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RESEARCH ARTICLE

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Dose-response relationships between internally-deposited uranium and select health outcomes in gaseous diffusion plant workers, 1948-2011

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Objective: To examine dose-response relationships between internal uranium exposures and select outcomes among a cohort of uranium enrichment workers.

Methods: Cox regression was conducted to examine associations between selected health outcomes and cumulative internal uranium with consideration for external ionizing radiation, work-related medical X-rays and contaminant radionuclides technetium (^{99}Tc) and plutonium (^{239}Pu) as potential confounders.

Results: Elevated and monotonically increasing mortality risks were observed for kidney cancer, chronic renal diseases, and multiple myeloma, and the association with internal uranium absorbed organ dose was statistically significant for multiple myeloma. Adjustment for potential confounders had minimal impact on the risk estimates.

Conclusion: Kidney cancer, chronic renal disease, and multiple myeloma mortality risks were elevated with increasing internal uranium absorbed organ dose. The findings add to evidence of an association between internal exposure to uranium and cancer. Future investigation includes a study of cancer incidence in this cohort.

KEYWORDS
absorbed organ doses, dose-response, gaseous diffusion, radiation, uranium enrichment

1 | INTRODUCTION

Due to the increasing global demand for nuclear power, fuel cycle industries are currently undergoing expansion in the U.S. and elsewhere (http://world-nuclear.org/information-library/current-and-future-generation/the-nuclear-renaissance.aspx, Accessed 3/1/2017). Operations at fuel cycle facilities present a potential for worker exposures to various uranium compounds that are known or suspected to cause adverse human health effects. Yiin et al[1] examined the patterns of cause-specific mortality in a combined cohort of 29 303 workers from three gaseous diffusion plants (GDP) in the United States: 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). Although workers at these former uranium enrichment facilities had significantly lower standardized mortality ratios (SMRs) for most diseases than the U.S. population, excess SMRs that were not statistically significant were observed in kidney cancer, bone cancer, non-Hodgkin's lymphoma (NHL), and chronic renal diseases. In an internal comparison with dose-response analysis, positive relations were observed between internal absorbed organ doses and mortality from kidney cancer, chronic renal diseases, and multiple myeloma.

This aim of the current study was a more in-depth examination of the dose-response relationships found for these health outcomes in the previously assembled cohort of uranium enrichment workers by including estimated doses to the kidney, bone surface, and red bone marrow from contaminant radionuclides plutonium-239 (^{239}Pu) and

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technetium (^{99}Tc) in recycled uranium as potential confounders. This current study also includes evaluation of linear-quadratic and restricted cubic splines regression models in addition to the linear excess relative risk (ERR) model reported in the previous study.[1] The clarification of the relationship between kidney and red bone marrow dose from occupational exposure to uranium and health risk will aid in evaluating current levels of protection and ultimately reduce cancer mortality for workers in the uranium fuel cycle.

2 | MATERIALS AND METHODS

2.1 | Study cohort

The details on the cohort and case ascertainment were described previously.[1] Briefly, the study subjects included a pooled cohort of workers from three uranium enrichment facilities: K-25, PORTS, and PGDP. 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, and the end of major facility construction at K-25 to minimize inclusion of short-term and construction workers.

Vital status was ascertained through 2011 using the National Death Index (NDI) Plus service, 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.

2.2 | Internal uranium exposure

A detailed description of the methods is found in the papers by Anderson et al[2] and Anderson and Apostoaei.[3] Briefly, uranium gravimetric and radioactivity concentration for >600 000 urine samples was abstracted from facility bioassay records. For workers with no reported bioassay data, urine uranium excretion was imputed using department-specific uranium concentrations averaged from reported bioassay data. Novel methods were used to estimate effective enrichment for workers by linking department numbers from work history records with calculated department- and facility-specific enrichments. Workers were then assigned an enrichment level for each record in their work history associated with a department number and then an effective enrichment was calculated for each worker. The effective enrichment was converted to specific activity which was used to convert gravimetric uranium data to radioactivity concentration. Reported and imputed bioassay data were used to calculate intakes assuming a chronic exposure from the first date through the last date of employment. Annual absorbed organ doses to lungs, bone surface, red bone marrow, kidneys, and liver were calculated from the intakes and accumulated for each worker until the date of last observation (ie, date of death, date lost to follow-up, or the study end date of December 31, 2011). Absorbed organ doses to lungs and liver are not used in this report as they are not applicable to the health outcomes investigated.

