in Oak Ridge, Tennessee.²¹ Polednak reported no excess mortality for all-cancers (SMR: 0.88; 95% CI: 0.60–1.23), but reported mortality excesses for respiratory system cancers (SMR: 1.39; 95% CI: 0.81–2.22) and lung cancer (SMR: 1.50; 95% CI: 0.87–2.40) among 1059 white male welders exposed to uranium, fluoride, lead, nickel, mercury, chromium, and technetium at three Oak Ridge plants from 1943 to 1977.²² Frome, *et al*, observed no excess in all-cancer, lung, or respiratory system mortality among 106 020 nuclear industry workers in Oak Ridge, employed between 1943 and 1985.²³ In another investigation, National Institute for Occupational Safety and Health (NIOSH) investigators did not observe excess all-cancer mortality (SMR: 0.82; 95% CI: 0.73–0.92), but observed statistically non-significant mortality excesses for stomach (SMR: 1.18; 95% CI: 0.65–1.94), female genital organs (SMR: 1.27; 95% CI: 0.47–2.77), bone (SMR: 1.68; 95% CI: 0.20–6.05), lympho-reticulosarcoma (SMR: 1.37; 95% CI: 0.55–2.82), and Hodgkin's disease (SMR: 1.38; 95% CI: 0.45–3.23).²⁴ Similarly, Charles, *et al*, observed an increase in cancer mortality associated with occupational exposure to metals and solvents.²⁵

Recently, Chan, *et al*, reported that excess mortality occurred among Paducah uranium gaseous diffusion plant (PGDP) workers who developed cancers of pancreas, myeloproliferative neoplasms and lymphomas.²⁰ However, Chan, *et al*, did

For more information on suicide risk among workers of the Paducah gaseous diffusion plant see www.thejioem.com/ijioem/index.php/ijioem/article/view/113

not observe excess mortality among lung cancer victims even though toxic metal and radiation exposures were likely higher among PGDP workers than the general population and IARC's earlier report that several of the metals were potential carcinogens.²⁶ Aware of the potential biases and constraints associated with SMR analyses, this investigation re-examines the relationship between lung cancer mortality and uranium exposure with specific emphasis on uranium exposure and radiation applying logistic regression analysis to case-control designs and proportional hazards regression to the entire cohort.

Materials and Methods

Population sampling frame

The PGDP is located on 3425-acres near Paducah, Kentucky. It was built in the early 1950s to process uranium. Although owned by the US Department of Energy (DOE), since construction the facility was leased to Union Carbide (1950–1984), Martin Marietta (1984–1995), and Lockheed Martin Utilities Services (1995–2005).²⁷ The PGDP cohort is described elsewhere in detail.^{28,29}

Workers had to work at least six continuous months from September 1, 1952 to December 31, 2003 to be eligible for the study. Person-time accrued from the worker's initial PGDP hiring date until their death or December 31, 2004. Briefly, 6859 worker files were assembled from DOE contractors, unions, and Oak Ridge affiliated universities.³⁰ Nosologists used state vital records agency death certificates to verify the vital status of workers dying before 1980. National Death Index (NDI) queries were used to verify post-1979 deaths. The vital status of two workers was undetermined. Thirty-nine worker files were duplicates.³¹ The final analysis file contained 6820 workers. Cancer mortality was followed until December 31, 2004.

Exposure assessment

Metals

A detail description of the job-specific metal exposure matrix is reported elsewhere.^{32,33} Briefly, all job titles were grouped, ranked for specific metal exposures, and consolidated using worker interviews, plant production records, and job-site maps. Metal exposure rankings were based on qualitative and quantitative factors such as environmental monitoring data, location of plant processes, and interviews with long-term workers. Company representatives and long-term workers reviewed job titles and were asked to comment on whether each job title would have less, the same, or more exposure than another job title. Rankings (categories) ranged from zero to five—zero representing “no exposure expected” and five “the most exposure expected.” Rankings were categorical and unrelated to quantitative exposure intensity (concentration) or dose. Therefore, exposure rankings for a unique metal were not additive or multiplicative (*ie*, a category ‘2’

