AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 60:96–108 (2017)

Mortality in a Combined Cohort of Uranium Enrichment Workers

James H. Yiin, PhD,[1]* Jeri L. Anderson, PhD,[1] Robert D. Daniels, PhD,[1] Stephen J. Bertke, PhD,[1] Donald A. Fleming, MS,[1] David J. Tollerud, MD,[2] Chih-Yu Tseng, MS,[1] Pi-Hsueh Chen, MS,[1] and Kathleen M. Waters, BS[1]

Objective *To examine the patterns of cause-specific mortality and relationship between internal exposure to uranium and specific causes in a pooled cohort of 29,303 workers employed at three former uranium enrichment facilities in the United States with follow-up through 2011.*

Methods *Cause-specific standardized mortality ratios (SMRs) for the full cohort were calculated with the U.S. population as referent. Internal comparison of the dose-response relation between selected outcomes and estimated organ doses was evaluated using regression models.*

Results *External comparison with the U.S. population showed significantly lower SMRs in most diseases in the pooled cohort. Internal comparison showed positive associations of absorbed organ doses with multiple myeloma, and to a lesser degree with kidney cancer.*

Conclusion *In general, these gaseous diffusion plant workers had significantly lower SMRs than the U.S. population. The internal comparison however, showed associations between internal organ doses and diseases associated with uranium exposure in previous studies.* Am. J. Ind. Med. 60:96–108, 2017. Published 2016. This article is a U.S. Government work and is in the public domain in the USA.

KEY WORDS: uranium enrichment; gaseous diffusion; absorbed organ doses; radiation; standardized mortality ratios; exposure-response

INTRODUCTION

Commercial nuclear power production in the United States is currently experiencing resurgence with associated expansion in commercial fuel cycle industries including mining, milling, uranium enrichment, and fuel fabrication. Operation of these fuel cycle facilities presents a potential for worker exposures to various uranium compounds that are known or suspected to cause adverse human health effects. The purpose of this study was to examine the patterns of cause-specific mortality in a pooled cohort of workers employed at three former uranium enrichment facilities in the United States. All three facilities were gaseous diffusion plants (GDP) with various years in operation beginning in the 1940s [Anderson and Apostoaei, 2015]: the Oak Ridge Gaseous Diffusion Plant (also known as K-25) in Oak Ridge, Tennessee (TN), the Portsmouth Gaseous Diffusion Plant (PORTS) in Piketon, Ohio (OH), and the Paducah Gaseous Diffusion Plant (PGDP) in Paducah, Kentucky (KY).

The process of uranium enrichment is described in Anderson and Apostoaei [2015]. The primary chemical form of uranium used in gaseous diffusion is uranium hexafluoride (UF_6), which does not react with oxygen, nitrogen, carbon dioxide, or dry air. UF_6 does react violently with water or moisture in the atmosphere, resulting in uranyl fluoride

[1]Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, Ohio

[2]School of Public Health and Information Sciences, University of Louisville, Louisville, Kentucky

*Correspondence to: James H. Yiin, PhD, Industrywide Studies Branch, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 1090 Tusculum Ave, MailStop R-15, Cincinnati, OH 45226, E-mail: jcy5@cdc.gov

Accepted 23 September 2016

DOI 10.1002/ajim.22668. Published online 18 October 2016 in Wiley Online Library (wileyonlinelibrary.com).

(UO_2F_2), a soluble uranium compound and the primary exposure of interest in this study. Internally deposited uranium accumulates primarily in the kidneys and skeleton when soluble compounds are inhaled, whereas insoluble forms are retained in the lung [Eidson, 1994]. Compared with other ionizing radiation sources, the available epidemiologic research on the health effects of uranium is sparse and study findings are inconsistent. A few studies have found significant increases in the risk of respiratory tract and hematopoietic cancers in workers exposed internally to uranium [Dupree et al., 1987; Ritz et al., 2000; Pinkerton et al., 2004; Canu et al., 2008]. A recently published study of the French uranium enrichment cohort found these workers healthier than the general population with substantially lower mortality rates for call causes and all cancers. The only significant excess in mortality was reported for pleural cancer but based on only nine deaths [Zhivin et al., 2016]. The variability in the reported risks associated with internal uranium exposure is largely due to several limitations, including low statistical power due to smaller cohort size of shorter follow-up period, and imprecise methods of internal exposure assessment. Furthermore, few studies have focused on a specific stage of the fuel cycle (e.g., uranium enrichment), and those that have not are subject to the effects of the variability in organ doses per unit intake resulting from exposures to differing uranium compounds [Canu et al., 2008; Zhivin et al., 2014].

Previous analyses have been conducted for the K-25, PORTS, and PGDP workers included in the current study. A case-control study of 581 workers at K-25 found a small but statistically significant elevation in risk of mortality from multiple myeloma [Yiin et al., 2009]. That study showed a weak association of multiple myeloma and absorbed bone marrow dose from internal exposure to uranium. The National Institute for Occupational Safety and Health (NIOSH) performed a mortality study of a cohort of workers at PORTS which included 8,877 workers employed for at least one day between September 1, 1954 and December 31, 1991. Vital status of that cohort was ascertained through December 31, 1991, at which time approximately 88% of the cohort was still alive. The study found no statistically significant excess in cause-specific mortality, although there was a non-significant excess of mortality from stomach cancer [NIOSH, 2001]. Another recently completed mortality study of workers at PGDP reported modest excess mortality from lymphatic and hematopoietic cancers, although standardized mortality ratios (SMRs) were not statistically significant [Chan et al., 2010].

The current study examines the patterns of cause-specific mortality with extended vital status follow-up and combined cohorts to increase statistical power. In addition to external comparisons using SMRs, the dose–response relationship within the study population was examined using regression models between mortality of selected outcomes and our main exposure of interest, the individual absorbed organ dose from internally deposited soluble uranium. The potential impact of external radiation exposure including work-related medical X-ray examinations on the estimates of internal uranium exposure was also investigated. The non-radiological exposures in GDP under consideration included in the study were nickel and trichloroethylene (TCE).

METHODS

Study Cohort

The study subjects were drawn from a pooled cohort of production workers from the three uranium enrichment facilities. Eligible workers were limited to those who worked for at least 1 year continuously at K-25 between January 1, 1948 and December 31, 1985, PORTS between March 1, 1956 and May 31, 2001, or PGDP between September 1, 1952 and December 31, 2003. The beginning dates of eligibility represent the start of operations for PORTS and PGDP. K-25 facility construction continued concurrently with operations into the late 1940s. During this time, K-25 workers comprised a mixture of process and construction workers that was difficult to disentangle. To limit recruitment to uranium workers, we set the employment year ahead to 1948, which essentially excluded approximately 60% of short-term and construction workers who left K-25 employment at the end of major facility construction.

Vital status was updated through 2011 using the National Death Index, Social Security Administration mortality database, and Internal Revenue Service records. Underlying cause of death information was coded according to the International Classification of Diseases revision in effect at the time of death.