2.3 | Exposure to contaminant radionuclides

Individual bioassay data consisting of activity concentrations of ^{238}Pu, ^{239}Pu, ^{237}Np, and ^{99}Tc or gross beta were abstracted from electronic databases, and historical plant records were examined to ascertain bioassay program procedures, analytical methods, and detection levels for the radionuclides of interest. Urinalysis data for contaminant radionuclides were available for <10% of the cohort, so bioassay data were imputed using the same methods as for uranium and are described in detail by Anderson et al.[4] Intakes were calculated assuming a chronic exposure from the first date through the last date of employment. Absorbed dose to the bone surface, red bone marrow, and kidney were calculated as these were the target organs associated with a priori outcomes of interest. For technetium, the current International Commission on Radiological Protection (ICRP)[5] biokinetic model and the new systemic model proposed by Leggett and Giussani[6] were used for intake and organ dose calculation. Organ doses from exposure to ^{99}Tc were estimated for 66, 9.7, and 12% of the K-25, PORTS, and PGDP cohorts, respectively. Individuals with no reported or imputed bioassay data were assumed to be unexposed. This report also estimated intakes using the new systemic model for technetium, which resulted in significantly higher calculated intakes (by a factor of 1.5) and doses (by a factor of 30, 8, and 15 for bone surfaces, red bone marrow, and kidneys, respectively) for the organs of interest than those calculated using the current ICRP model. For ^{239}Pu exposure, organ doses were estimated for about 16% of the K-25 cohort. There were too few reported data (<0.1%) for ^{238}Pu and ^{237}Np in the combined cohort, and ^{239}Pu in PORTS or PGDP for their inclusion in analyses.

2.4 | Ionizing radiation exposure from external sources

The dose estimation process for external ionizing radiation was described in detail in Yiin et al.[1] For each worker, all sources of external ionizing radiation were included. Exposure data from other employment were obtained from the U.S. Department of Energy's Radiation Exposure Monitoring System (REMS) and the U.S. Nuclear Regulatory Commission's Radiation Exposure Information and Reporting System (REIRS). Dose from routine photofluorographic chest X-rays performed at K-25 mid-1945 through 1956 was also included.[7–8]

2.5 | Statistical analysis

Cox proportional hazards regression was performed to estimate the effect of exposure on cause-specific mortality. For each selected outcome, risk sets for each case included all cohort members who started working at a younger age than the index case's age at death (effectively matching on age). Risk sets were further matched on gender, race, birth date (within 5 years), and plant.[9,10] The a priori outcomes of interest included kidney and bone cancers where internally-deposited uranium primarily accumulates,[11] individual hematopoietic cancers (ie, NHL, leukemia, and multiple myeloma),[8,12,13] and chronic and unspecified nephritis and renal disease (including chronic renal failure, nephritis, renal sclerosis, and other nephritic syndromes grouped as a UCOD

category in the NIOSH-92 rate file[14]). Methods described by Langholz and Richardson[15] were used to fit general non-loglinear relative risk models. The general model form is $H(X_1) = H(X_0)^*f(X_1)$, where H(.) is the hazard rate at a specified dose, and f(.) is the effect of dose on the hazard relative to a reference dose, X_0.

Several regression models were used to evaluate the relation between each outcome and corresponding internal uranium organ dose. The primary models included: 1) linear, $f(X) = 1 + \beta X$ where β is the estimated model parameter for the main exposure of interest X; and 2) linear-quadratic, $f(X) = 1 + \beta_1 X + \beta_2 X^2$. Additionally, a categorical model was examined with three exposed groups, with cut points at the 33rd and 66th percentile of the exposed cases' exposure distribution, compared to the non-exposed reference group. The shape of the dose-response was further examined by restricted cubic splines (RCS) with three knots at equally spaced points (ie, at the 95th percentile and at 1/3 and 2/3 of the 95th percentile) across the dose distribution. The Akaike Information Criterion (AIC)[16] was used to evaluate model fit. In addition, for each outcome, a grid search was used to find the lag that maximized the likelihood function.[17] The hazard ratio (HR) at 50th and 75th percentiles of dose compared with the non-exposed and corresponding 95% profile likelihood-based confidence intervals (CIs) were derived with restriction to workers with no more than the 95th percentile of dose. To account for choosing the best fitting lag for each model, 95% CIs were calculated with 2 degrees of freedom.[18]