TAKE-HOME MESSAGE

- Workers of uranium gaseous diffusion plants are at higher risk of lung cancer mortality.
- Limiting the work to 42 months (3.5 years) at high radiation levels (1096 mrem) may reduce lung cancer mortality.
- Nuclear industry employers should biomonitor workers for metals (nickel, beryllium, arsenic, *etc*) other than radioactive metals.
- Comprehensive metal biomonitoring methods need to be developed, improved, and adopted for workers similarly exposed.

exposure ranking was not twice a category '1' exposure ranking). Inter-rank comparisons were invalid.

Categories '0' and '1' were combined for this analysis.

Arsenic, hexavalent chromium, nickel, beryllium, and uranium exposure categories were tabulated to construct a study-specific, job exposure matrix (JEM) by modifying methods described elsewhere.³² Discrete exposure ranking categories ranging from zero to five were entered into each unique metal (row)/job-title (column) cell. More than one ranking was allowed per cell in the JEM to account for changes in plant processes over time. A supplemental table provided additional ranking information.³²

Categories '0' and '1' were combined for the analysis below.

Radiation

External radiation exposure intensity was determined by monitoring personal radiometric badges. Data were recorded as decimal, interval data in millirems. Millirem exposures were natural logarithm (\ln) transformed to mitigate skewness and kurtosis. Tertile categories were devised in which the lowest exposure ("Low") represented all millirem values ≤ 427.63 mrem. Intermediate exposures ("Intermediate") represented all millirem values > 427.63 and ≤ 1069.25 mrem. The highest tertile ("High") represented all millirem values > 1069.25 mrem.

Duration of exposure to radiation

Employment duration was a proxy estimate for the duration of radiation exposure. Employment duration was determined as the difference in total days between the dates last observed and initially hired. To calculate years of employment, days were divided by 365.25. Total years were stratified by tertiles. Workers employed 3.51 years or less were consid-

ered "Short" duration employees. Workers employed > 3.51 years and ≤ 11.8 years were "Intermediate" duration workers. Those who worked > 11.8 years were "Long" duration workers.

Case ascertainment

All death certificates with "Underlying Cause of Death" (UCD) fields containing International Classification for Disease (ICD) codes 161, 162.0-162.5, 162.8, 163 (ICD-6 and ICD-7), or codes 161, 162.0-162.5, 162.8, 163.1, 163.9 (ICD-8), or codes 162.0-162.9, 163, 164, 165, (ICD-9), or codes C33.0-C34.0-C34.3, C34.8, C34.9, C37, C38.0-C38.3, C38.8, C39, C45 (ICD-10) and dying before December 31, 2003 were considered lung cancer cases.³⁴

Control selection

Case-control design

Cumulative incidence and incidence density sampling was used to select controls. Five-hundred and eighteen controls were selected by incidence density sampling ($\sim 4:1$ controls per case without age-group frequency matching). A parallel case-control design is also applied because assuming that the hazard ratio (HR) is constant over time may be invalid for specific proportional hazards models.^{35,36}

Statistical analysis

All statistics were estimated using STATA™ ver 10.1 Statistics/Data Analysis Special Edition (Stata Corp, 4905 Lakeway Drive, College Station, TX 77845, USA).

Initially, all lung cancer mortality risk estimates associated with radiation exposure were derived from Cox proportional hazards regression models.³⁵ However, test that the relative hazard (hazard in the exposed divided by hazard in the unexposed) was fixed over time often in-

licated that a single HR was marginally appropriate or inappropriate for some models. Since fixed proportional hazards (the assumption that the ratio of hazards between exposed and unexposed is the same at all possible survival times) is not an assumption of case-control designs, a parallel nested case-control design was pursued.

