



Increased Suicide Risk among Workers following Toxic Metal Exposure at the Paducah Gaseous Diffusion Plant From 1952 to 2003: A Cohort Study

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Abstract

Background: Suicide is a problem worldwide and occupation is an important risk factor. In the last decade, 55 200 deaths in the US were attributed to occupational risk factors.

Objective: To determine if toxic metal exposure was associated with suicide risk among Paducah gaseous diffusion plant (PGDP) workers.

Methods: We assembled a cohort of 6 820 nuclear industry workers employed from 1952 to 2003. A job-specific exposure matrix (JEM) was used to determine metal exposure likelihood. Uranium exposure was also assessed by urinalysis. All suicide/self-injury International Classification for Disease (ICD) codes were used to identify suicides. Standardized mortality ratios (SMR), odds ratios (OR), and hazard ratios (HR) were used to estimate suicide risk.

Results: PGDP suicide victims typically were younger white men. Within exposure likelihood categories, several suicide SMRs were typically elevated for several metals. Only beryllium exposure likelihood was associated with an increased HR. Uranium urine concentration was associated with an elevated suicide risk after stratification by urinalysis frequency.

Conclusion: Suicide risk is associated with uranium exposure.

Keywords: Toxic; environmental toxic substances; JEM; Exposure assessment; Uranium; Suicide; Atomic energy; Gaseous diffusion; Epidemiology; Proportional hazard

Introduction

Suicide is a problem worldwide¹ and occupation is an important risk factor.² In the last decade, 55 200 deaths in the US were attributed to occupational risk factors.^{2,3} The US Bureau of Labor statistics classifies less than 0.5% of suicides as work-related (occurring at the work site, during work time, or related to work

and occurring elsewhere) since 1992.⁴ Often the specific occupational factor(s) elevating suicide risk is unclear because job titles,^{5,6} specific careers,^{7,8} trades,^{2,9,10} or social classes within occupations^{3,11,12} are typically studied rather than work site toxic agent exposure. One explanation for so few studies is a low suicide frequency at work sites.⁴ Another explanation is a lack of evidence that work site toxicants are as-

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sociated with increased suicide risk.^{9,13}

Suicides related to toxic hazard exposures are often more difficult to identify because the toxic exposure may also occur outside the work site, the suicide may be classified as non-work-related, or it may be under-reported.^{4,14} In addition, if a toxic chemical unique to the work site is suspected, employers may not monitor that agent. Metals are among the potential toxicants monitored and regulated at nuclear industry work sites, some with the potential to cause brain and/or mind dysfunctions.¹⁵⁻¹⁹ Typically, workers involved in uranium gaseous diffusion processing may be routinely exposed to arsenic, lead, mercury, nickel, and uranium. Paducah gaseous diffusion plant (PGDP) workers, in particular, were exposed to arsenic, beryllium, chromium, nickel, and uranium, all potentially neurotoxic.¹⁶ Arsenic exposure induces Ca^{2+} influx, axonopathy, toxic delirium, and encephalopathy.^{15,17,18} Chromium and nickel exposure results in disturbances in memory and concentration, affective changes, and sympathetic nervous system symptoms such as erectile dysfunction, dizziness, heat intolerance, dry mouth and eyes, urinary bladder (incontinence) and bowel (constipation/diarrhea) dysfunction.¹⁹ In a 2004 review, Craft, *et al*, observed that human exposure to uranium induced extra-pyramidal symptoms (ataxia, nystagmus, peripheral neuropathy) and poor neuro-cognitive test performance.²⁰ Craft, *et al*, also cited investigations in which rats chronically exposed to uranium showed significant uranium accumulation in the cortex, cerebellum, midbrain, and vermis as well as electrophysiological changes in hippocampus neurons. In 2007, Kreiss, *et al*, reviewed 75 journal articles addressing beryllium hazards in the workplace and found no neurotoxic hazards.²¹

Therefore, investigating potential work site-specific toxicants associated with

suicide requires at least two things: 1) a worker population exposed to the neurotoxic or psychotoxic agents unique to that workplace; and 2) strong stakeholder support to conduct the investigation. The PGDP worker cohort is such a cohort. Paducah Kentucky's residents, PGDP workers, and government officials raised health and safety concerns about PGDP toxic hazard exposures. Initial studies emphasized polychlorinated biphenyl (PCB) exposure and nearby wildlife.²² That effort was followed by US Department of Energy (DOE) funding to investigate morbidity and mortality among PGDP workers employed there from 1952 to 2003.²³ Among the mortal events to receive attention was suicide. Recently, Aldrich, *et al*, using a retrospective cohort design, observed elevated suicide risk among 754 PGDP workers who were compared to two internal standard populations. Exposed workers were employed only during the plant's refitting years—1975 to 1979.²⁴ Investigators used a job-specific exposure matrix (JEM) to ascertain worker exposures. In addition, Aldrich, *et al*, created time-dependent, dichotomized exposure categories of “ever” or “only worked” during the “refitting” years. Aldrich, *et al*, observed elevated suicide risk, but concluded that the elevated risk was not due to workplace metal exposure.