TABLE 1 Demographics of gaseous diffusion plant workers with follow-up through 12/31/2011

	Primary facility							
	K-25		PORTS		PGDP		All facilities	
Characteristics	*n* (%) or mean (SD)		*n* (%) or mean (SD)		*n* (%) or mean (SD)		*n* (%) or mean (SD)	
Sex								
Male	13 529	(80%)	5772	(83%)	4450	(83%)	23 751	(81%)
Female	3449	(20%)	1163	(17%)	940	(17%)	5552	(19%)
Race								
White	15 931	(94%)	6489	(94%)	4861	(90%)	27 281	(93%)
Other race	1046	(6%)	441	(6%)	529	(10%)	2016	(7%)
Unknown[a]	1	(0%)	5	(0%)	0	(0%)	6	(0%)
Age at hire								
<20	1682	(10%)	663	(10%)	273	(5%)	2618	(9%)
20 to <25	5023	(30%)	2074	(30%)	1653	(31%)	8750	(30%)
25 to <30	4090	(24%)	1610	(23%)	1469	(27%)	7169	(24%)
30 to <35	2523	(15%)	1063	(15%)	855	(16%)	4441	(15%)
35 to <40	1571	(9%)	718	(10%)	505	(9%)	2794	(10%)
40 to <50	1613	(10%)	601	(9%)	492	(9%)	2706	(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	5656	(33%)	60	(1%)	2	(0%)	5718	(20%)
1950-1959	4133	(24%)	2787	(40%)	2102	(39%)	9022	(31%)
1960-1969	1750	(10%)	341	(5%)	372	(7%)	2463	(8%)
1970-1979	4913	(29%)	2427	(35%)	1793	(33%)	9133	(31%)
1980+	526	(3%)	1320	(19%)	1121	(21%)	2967	(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	8087	(48%)	4458	(64%)	3491	(65%)	16 036	(55%)
Deceased	8891	(52%)	2477	(36%)	1899	(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 2 Summary statistics of the cumulative absorbed dose (mGy) by primary facility and all facilities

	Primary facility			All facilities
Exposure estimate	**K-25 *n* = 16 978**	**PORTS *n* = 6935**	**PGDP *n* = 5390**	***n* = 29 303**
Internal uranium absorbed organ dose (mGy)				
Kidneys				
Average (SD)	1.28 (8.50)	0.33 (1.79)	0.69 (1.57)	0.95 (6.57)
50%	0.49	0.00	0.31	0.30
75%	1.21	0.25	0.87	0.93
90%	2.36	0.84	1.64	1.92
95%	3.48	1.43	2.35	2.91
Max	513	88.6	46.1	513
Bone surface				
Average (SD)	3.22 (22.7)	0.82 (4.34)	1.68 (3.86)	2.37 (17.5)
50%	1.21	0.00	0.75	0.74
75%	2.95	0.60	2.12	2.30
90%	5.87	2.04	4.01	4.78
95%	8.72	3.53	5.85	7.32
Max	1491	212	129	1491
Red bone marrow				
Average (SD)	0.38 (2.63)	0.09 (0.49)	0.20 (0.47)	0.28 (2.03)
50%	0.14	0.00	0.09	0.09
75%	0.35	0.07	0.26	0.27
90%	0.69	0.23	0.49	0.56
95%	1.02	0.40	0.70	0.86
Max	172	24.5	13.9	172
External radiation organ dose[a] (mGy)				
Kidneys				
Average (SD)	21 (24)/3.8 (12)	2.1 (4.1)	4.5 (11)	3.5 (11)
50%	13/1.32	0.70	0.76	1.08
75%	37/3.65	2.24	3.63	3.28
90%	54/6.37	5.28	10.5	6.68
Bone surface				
Average (SD)	58 (64)/5.4 (18)	3.0 (5.9)	6.4 (16)	5.0 (16)
50%	39/1.90	1.00	1.10	1.55
75%	103/5.25	3.22	5.23	4.72
90%	157/9.15	7.59	15.0	9.61
Red bone marrow				
Average (SD)	25 (29)/4.8 (16)	2.6 (5.3)	5.7 (15)	4.5 (14)
50%	15/1.70	0.89	0.98	1.38
75%	44/4.69	2.87	4.67	4.21
90%	63/8.18	6.78	13.4	8.58
Dose to $^{99}Tc/^{239}Pu$[b] (mGy)				
Kidneys				
Average (SD)	95 (2070)/0.18 (1.22)	4.1 (281)	6.6 (307)	57 (1588)
50%	0.13/0.00	0.00	0.00	0.00
75%	0.37/0.00	0.00	0.00	0.20