Odds ratios (ORs) were estimated by logistic regression analysis³⁷ and adjusted using the available confounding variables. Bias introduced by ignoring smoking (subject-level tobacco smoking histories unavailable) was addressed by probabilistic sensitivity analyses, assuming that lung cancer mortality relative risk attributable to tobacco smoking was 1.5 and tobacco smoke exposure prevalence among workers ranged from 0.10 to 0.25.³⁸

χ^2 statistics with degrees of freedom and *p* value,³⁹ and crude and adjusted ORs⁴⁰ with 95% CI are provided where appropriate.

Cohen's *k* was used to assess inter-method agreement between the JEM and urine uranium concentration and external radiation.^{41,42} The JEM was converted to a dichotomous (exposed *vs.* unexposed) matrix by collapsing all values '1' and '2' into one "unexposed" category. JEM categories 3–5 were classified as "exposed." Urine uranium concentration was divided into two exposure categories in which unexposed workers had values less than or equal to the median. Similarly, natural log-transformed millirem values were divided into two exposure categories in which unexposed workers had values less than or equal to the median.

Tobacco smoking effects were assessed using probabilistic sensitivity analysis.⁴³

Institutional review board (IRB) approval

Only de-identified data were available for this analysis. The PDGP, University of

Louisville, University of Kentucky, and University of Cincinnati IRB annually approved all data collection methods and verified investigators training to conduct ethical scientific investigations. Consent to collect worker information was obtained from employers and employee union representatives.

Results

There were 1674 total deaths. Four-hundred and thirty-five were classified as cancers. One-hundred forty-seven were lung cancer deaths. The first cancer death occurred April 11, 1953; the last occurred December 23, 2003. Eighteen percent (*n*=1223) of PGDP workers initially hired as chemical operators accounted for 29% (*n*=42) of all lung cancer deaths (*p*<0.07). Thirty-two percent (*n*=2190) of all PGDP workers were initially hired in maintenance categories and accounted for one-third (*n*=49) of all lung cancer deaths. Sixteen and a half percent (*n*=1129) of PGDP workers initially hired as office workers accounted for 10% (*n*=15) of all lung cancer deaths. Four and a half percent (*n*=300) of workers initially hired in a security title accounted for seven and a half percent (*n*=11) of all lung cancer deaths. The remainder of the cancer deaths occurred among other job title groups, however none with frequencies higher than those described above.

Table 1 compares the means or percent distribution of demographic and exposure characteristics between workers dying from lung cancer and those who did not die from lung cancer. Workers dying from lung cancer were typically older, white men compared to workers who did not die from lung cancer. Workers who died from lung cancer likely experienced higher arsenic, beryllium, chromium, nickel, uranium, and trichloroethylene (TCE) exposures compared to those who

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did not, and proportional differences in these exposures were significantly different for all but arsenic. Radiation exposure (film badge readings) among lung cancer cases was also significantly higher compared to other workers.

Table 2 summarizes univariate (crude) and multivariate (adjusted) logistic regression analysis derived ORs for lung cancer mortality risk. From left to right are the JEM exposure categories, the number of lung cancer cases, the number of controls, a crude OR estimate, and finally the adjusted OR. ORs show a 20% increase (OR: 1.20; 95% CI: 0.54–2.63) in lung cancer deaths among PGDP workers exposed to “any metal” compared to unexposed workers after adjusting for race, age, and gender. Lung cancer mortality risk was consistently elevated for nickel, uranium, and TCE job exposure matrix categories.

Uniquely, uranium exposure was assessed using the JEM and results of urine analysis for uranium. There was substantial agreement ($0.61 < k < 0.80$; 83% agreement; $k=0.68$) between a modified dichotomous JEM (see Methods) and urine uranium, but only fair agreement ($0.21 < k < 0.40$; 67% agreement; $k=0.34$) between the dichotomous JEM and radiation badge data.^{41,42} Consequently, similar comparisons were not possible for the other metals and TCE.