Internal Uranium Exposure

A detailed description of the methods is found in the paper by Anderson et al. [2016]. Briefly, uranium gravimetric and radioactivity concentration for >600,000 urine samples was abstracted from facility bioassay records. Department- and facility-specific enrichment levels were estimated using the ratio of activity concentration to gravimetric concentration and department numbers reported for each urine sample. Novel methods were used to estimate effective enrichment to which each individual worker was chronically exposed by combining department numbers from work history records with department- and facility-specific enrichments. Gravimetric uranium concentration (in $mg\,L^{-1}$) for each urine sample was converted to 24-hr activity excretion (becquerel (Bq) d^{-1}) by multiplying the by the 24-hr urinary excretion rate ($1.6\,L\ d^{-1}$) and the

department- or facility-specific uranium specific activity. For each study subject with at least one positive bioassay sample (i.e., greater than the facility detection limit or administrative limit, L), data points recorded as zero or less than L were assigned an imputed value, GM:

$$GM = L\,(1 - f)$$

where GM represents the geometric mean of the distribution of urine samples below L and f is the fraction of samples below L [Anderson and Apostoaei, 2015]. Bioassay data were imputed for study subjects with no reported data using department-specific uranium concentration combined with department numbers from each individual's work history. Study subjects with all bioassay data points reported or imputed as zero or below the detection level and who had worked in jobs with uranium exposure potential, or who had no reported bioassay data and worked in jobs with no uranium exposure potential, were assumed to be unexposed and assigned intakes and doses of zero. Reported and imputed bioassay data were used to calculate intakes assuming a chronic exposure to a 5-μm activity median aerodynamic diameter aerosol of a soluble uranium compound (Absorption Type F). The intakes were then used in combination with the effective enrichment to calculate absorbed organ doses to the lungs, bone surface, red bone marrow, kidneys, and liver, which were selected a priori because of the tendency for these organs to take up uranium. Annual absorbed organ doses were calculated and accumulated for each worker until the date of last observation (i.e., date of death, date lost to follow-up, or the study end date of December 31, 2011).

Ionizing Radiation Exposure from External Sources

Workers had a risk of exposure to external ionizing radiation due to relatively low-level radioactive emissions associated with uranium products and wastes in contaminated equipment and systems. Measurements obtained from personal monitors (i.e., film badges and thermoluminescent dosimeters) were abstracted from facility records, the U.S. Department of Energy's (DOE) Radiation Exposure Monitoring System, the Nuclear Regulatory Commission's (NRC) Radiation Exposure Information and Reporting System, and previous study records. Potentially overlapping information was resolved by manual review, with preference given to facility records, followed by national dose registries, and then other sources such as previous study records. Monitoring protocols, work history information (job titles and departments), and exposure distributions among monitored workers were used to create job-exposure matrices for estimating exposures during periods of incomplete personal monitoring. Records of positive neutron and tritium exposures were available for a small number of subjects. However, this information was not included in analyses because the contribution to total dose was negligible. Given low linear energy transfer (low-LET) radiations, external exposure values were considered reasonable approximations of personal dose equivalent. These doses were further adjusted using International Commission on Radiological Protection conversion coefficients [Petoussi-Henss et al., 2010] to produce final estimates of absorbed dose to organs of interest (i.e., lungs, bone surface, red bone marrow, kidneys, and liver).

Work-Related Medical X-Rays

Routine physical examinations that included stereo photofluorographic posterior-to-anterior chest X-rays were performed at K-25 from mid-1945 through 1956 [Yiin et al., 2009]. Chest photofluorography was common in this period as a means of tuberculosis screening. These exams were a condition of employment and the dose received as a result of these exams was non-trivial relative to other occupational dose from other sources. Therefore, organ doses were estimated using methods similar to those described in Anderson and Daniels [2006]. Briefly, dose per procedure was calculated for each organ of interest and were assigned to K-25 study subjects on their hire date (pre-employment screening) and once every year thereafter from 1945 through 1956. The exposure from X-ray examinations was then added to the external radiation dose estimates. Records suggest that photofluorographic X-ray examinations were rarely used at PORTS or PGDP, so no doses were assigned for employment at those facilities.

Non-Radiological Exposure

Due to the nickel content of gaseous diffusion process equipment and piping, and the historic use of TCE as a degreasing agent for this equipment, these two chemicals were selected for exposure assessment. The exothermic reaction requires that UF_6 be handled in leak-tight containers and processing equipment to prevent reaction with water vapor in air. The corrosive effects of UF_6 require that certain non-reactive metals be used in gaseous diffusion plant processing equipment. Nickel is primarily used to form alloys which are corrosion and heat resistant [ATSDR, 2005]. TCE is used primarily as a solvent for degreasing metal parts, although it is also a component in paint thinners and adhesives [ATSDR, 1997].

A modified job-exposure matrix approach that incorporated available chemical hazard information to link study subjects with historic potential for nickel and TCE exposure was the basis of the chemical exposure assessment. The

exposure matrix included a factor based on professional judgement that represented an estimate of the exposed fraction of time per day for each unique department number and job title combination, ranging from administrative titles assigned a factor of zero, to workers performing the exposure activity assigned a factor of one. An algorithm was developed to calculate modified cumulative exposure duration (days) for nickel and TCE for each study subject as follows:

$$\text{Modified Cumulative Exposure Duration (days)} = \sum_i \sum_j D_{ij} \times f_{ij,}$$

where: D is the number of days the subject worked in a department associated with an exposure activity work area i, during work history period j; f is a factor representing the relative fraction of time/day the subject spent in the exposure activity work area i, during work history period j.

For this study, the modified cumulative exposure duration provided a relative measure of exposure to nickel and TCE for each study subject being evaluated. As a semi-quantitative estimate, these durations are not comparable to any absolute exposure values or occupational health limits. Workers not employed in an exposure-associated department during their tenure at these facilities were considered unexposed.

Statistical Analysis

The NIOSH Life Table Analysis System (LTAS.NET) was used to calculate SMRs with the U.S. rates as referent. Observed deaths were classified into 1 of 92 cause-of-death categories [Robinson et al., 2006]. The expected numbers of deaths were estimated for all-deaths combined, all-cancer deaths combined, and each cause-specific death category as the product of U.S. population death rates and the person years at risk of dying (PYARS) in strata of sex, race (White, others), age (15–19, . . . 85+ years in 5-year categories), and calendar time (in 5-year periods starting with 1940–44) [Schubauer-Berigan et al., 2011]. Observed deaths and PYARS were accumulated from the date of cohort inclusion through the end of the study (December 31, 2011), date last observed, or the date of death, whichever occurred first. Numbers of deaths observed for each cause were divided by the expected number of deaths to calculate standardized mortality ratios. Two-sided 95% confidence intervals (CI) were calculated as described elsewhere [Steenland et al., 1990]. A sensitivity analysis was conducted to generate SMRs based on state general population mortality rates (TN for K-25, Ohio for PORTS, and Kentucky for PGDP, and three states combined for the pooled cohort).

For internal comparisons, regression models were used to evaluate the relation between selected outcomes and estimated internal organ doses. The a priori outcomes of interest included lung cancer [Checkoway et al., 1988; Dupree et al., 1995; Loomis and Wolf, 1996], kidney, and bone cancers where internally deposited uranium primarily accumulates [Eidson, 1994], hematopoietic cancers (non-Hodgkin lymphoma (NHL), leukemia, and multiple myeloma) [Ritz et al., 2000; Pinkerton et al., 2004; Yiin et al., 2009] and non-malignant respiratory disease [Pinkerton et al., 2004]. Additionally, because the kidney is a uranium target organ, chronic and unspecified nephritis and renal disease (minor 70 as defined in NIOSH-92 rate file [NIOSH, 2013]) was investigated. Diseases with significant excess in SMRs were also explored further.