Below, we reexamine the PGDP worker cohort, focusing on suicides and potential JEM exposure misclassification error.

Among the nuclear industry studies basing their risk estimates on standardized mortality ratios (SMRs), suicide mortality is inconsistently reported. For example, Godbold and coworkers reported SMRs among 814 nickel-exposed “barrier workers” employed at the Oak Ridge gaseous diffusion plant in Oak Ridge, Tennessee, USA, but suicide excess was not reported.²⁵ Conversely, Polednak reported suicide excess (SMR=1.67; 95% CI: 0.79–

3.02) among 1059 white, male welders exposed to uranium, fluoride, lead, nickel, mercury, chromium, and technetium at three Oak Ridge plants from 1943 to 1977.²⁶ Subsequently, Frome, *et al*, reported an SMR of 0.93 among 106 020 nuclear industry workers in Oak Ridge, Tennessee, employed between 1943 and 1985.²⁷ In another investigation, National Institute for Occupational Health (NIOSH) investigators reported a suicide SMR of 0.6.²⁸ Unfortunately, SMRs frequently underestimate mortality risk because employed populations are typically healthier than the general population. Since the above investigators used SMRs to assess risk, suicide risk may have been underestimated.

To address these concerns, we emphasized case ascertainment, an appropriate comparison group, exposure assessment, and the impact of unmeasured confounding. Next, we used proportional hazards regression²⁹ in addition to SMRs, because hazard ratios compare hazard rates (risk) between the exposed and unexposed in the same employed cohort. In addition, we looked at the JEM's potential for exposure misclassification. Finally, we evaluated the impact of an unmeasured confounder (*i.e.*, mental illness prevalence) on the association between specific metal exposure and suicide risk.

Although the JEM was used to assess all metal exposure in prior PGDP studies,^{24,30} uranium urine concentration was also used to assess uranium internal dose. Furthermore, PGDP JEM exposure classifications were based on an ordinal scale. In contrast, uranium urinalyses were based on an interval scale. We additionally examined agreement between the JEM's uranium exposure categories on an ordinal scale with urine uranium concentrations on an interval scale—assuming that urine uranium concentration was a more valid, internal dose, exposure measure.

Typically, urines were monitored from

a single void, but their frequency varied. For example, chemical operators and maintenance mechanic urines were monitored monthly. Other workers were monitored quarterly. Non-uranium area workers were monitored annually. Frequency was also influenced by the analytic method's sensitivity, solubility of the uranium, and administrative or regulatory requirements to limit a worker's dose. Uranium aerosol size and solubility influence its *in vitro* transport. If insoluble, aerosols may remain in the lungs for up to 16 years.³¹ However, once in the blood stream, uranium is excreted in a few days—60% in the first 24 hours.

We conducted this study to determine if a suicide risk was associated with arsenic, beryllium, chromium, nickel, and/or uranium exposure among PGDP workers.

Materials and Methods

Study cohort

Investigators assembled a dynamic, retrospective cohort of all PGDP workers employed for 30 or more days from September 1, 1952 to December 31, 2003. Person-time accrued from the worker's initial hiring date to their death or December 31, 2004. The PGDP is located on 3425-acres near Paducah, Kentucky, USA. 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).³²

Briefly, 6859 worker files were assembled from DOE contractors, unions, and Oak Ridge affiliated universities.³³ 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

TAKE-HOME MESSAGE

- Many factors such as employment status, income, religiosity, marital status, illness, and loss of a family member, are associated with suicide.
- Occupation also is an important risk factor for suicide. Less than 0.5% of suicides are work-related (occurring at the work site, during work time, or related to work and occurring elsewhere).
- Suicides related to toxic hazard exposures are often more difficult to identify because the toxic exposure may also occur outside the work site, the suicide may be classified as non-work-related, or it may be under-reported.
- Metals are among the potential toxicants monitored and regulated at nuclear industry work sites, some with the potential to cause brain and/or mind dysfunctions.
- Workers involved in uranium gaseous diffusion processing may be routinely exposed to arsenic, lead, mercury, nickel, and uranium.
- Human exposure to uranium induces extra-pyramidal symptoms (ataxia, nystagmus, peripheral neuropathy) and poor neuro-cognitive test performance.
- Suicide risk is associated with uranium exposure.

verify post-1979 deaths. The vital status of two workers was undetermined. Thirty-nine worker files were duplicates.³³ The final analysis file contained 6820 workers. Suicide morality was followed until December 31, 2004.