Table 3 summarizes the relative lung cancer mortality OR estimates for employment duration tertiles (far left column). Columns two and three contain the number of cases and controls, respectively in each stratum. The last two columns represent the crude and adjusted OR estimates compared using the “Short” duration stratum as the reference worker population. The risk of lung cancer mortality among workers employed >3.51 years is not different from the reference population.

Table 4 summarizes the relative lung cancer mortality OR between radiation exposure— $\ln(\text{mrem})$ —tertiles (far left column), with the lowest tertile as the reference group. Relative lung cancer mortality risk increased as the exposure level increased, compared to the reference group. However, workers receiving the highest radiation exposure were at a lower risk of dying than workers receiving

Table 1: A comparison of the mean and proportional differences of important traits and exposures between Paducah Gaseous Diffusion Plant workers dying from lung cancer and workers who did not.

Population trait	Lung cancer deaths n = 147	All other workers n = 6673
Person-Years (mean)	12.3	11.0
Age (mean, 95% CI)	68.4 (66.9–70.0)	59.9 (59.6–60.3)
Female gender (%)	7.5	18.4 ^a
Race (%)		
White	85	71 ^b
Non-white	5	11
Unknown	11	17
Likely higher metal exposure based on the Job Exposure Matrix:		
Arsenic exposure (%)	24	27
Beryllium exposure (%)	45	36 ^a
Chromium exposure (%)	50	41 ^a
Nickel exposure (%)	48	38 ^b
Uranium exposure (%)	53	41 ^c
TCE exposure (%)	47	38 ^a
^d Radiation exposure ($\ln(\text{mrem})$)		
Low (%)	54	46 ^e
Medium (%)	27	31 ^f
High (%)	22	31
	51	37

^a $p < 0.03$, ^b $p < 0.02$, ^c $p < 0.005$, ^d $p < 0.015$, ^e $p < 0.001$ for all radiation strata
 Higher metal exposure = JEM categories 4 and 5 combined
 Lower metal exposure = all other JEM categories
 TCE = trichloroethylene
^dStrata derived from natural log (ln) transformed mrem values of film badge readings

Table 2: Lung cancer odds ratio (OR) estimates within Job Exposure Matrix categories

Job Exposure Matrix	Lung Ca cases (n = 147)*	Non-cases (n = 6673)*	Crude OR (95% CI)	Adjusted OR† (95% CI)
Any metal				
No	9	551	Reference	Reference
Yes	138	6122	1.38 (0.70–3.10)	1.20 (0.54–2.63)
Arsenic				
1	48	2068	Reference	Reference
2	21	1767	0.51 (0.29–0.88)	0.45 (0.25–0.84)
3	43	1044	1.77 (1.14–2.75)	0.91 (0.61–1.37)
4	6	213	1.21 (0.42–2.88)	0.89 (0.64–1.24)
5	26	1444	0.78 (0.46–1.28)	0.81 (0.68–0.97)
Beryllium				
1	51	2947	Reference	Reference
2	20	1039	1.11 (0.62–1.91)	0.92 (0.51–1.66)
3	10	288	2.00 (0.90–4.05)	1.00 (0.64–1.57)
4	5	121	2.39 (0.73–6.09)	1.17 (0.81–1.68)
5	58	2141	1.57 (1.05–2.34)	0.95 (0.83–1.09)
Chromium				
1	64	3360	Reference	Reference
2	10	591	0.89 (0.40–1.75)	0.92 (0.44–1.91)
3	—	—	—	—
4	22	1183	0.98 (0.57–1.62)	0.97 (0.80–1.67)
5	48	1402	1.80 (1.20–2.67)	1.12 (0.89–1.41)
Nickel				
1	41	3134	Reference	Reference
2	31	897	2.64 (1.59–4.34)	2.16 (1.23–3.79)
3	5	106	3.61 (1.08–9.37)	1.60 (0.92–2.77)
4	9	251	2.74 (1.15–5.81)	1.12 (0.81–1.56)
5	58	2148	2.06 (1.35–3.17)	1.03 (0.89–1.20)
Uranium				
1	41	2804	Reference	Reference
2	24	954	1.72 (0.99–2.93)	1.56 (0.87–2.82)
3	4	146	1.87 (0.48–5.28)	1.22 (0.66–2.25)
4	17	484	2.40 (1.26–4.36)	1.15 (0.91–1.46)
5	58	2148	1.85 (1.21–2.84)	1.00 (0.87–1.16)
TCE				
1	24	1652	Reference	Reference
2	51	1829	1.92 (1.15–3.28)	1.52 (0.84–2.75)
3	3	640	0.32 (0.06–1.07)	0.62 (0.33–1.16)
4	16	786	1.40 (0.69–2.77)	1.05 (0.82–1.34)
5	48	1387	2.38 (1.42–4.09)	1.17 (1.00–1.38)