For each selected outcome, risk sets were drawn from the study cohort using incidence density matching on gender, race, attained age, birth date (within 5 years) of the case, and plant [Beaumont et al., 1989; Langholz and Goldstein, 1996]. General relative risk models using methods analogous to the Cox proportional hazards analysis were developed [Callas et al., 1998; Langholz and Richardson 2010]. A linear excess relative risk (ERR) model was used to describe the effects of internal soluble uranium exposure as it is preferred in radiation research. ERR per milligray (mGy) of absorbed internal organ dose and corresponding 95% profile likelihood-based CI were derived with restriction to workers with less than the 95th percentile of exposure. Risk heterogeneity by facility was examined by likelihood ratio test. A lag discounting exposures 10 years prior to attained age was used, although analyses with a 5- and 15-year lags were also conducted to explore the effect of latency periods between exposure and mortality. Dose–response was also explored using categorical models with the non-exposed after lagging as reference (Q1). Cut-points for the exposed were selected by dividing the deceased with positive cumulative internal organ dose estimates into three groups (Q2, Q3, and Q4) with an approximately equal number of observed deaths in each group. The impact of potential confounders such as external radiation with or without X-ray, nickel, TCE, and employment duration was investigated by including one covariate at a time in the model and examining the percent change relative to the width of the confidence interval. All regression modeling analyses on internal comparisons were conducted using SAS software [SAS Institute Inc., 2002–2010].

RESULTS

The study included 29,303 eligible workers who worked for at least 1 year continuously within the specified time periods at the three uranium enrichment facilities. A primary site was associated with a worker in which he or she became eligible (i.e., the facility where the worker first worked 1 or more years continuously within the eligibility period). Most workers (72%) worked at only one of these facilities and 23%

worked at K-25 and surrounding sites. The cohort is predominantly male (81%) and White (93%). A total of 1,099,370 person-years were accumulated: 655,550 from 16,978 K-25 workers, 251,201 from 6,935 PORTS workers, and 192,619 from 5,390 PGDP workers. Less than 0.1% of the total person-years from 17 workers were lost to follow-up. Males contributed 81% of the person-years and Whites 94%, similar to the proportions of male and White workers in the cohort. Over half of the workers were hired in their 20s (54%) and the mean age at hire was 29.2 years. The years of hire varied among facilities due to differences in facility operations. The mean duration of employment ranged from 11.6 years at PORTS to 15.1 years at K-25. Approximately, 45% (n = 13,267) of the cohort was deceased. Because K-25 was an older facility with more early years in operation, more deaths were observed for those workers (52%) than those at the other two facilities (35–36%) (Table I).

Bioassay data were available for 58% of the cohort and were imputed for an additional 33%. The remaining 9% had no reported data. Approximately 29% of the cohort was considered to be unexposed because of bioassay data reported or imputed to be zero or less than the facility administrative limit or because of a combination of work history and no reported or imputed data. Estimated internal organ doses were highest in bone surface with mean of 2.4 mGy and lowest in lungs with mean of 0.07 mGy. All internal organ doses were highest among K-25 workers likely due to earliest operation and longest duration

TABLE I. Demographics of Gaseous Diffusion Plant Workers With Follow-Up Through December 31, 2011

	Primary site			
	K-25	PORTS	PGDP	All sites
Characteristics	n (%) or Mean (SD)	n (%) or Mean (SD)	n (%) or Mean (SD)	n (%) or Mean (SD)
Sex				
Male	13,529 (80%)	5,772 (83%)	4,450 (83%)	23,751 (81%)
Female	3,449 (20%)	1,163 (17%)	940 (17%)	5,552 (19%)
Race				
White	15,931 (94%)	6,489 (94%)	4,861 (90%)	27,281 (93%)
Other race	1,046 (6%)	441 (6%)	529 (10%)	2,016 (7%)
Unknown[a]	1 (0%)	5 (0%)	0 (0%)	6 (0%)
Age at hire				
<20	1,682 (10%)	663 (10%)	273 (5%)	2,618 (9%)
20 to <25	5,023 (30%)	2,074 (30%)	1,653 (31%)	8,750 (30%)
25 to <30	4,090 (24%)	1,610 (23%)	1,469 (27%)	7,169 (24%)
30 to <35	2,523 (15%)	1,063 (15%)	855 (16%)	4,441 (15%)
35 to <40	1,571 (9%)	718 (10%)	505 (9%)	2,794 (10%)
40 to <50	1,613 (10%)	601 (9%)	492 (9%)	2,706 (9%)
50+	476 (3%)	206 (3%)	143 (3%)	825 (3%)
Age at hire (years)	29.1 (8.5)	29.2 (8.5)	29.5 (8.1)	29.2 (8.4)
Year of hire				
<1950	5,656 (33%)	60 (1%)	2 (0%)	5,718 (20%)
1950–1959	4,133 (24%)	2,787 (40%)	2,102 (39%)	9,022 (31%)
1960–1969	1,750 (10%)	341 (5%)	372 (7%)	2,463 (8%)
1970–1979	4,913 (29%)	2,427 (35%)	1,793 (33%)	9,133 (31%)
1980+	526 (3%)	1,320 (19%)	1,121 (21%)	2,967 (10%)
Duration of employment (years)	15.1 (11.1)	11.6 (9.8)	13.3 (10.7)	13.9 (10.8)
Age at last follow-up (years)[b]	70.6 (12.1)	67.1 (12.3)	66.2 (13.1)	69.0 (12.5)
Vital status (as of 12/31/2011)				
Alive	8,087 (48%)	4,458 (64%)	3,491 (65%)	16,036 (55%)
Deceased	8,891 (52%)	2,477 (36%)	1,899 (35%)	13,267 (45%)

K-25, Oak Ridge gaseous diffusion plant, Tennessee; PORTS, Portsmouth gaseous diffusion plant in Piketon, Ohio; PGDP, Paducah gaseous diffusion plant, Kentucky; SD, standard deviation.

[a]Assigned to White in analyses.

[b]Age at lost to follow-up, death or study end, whichever is the earliest.

(Table II). Overall the doses were low but not unexpected compared to exposure at other facilities. For example, median organ absorbed doses estimated were 0.053, 0.0015, and 0.0044 mGy for lung, red bone marrow, and kidney, respectively for the Fernald cohort [Anderson et al., 2012]. The median lung, red bone marrow, and kidney organ absorbed doses, respectively in our cohort were 0.0204, 0.0878, and 0.2995 mGy. The average cumulative external dose ranged from 13 mGy in kidneys to 40 mGy in lungs. External dose were also highest among K-25 workers due to dose from work-related medical X-ray examinations administered as a condition of work in the early years, and lowest among PORTS workers, which did not have significant exposures from work-related medical X-rays.

Correlation analysis showed that employment duration was weakly to moderately associated with estimated internal organ doses, while the association with estimated external organ doses was marginally stronger. It was expected as external organ doses for most workers were mainly based on work history/employment duration, while internal doses were accumulated beyond last employment date until the last observation date of each study subject. There was no association between internal dose estimates and X-ray among K-25 workers.

Nickel and TCE exposure duration-days were estimated but only a limited number of workers were exposed. In correlation analysis, nickel and TCE, whether treated dichotomously or as continuous variables representing exposure-days, were poorly correlated with internal organ dose and were thus unlikely to confound radiation effects in this study.