Exposure assessment

Job exposure matrix: We further modified the metal exposure assessments methods described by Chan, *et al.*³⁰ Briefly, all job titles were grouped, ranked for specific metal exposures, and consolidated using worker interviews, plant production records, and job site maps.³⁴ 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 with zero representing “no exposure expected” and five the “most exposure expected.” Rankings were categorical and unrelated to a quantitative exposure intensity (concentration) or dose. Therefore, exposure rankings for a unique metal were not additive or multiplicative (*i.e.*, a category ‘2’ exposure ranking was not twice a category ‘1’ exposure ranking), thus, 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.³⁴ 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.³⁴

Using the JEM, each worker was assigned an expected metal exposure category for each job-title during the work-

er's job history. When a worker's job title changed, the expected exposure category for each metal also changed. Follow-up was based on actual time employed. For uranium, the JEM algorithm was applied during periods in which workers held jobs that did not require uranium urinalysis (*see Uranium urinalyses below*).

A detailed description of the JEM is described elsewhere.³⁴

Uranium urinalyses: Each worker provided a single void urine specimen for job title-specific uranium exposure monitoring. Uranium urine concentration ($\mu\text{g/L}$) was recorded as a “yearly” mean. Urinalysis frequency was job title- and program-specific. Workers could have several yearly means recorded per calendar year. For example, a worker with one job title during the calendar year might have one yearly mean recorded. A worker with two job titles during the calendar year, would have at least two means recorded—one for each job title, and so on. Additional urine yearly means could be recorded because of specific program requirements.

Urinalysis cohorts: There were 21 urinalysis cohorts that contained workers who committed suicide. Urine Cohort 1 included only the first urinalysis of all workers. Urine Cohort 2 included the second urinalysis of all workers. Urine Cohort 3 contained the third urinalysis of all workers, and so on. Urinalysis cohorts were divided into dichotomous concentration categories. “High” represented urines with uranium “yearly” means greater than the cohort median, and “Low” represented urines with uranium “yearly” means less than or equal to the cohort median. Urine cohorts were neither period- nor job-specific. For example, Cohort 1 contained the first urinalysis of all workers, regardless of urinalysis year, the year hired, or job title. We analyzed 15 urinalysis cohorts. Arbitrarily, we report the results for the 1st, 5th, 10th, and 15th yearly

mean estimate since the overall pattern (a progressively lower yearly mean than the previous yearly mean) was consistent for workers who committed suicide and those who did not.

Case ascertainment

All death certificates with “Underlying Cause of Death” (UCD) fields containing International Classification for Disease (ICD) codes E963, E970-E979 (ICD-6 & ICD-7), or codes E950-E959 (ICD-8), or codes E950-E952, E952.0, E953, E953.0-E953.9, E954, E954.0-E954.9, E955.0-E955.9, E956, E957.0-E957.9, E958.0, E958.1-E959.9, E976 (ICD-9), or codes X60-X69, X70, X71, X72-X74.9, X75-X77, X78, X79, X80-X81, X82-X84, Y87.0 (ICD-10) were considered “suicide/self injury” cases.³⁵

Statistical analysis

χ^2 , crude and adjusted odds ratios (ORs) with 95% confidence interval (CI), and crude and adjusted Cox proportional hazard statistics with 95% CI were estimated where appropriate.^{36,37,29}

Standardized mortality ratios (SMRs) were determined by applying 1977 age-specific US suicide rates to person-years accumulated from September 1, 1952 to December 31, 2004,³⁸ as 1977 US suicide rates are the approximate midpoint between January 1953 and December 2004.

Hazard ratios (HRs) were assessed using proportional hazard regressions²⁹ using *STATA™ 10.1 Statistics/Data Analysis Special Edition* (StataCorp, 4905 Lakeway Drive, College Station, TX 77845 USA). Hazard ratios were adjusted for confounding variables in two ways. First, HRs were calculated using fixed-covariate (time-independent) models,²⁹ then calculated using variable-covariate (time-dependent) models.³⁹ Unless otherwise indicated, all HRs were calculated using fixed-covariate models. Follow-up time

was based on actual time employed and accrued in a specific exposure likelihood category. Females were omitted from the final model because there were only two (5.0%) female suicides.

Cohen's κ was used to determine agreement between the JEM and uranium urinalysis.⁴⁰ The JEM was recoded as High_{jem} and Low_{jem}. High_{jem} included original JEM categories 4 and 5. Low_{jem} contained the remainder. Similarly, the uranium urinalyses were recoded as High_{urn} and Low_{urn} as described earlier (see *Exposure assessment*). Although exposure likelihood and internal dose are not equivalent exposure measures and represent ordinal and interval scales, respectively, we assessed the JEM's sensitivity and specificity using urinalysis categories as our "gold standard."