*Sum may not equal n because some data are missing. †Adjusted for race, gender, and age. “Any metal” is dichotomous: No metal exposure = category 1, any metal exposure = categories 2–5. Controls were selected by cumulative incidence sampling.

Table 3: Lung cancer odds ratio (OR) estimates by duration of employment

Employment duration*	Lung Ca cases (n = 147) [†]	Non-cases (n = 6673)	Crude OR (95% CI)	Adjusted OR [‡] (95% CI)
Short	47	2204	Reference	Reference
Intermediate	43	2207	0.91 (0.60–1.41)	1.04 (0.67–1.67)
Long	57	2262	1.24 (0.83–1.89)	1.00 (0.77–1.19)

*Short: ≤3.51 years; Intermediate: >3.51 and ≤11.84 years; Long: >11.84 years

[†]Sum may not equal n because some data are missing. [‡]Adjusted for race, gender, and age group.

ing the intermediate radiation exposure. In summary, lung cancer mortality risk is modestly higher among workers who were exposed to more external radiation for longer periods of time, when compared to workers who were exposed to less external radiation for shorter intervals.

Table 5 summarizes comparisons of lung cancer mortality OR estimates stratified by radiation exposure and employment duration. In the far left column are radiation and employment duration strata. The next two columns enumerate the cases and controls within each stratum. The numbers in columns two and three were used to calculate risk estimates in columns four and five. Column four is the crude lung cancer mortality risk estimate based on a 4:1 incidence density sample of the cohort. At the very bottom of column four is the tobacco smoke adjusted estimate of the crude risk. Column five contains logistic regression analysis de-

rived cancer mortality risk estimates for the same incidence density derived sample, adjusted for race, gender, age group, arsenic, beryllium, chromium, nickel, and TCE. The risk is elevated nearly two fold among workers who worked >3.51 years and experienced higher external radiation exposures compared to workers who worked ≤3.51 years and experienced the lowest external radiation exposure, after adjusting for race, gender, age, arsenic, beryllium, chromium, nickel, and TCE. Tobacco smoking changed the estimated precision, but not the magnitude of the mortality risk.

Table 6 is a comparison of HRs associated with metal exposure stratified by radiation exposure and employment duration. Adjusted HRs are initially displayed for uranium and nickel exposure in the first three strata. Lung cancer mortality HRs are elevated for uranium exposed workers in the lowest radiation and short

Table 4: Lung cancer odds ratio (OR) estimates by external radiation exposure levels

External radiation exposure dose* ln(mrem)	Lung Ca cases (n = 147)	Non-cases (n = 6673)	Crude OR (95% CI)	Adjusted OR [†] (95% CI)
Low	40	2111	Reference	Reference
Intermediate	32	2120	0.80 (0.48–1.31)	1.30 (1.00–1.80)
High	75	2442	1.62 (1.08–2.45)	1.12 (0.86–1.53)

Roentgen equivalent in man (rem)

*Low (exposure ≤427.63 mrem); Intermediate (exposure >427.63 and ≤1096.25 mrem); High (exposure >1096.25 mrem)

[†]Adjusted for race, gender, and age group.