SMR Analysis

These gaseous diffusion plant workers had significantly decreased mortality from all-causes (SMR = 0.83, 95%CI 0.82–0.85, n = 13,267) as well as from all-cancers (SMR = 0.87, 95%CI 0.84–0.90, n = 3,530) and from various cancers comparing to the U.S. population referent (Table III). For the a priori outcomes, kidney (SMR = 1.10, 95%CI 0.90–1.32, n = 110) and bone cancers (SMR = 1.23, 95%CI 0.61–2.20, n = 11) were slightly but not statistically elevated. There was significantly decreased mortality from lung cancer (SMR = 0.88, 95%CI 0.83–0.94, n = 1,172) and diseases of the respiratory system (SMR = 0.85, 95%CI 0.80–0.90, n = 1,194). Mortality from hematopoietic cancers (SMR = 0.91, 95%CI 0.82–1.01, n = 362) including multiple myeloma (SMR = 0.98, 95%CI 0.77–1.24, n = 69) were non-significantly decreased. In addition to non-malignant respiratory diseases including chronic obstructive pulmonary disease (COPD; SMR = 0.83, 95%CI 0.77–0.90,

TABLE II. Exposure Estimate Summary Statistics: Mean (Standard Deviation)

	Primary site			
	K-25	PORTS	PGDP	All sites
Exposure estimate	**n = 16,978**	**n = 6,935**	**n = 5,390**	**n = 29,303**
Internal uranium absorbed organ dose (mGy)				
Lungs	0.10 (0.78)	0.02 (0.12)	0.05 (0.12)	0.07 (0.60)
Bone surface	3.22 (22.7)	0.82 (4.34)	1.68 (3.86)	2.37 (17.5)
Red bone marrow	0.38 (2.63)	0.09 (0.49)	0.20 (0.47)	0.28 (2.03)
Kidneys	1.28 (8.50)	0.33 (1.79)	0.69 (1.57)	0.95 (6.57)
Liver	0.44 (3.12)	0.11 (0.61)	0.23 (0.53)	0.33 (2.41)
External organ dose (mGy)[a]				
Lungs	67 (73)/4.8 (16)	2.6 (5.3)	5.7 (15)	40 (64)/4.5 (14)
Bone surface	58 (64)/5.4 (18)	3.0 (5.9)	6.4 (16)	35 (56)/5.0 (16)
Red bone marrow	25 (29)/4.8 (16)	2.6 (5.3)	5.7 (15)	16 (25)/4.5 (14)
Kidneys	21 (24)/3.8 (12)	2.1 (4.1)	4.5 (11)	13 (21)/3.5 (11)
Liver	26 (30)/4.5 (15)	2.5 (5.0)	5.4 (14)	17 (26)/4.2 (13)
Nickel (Exposure duration—days)				
	821 (1717)	651 (1479)	549 (1712)	731 (1666)
Trichloroethylene (Exposure duration—days)				
	419 (1247)	238 (761)	464 (1298)	385 (1164)

K-25, Oak Ridge gaseous diffusion plant, Tennessee; PORTS: Portsmouth gaseous diffusion plant in Piketon, Ohio; PGDP, Paducah gaseous diffusion plant, Kentucky; mGy, milligray.

[a]External organ dose including gamma radiation, and for K-25 and all sites, with or without exposure to X-radiation from work-required photofluorographic chest X-rays.

TABLE III. Select Mortality Among Gaseous Diffusion Plant Workers With Follow-Up Through December 31, 2011 Using U.S. Referent Rates

Underlying cause of death	Observed	SMR	95% CL
All causes	13,267	0.83**	(0.82, 0.85)
All cancers	3,530	0.87**	(0.84, 0.90)
MN of buccal cavity and pharynx	46	0.56**	(0.41, 0.75)
MN of tongue	8	0.42**	(0.18, 0.83)
MN of pharynx	21	0.52**	(0.32, 0.80)
MN of digestive organs and peritoneum	780	0.79**	(0.74, 0.85)
MN of esophagus	74	0.67**	(0.52, 0.84)
MN of stomach	84	0.73**	(0.58, 0.91)
MN of intestine except rectum	300	0.87*	(0.78, 0.98)
MN of rectum	55	0.73*	(0.55, 0.95)
MN of biliary passages and liver	70	0.60**	(0.47, 0.76)
MN of pancreas	187	0.89	(0.76, 1.02)
MN of respiratory system	1,224	0.89**	(0.84, 0.94)
MN of larynx	38	0.89	(0.63, 1.23)
MN of trachea, bronchus, and lung	1,172	0.88**	(0.83, 0.94)
MN of pleura	7	2.25	(0.90, 4.63)
MN of breast	92	0.92	(0.74, 1.12)
MN of female genital organs	55	0.91	(0.69, 1.19)
MN of male genital organs	287	0.86**	(0.76, 0.97)
MN of prostate	282	0.87*	(0.77, 0.98)
MN of urinary organs	198	0.93	(0.81, 1.07)
MN of kidney	110	1.10	(0.90, 1.32)
MN of bladder and other urinary organs	88	0.78*	(0.63, 0.96)
MN of other and unspecified sites	486	0.93	(0.85, 1.02)
MN of skin	72	0.84	(0.66, 1.06)
Mesothelioma	25	2.21**	(1.43, 3.27)
MN of brain and other parts of nervous system	105	1.05	(0.86, 1.27)
MN of bone	11	1.23	(0.61, 2.20)
MN of connective tissue	17	0.78	(0.45, 1.25)
MN of other and unspecified sites	249	0.88	(0.78, 1.00)
Neoplasms of lymphatic and hematopoietic tissue	362	0.91	(0.82, 1.01)
Non-Hodgkin's Lymphoma	163	1.06	(0.90, 1.23)
Leukemia and aleukemia	117	0.76**	(0.63, 0.91)
Multiple myeloma	69	0.98	(0.77, 1.24)
Benign and unspecified neoplasms	45	0.85	(0.62, 1.13)
Diabetes mellitus	277	0.76**	(0.67, 0.86)
Diseases of the blood and blood forming organs	63	0.93	(0.72, 1.19)
Mental, psychoneurotic, and personality disorders	211	0.77**	(0.67, 0.88)
Alcoholism	23	0.38**	(0.24, 0.57)
Other mental disorders	188	0.88	(0.76, 1.01)
Disorders of the nervous system and sense organs	456	1.07	(0.97, 1.17)
Multiple sclerosis	15	0.90	(0.51, 1.49)
Other diseases of the nervous system and sense organs	441	1.08	(0.98, 1.18)
Diseases of the heart	4,247	0.81**	(0.78, 0.83)
Rheumatic heart disease, including fever	34	0.54**	(0.37, 0.75)
Ischemic heart disease	3,488	0.83**	(0.80, 0.86)
Chronic disease of endocardium	64	0.70**	(0.54, 0.89)
Hypertension with heart disease	75	0.47**	(0.37, 0.59)
Other diseases of the heart	586	0.80**	(0.74, 0.87)

(*Continued*)

TABLE III. (*Continued*)