Probabilistic sensitivity analyses were used to assess the effects of unmeasured confounding due to prevalent mental illness.⁴¹ We assumed a 20% prevalence of all mental illnesses and a 5.4% prevalence of severe mental illnesses (in combination) among PDGP workers.⁴²

Institutional review board (IRB) approval

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

Results

Six-thousand eight-hundred and twenty PGDP workers accrued 111 310.25 person-years at risk of exposure ranging from 0.50 to 45.0 person-years per worker. The per-capita person-years at risk of exposure was 16.3 person-years. There were 1634 total deaths. Forty were classified as suicide/intentional injury. The first suicide occurred

December 7, 1957; the last occurred October 12, 2002. PGDP workers initially hired as chemical operators (n=1223 or 17.9% of all workers) accounted for 12 (30%) of all 40 suicides. Thirty-two percent (n=2174) of all PGDP workers were initially hired in maintenance categories and accounted for 11 (28%) of the 40 suicides. PGDP workers initially hired in engineering categories (n=608, or 8.9% of all workers) accounted for three (8%) of all suicides. PGDP workers initially hired as security workers (n=300 or 4.4% of all workers) accounted for five (13%) of all suicides. Except for chemical operators and security workers, suicide prevalence was approximately proportional to the number of workers in all other job title groups.

Table 1 compares the means or frequency distribution of demographic and exposure characteristics between workers committing suicide and those who did not commit suicide. Workers committing suicide typically were younger, white men who accrued less person-time than workers who did not commit suicide. With the exception of likely arsenic exposure, workers committing suicide spent a significantly larger proportion of their time at the highest likely metal exposure category. In addition, the proportion of workers committing suicide was higher among the high uranium urinalysis cohort categories than workers not committing suicide (Table 1).

A further comparison of job exposure categories by PGDP workers committing suicide vs. workers not committing suicide by exposure category indicated that the distributions of suicide victims among several job exposure categories (chromium, uranium, and trichloroethylene [TCE]) were probably not chance events and probably higher than expected (not shown). TCE exposure was included because it was available and has recognized central nervous system effects.

An analysis of suicide mortality excess

Table 1: A comparison of the mean and proportional differences of important traits and exposures between workers committing suicide and those who did not.

Population Trait	Workers Committing Suicide	Workers Not Committing Suicide	p value
Person-yrs (mean)	8.7	16.4 ^a	0.01
Age (mean)	50.8	68.3 ^b	<0.001
Gender female (%)	5	18 ^c	0.03
African-American race (%)	<1	1	
Proportion of total person-time with highest likelihood of:			
Arsenic exposure (%)	36	32	<0.001
Beryllium exposure (%)	73	44 ^d	<0.001
Chromium exposure (%)	70	29 ^d	<0.001
Nickel exposure (%)	73	44 ^d	<0.001
Uranium exposure (%)	73	44 ^d	<0.001
TCE exposure (%)	71	33 ^d	<0.001
Greater than the median urine uranium concentration			
1 st Urinalysis Cohort 1 (%)	40.0	39.9	NS*
5 th Urinalysis Cohort 5 (%)	77.5	60.1 ^e	0.03
10 th Urinalysis Cohort 10 (%)	87.5	70.4 ^e	0.03
15 th Urinalysis Cohort 15 (%)	97.5	77.4 ^f	0.002

*NS: Not significant; ^aStudent's *t* test=2.7; ^bStudent's *t* test=8.01; ^cMantel-Haenszel $\chi^2=4.70$, df=1; ^dZ statistic=3.68; ^eMantel-Haenszel $\chi^2=5.02$, df=1; ^fMantel-Haenszel $\chi^2=9.21$, df=1

and risk is presented in Table 2. SMRs, using 1977 US suicide rates, showed a significant, two-fold overall excess of suicide deaths among PGDP workers exposed to any metal compared to 1977 US standard population suicide rates. Further SMR analyses, stratifying by likely job exposure category, revealed several significant suicide excesses among workers. For example, workers with arsenic exposure likelihoods 1 and 2, or beryllium exposure likelihood 5, or nickel exposure likelihoods 1 and 5, or uranium exposure likelihoods 2 and 5, or TCE exposure likelihoods 2 and 5 demonstrated excess suicides. As expected, there were no intra-category SMR trends because the exposure categories are nominal

and not interval (see *Exposure assessment section*). Suicide HR analysis, adjusted for “any metal” exposure, TCE exposure likelihood, age, and race was not elevated (HR=0.9; 95% CI: 0.7–1.2). Suicide HR analysis revealed no statistically significant increase in suicide risk for workers with a varied history of likely arsenic, chromium, nickel, or uranium exposures compared to workers with no such history—adjusting for age, race, likely exposure to TCE, and the potential “confounder” metals. Only among workers with a varied history of likely beryllium exposures was suicide risk elevated (HR=2.6; 95% CI: 0.9–7.9) compared to workers with no such beryllium history—adjusting for

Table 2: Likely exposure category by observed suicides, expected suicides, standardized mortality ratio (SMR), and hazard ratio (HR).