(Continues)

TABLE 2 (Continued)

	Primary facility			All facilities
Exposure estimate	K-25 *n* = 16 978	PORTS *n* = 6935	PGDP *n* = 5390	*n* = 29 303
90%	0.83/0.24	0.00	0.03	0.59
Bone surface				
Average (SD)	73 (1619)/14 (99)	3.4 (230)	4.7 (223)	44 (1241)
50%	0.10/0.00	0.00	0.00	0.00
75%	0.27/0.00	0.00	0.00	0.14
90%	0.60/18	0.00	0.02	0.41
Red bone marrow				
Average (SD)	51 (1106)/2.0 (14)	2.2 (150)	3.5 (164)	30 (848)
50%	0.07/0.00	0.00	0.00	0.00
75%	0.20/0.00	0.00	0.00	0.11
90%	0.43/2.73	0.00	0.01	0.30

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

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

[b]Technetium (^{99}Tc) for primary facility and combined facilities, plutonium (^{239}Pu) for K-25 only.

As in the previous study, analyses were also conducted with adjustment for potential confounding exposures such as external ionizing radiation dose with or without X-rays and dose from contaminant radionuclides (^{239}Pu and ^{99}Tc), by including one potential confounder (entered as a continuous variable) at a time in the model. Non-radiological exposures to nickel and trichloroethylene (TCE) were not included in the present study as they were unlikely confounders due to poor correlations with internal uranium organ doses in the previous report.[1] All analyses were conducted using SAS software.[19]

3 | 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. There were 16 978, 6 935, and 5 390 workers with K-25, PORTS, and PGDP, respectively, as the primary facility. The cohort was mostly male (81%) and white (93%), and had an average age at hire of 29.2 years and employment duration of 13.9 years. Approximately 45% of the cohort was deceased at the end of follow-up (Table 1).

Bioassay data on internal uranium were available for 58% of the cohort and were imputed for an additional 33%. The remaining 9% who had no reported or imputed bioassay data were assumed to be unexposed. K-25 had the highest number of workers with imputed uranium data (45% of the cohort). Only 13% of PORTS workers had imputed uranium data. Table 2 shows the distributions of cumulative organ absorbed doses calculated from reported and imputed bioassay data. Estimated mean cumulative internal uranium organ doses in the combined cohort ranged from 0.28 mGy in red bone marrow and 0.95 mGy in kidneys, to 2.37 mGy in bone surface. Internal uranium doses were highest among K-25 workers at mean, median, 75 and 95% of exposure, likely due to earliest operation and longest duration. Overall the doses were low but not unexpected compared to exposure at other facilities. External doses were also highest among K-25 workers due to dose from work-related medical X-ray examinations. The range of cumulative doses from ^{99}Tc was very wide with a few extreme values resulting in higher means and large standard deviations (SD) in all facilities. For example, the median and 90% of cumulative dose from ^{99}Tc in kidneys at K-25 were 0.13 and 0.83 mGy, respectively, but the mean was 95 with SD of 2070. Because medical X-ray examinations were performed at K-25 only and there were very few workers with estimated ^{239}Pu exposures at other facilities, summary statistics and analyses with external ionizing radiation dose with X-rays and dose from contaminant radionuclide ^{239}Pu were restricted to K-25 workers only. Workers with extremely high exposures (>95th percentile) were excluded from regression analyses, as these high exposures were due to extreme bioassay values that may have been part of non-routine monitoring immediately following an incident or that may have been used as spikes for quality control.

Spearman correlation coefficients suggested that the estimated organ doses from internal uranium exposure were moderately associated with external radiation dose and ^{99}Tc dose to kidney, red bone marrow, and bone surface, among the combined cohort and K-25 only workers. There appeared to be more correlation between internal uranium and external radiation in the combined cohort (approximately 0.44 for each of the three organ doses, $P < 0.01$) than among K-25 only workers (about 0.35, $P < 0.01$). Note that the external radiation dose for K-25 workers included dose from medical X-ray examinations. The correlation coefficients between internal uranium dose and ^{99}Tc dose in the combined cohort or K-25 only workers were consistent and ranged from 0.40 to 0.43 ($P < 0.01$).