Table 5: A comparison of odds ratio (OR) (95% CI) estimates by radiation exposure and employment duration using a 4:1 incidence density sample

Uranium exposure by radiation and employment duration strata ^a	Cases	Controls	Crude OR (n = 406)	Adjusted OR ^b (n = 406)
Low and Short	24	120	Reference	Reference
Intermediate and Intermediate	14	89	1.3 (0.6–2.8)	1.6 (0.7–3.2)
High and Long	41	118	1.7 (1.0–3.2)	1.9 (1.1–3.4)
Cigarette smoking adjusted ^c	—	—	1.7 (0.8–3.4)	—

Low (exposure ≤ 427.63 mrem); Intermediate (exposure >427.63 and ≤ 1096.25 mrem); High (exposure >1096.25 mrem)
 Short (Employment ≤ 3.51 years); Intermediate (Employment >3.5 and ≤ 11.8 years); Long (Employment >11.8 yrs)

^aWithin each stratum is workers exposed and unexposed to uranium.

^bAdjusted for race, gender, age group, and exposure to arsenic, beryllium, chromium, nickel, and TCE.

^cAdjusted for cigarette smoking using probabilistic sensitivity analysis assuming nondifferential exposure assessment.

employment duration stratum (HR: 1.8; 95% CI: 0.32–9.64) as well as the high radiation and long employment duration stratum (HR: 8.4; 95% CI: 1.78–39.42). As for nickel, lung cancer mortality HRs are elevated in all three exclusive strata; the lowest radiation and short employment duration stratum (HR_{nickel}: 1.7; 95% CI: 0.44–6.72), the intermediate stratum (HR: 1.4; 95% CI: 0.25–7.71), and the high radiation and long employment duration stratum (HR_{nickel}: 1.2; 95% CI: 0.46–2.92). Lung cancer mortality risk associated with arsenic, beryllium, chromium and TCE were not elevated and are not shown to save space in the final Table. When “Low and Short” categories were combined with “Intermediate” radiation and employment duration categories, the risk of death associated with lung cancer is not elevated for uranium (HR: 0.5; 95% CI: 0.14–2.02), but it remains elevated for nickel (HR: 1.9; 95% CI: 0.65–5.77). Lung cancer mortality risk associated with arsenic, beryllium, chromium and TCE was not elevated. However, when “Low and Short” categories were combined with “High and Long” radiation and employment duration categories, lung cancer mortality risk is elevated for uranium

(HR: 4.2; 95% CI: 1.49–11.8) and nickel (HR: 1.9; 95% CI: 0.87–3.89). Lung cancer mortality risk associated with arsenic, beryllium, chromium and TCE was not elevated.

Discussion

These results suggests that lung cancer mortality risk among gaseous diffusion plant workers is likely elevated (Table 6) and is what one would expect based on beliefs about the health effects of radiation and uranium exposure. The lack of an elevated risk in the intermediate exposure group suggests that there may have been two groups of workers with different (unique?) sensitivity to radiation. For example, there may have been a group of workers who were most sensitive to developing radiation-induced lung cancers early on (in the first 3.5 years) (Table 6). Intermediate level exposed workers may represent a group more resistant to the effects of radiation and may not develop disease until approximately eight years later or longer (Table 6). This also may suggest that there are two etiologically specific lung tissue variants among humans—one highly susceptible to on-

cological radiation and another more resistant. Still, this is the first report that uranium exposed PDGP workers experienced increased lung cancer mortality risk compared to unexposed workers.²⁹ The disparity between this and earlier efforts may be explained, in part, by inherent methodological differences between standardized mortality, case-control, and proportional hazards analyses. Key is this study's reliance on intra-cohort coworker comparisons. Coworker comparisons inherently mitigate the impact of potentially confounding or effect-modifying covariates (socioeconomic status, access to care, education, smoking, etc). Furthermore, coworker comparisons mitigate a potential healthy-worker bias (selection bias associated with the ability to perform certain work-related task) typically associated with occupational cohorts comprised of workers who were followed and worked for a long time.⁴⁴

This is not the first observations that nickel is associated with lung cancer mortality in similarly occupied workers, but is the first report of this association among these workers. Notable was the observation that the risk was nearly the same across each stratum in Table 6, suggesting a risk-independent of these strata. The association (Tables 2 and 6) is consistent with reports cited above (see Introduction) and provided some assurance that these methods were at least sensitive enough to detect a previously observed association.