Underlying cause of death	Observed	SMR	95% CL
Other diseases of the circulatory system	1,147	0.86**	(0.81, 0.91)
Hypertension without heart disease	62	0.74*	(0.57, 0.95)
Cerebrovascular disease	746	0.86**	(0.80, 0.92)
Diseases of the arteries, veins and pulmonary circulation	339	0.89*	(0.80, 0.99)
Diseases of the respiratory system	1,194	0.85**	(0.80, 0.90)
Pneumonia (except newborn)	300	0.79**	(0.70, 0.89)
Chronic obstructive pulmonary disease	634	0.83**	(0.77, 0.90)
Asthma	10	0.44**	(0.21, 0.81)
Pneumoconioses and other respiratory diseases	238	1.03	(0.90, 1.17)
Diseases of the digestive system	412	0.64**	(0.58, 0.70)
Diseases of the stomach and duodenum	32	0.57**	(0.39, 0.80)
Hernia and intestinal obstruction	23	0.62*	(0.39, 0.93)
Cirrhosis and other chronic liver disease	157	0.53**	(0.45, 0.62)
Other diseases of digestive system	200	0.77**	(0.67, 0.89)
Diseases of the genitourinary system	234	0.81**	(0.71, 0.92)
Acute glomerulonephritis, nephrotic syndrome and acute renal failure	31	0.95	(0.64, 1.34)
Chronic and unspecified nephritis and renal failure	117	0.72**	(0.60, 0.86)
Infection of kidney	9	0.82	(0.37, 1.55)
Other genitourinary system diseases	68	0.98	(0.76, 1.24)
Diseases of the skin and subcutaneous tissue	9	0.57	(0.26, 1.08)
Diseases of the musculoskeletal system and connective tissue	53	1.11	(0.83, 1.45)
Arthritis and spondylitis	22	1.23	(0.77, 1.87)
Other diseases of musculoskeletal system	28	1.16	(0.77, 1.67)
Symptoms and ill-defined conditions	234	1.45**	(1.27, 1.65)
Accidents	561	0.80**	(0.74, 0.87)
Transportation accidents	262	0.83**	(0.73, 0.93)
Accidental poisoning	22	0.43**	(0.27, 0.65)
Accident falls	99	0.85	(0.69, 1.04)
Other accidents	166	0.84*	(0.72, 0.98)
Violence	242	0.70**	(0.62, 0.80)
Suicide	198	0.78**	(0.68, 0.90)
Homicide	44	0.49**	(0.35, 0.65)
Other and unspecified causes	344	0.79**	(0.71, 0.87)

MN, malignant neoplasm; SMR, standardized mortality ratio; 95% CL, 95% confidence limits.
*Two-sided $P < 0.05$; **Two-sided $P < 0.01$.

n = 634), mortality was also significantly decreased in other outcomes that may be related to healthy worker selection and survivor effects, such as diabetes mellitus (SMR = 0.76, 95% CI 0.67–0.86, n = 277), diseases of the heart (SMR = 0.81, 95%CI 0.78–0.83, n = 4,247) including ischemic heart disease (SMR = 0.83, 95%CI 0.80–0.86, n = 3,488), cerebrovascular disease (SMR = 0.86, 95%CI 0.80–0.92, n = 746), and alcoholism (SMR = 0.38, 95%CI 0.24–0.57, n = 23). Mortality from diseases of the digestive system (SMR = 0.64, 95%CI 0.58–0.70, n = 412) and genitourinary system (SMR = 0.81, 95%CI 0.71–0.92, n = 234) was also significantly lower than that of the U.S. population. The only significant elevation in disease-specific mortality observed in the cohort was malignant mesothelioma with 25 deaths (SMR = 2.21, 95%CI 1.43–3.27).

Mortality results based on the combined three-state (TN, OH, and KY) population mortality rates for the full cohort are shown in Supplemental Table SI, and for each facility in Tables SII–IV. Results for all-cause, all-cancer, and cause-specific diseases in general followed the same pattern of those based on U.S. mortality rates, in terms of direction and significance. Using corresponding state rates as reference, all-cause and all-cancer mortality in each facility remained significantly lower than that in the state population. Kidney cancer was statistically significantly higher at K-25 (SMR = 1.30, 95%CI 1.03–1.61, n = 82), significantly

lower at PORTS (SMR = 0.48, 95%CI 0.24–0.85, n = 11), and at the population level at PGDP (SMR = 0.95, 95%CI 0.55–1.52, n = 17). Mesothelioma was statistically significantly higher at K-25 (SMR = 3.02, 95%CI 1.73–4.91, n = 16) and non-significantly higher at the other two facilities (SMR = 2.27 and n = 7 at PORTS and SMR = 1.33 and n = 2 at PGDP with 95%CI including one at both sites). The SMR for symptoms and ill-defined conditions was significantly elevated (SMR = 1.45, 95%CI 1.27–1.65, n = 234) with U.S. rates but became non-significant (SMR = 1.03, 95%CI 0.90–1.17) with combined state rates. As this category is reserved for coding non-specific causes of death listed on the death certificate, it suggests that the increased SMR is likely due to an increased number of earlier unattended deaths among K-25 workers who resided in a predominantly rural area of Tennessee.

Exposure-Response Analysis

Table IV shows the exposure-response of selected mortality and absorbed organ dose from internally deposited soluble uranium with a 10-year lag. The categorical model included full cohort, but the ERR estimates included workers with less than the 95th percentile of exposure to avoid underestimating risk at the lower doses. Each of the exposed categories showed elevated risk compared to the non-exposed (baseline) for lung cancer, kidney cancer, mesothelioma, leukemia, and chronic and unspecified nephritis and renal failure in the categorical model. The workers in the highest internal red bone marrow dose category had significantly higher risk for multiple myeloma than those with no exposure. The ERR models show positive non-significant associations between internal absorbed organ doses and mortality of kidney cancer, mesothelioma, hematopoietic cancers, leukemia, and chronic and unspecified nephritis and renal failure. The ERR estimates were almost zero for respiratory diseases and non-significantly negative for lung cancer, NHL, and COPD. The association between internal red bone marrow dose and multiple myeloma mortality was statistically significant with ERR of 2.92 (95%CI 0.51–7.86) per mGy of exposure, and there was no evidence of heterogeneity among facilities ($P = 0.46$).

The impact of potential confounders was investigated by the percent change relative to the width of the confidence interval. Employment duration had more impact (72–79% change) for respiratory diseases and COPD but less (up to 33% change) on other a priori outcomes. For external radiation with or without X-ray, the impact was minimal with the largest changes of 26% on COPD and 18–23% on kidney cancer. The changes were smaller or not calculable for nickel and TCE.

Analyses with 5- and 15-year lags had similar findings with a 10-year lag, with each of the exposed categories

TABLE IV. Relative Risk (RR) and Excess Relative Risk (ERR) of Selected Mortality and Internal Absorbed Organ Doses with a 10-Year Lag

	Internal absorbed organ dose											Impact of potential confounders[b]			
	Q1		Q2		Q3		Q4		ERR per mGy						
Cause of death/target organ	n	Ref	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	95% CI[a]	ED	EX	EN	Ni
Lung cancer/lungs	293	1.0	291	1.13 (0.96, 1.34)	290	1.01 (0.86, 1.20)	298	1.04 (0.88, 1.24)	−0.75 (−2.31, 1.12)	29%	−4%	−13%	−18%
Kidney cancer/kidneys	21	1.0	30	1.27 (0.72, 2.26)	29	1.20 (0.67, 2.17)	30	1.37 (0.77, 2.49)	0.14 (−0.16, 0.66)	−31%	−18%	−23%	2%
Mesothelioma/lungs	5	1.0	7	1.14 (0.36, 3.95)	7	2.46 (0.75, 8.65)	6	1.78 (0.50, 6.57)	11.1 (−4.39, 65.3)	19%	NC	−7%	−15%
Bone cancer/bone surface	2	1.0	3	2.30 (0.36, 17.9)	3	1.61 (0.26, 12.4)	3	0.94 (0.15, 7.65)	NC	NC	NC	NC	NC
Hematopoietic cancers/RBM	94	1.0	89	1.06 (0.78, 1.44)	88	0.94 (0.69, 1.29)	91	1.23 (0.89, 1.69)	0.50 (−0.20, 1.44)	8%	−4%	0%	4%
NHL/RBM	49	1.0	38	0.90 (0.58, 1.39)	38	0.80 (0.51, 1.27)	38	0.90 (0.56, 1.44)	−0.14 (−0.85, 0.97)	30%	7%	14%	3%
All leukemia/RBM	27	1.0	30	1.39 (0.80, 2.44)	30	1.19 (0.67, 2.12)	30	1.32 (0.74, 2.39)	0.39 (−0.70, 2.32)	−16%	−16%	−12%	6%
Multiple myeloma/RBM	14	1.0	19	0.88 (0.44, 1.82)	18	1.07 (0.51, 2.29)	18	2.12 (1.01, 4.56)	2.92 (0.51, 7.86)	−6%	12%	6%	−1%
Respiratory diseases/lungs	309	1.0	293	0.94 (0.80, 1.11)	292	0.99 (0.84, 1.17)	300	0.92 (0.77, 1.08)	0.08 (−0.33, 1.88)	79%	0%	15%	−5%
COPD/lungs	163	1.0	156	1.05 (0.84, 1.31)	155	0.94 (0.75, 1.18)	160	0.88 (0.70, 1.10)	−1.49 (−3.21, 0.72)	72%	7%	26%	−5%
Renal diseases/kidneys	18	1.0	33	2.27 (1.26, 4.23)	33	1.65 (0.91, 3.12)	33	1.86 (1.01, 3.54)	0.26 (−0.08, 0.85)	33%	−11%	−9%	3%