TABLE 3 Hazard ratios and 95% confidence intervals of internal absorbed organ doses at 50th and 75th percentiles of dose vs. non-exposed, and with adjustment for external radiation without X-ray or contaminant radionuclide ^{99}Tc: combined cohort

Cause of death/target organ	Cases	Lag in years[a]	50th percentile				75th percentile			
			mGy	Internal uranium	With external	With ^{99}Tc	mGy	Internal uranium	With external	With ^{99}Tc
Linear										
Kidney cancer/kidneys	101	35	0.30	1.28 (0.94, 2.06)	1.23 (0.92, 2.05)	1.27 (0.94, 2.09)	0.93	1.86 (0.83, 4.30)	1.73 (0.77, 4.26)	1.85 (0.81, 4.45)
NHL/RBM	151	9	0.09	0.99 (0.92, 1.12)	1 (0.99, 1.15)	0.98 (0.91, 1.12)	0.27	0.96 (0.75, 1.38)	1 (0.97, 1.48)	0.94 (0.72, 1.36)
All leukemia/RBM	111	2	0.09	1.08 (0.96, 1.31)	1.07 (0.95, 1.30)	1.11 (0.97, 1.39)	0.27	1.24 (0.87, 1.94)	1.21 (0.86, 1.91)	1.34 (0.92, 2.19)
Multiple myeloma/RBM	65	24	0.09	**1.78 (1.11, 3.80)**	**1.60 (1.04, 3.37)**	**1.74 (1.09, 3.74)**	0.27	**3.42 (1.35, 9.64)**	**2.84 (1.12, 8.32)**	**3.28 (1.27, 9.46)**
Renal diseases/kidneys	107	30	0.30	1.04 (0.90, 1.36)	1.04 (0.90, 1.40)	1.04 (0.90, 1.36)	0.93	1.12 (0.68, 2.12)	1.12 (0.68, 2.23)	1.11 (0.68, 2.12)
Linear-quadratic										
Kidney cancer/kidneys	101	35	0.30	1.30 (NC, 2.35)	1.23 (NC, 2.35)	1.29 (NC, 2.40)	0.93	1.88 (NC, 4.38)	1.72 (0.66, 4.37)	1.86 (NC, 4.49)
NHL/RBM	151	9	0.09	0.84 (NC, 1.12)	0.87 (NC, 1.17)	0.83 (NC, 1.10)	0.27	0.70 (NC, 1.28)	0.75 (NC, 1.40)	0.68 (NC, 1.25)
All leukemia/RBM	111	2	0.09	0.91 (NC, 1.31)	0.89 (NC, 1.28)	0.94 (NC, 1.40)	0.27	0.91 (NC, 1.82)	0.86 (NC, 1.76)	1.02 (0.93, 2.07)
Multiple myeloma/RBM	65	24	0.09	**2.30 (1.06, 5.70)**	**2.00 (NC, 5.11)**	**2.24 (1.02, 5.63)**	0.27	**3.86 (1.48, 10.7)**	**3.23 (1.19, 9.47)**	**3.73 (1.38, 10.6)**
Renal diseases/kidneys	107	30	0.30	DNC	DNC	DNC	0.93	DNC	DNC	DNC

Bold values indicate statistically significant results.

NHL, Non-Hodgkin's lymphoma; RBM, red bone marrow; mGy, milligray; DNC, did not converge; NC, not calculable.

[a]lag with the best fit for the model; no bone cancer results as neither model converged.

Tables 3 and 4 show the linear and linear-quadratic model results of estimated hazard ratios of internal uranium absorbed organ doses at the 50th and 75th percentiles of dose compared to the non-exposed, with or without adjustment for external radiation/X-ray dose or contaminant radionuclide dose. The lags with the best fit for the model varied by cancer type, ranging from 2 years for leukemia and 35 years for kidney cancer. Many of the estimates for the linear-quadratic models had lower 95% confidence intervals that were not calculable, which indicated imprecision for these statistically non-significant results. The linear-quadratic model for chronic kidney diseases did not converge.

There were 101 kidney cancer deaths in the combined cohort, and the lag with the best model fit was 35 years. The better fitted kidney cancer model was linear, although the difference in AIC values was small when compared with the linear-quadratic model (Figure 1). Monotonically, but non-statistically significant, increasing kidney cancer mortality risk was observed, with the HR increasing from 1.28 (95%CI 0.94-2.06) at 50th to 1.86 (95%CI 0.83-4.30) at 75th percentile of internal uranium dose. Similar results were observed with adjustment for external dose (with or without including medical X-ray) or contaminant radionuclide (^{99}Tc or ^{239}Pu), either in the combined cohort or K-25-only workers.