Exposure likelihood	Observed	Expected	SMR (95% CI)	HR (95% CI)
Any metal*	39	18.71	2.1 (1.4–2.7)	0.9 (0.7–1.2)[†]
Arsenic				0.7 (0.4–1.0)
1	9	2.84	3.2 (1.1–5.2)	
2	6	4.96	1.2 (0.2–2.2)	
3	12	4.22	2.8 (1.2–4.5)	
4	1	0.97	1.0 (0.0–3.1)	
5	8	6.80	1.2 (0.4–2.0)	
Beryllium				2.3 (0.5–8.0)
1	10	5.48	1.8 (0.7–2.9)	
2	7	3.34	2.0 (0.5–3.6)	
3	2	0.95	2.1 (0.0–5.0)	
4	0	0.62	—	
5	19	9.34	2.0 (1.1–2.9)	
Chromium				0.7 (0.4–1.3)
1	15	7.29	2.1 (1.0–3.1)	
2	4	1.51	2.7 (0.1–5.2)	
3	0	0.00	0.0	
4	5	4.20	1.2 (0.2–2.2)	
5	14	6.78	2.1 (1.0–3.2)	
Nickel				0.9 (0.6–1.3)
1	13	6.28	2.1 (1.0–3.2)	
2	3	2.90	1.0 (0.8–1.2)	
3	0	0.00	0.0	
4	1	4.19	0.2 (0.5–1.5)	
5	19	9.40	2.0 (1.1–2.9)	
Uranium				0.9 (0.4–2.0)
1	10	5.97	1.7 (0.3–2.7)	
2	6	2.05	2.9 (1.7–4.1)	
3	2	0.74	2.7 (0.0–6.4)	
4	1	1.62	0.6 (0.0–1.8)	
5	19	9.40	2.0 (1.1–2.9)	
TCE				0.9 (0.6–1.3)
1	6	1.35	4.4 (0.9–8.0)	
2	14	2.56	5.5 (3.7–7.2)	
3	1	0.66	1.5 (-1.4–4.5)	
4	1	1.48	0.7 (-0.6–2.0)	
5	16	4.80	3.3 (1.7–5.0)	

*Any Metal is dichotomous: No exposure=likelihood 1, any metal exposure=likelihoods 2–5

[†]Adjusted for TCE likelihoods, age and race

age, race, and likely exposure to arsenic, chromium, nickel, uranium, and TCE. However, a history of likely beryllium exposure approached the null (HR=1.1; 95% CI: 0.9–1.2) in the time-dependent model. A global test of nonproportional-hazards⁴³ of our model was not significant (p=0.67).

Since there was plausible evidence that arsenic, chromium, nickel, and uranium were neurotoxic and psychotoxic, we pursued additional risk analyses associated with these metals using time-dependent models (data not shown). Using time-dependent covariate models in which age,

Table 3: Agreement between job exposure matrix (JEM) Uranium Exposure Likelihoods and Urine Uranium Concentration Categories by Uranium Urinalysis Cohort.

JEM Categories	Urine Cohort 1: All 1 st Urinalysis		Kappa	Percent agreement (Expected)
	High _{urn}	Low _{urn}		
High _{jem}	1499	1345	0.126	61.74
Low _{jem}	1228	2745		
Total*	2727	4090		
	Urine Cohort 5: All 5 th Urinalysis			
	High _{urn}	Low _{urn}		
High _{jem}	2096	751	0.113	49.97
Low _{jem}	2010	1963		
Total	4106	2714		
	Urine Cohort 10: All 10 th Urinalysis			
	High _{urn}	Low _{urn}		
High _{jem}	2317	530	0.110	44.09
Low _{jem}	2492	1481		
Total	4809	2011		
	Urine Cohort 15: All 15 th Urinalysis			
	High _{urn}	Low _{urn}		
High _{jem}	2410	437	0.091	38.90
Low _{jem}	2877	1096		
Total	5287	1533		
	All Urines Unstratified			
	High _{urn}	Low _{urn}		
High _{jem}	1252	28	0.4693	76.20
Low _{jem}	1595	3945		
Total	2847	3973		

High_{jem}: Original JEM categories 4 and 5; Low_{jem}: Original JEM categories 0–3

High_{urn}: Urine yearly means > median; Low_{urn}: Urine yearly means < median

Kappa: Cohen's $\kappa = (p - p_e) / (1 - p_e)$, where p is the proportion in agreement and p_e is the proportion expected to agree by chance.⁴⁰

race, and the exposure of interest were fixed, we observed no increase in suicide mortality risk when the other exposure covariates were allowed to continuously vary with respect to time.³⁹ Typically, HRs ranged from 0.8 to 1.0 with 95% CI lower limit of 0.7 to 0.9 and 95% CI upper limit

of 1.0 to 1.2.

Overall, there were 119 474 uranium urine yearly means recorded—about 18 per worker. Estimated concentrations ranged from zero to 2900 $\mu\text{g/L}$. The overall median was 3.5 $\mu\text{g/L}$.

There was weak agreement (Cohen's κ)

Table 4: Suicide odds ratios (ORs) and hazard ratios (HRs) by dichotomous urine uranium concentration and JEM Uranium Exposure Likelihood Categories.