RBM, red bone marrow; NHL, Non-Hodgkin's Lymphoma; COPD, chronic obstructive pulmonary disease; mGy, milligray; CI, confidence intervals; NC, not calculable; ED, employment duration; EX, external radiation with X-ray; EN, external radiation without X-ray; Ni, Nickel.

[a]Linear ERR per mGy and corresponding 95% profile-likelihood-based CI with restriction to workers with less than the 95th percentile of exposure.

[b]Measured by percent change relative to the width of CI; models with trichloroethylene not calculable.

showing elevated risk compared to the non-exposed for lung cancer, kidney cancer, mesothelioma, and chronic and unspecified nephritis and renal failure in the categorical model (Supplemental Tables SV–VI). The results also show elevated risk in every exposed category for bone cancer, hematopoietic cancers, and multiple myeloma with positive ERR estimates with a 15-year lag and for leukemia with a 5-year lag. The models with a 10-year lag fit best for lung cancer, kidney cancer, leukemia, respiratory diseases, and chronic and unspecified nephritis and renal failure, while those with a 15-year lag best for NHL, COPD, and mesothelioma, and 5-year lag for bone cancer, hematopoietic cancers, and multiple myeloma. The difference in fit statistics among models with various lags; however, are small (0.16–2.45) and not statistically significant. The association between internal red bone marrow dose and multiple myeloma mortality remained positive and statistically significant with either a 5- or 15-year lag and the ERR estimates increase with longer lag. The impact of potential confounders using a 15-year lag was similar to that using a 10-year lag for mortality with positive ERR estimates.

DISCUSSION

The NRC currently regulates 14 uranium fuel cycle facilities, including uranium enrichment facilities, in 10 states [NRC, 2011]. This study examined the patterns of cause-specific mortality in a pooled cohort of workers employed at three previously studied uranium enrichment facilities in the United States. This study was designed to overcome the common limitations encountered in past studies of health effects in uranium workers by assembling a large pooled cohort of workers for increased power, focusing on one stage of the uranium fuel production cycle, and improving the assessment of internal uranium exposure by calculating organ absorbed dose from urinary uranium results.

Our results from external comparisons were similar to those reported in previous studies of the PORTS [NIOSH, 2001] and PGDP [Chan et al., 2010] cohorts, as well as the French uranium enrichment workers in terms of lower mortality than the reference population [Zhivin et al., 2016]. Deficits in mortality risk were observed for most outcomes in our cohort, the strongest of which were for outcomes most associated with lifestyle factors. Therefore, there is substantial evidence of healthy worker effects. Deficits were also observed among most a priori outcomes. However, there was evidence of modest excess mortality from cancers of the kidney and bone compared to the U.S. population. Examining individual facilities, the kidney cancer mortality was statistically significantly elevated in K-25, but not in the other two facilities. Heterogeneity tests also show significant differences in kidney cancer mortality among facilities ($P < 0.01$). The causes of facility differences are unknown; however, we note that estimated kidney doses were highest among K-25 workers compared to others.

The French uranium enrichment cohort reported a near twofold increase (SMR = 1.9) in mesothelioma mortality compared to the French general population [Zhivin et al., 2016]. We also observed a twofold increase in malignant mesothelioma mortality compared with the U.S. population. The SMRs differed among facilities, which corresponded to differing follow-up times (35 years at K-25 with SMR of 3.02, 31 years at PORTS with SMR of 2.27 and 24 years at PGDP with SMR of 1.33). Malignant mesothelioma is primarily attributable to asbestos exposure and has extremely long latency [Mossman and Gee, 1989; Burdorf et al., 2003]. McGeoghegan and Binks [2000] previously reported strong relationship between exposure to asbestos and risk of mesothelioma among uranium enrichment workers. The longer follow-up time may partially explain higher mesothelioma mortality at K-25 and PORTS. A study of construction and craft workers intermittently employed by subcontractors at the DOE sites that included the three GDP sites in our study found significantly elevated SMRs for mesothelioma [Ringen et al., 2015]. Similar results have been reported elsewhere [Tsai et al., 1996]. Evidence suggests that the association of mesothelioma with work involving certain mineral species of asbestos (e.g., crocidolite and amosite) is far greater than with other species (e.g., chrysotile) [ACGIH, 2001]. Large amounts of asbestos-containing-materials were installed at these GDP production facilities during construction and work was likely performed by subcontracted workers. Subsequent facility additions, upgrades and removals also likely involved installation and/or handling of asbestos-containing-material. Some work activities (e.g., routine maintenance and repair work on asbestos-containing-materials in process systems, equipment and facilities) were performed during all of the years of GDP site operations and these activities would likely have involved workers included in this study.

We found a significantly positive association between absorbed dose from internal uranium deposition and multiple myeloma mortality in these workers. This finding is consistent with the study by Yiin et al. [2009], who previously reported a weak association between multiple myeloma and internal absorbed bone marrow dose among K-25 workers. Other studies with internal exposure; however, found no excess mortality from multiple myeloma [Faber, 1979; Stebbings et al., 1984]. We also found positive but not statistically significant dose–response relation for kidney cancer and chronic nephritis and renal failure, conditions associated with exposure to soluble uranium [Leggett, 1989]. Additionally the associations between absorbed doses and hematopoietic cancers and mesothelioma mortality were also positive but non-significant.

Exposure to nickel via inhalation has been shown to increase risk of lung and nasal cancer in cohorts of nickel refinery workers [Doll et al., 1977; Enterline and Marsh, 1982;

Andersen et al., 1996; Anttila et al., 1998; Grimsrud et al., 2003]. However, studies of other nickel workers, such as those employed in mining and smelting [Shannon et al., 1984; Shannon et al., 1991], and nickel-alloy [Enterline and Marsh, 1982] and barrier production facilities [Godbold and Tompkins, 1979; Cragle et al., 1984] have found no significant increases in respiratory tract cancers. Exposure to TCE can occur through inhalation, ingestion, or absorption through skin. Several studies of workers occupationally exposed to TCE have suggested increased risk of mortality from multiple myeloma, NHL, kidney, and liver cancer [Axelson et al., 1978; Shindell and Ulrich, 1985; Spirtas et al., 1991; Axelson et al., 1994; Lipworth et al., 2011; Scott and Jinot, 2011]. The International Agency for Research on Cancer (IARC) classifies TCE as a probable human carcinogen (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of TCE [IARC, 1995]. In the current study, there were limited workers with estimated nickel and TCE exposure and these non-radiological chemicals were too poorly correlated with internal organ dose to confound radiation effects.