There were 11 bone cancer deaths in the combined cohort, eight of which were among K-25 workers. There was lack of convergence as neither the linear nor the linear-quadratic model yielded risk estimates, but both the categorical and spline models showed a dip in risk estimates among the highest exposed (Figure 1). For NHL and leukemia, there was virtually no difference in AIC values between the linear and linear-quadratic models, although examining the shape of the dose-response shows that the linear-quadratic was closer to the spline model (Figure 1). HRs at the 50th and 75th percentiles in linear-quadratic models for NHL and leukemia were lower than or close to 1.

Elevated and monotonically increasing multiple myeloma mortality risk was observed in the combined cohort and was statistically significant in the linear model. The HR increased from 1.78 (95%CI 1.11-3.80) at 50th percentile to 3.42 (95%CI 1.35-9.64) at 75th percentile of exposure. The significant results did not change when external radiation dose or ^{99}Tc dose was included in the analysis. The HRs were higher in the linear-quadratic model. Similar trends were observed among K-25 workers, although the risk estimates were not statistically significant in the linear model.

For chronic kidney diseases, monotonically, but non-statistically significant, increasing risk was observed among K-25 workers, with the HR increasing from 1.15 (95%CI 0.92-1.86) at 50th to 1.48 (95%CI 0.76-3.67) at 75th percentile of internal uranium dose using the linear model. HRs in the combined cohort increased slightly from 1.04 at 50th to 1.12 at 75th percentile of dose. Adjustment for external dose or contaminant radionuclide had minimal impact on the HR estimates.

4 | DISCUSSION

In the previous study, we pooled information from uranium worker cohorts and extended follow-up to examine mortality patterns in the

TABLE 4 Hazard ratios and 95% confidence intervals of internal absorbed organ doses at 50th and 75th percentiles of dose vs. non-exposed, and with adjustment for external radiation plus X-ray or contaminant radionuclide ^{239}Pu: K-25 workers only

			50th percentile				75th percentile			
Cause of death/target organ	Cases	Lag in years[a]	mGy	Internal uranium	With external	With ^{239}Pu	mGy	Internal uranium	With external+	With ^{239}Pu
Linear										
Kidney cancer/kidneys	74	35	0.30	1.25 (0.88, 2.17)	1.22 (0.91, 2.22)	1.23 (0.91, 2.13)	0.93	1.77 (0.62, 4.63)	1.70 (0.72, 4.79)	1.71 (0.73, 4.50)
NHL/RBM	84	9	0.09	1 (0.99, 1.19)	1 (0.98, 1.19)	0.99 (0.95, 1.18)	0.27	1 (0.97, 1.59)	0.99 (0.92, 1.58)	0.97 (0.85, 1.55)
All leukemia/RBM	75	2	0.09	1.08 (0.95, 1.37)	1.07 (0.95, 1.35)	1.09 (0.95, 1.38)	0.27	1.26 (0.86, 2.15)	1.23 (0.84, 2.08)	1.27 (0.86, 2.19)
Multiple myeloma/RBM	44	24	0.09	1.55 (0.96, 3.83)	1.38 (0.91, 3.19)	1.49 (0.94, 3.60)	0.27	2.70 (0.87, 9.72)	2.17 (0.73, 7.77)	2.51 (0.82, 9.04)
Renal diseases/kidneys	53	30	0.30	1.15 (0.92, 1.86)	1.16 (0.92, 1.96)	1.12 (0.91, 1.75)	0.93	1.48 (0.76, 3.67)	1.51 (0.76, 3.97)	1.36 (0.72, 3.34)
Linear-quadratic										
Kidney cancer/kidneys	74	35	0.30	1.25 (NC, 2.48)	1.21 (NC, 2.58)	1.21 (NC, 2.41)	0.93	1.77 (NC, 4.73)	1.68 (NC, 4.96)	1.69 (NC, 4.58)
NHL/RBM	84	9	0.09	0.86 (NC, 1.23)	0.85 (NC, 1.22)	0.85 (NC, 1.21)	0.27	0.73 (NC, 1.55)	0.72 (NC, 1.53)	0.71 (NC, 1.50)
All leukemia/RBM	75	2	0.09	0.89 (NC, 1.38)	0.89 (NC, 1.36)	0.90 (NC, 1.40)	0.27	0.89 (NC, 2.01)	0.86 (NC, 1.94)	0.90 (NC, 2.05)
Multiple myeloma/RBM	44	24	0.09	**2.67 (1.14, 8.04)**	**2.29 (1.01, 6.86)**	**2.55 (1.10, 7.63)**	0.27	**3.76 (1.23, 12.8)**	3.10 (1.00, 10.8)	**3.53 (1.14, 12.1)**
Renal diseases/kidneys	53	30	0.30	DNC	DNC	DNC	0.93	DNC	DNC	DNC

Bold values indicate statistically significant results.