Uranium Categories	Suicide	No Suicide	OR (95% CI)	HR (95% CI)
All Urinalyses				
High	18	3399	0.8 (0.4–1.5)*	1.1 (0.5–2.2)*
Low	22	3381	0.8 (0.4–1.7)†	
Total	40	6780		
1 st Urinalysis (Cohort 1)				
High	16	2711	1.0 (0.5–1.9)*	1.2 (0.6–2.3)§
Low	24	4069	0.8 (0.4–1.6)†	
Total	40	6780		
5 th Urinalysis (Cohort 5)				
High	31	4075	2.3 (1.1–4.8)*	2.7 (1.2–6.1)§
Low	9	2705	1.7 (0.8–3.9)†	
Total	40	6780		
10 th Urinalysis (Cohort 10)				
High	35	4774	2.9 (1.2–7.5)*	3.6 (1.4–9.7)§
Low	5	2006	1.6 (0.6–4.5)†	
Total	40	6780		
15 th Urinalysis (Cohort 15)				
High	39	5248	11.4 (1.6–82.9)*	9.1 (1.2–66.9)§
Low	1	1532	4.4 (0.6–32.2)†	
Total	40	6780		
JEM Category				
High exposure likelihood	22	2825	1.4 (0.7–2.7)*	1.1 (0.5–2.5)
Low exposure likelihood	18	3955	1.3 (0.6–2.7)†	
Total	40	6780		

A "High" urine uranium concentration is greater than the median concentration of all workers.

A "High" exposure likelihood is equal to likelihood categories 4 or 5.

*Adjusted for age; †Adjusted for age, race, and TCE exposure categories. §Adjusted for age, race, and TCE.

between the JEM's high/low uranium exposure likelihood categories and the uranium urinalysis cohort high/low categories (Table 3). Uranium yearly mean concen-

trations ranged from 0.0 to 259 µg/L with a median of 3.7 µg/L for workers in Urinalysis Cohort 1. In Urinalysis Cohort 5 uranium yearly mean concentrations ranged

from 0.0 to 2900 $\mu\text{g/L}$ with a median of 3.5 $\mu\text{g/L}$. In Urinalysis Cohort 10 uranium yearly mean concentrations ranged from 0.0 to 404.3 $\mu\text{g/L}$ with a median of 1.0 $\mu\text{g/L}$. Uranium yearly mean concentrations ranged from 0.0 to 774.2 $\mu\text{g/L}$ with a median of 0.0 $\mu\text{g/L}$ for workers in the Urinalysis Cohort 15. We observed slight agreement ($\kappa=0.126, 0.113, 0.110, 0.091$) between the JEM and Urinalysis Cohorts 1 to 15, respectively. When the JEM's dichotomous categories were compared to dichotomous categories of the cohort's median uranium urine level, we observed moderate agreement ($\kappa=0.470$).

Using uranium urine measurements as the "gold standard," we estimated the JEM's sensitivity and specificity (or inter-method reliability). In Urinalysis Cohort 1, the JEM had low sensitivity (0.40; 95% CI: 0.39–0.41) or ability to assign high exposure likelihood to workers with high (>median) urine uranium measurements, but had only moderate specificity (0.60; 95% CI: 0.43–0.75) or ability to assign a low exposure likelihood to workers with low (\leq median) urine uranium measurements. In Urinalysis Cohort 5, the JEM had a slightly higher sensitivity (0.60; 95% CI: 0.59–0.61), but an even lower specificity (0.23; 95% CI: 0.11–0.39). In Urinalysis Cohort 10, the JEM had even higher sensitivity (0.70; 95% CI: 0.69–0.72), but an even lower specificity (0.13; 95% CI: 0.05–0.28). In uranium Urinalysis Cohort 15, the JEM was most sensitive (0.77; 95% CI: 0.76–0.78) and least specific (0.03; 95% CI: 0.00–0.15).

Table 4 compares suicide ORs and HRs when uranium exposure was assessed using high/low urine analysis and JEM categories. High urine uranium concentration was associated with increased suicide risk estimates. High JEM-derived uranium exposure likelihoods were not associated with higher suicide risk estimates. Estimated suicide risk increased as urine year-

ly mean frequency increased (*i.e.*, from urine Cohort 1 to Cohort 15), but this trend was not statistically significant in a linear test ($p=0.08$; slope not equal to zero) or a nonparametric trend test across ordered groups ($p=0.08$). The median uranium urine concentration decreased from 4.3, to 4.1, to 3.9, and finally 3.7 $\mu\text{g/L}$ for the 1st, 5th, 10th, and 15th urinalysis, respectively.

Discussion

Overall, the suicide mortality among metal-exposed workers was twice the expected mortality (SMR=2.1; 95% CI: 1.4–2.7) of the general population standard (Table 2). In addition, several metal-specific exposure likelihoods had higher than expected suicide deaths. This is in contrast to our proportional hazards regression analysis (Table 2) that indicates no elevated suicide mortality risk when toxic metal exposed workers are compared with PGDP peers who were not exposed. In the discussion below we examine these contrasting estimates.