Exposure to hydrofluoric acid was a unique exposure at all three sites. An exposure assessment; however, was determined to not be feasible. It was not performed for the following reasons to avoid the likelihood of large potential for misclassification: (i) work history data (e.g., department-job) could not be clearly associated with processes with potential for hydrofluoric acid exposure to allow identification or meaningful categorization of potentially exposed workers; (ii) industrial hygiene air monitoring results for hydrofluoric acid were very sparse; and (iii) industrial hygiene air monitoring results for fluoride, and urine bioassay results for fluoride were available but could not be used to distinguish hydrofluoric acid exposure from other fluoride exposures, which were more common at the GDP sites. Workers with potential for uranium exposure generally also had potential for exposure to fluorine-containing compounds that occurred at the GDP sites. As sufficient data were not available to categorize and assess workers' exposure potential to specific fluorine-containing compounds (i.e., those which have the potential to result in acid gas exposure—e.g., hydrofluoric acid, hydrogen fluoride gas, and fluorine gas), this limited the ability to evaluate any possible effects of these compounds on respiratory system or related mortality outcomes.

Asbestos was not identified a priori as an important exposure agent so asbestos exposure was not assessed. In retrospect, the lack of asbestos exposure data was a limitation in our study as the SMR for mesothelioma was elevated. The asbestos literature is extensive and any future GDP asbestos exposure assessment should consider the potential for exposure to the individual mineral species of asbestos that have been associated with mesothelioma (e.g., crocidolite and amosite) [ACGIH, 2001].

Internal exposures to uranium from employment at facilities not recorded in the work history were not quantified which may impact the results. Also, significant uncertainty is associated with intake and dose calculations [Anderson et al., 2016] which are not accounted for in the epidemiological analyses. The largest sources of uncertainty in the intake calculations are due to variation in the enrichment of uranium to which the workers are exposed and inter- and intra-individual variability in 24-hr urine excretion by volume. Particle size and solubility contribute to uncertainty to a lesser extent.

Although, our internal and external dose estimates improved the dose–response analysis, major factors to cancer risk such as family history of cancer, socioeconomic status, and lifestyle factors such as diet, smoking, and alcohol consumption, were still lacking. Additionally, because of better diagnostic capability and medical treatment, the survivability of many cancers has improved. Therefore, a cancer incidence study in this pooled cohort is underway to evaluate health effects in this cohort not revealed in the mortality analysis.

CONCLUSION

We pooled information from previously studied uranium worker cohorts and extended follow-up to examine mortality patterns in the largest group of uranium enrichment workers assembled. Despite evidence of strong "healthy worker effects," there was weak evidence suggesting excess mortality from kidney and bone cancers in these workers compared to the U.S. population. Furthermore, positive but not statistically significant dose–response relations between absorbed kidney dose from internally deposited soluble uranium and kidney cancer and chronic non-malignant kidney diseases were observed. We also observed statistically significantly positive association between red bone marrow dose and multiple myeloma. These findings improve our understanding of the relationship between protracted exposures to uranium compounds and cancer. Continued follow-up of these uranium cohorts may help to clarify exposure-response relationships and thus be useful in evaluating current levels of protection for workers in the uranium fuel cycle.

AUTHORS' CONTRIBUTIONS

All authors meet the authorship criteria: (i) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (ii) drafting the work or revising it critically for important intellectual content; (iii) final approval of the version to be published; and (iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

This study was made possible by the cooperation and support of the U.S. Department of Energy and its employees and contractors. We thank the National Death Index and various state vital statistics office for providing death data and death certificates for the study. We also thank NIOSH staff and contractors for their contribution to the collection, coding, and management of study data.

FUNDING

This work was supported in part through an inter-agency agreement with the U.S. Department of Energy.

ETHICS APPROVAL AND INFORMED CONSENT

This research was approved by the Institutional Review Boards of the National Institute for Occupational Safety and Health (NIOSH) and the Central DOE (CDOE).

DISCLOSURE (AUTHORS)

The authors report no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Rodney Ehrlich declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

REFERENCES

ACGIH. 2001. Asbestos: TLV(R) chemical substances. 7th Edition Cincinnati, Ohio: Documentation, American Conference of Governmental Industrial Hygienists.

Andersen A, Berge SR, Engeland A, Norseth T. 1996. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. Occup Environ Med 53:708–713.

Anderson JL, Apostoaei AI. 2015. Method of analyzing left-censored bioassay data in large cohort studies. J Exp Sci Environ Epidemiol DOI: 10.1038/jes.2015.36 [Epub ahead of print].

Anderson JL, Apostoaei AI, Yiin JH, Fleming DA, Tseng C-Y, Chen P-H. 2016. Internal exposure to uranium in a pooled cohort of gaseous diffusion plant workers. Radiat Prot Dosim 168:471–477.

Anderson JL, Daniels RD. 2006. Bone marrow dose estimates from work-related medical X-ray examinations given between 1943 and 1966 for personnel from five U.S. nuclear facilities. Health Phys 90:544–553.

Anderson JL, Daniels RD, Fleming DA, Tseng CY. 2012. Exposure assessment for a cohort of workers at a former uranium processing facility. J Expo Sci Environ Epidemiol 22:324–330.

Anttila A, Pukkala E, Aitio A, Rantanen T, Karjalainen S. 1998. Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. Int Arch Occup Environ Health 71:245–250.

ATSDR. 2005. Toxicological profile for nickel, Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services.

ATSDR. 1997. Toxicological profile for trichloroethylene, Agency for Toxic Substances and Disease Registry, Public Health Service, U.S. Department of Health and Human Services.

Axelson O, Andersson K, Hogstedt C, Holmberg B, Molina G, de Verdier A. 1978. A cohort study on trichloroethylene exposure and cancer mortality. J Occup Med 20:194–196.

Axelson O, Selden A, Andersson K, Hogstedt C. 1994. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. J Occup Environ Med 36:556–562.

Beaumont JJ, Steenland K, Minton A, Meyer S. 1989. A computer-program for incidence density sampling of controls in case-control studies nested within occupational cohort studies. Am J Epidemiol 129:212–219.

Burdorf A, Dahhan M, Swuste P. 2003. Occupational characteristics of cases with asbestos-related diseases in The Netherlands. Ann Occup Hyg 47:485–492.

Callas PW, Pastides H, Hosmer DW. 1998. Empirical comparisons of proportional hazards, poisson, and logistic regression modeling of occupational cohort data. Am J Ind Med 33:33–47.

Canu IG, Ellis ED, Tirmarche M. 2008. Cancer risk in nuclear workers occupationally exposed to uranium-emphasis on internal exposure. Health Phys 94:1–17.

Chan C, Hughes TS, Muldoon S, Aldrich T, Rice C, Hornung R, Brion G, Tollerud DJ. 2010. Mortality patterns among paducah gaseous diffusion plant workers. J Occup Environ Med 52:725–732.

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

Cragle DL, Hollis DR, Newport TH, Shy CM. 1984. A retrospective cohort mortality study among workers occupationally exposed to metallic nickel powder at the Oak Ridge Gaseous Diffusion Plant. IARC Sci Pub l:57–63.