NHL, Non-Hodgkin's lymphoma; RBM, red bone marrow; mGy, milligray; DNC, did not converge; NC, not calculable.

[a]lag with the best fit for the model; no bone cancer results as neither model converged.

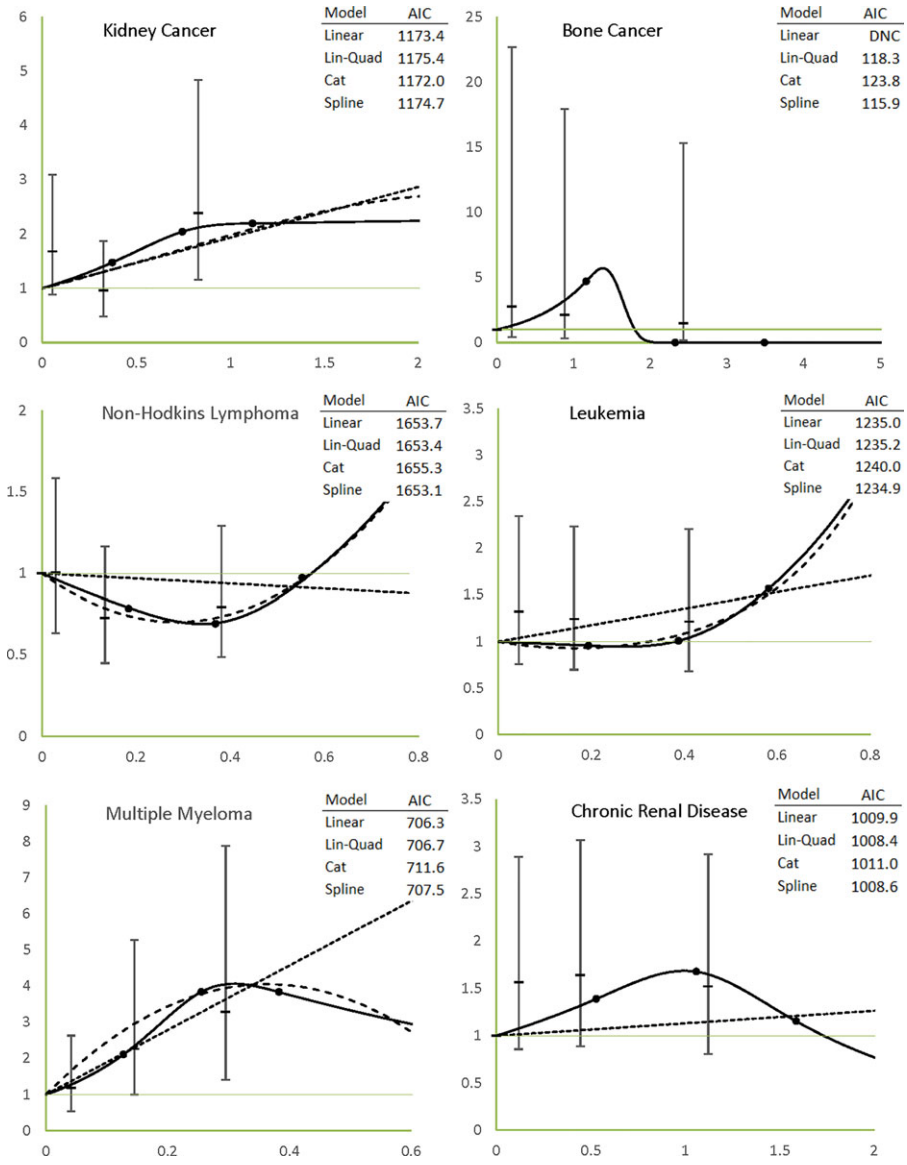

FIGURE 1 Hazard ratios (HR; Y axis) versus internal uranium organ doses (in mGy; X axis) in various models in combined cohort. AIC: Akaike Information Criterion; Linear – – –; Linear-Quadratic (Lin-Quad) – – –; Categorical (Cat): vertical lines; Spline: solid line with 3 knots at equally spaced point