First, SMR estimates frequently show no mortality excess when the employed cohort is compared to a standard population (healthy worker effect).⁴⁴ A significantly elevated suicide SMR suggests that when an increased mortality risk is observed, the exposure/mortality association is sufficient to overcome any healthy worker bias derived from hiring "healthier" workers. In contrast, the overall HR estimates suggest no increased mortality risk associated with toxic metal exposure (Table 2). However, the SMR estimates were exposure level-specific without accounting for the exposure categories of the other metals. In contrast, the HR is an estimate that accounts for all other exposure likelihoods.

Next, other than differences in the comparison groups, the differences between the two estimates may be linked to exposure misclassification. Note that our

attempts to validate JEM uranium categories with uranium urinalysis categories suggested that the two methods differed in classifying worker uranium exposure. It is also likely that the two methods (JEM *vs.* urinalysis) redistribute person-years differently resulting in disparate risk estimates. It is also likely that the assumptions made to derive the SMR or HR were violated and were inappropriate for this analysis. For example, proportional hazards regression assumes that hazards are proportional between events. If this assumption is violated, it suggests that the chosen model is inappropriate. However, we tested our model for nonproportional hazards and found that the assumption is not violated in this instance ($p=0.062$) suggesting that our model is appropriate.

Still, with the exception of likely beryllium exposure, HR estimates were near or below 1.0 (Table 2).

Another reason why the SMR and HR estimates differed is that likely metal exposure categories confound mortality risk estimates, even though some metals may fail as classic confounders (related to both metal exposure and suicide outcomes).⁴⁵ Since arsenic is routinely found in our drinking water, some exposure occurs among PGDP workers and the general population. The question is whether food and drinking water exposures are of the same duration and intensity as those experienced on the job. More important, it is unlikely that beryllium, chromium, nickel, and uranium are routinely encountered in the general population at levels comparable to the PGDP workplace. Toxic metal exposure must also indicate a pathway to suicide outcomes¹⁹⁻²¹ to confound suicide risk estimates. Clearly, our SMR estimates are adjusted for age/exposure-specific strata, but not at the level of sophistication and convenience we also were able to adjust using proportional hazards regression. Adjusting for the few demo-

graphic and other exposure likelihoods suggested a null exposure/mortality association prior to stratification by urinalysis cohort (or indirectly urinalysis frequency). Using the data available, it was apparent that repeated uranium urine monitoring clearly had three effects on suicide mortality HR estimates. First, the percent agreement between the JEM and uranium urinalysis categories increased (Table 3). Second, the association between uranium exposure and suicide strengthened (Table 4). Finally, JEM sensitivity increased and specificity decreased (Table 4). The latter two observations can be explained, in part by a fall in urine cohort yearly medians. However, the increase in percent agreement may also reflect a worker's conscious preparation prior to each urinalysis, a learned awareness of how to avoid hazards over time, and the consequences (health, loss of pay, termination) of repeated overexposure to hazards. Since repeated urinalyses (*i.e.*, urinalysis cohorts) show a nearly monotonic rise in mortality risk by cohort, it is likely that proportional hazards regression estimates in Table 2 are confounded by membership in urinalysis cohorts. Once adjusted for urinalysis cohort, an elevated suicide mortality risk is observed.

How do our estimates compare with previous reports? Aldrich, *et al*,²⁴ observed an elevated suicide mortality risk but concluded that it was not “due to PGDP employment exposures to metal dust.” We see distinct differences between the two studies. First, we used indirect standardization based on the 1977 US standard population suicide rates to calculate SMRs. In contrast, Aldrich, *et al*, used direct standardization using internal populations standards to generate SMRs. Second, we counter with HRs to address indirect standardization weaknesses. Third, we identified and used 40 suicides. Aldrich, *et al*, reported only 11. Fourth, Aldrich, *et al*, based their ex-

posure assessment observations solely on the JEM. Fifth, the JEM agreed poorly with urinalysis categories based on actual urine levels (Table 3). Sixth, ordinal scale measurement errors impact exposure/disease associations differently than interval scale measurement errors.⁴⁶ Finally and most important, by focusing on the PGDP's refitting interval between 1975 and 1979, Aldrich, *et al*, differentially assessed suicide cases. As indicated earlier, nosologists examined death certificates alone to ascertain all "cases" occurring before 1980. After 1979, case ascertainment included the NDI (*see Methods*). Thus, nosologists used death certificates alone for workers during the refitting (exposed), but used death certificates and NDI methods for workers after the refitting (unexposed). The added impact of NDI-ascertained cases is well documented^{47,48} and leaves the lack of association reported by Aldrich, *et al*, unresolved.