Doll R, Mathews JD, Morgan LG. 1977. Cancers of the lung and nasal sinuses in nickel workers: A reassessment of the period of risk. Br J Ind Med 34:102–105.

Dupree EA, Cragle DL, Mclain RW, Crawford-Brown DJ, Teta MJ. 1987. Mortality among workers at a uranium processing facility, the Linde Air Products Company Ceramics Plant, 1943–1949. Scand J Work Environ Health 13:100–107.

Dupree EA, Watkins JP, Ingle JN, Wallace PW, West CM, Tankersley WG. 1995. Uranium dust exposure and lung cancer risk in four uranium processing operations. Epidemiology 6:370–375.

Eidson AF. 1994. The effect of solubility on inhaled uranium compound clearance: A review. Health Phys 67:1–14.

Enterline PE, Marsh GM. 1982. Mortality among workers in a nickel refinery and alloy manufacturing plant in West-Virginia. J Natl Cancer Inst 68:925–933.

Faber M. 1979. Twenty-eight years of continuous follow-up of patients injected with thorotrast for cerebral angiography. Environ Res 18:37–43.

Godbold JH, Jr., Tompkins EA. 1979. A long-term mortality study of workers occupationally exposed to metallic nickel at the Oak Ridge Gaseous Diffusion Plant. J Occup Med 21:799–806.

Grimsrud TK, Berge SR, Martinsen JI, Andersen A. 2003. Lung cancer incidence among Norwegian nickel-refinery workers 1953–2000. J Environ Monit 5:190–197.

IARC, Ed. 1995. IARC Monographs on the evaluation of carcinogenic risks to humans: Dry cleaning, some chlorinated solvents and other industrial chemicals. Lyon, France: International Agency for Research on Cancer. Vol. 63.

Langholz B, Goldstein L. 1996. Risk set sampling in epidemiologic cohort studies. Statist Sci 11:35–53.

Langholz B, Richardson DB. 2010. Fitting general relative risk models for survival time and matched case-control analysis. Am J Epidemiol 171:377–383.

Leggett RW. 1989. The behavior and chemical toxicity of U in the kidney: A reassessment. Health Phys 57:365–383.

Lipworth L, Sonderman JS, Mumma MT, Tarone RE, Marano DE, Boice JD, Jr, McLaughlin JK. 2011. Cancer mortality among aircraft manufacturing workers: An extended follow-up. J Occup Environ Med 53:992–1007.

Loomis DP, Wolf SH. 1996. Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947–1990. Am J Ind Med 29:131–141.

McGeoghegan D, Binks K. 2000. The mortality and cancer morbidity experience of workers at the Capenhurst uranium enrichment facility 1946–95. J Radiol Prot 20:381–401.

Mossman BT, Gee JBL. 1989. Asbestos-related diseases. N Engl J Med 320:1121–1130.

NIOSH. 2001. Mortality patterns among uranium enrichment workers at the Portsmouth Gaseous Diffusion Plant, Piketon, Ohio. Final Report Prepared by the Health-related Energy Research Branch, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health.

NIOSH. 2013. NIOSH life table analysis system, LTAS.NET ver. 3.1 Rate File Information. http://www.cdc.gov/niosh/ltas/rates.html. Accessed September 25, 2015.

NRC. 2011. Occupational Radiation Exposure at Commercial Nuclear Power Reactors and Other Facilities 2009: Forty-second Annual Report 31.

Petoussi-Henss N, Bolch WE, Eckerman KF, Endo A, Hertel N, Hunt J, Pelliccioni M, Schlattl H, Zankl M. International Commission on Radiological Protection; International Commission on Radiation Units and Measurements. 2010. Conversion coefficients for radiological protection quantities for external radiation exposures. ICRP Publication 116. Ann ICRP 40(2–5):1–257.

Pinkerton LE, Bloom TF, Hein MJ, Ward EM. 2004. Mortality among a cohort of uranium mill workers: An update. Occup Environ Med 61:57–64.

Ringen K, Dement J, Welch L, Bingham E, Quinn P, Chen A, Haas S. 2015. Mortality of older construction and craft workers employed at department of energy (DOE) nuclear sites: Follow-up through 2011. Am J Ind Med 58:152–167.

Ritz B, Morgenstern H, Crawford-Brown D, Young B. 2000. The effects of internal radiation exposure on cancer mortality in nuclear workers at Rocketdyne/Atomics International. Environ Health Perspect 108:743–751.

Robinson CF, Schnorr TM, Cassinelli RT II, Calvert GM, Steenland NK, Gersic CM, Schubauer-Berigan MK. 2006. Tenth revision U.S. mortality rates for use with the NIOSH life table analysis system. J Occup Environ Med 48:662–667.

SAS Software, Version 9.3, Copyright 2002–2010. SAS Institute Inc., Cary, NC.

Schubauer-Berigan MK, Hein MJ, Raudabaugh WM, Ruder AM, Silver SR, Spaeth S, Steenland K, Petersen MR, Waters KM. 2011. Update of the NIOSH life table analysis system: A person-years analysis program for the windows computing environment. Am J Ind Med 54:915–924.

Scott CS, Jinot J. 2011. Trichloroethylene and cancer: Systematic and quantitative review of epidemiologic evidence for identifying hazards. Int J Environ Res Public Health 8:4238–4172.

Shannon HS, Julian JA, Roberts RS. 1984. A mortality study of 11,500 nickel workers. J Natl Cancer Inst 73:1251–1258.

Shannon HS, Walsh C, Jadon N, Julian JA, Weglo JK, Thornhill PG, Cecutti AG. 1991. Mortality of 11,500 nickel workers-extended follow up and relationship to environmental conditions. Toxicol Ind Health 7:277–294.

Shindell S, Ulrich S. 1985. A cohort study of employees of a manufacturing plant using trichlorethylene. J Occup Environ Med 27:577–579.

Spirtas R, Stewart PA, Lee JS, Marano DE, Forbes CD, Grauman DJ, Pettigrew HM, Blair A, Hoover RN, Cohen JL. 1991. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiologic results. Br J Ind Med 48:515–530.

Steenland K, Beaumont J, Spaeth S, Brown D, Okun A, Jurcenko L, Ryan B, Phillips S, Roscoe R, Stayner L, et al. 1990. New developments in the life table analysis system of the national institute for occupational safety and health. J Occup Med 32:1091–1098.

Stebbings JH, Lucas HF, Stehney AF. 1984. Mortality from cancers of major sites in female radium dial workers. Am J Ind Med 5:435–459.

Tsai SP, Waddell LC Jr., Gilstrap EL, Ransdell JD, Ross CE. 1996. Mortality among maintenance employees potentially exposed to asbestos in a refinery and petrochemical plant. Am J Ind Med 29:89–98.

Yiin JH, Anderson JL, Daniels RD, Seel EA, Fleming DA, Waters KM, Chen P. 2009. A nested case-control study of multiple myeloma risk and uranium exposure among workers at the oak ridge gaseous diffusion plant. Radiat Res 171:637–645.

Zhivin S, Canu IG, Samson E, Laurent O, Grellier J, Collomb P, Zablotska LB, Laurier D. 2016. Mortality (1968–2008) in a French cohort of uranium enrichment workers potentially exposed to rapidly soluble uranium compounds. Occup Environ Med 73:167–174.

Zhivin S, Laurier D, Canu IG. 2014. Health effects of occupational exposure to uranium: Do physicochemical properties matter? Int J Radiat Biol 90:1104–1113.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Institution where work performed: National Institute for Occupational Safety and Health.