largest group of uranium enrichment workers assembled. Despite evidence of a strong "healthy worker effect" as found in a recent French uranium enrichment worker study,[20] there was weak evidence in the standardized mortality ratio (SMR) analysis suggesting excess mortality from kidney and bone cancers in these workers compared to the U.S. population. Furthermore, internal comparison using the linear ERR model showed 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.[1] We also observed a statistically significant positive association between red bone marrow dose and multiple myeloma.

Major factors to cancer risk such as family history of cancer, socioeconomic status, and lifestyle factors (diet, smoking, and alcohol consumption), were still lacking in the study. However, we improved upon the previous study by adopting various regression models and including contaminant radionuclides in recycled uranium as potential confounders to clarify the dose-response relationships. The ionizing radiation exposure from both external sources and work-related X-rays is due to relatively low-energy gamma rays with a relative biological effectiveness (RBE) of unity, whereas the internal exposure was due mostly to the alpha-emitting radioisotopes of uranium and plutonium and the beta emissions from ^{99}Tc. The analyses reported in this study indicate that there is no statistically significant confounding by external ionizing radiation exposure or internal exposure to the contaminant radionuclides.

Our best fit models for certain cancers had lags longer than the 10-20 years usually used in other studies. Daniels et al[17] reported that temporal risk patterns appeared to vary by cancer type, and the excess risk of certain cancers may span several decades. Our report of late onset of exposure-related mortality also suggested additional follow-up of these workers to fully describe their lifetime risks.

The suggestion of a dose-response between internal uranium exposure and kidney cancer and non-malignant kidney disease is not unexpected given that the kidney is a target organ for soluble uranium.[21] However, previous studies of uranium-exposed cohorts have not indicated any excess risk for these health outcomes, possibly due to low statistical power or limited cases. Bone surface is also a target organ for soluble uranium. Neither the linear nor the linear-quadratic models gave point estimates for bone cancer mortality, but the categorical and spline models showed attenuated risk among the highest exposed. Nonlinear dose-responses with an increasing slope at lower exposures followed by attenuated risk at higher exposures are common to occupational studies.[22] While a healthy worker survivor effect could cause negative or attenuated dose-response, it seems less likely to explain our findings in NHL and leukemia, as relatively short latency periods in these diseases (best fitted lags of 7-9 years) tend to reduce a healthy worker survivor effect. Also, the effect of imputing doses is unknown and could not be evaluated in this study due to the low number of deaths from the outcomes of interest. However, the effect of imputation on dose-response modeling will be investigated in a future study of cardiovascular disease mortality.

The finding of a statistically significant dose-response for bone marrow dose from internally-deposited uranium and multiple myeloma mortality is consistent with a previous case-control study of multiple myeloma mortality in the K-25 cohort.[8] Multiple myeloma is a cancer resulting in proliferation of abnormal plasma cells which crowd out normal bone marrow cells, such as red and white blood cells and platelets. Renal insufficiency has been associated with decreased overall survival among multiple myeloma patients,[23] so it is possible that uranium exposure of the kidneys results in increased mortality. A forthcoming cancer incidence study will be able to compare myeloma incidence to mortality in the cohort.

5 | CONCLUSION

Consistent with previous findings, we observed a statistically significantly positive association between red bone marrow dose and multiple myeloma mortality using different regression models in this pooled uranium worker cohort. Elevated and monotonically increasing mortality risks were also observed for kidney cancer and chronic renal diseases. Adjustment for potential confounders such as external radiation and contaminant radionuclides in recycled uranium did not alter the results in terms of direction and significance. These findings further improve our understanding of the relation between protracted exposures to uranium compounds and cancers and chronic renal diseases. Continued follow-up of these uranium cohorts may help to clarify dose-response relations and be useful in evaluating current levels of protection for workers in the uranium fuel cycle.

AUTHORS' CONTRIBUTIONS

All authors meet the authorship criteria: 1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; 2) drafting the work or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) 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.

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INSTITUTION AND ETHICS APPROVAL

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. The Department of Energy had no decision-making power with respect to the design, conduct, analysis, write-up or decision to publish with respect to the current study.

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven B. Markowitz 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 official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

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