Still we lacked important sociologic data about factors that disrupt social life routines (*i.e.*, employment status, income, religiosity, marital status, illness, and loss of a family member) and their prevalence.^{49,50} Instead of estimating each factor associated with suicide, we used sensitivity analyses⁴¹ to assess the effect of prevalent mental illness, an important unmeasured confounder. We used a prevalence of 20% for all mental illness and 5.7% for severe mental illness among PGDP workers⁴² assuming that mental illness is responsible for a suicide mortality risk of 1.5. As a result, our sensitivity analysis lowered the HR from 2.7 to 1.9 assuming 20% prevalent mental illness in the 5th urinalysis cohort—as an example. This estimate was also lowered to an HR of 1.8 assuming a 5.7% severe mental illness prevalence. Therefore, it is likely that the risk of suicide mortality among PGDP workers following uranium exposure is approximately two fold instead of nearly three fold in

the 5th urinalysis cohort (Table 4). Overall, adjusting for mental illness would have lowered suicide risk one fold among workers exposed to uranium.

Finally, differences in estimates can be the result of study strengths and weaknesses. Among our study's strengths are cohort size (6820 workers), a thorough case ascertainment, use of proportional hazard analyses to ensure peer-to-peer comparisons, use of urinalyses to assess the validity of uranium exposure likelihood categories, and use of methods to assess the impact of unmeasured confounders on suicide risk. Important weaknesses include exposure measurement error associated with the JEM and significant systematic bias leading to exposure misclassification. In addition, the study lacked primary sociologic data on factors that may confound or modify the effect of toxic metal-induced psychopathology and suicide.

Clearly, policies supporting research on toxic metal hazards in the workplace and suicide risk are necessary and should be linked to the confounding influences of community-based suicide risk factors.⁵¹⁻⁵³ This study demonstrates the difficulty in assessing mortality risk when the relationship between exposure and disease is not clearly understood. We further believe that the study demonstrates the importance of metal bio-monitoring programs, regardless of their demonstrated neurotoxicity. The policy implications suggest that "safe" levels should be periodically re-evaluated for outcomes not previously associated with exposure.

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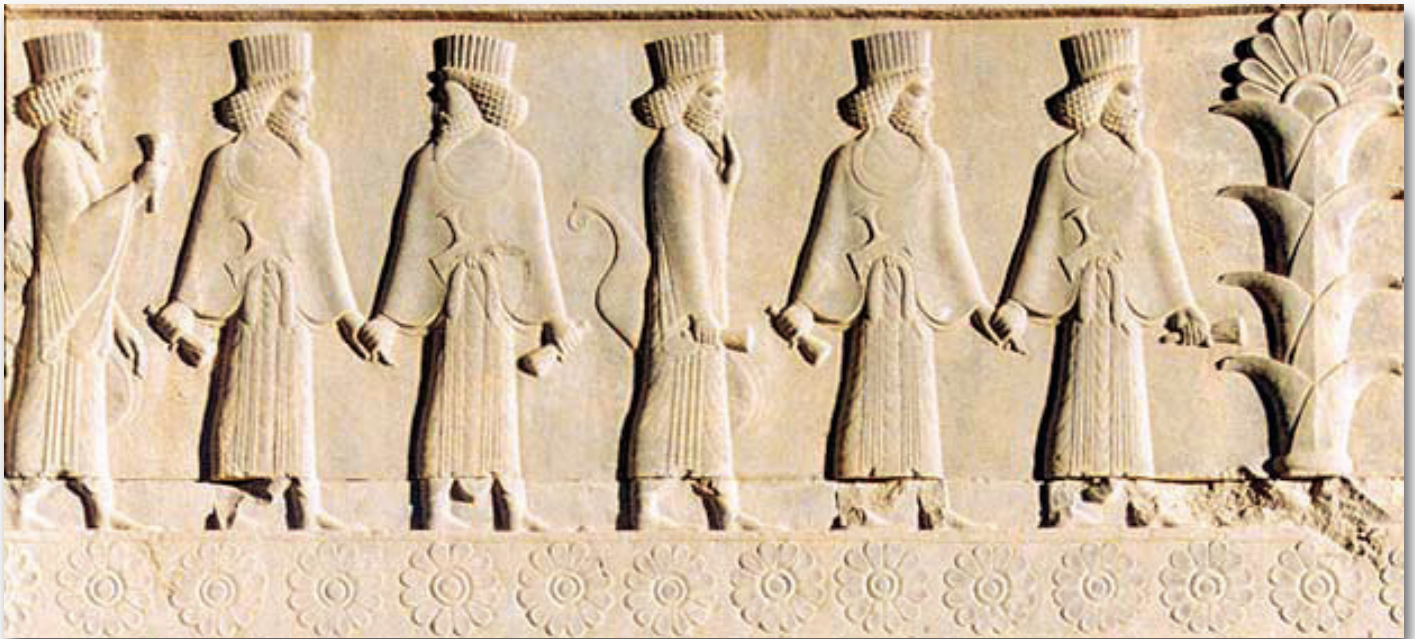
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One of the Persepolis carvings (near Shiraz, Iran).