Still, specific weaknesses suggest some degree of caution. Typically generic, dichotomous JEMs ecologically and non-differentially assign exposures. However, historically JEM validity has not been encouraging.^{45,46} The JEM applied in this investigation is based on five exposure "likelihoods." When these categories are collapsed (see Methods), the likelihood of exposure misclassification may increase.

Table 6: A comparison of proportional hazards regression lung cancer mortality risk estimates associated with metal exposure stratified by radiation exposure and employment duration.

Uranium exposure by radiation and employment duration strata ^a	^a Adjusted Hazard Ratios
Low and Short only	(n = 1064)
Uranium	1.8 (0.32–9.64)
Nickel	1.7 (0.44–6.72)
Intermediate and Intermediate only	(n = 839)
Uranium	0.3 (0.02–3.11)
Nickel	1.4 (0.25–7.71)
High and Long only	(n = 1590)
Uranium	8.4 (1.78–39.42)
Nickel	1.2 (0.46–2.92)
Low and Short + Intermediate and Intermediate	(n = 1903)
Uranium	0.5 (0.14–2.02)
Nickel	1.9 (0.65–5.77)
Arsenic	0.5 (0.24–1.09)
Beryllium	1.0 (0.38–2.83)
Chromium	1.0 (0.60–1.57)
TCE	1.0 (0.66–1.52)
Low and Short + High and Long	(n = 2654)
Uranium	4.2 (1.49–11.8)
Nickel	1.9 (0.87–3.98)
Arsenic	0.6 (0.45–0.90)
Beryllium	0.5 (0.27–0.98)
Chromium	1.0 (0.70–1.50)
TCE	0.9 (0.64–1.20)

Low (exposure ≤427.63 mrem); Intermediate (exposure >427.63 and ≤1096.25 mrem); High (exposure >1096.25 mrem)
 Short (employment ≤3.51 years); Intermediate (employment >3.5 and ≤11.8 years); Long (employment >11.8 years)
^aAdjusted for race, gender, age group, and exposure to arsenic, beryllium, chromium, nickel, and TCE.

Fortunately, bias associated with the JEM's assessment of uranium exposure was mitigated by use of available radiation and uranium exposure monitoring data, both collected at the individual level by film badge and urinalysis, respectively. A simple, linear, bivariate regression model of film badge radiation and uranium urinalysis produced a coefficient of determination of 0.49 (data not shown),

suggesting that urine uranium concentration predicts about half of the variation in film badge radiation readings. This variability may be explained by workers not wearing their film badges at all times and PDGP policies that base urine uranium levels on mean values for a one-year interval. Although uranium urinalysis data strongly agreed with a dichotomous JEM assessment of uranium exposure, this analysis focuses on radiation (film badge) exposure because of the important role that radiation is believed to play in carcinogenesis and the awareness that there are potentially other sources of radiation exposure in the workplace.

A critical hurdle was the lack of individual-level tobacco smoke exposure information. To counter this, probabilistic sensitivity analyses were used to estimate the potential cigarette smoking impact on mortality estimates, assuming that cigarette smoking prevalence ranged from 10% to 25%. This suggests that cigarette smoking would have more of an impact on the estimated precision of the risk estimate than its magnitude (Table 5).

Overall, this study suggests that lung cancer is likely elevated among PGDP workers exposed to more than 1000 mrem for >3.5 years. Therefore, further attempts to reduce the duration of external radiation exposure and its intensity in the workplace may lower lung cancer mortality among similarly employed workers.

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